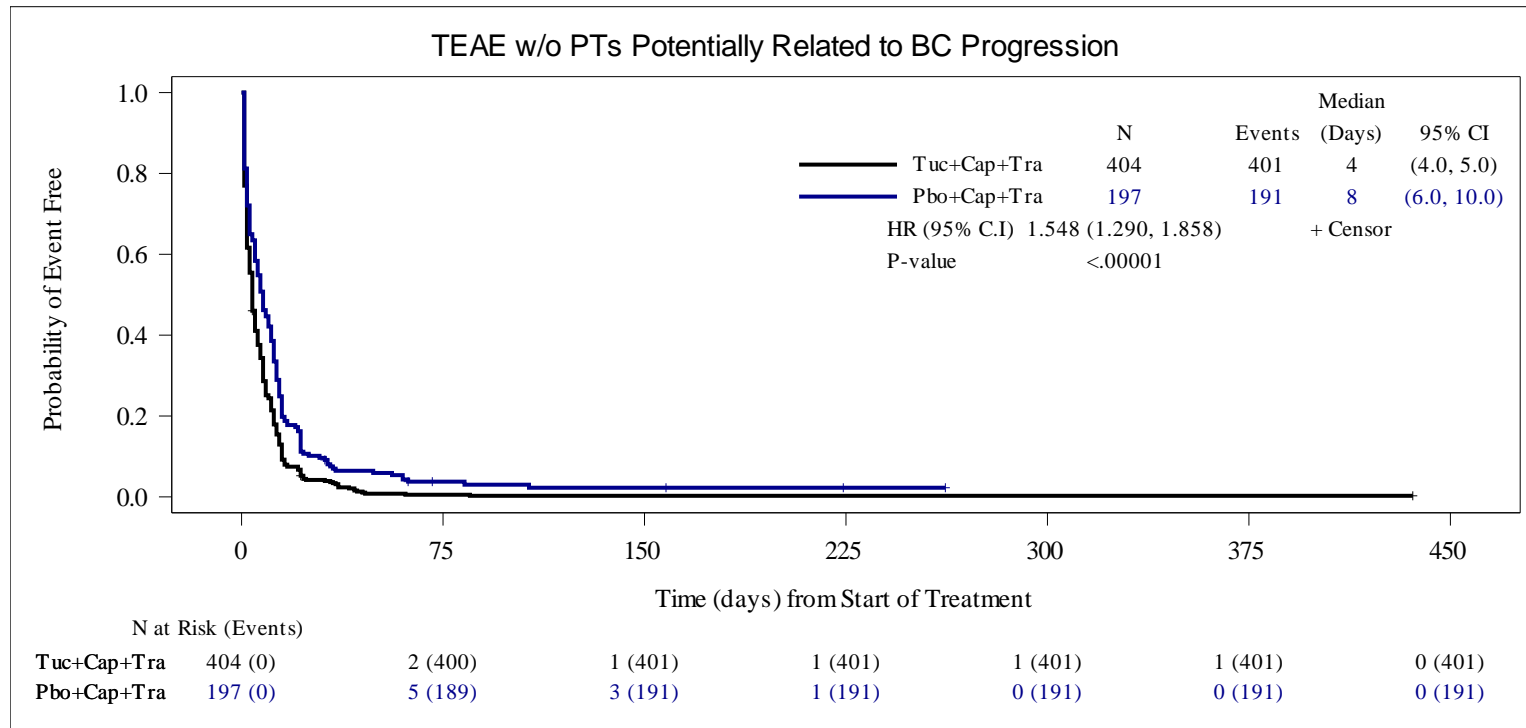


Seattle Genetics Protocol ONT-380-206

**Figure 2.5.2 Kaplan-Meier Estimate of Time to First Onset of Treatment-Emergent Adverse Events (Sensitivity Analysis)
Safety Analysis Set**



HR is computed from the Cox proportional hazards model using stratification factors (Presence or history of brain metastases: Yes/No, ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization. When the number of subjects with at least one event was ≤ 30 , an unstratified Cox model was run.

Two-sided p-value calculated from Cox proportional hazards model .

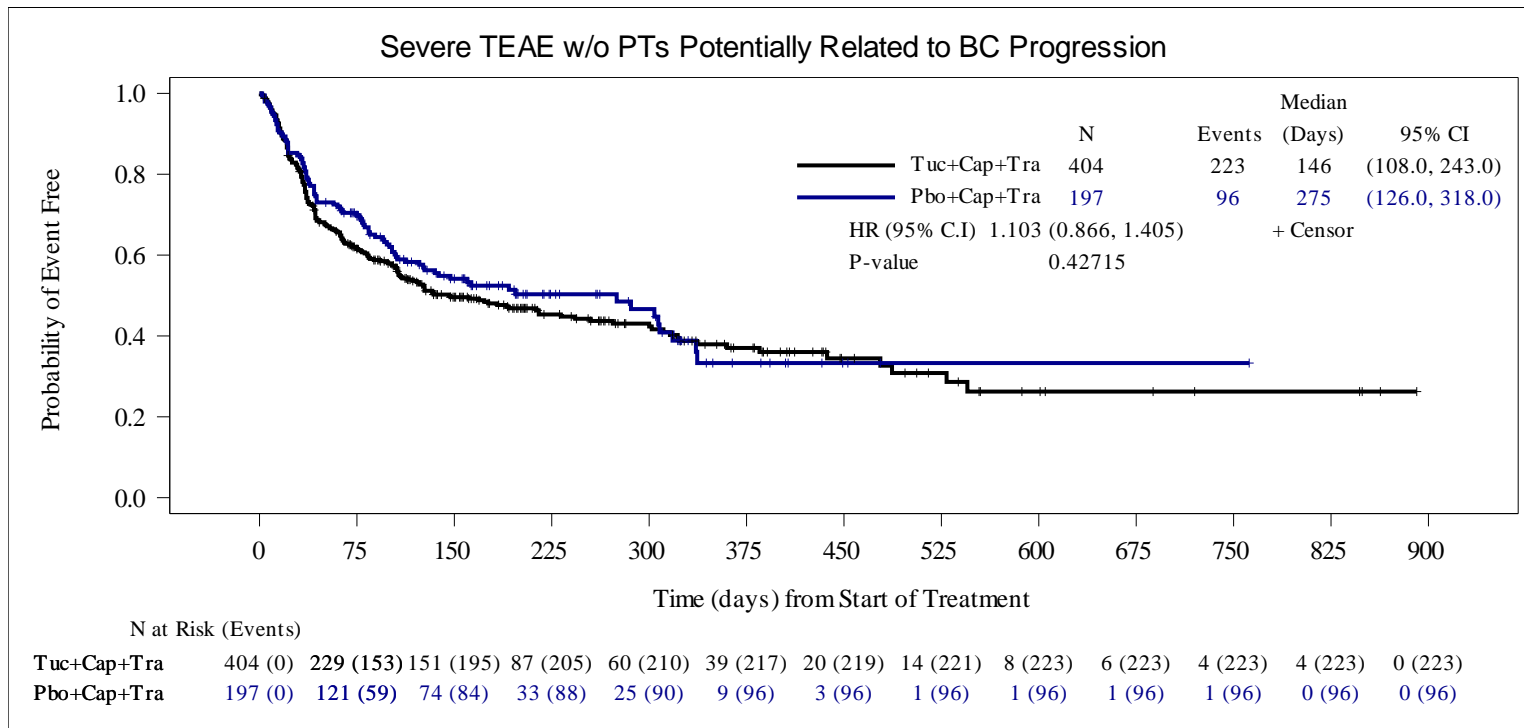
Data Snapshot: 14OCT2019, Data Cutoff Date: 04SEP2019

Source: O:\Projects\Tucatinib\ONT380-206_germanreimburse_1753\v01\outputs\tlfs\pgms\f-ae-km-overall-sens-safs.sas Output: f-ae-km-overall-sens-safs.rtf(17JUL20:16:07)

Data: adsl, adae, adtesaf

Seattle Genetics Protocol ONT-380-206

**Figure 2.5.2 Kaplan-Meier Estimate of Time to First Onset of Treatment-Emergent Adverse Events (Sensitivity Analysis)
Safety Analysis Set**



HR is computed from the Cox proportional hazards model using stratification factors (Presence or history of brain metastases: Yes/No, ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization. When the number of subjects with at least one event was ≤ 30 , an unstratified Cox model was run.

Two-sided p-value calculated from Cox proportional hazards model .

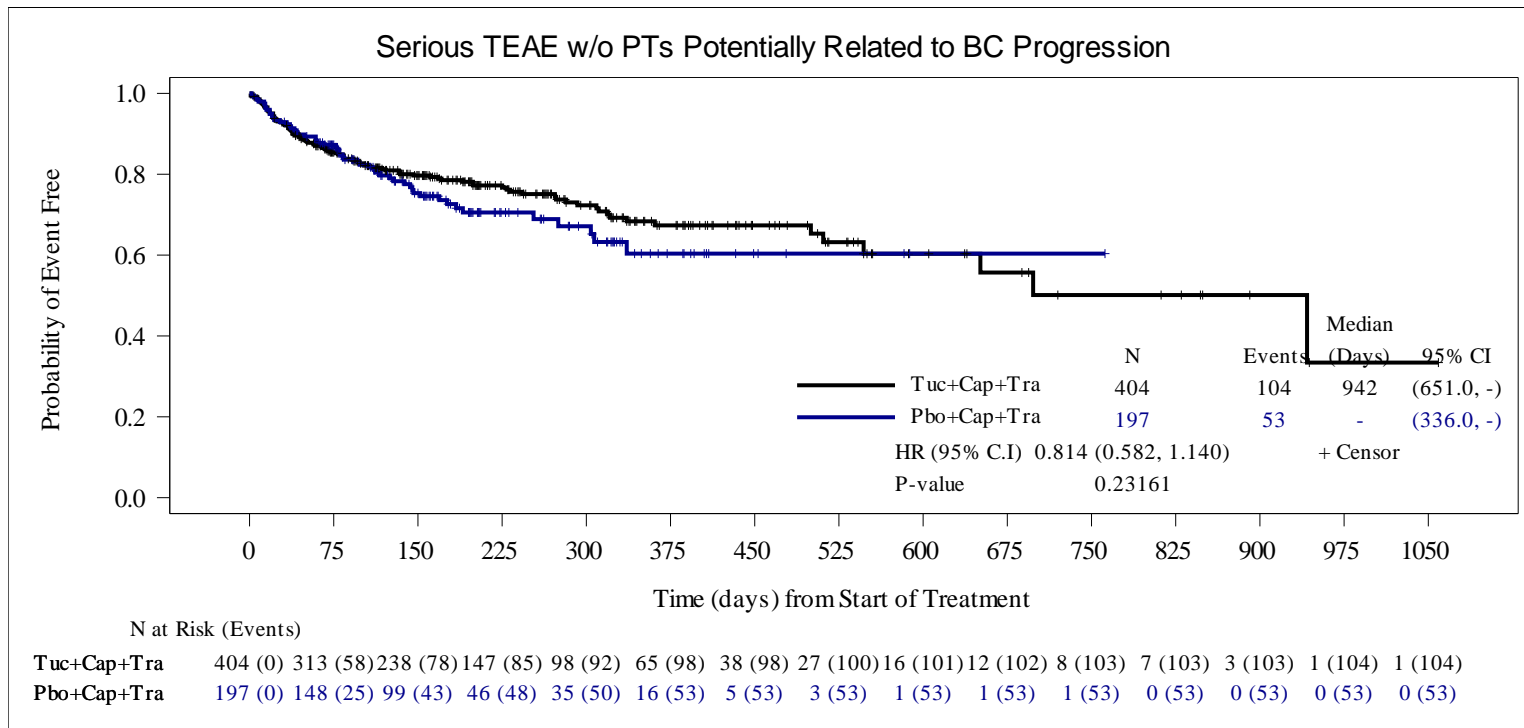
Data Snapshot: 14OCT2019, Data Cutoff Date: 04SEP2019

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_1753\v01\outputs\tlfs\pgms\f-ae-km-overall-sens-safs.sas Output: f-ae-km-overall-sens-safs.rtf(17JUL20:16:07)

Data: adsl, adae, adttesaf

Seattle Genetics Protocol ONT-380-206

**Figure 2.5.2 Kaplan-Meier Estimate of Time to First Onset of Treatment-Emergent Adverse Events (Sensitivity Analysis)
Safety Analysis Set**



HR is computed from the Cox proportional hazards model using stratification factors (Presence or history of brain metastases: Yes/No, ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization. When the number of subjects with at least one event was ≤ 30 , an unstratified Cox model was run.

Two-sided p-value calculated from Cox proportional hazards model .

Data Snapshot: 14OCT2019, Data Cutoff Date: 04SEP2019

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_1753\v01\outputs\tlfs\pgms\f-ae-km-overall-sens-safs.sas Output: f-ae-km-overall-sens-safs.rtf(17JUL20:16:07)

Data: adsl, adae, adttesaf

Seattle Genetics Protocol ONT-380-206**Table 2.4.2 Summary of Treatment-Emergent Adverse Events - Time-to-Event Analysis (Sensitivity Analysis)
Safety Analysis Set**

| Parameters | | Tuc+Cap+Tra (N=404) | Pbo+Cap+Tra (N=197) |
|---|--|------------------------|------------------------|
| TEAE w/o PTs Potentially Related to BC Progression | Number of Subjects With at Least One Event, n (%) | 401 (99.3) | 191 (97.0) |
| | Number of Censored Subjects, n (%) | 3 (0.7) | 6 (3.0) |
| | Stratified Hazard Ratio ^{a, b} (95% C.I.) | 1.548 (1.290, 1.858) | |
| | P-value ^{b, c} | <.00001 | |
| | Median Time to Onset of the First Event (Days) (95% C.I.) ^d | 4.0 (4.0, 5.0) | 8.0 (6.0, 10.0) |
| | 25 th , 75 th Percentile | 2.0, 10.0 | 2.0, 14.0 |
| | Observed Min, Max ^e | 1, 436+ | 1, 262+ |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (Presence or history of brain metastases: Yes/No, ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization. When the number of subjects with at least one event was ≤ 30 , an unstratified Cox model was run.

c. Two-sided p-value calculated from Cox proportional hazards model .

d. Calculated using the complementary log-log transformation method (Collett, 1994).

e. '+' means the observed time is from censored subjects.

Data Snapshot: 14OCT2019, Data Cutoff Date: 04SEP2019

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_1753\v01\outputs\tlfs\pgms\t-ae-km-overall-sens-safs.sas Output: t-ae-km-overall-sens-safs.rtf (17JUL20:17:18) Data: adsl, adae, adttesaf

Seattle Genetics Protocol ONT-380-206**Table 2.4.2 Summary of Treatment-Emergent Adverse Events - Time-to-Event Analysis (Sensitivity Analysis)
Safety Analysis Set**

| Parameters | | Tuc+Cap+Tra (N=404) | Pbo+Cap+Tra (N=197) |
|---|--|-------------------------|-------------------------|
| Severe TEAE w/o PTs Potentially Related to BC Progression | Number of Subjects With at Least One Event, n (%) | 223 (55.2) | 96 (48.7) |
| | Number of Censored Subjects, n (%) | 181 (44.8) | 101 (51.3) |
| | Stratified Hazard Ratio ^{a, b} (95% C.I.) | 1.103 (0.866, 1.405) | |
| | P-value ^{b, c} | 0.42715 | |
| | Median Time to Onset of the First Event (Days) (95% C.I.) ^d | 146.0 (108.0, 243.0) | 275.0 (126.0, 318.0) |
| | 25 th , 75 th Percentile | 36.0, - | 43.0, - |
| | Observed Min, Max ^e | 1, 891+ | 2, 762+ |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (Presence or history of brain metastases: Yes/No, ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization. When the number of subjects with at least one event was ≤ 30 , an unstratified Cox model was run.

c. Two-sided p-value calculated from Cox proportional hazards model .

d. Calculated using the complementary log-log transformation method (Collett, 1994).

e. '+' means the observed time is from censored subjects.

Data Snapshot: 14OCT2019, Data Cutoff Date: 04SEP2019

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_1753\v01\outputs\tlfs\pgms\t-ae-km-overall-sens-safs.sas Output: t-ae-km-overall-sens-safs.rtf (17JUL20:17:18) Data: adsl, adae, addtesaf

Seattle Genetics Protocol ONT-380-206**Table 2.4.2 Summary of Treatment-Emergent Adverse Events - Time-to-Event Analysis (Sensitivity Analysis)
Safety Analysis Set**

| Parameters | | Tuc+Cap+Tra (N=404) | Pbo+Cap+Tra (N=197) |
|--|--|------------------------|------------------------|
| Serious TEAE w/o PTs Potentially Related to BC Progression | Number of Subjects With at Least One Event, n (%) | 104 (25.7) | 53 (26.9) |
| | Number of Censored Subjects, n (%) | 300 (74.3) | 144 (73.1) |
| | Stratified Hazard Ratio ^{a, b} (95% C.I.) | 0.814 (0.582, 1.140) | |
| | P-value ^{b, c} | 0.23161 | |
| | Median Time to Onset of the First Event (Days) (95% C.I.) ^d | 942.0 (651.0, -) | - (336.0, -) |
| 25 th , 75 th Percentile | 272.0, - | 152.0, - | |
| Observed Min, Max ^e | 1, 1059+ | 2, 762+ | |

Page 3 of 4

a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (Presence or history of brain metastases: Yes/No, ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization. When the number of subjects with at least one event was ≤ 30 , an unstratified Cox model was run.

c. Two-sided p-value calculated from Cox proportional hazards model .

d. Calculated using the complementary log-log transformation method (Collett, 1994).

e. '+' means the observed time is from censored subjects.

Data Snapshot: 14OCT2019, Data Cutoff Date: 04SEP2019

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_1753\v01\outputs\tlfs\pgms\t-ae-km-overall-sens-safs.sas Output: t-ae-km-overall-sens-safs.rtf (17JUL20:17:18) Data: adsl, adae, adttesaf

Seagen Protocol ONT-380-206**Table 2.4.2 Summary of Treatment-Emergent Adverse Events - Time-to-Event Analysis (Sensitivity Analysis)
Safety Analysis Set**

| Parameters | | Tuc+Cap+Tra (N=404) | Pbo+Cap+Tra (N=197) |
|---|--|------------------------|------------------------|
| TEAE w/o PTs Potentially Related to BC Progression | Number of Subjects With at Least One Event, n (%) | 401 (99.3) | 191 (97.0) |
| | Number of Censored Subjects, n (%) | 3 (0.7) | 6 (3.0) |
| | Stratified Hazard Ratio ^{a, b} (95% C.I.) | 1.552 (1.293, 1.862) | |
| | P-value ^{b, c} | <.00001 | |
| | Median Time to Onset of the First Event (Days) (95% C.I.) ^d | 4.0 (3.0, 5.0) | 8.0 (6.0, 10.0) |
| | 25 th , 75 th Percentile | 2.0, 9.0 | 2.0, 14.0 |
| Observed Min, Max ^e | 1, 436+ | 1, 265+ | |

Page 1 of 4

a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (Presence or history of brain metastases: Yes/No, ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization. When the number of subjects with at least one event was ≤ 30 , an unstratified Cox model was run.

c. Two-sided p-value calculated from Cox proportional hazards model .

d. Calculated using the complementary log-log transformation method (Collett, 1994).

e. '+' means the observed time is from censored subjects.

Snapshot date: 10SEP2020, data cutoff date: 29MAY2020.

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_may2020_dco_1943\v01\outputs\tlfs\pgms\t-ae-km-overall-sens-safs.sas Output:
t02-04-02-ae-km-overall-sens-safs.rtf (14DEC20:17:13) Data: adsl, adae, adttesaf

Seagen Protocol ONT-380-206**Table 2.4.2 Summary of Treatment-Emergent Adverse Events - Time-to-Event Analysis (Sensitivity Analysis)
Safety Analysis Set**

| Parameters | | Tuc+Cap+Tra (N=404) | Pbo+Cap+Tra (N=197) |
|---|--|-------------------------|-------------------------|
| Severe TEAE w/o PTs Potentially Related to BC Progression | Number of Subjects With at Least One Event, n (%) | 239 (59.2) | 101 (51.3) |
| | Number of Censored Subjects, n (%) | 165 (40.8) | 96 (48.7) |
| | Stratified Hazard Ratio ^{a, b} (95% C.I.) | 1.112 (0.879, 1.406) | |
| | P-value ^{b, c} | 0.37632 | |
| | Median Time to Onset of the First Event (Days) (95% C.I.) ^d | 134.0 (107.0, 215.0) | 243.0 (123.0, 308.0) |
| | 25 th , 75 th Percentile | 36.0, 697.0 | 43.0, 576.0 |
| | Observed Min, Max ^e | 1, 1131+ | 2, 762+ |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (Presence or history of brain metastases: Yes/No, ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization. When the number of subjects with at least one event was ≤ 30 , an unstratified Cox model was run.

c. Two-sided p-value calculated from Cox proportional hazards model .

d. Calculated using the complementary log-log transformation method (Collett, 1994).

e. '+' means the observed time is from censored subjects.

Snapshot date: 10SEP2020, data cutoff date: 29MAY2020.

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_may2020_dco_1943\v01\outputs\tlfs\pgms\t-ae-km-overall-sens-safs.sas Output:
t02-04-02-ae-km-overall-sens-safs.rtf (14DEC20:17:13) Data: adsl, adae, adttesaf

Seagen Protocol ONT-380-206**Table 2.4.2 Summary of Treatment-Emergent Adverse Events - Time-to-Event Analysis (Sensitivity Analysis)
Safety Analysis Set**

| Parameters | | Tuc+Cap+Tra (N=404) | Pbo+Cap+Tra (N=197) |
|--|--|------------------------|------------------------|
| Serious TEAE w/o PTs Potentially Related to BC Progression | Number of Subjects With at Least One Event, n (%) | 118 (29.2) | 58 (29.4) |
| | Number of Censored Subjects, n (%) | 286 (70.8) | 139 (70.6) |
| | Stratified Hazard Ratio ^{a, b} (95% C.I.) | 0.784 (0.568, 1.081) | |
| | P-value ^{b, c} | 0.13685 | |
| | Median Time to Onset of the First Event (Days) (95% C.I.) ^d | 942.0 (577.0, -) | - (336.0, -) |
| | 25 th , 75 th Percentile | 260.0, - | 152.0, - |
| | Observed Min, Max ^e | 1, 1327+ | 2, 839+ |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (Presence or history of brain metastases: Yes/No, ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization. When the number of subjects with at least one event was ≤ 30 , an unstratified Cox model was run.

c. Two-sided p-value calculated from Cox proportional hazards model .

d. Calculated using the complementary log-log transformation method (Collett, 1994).

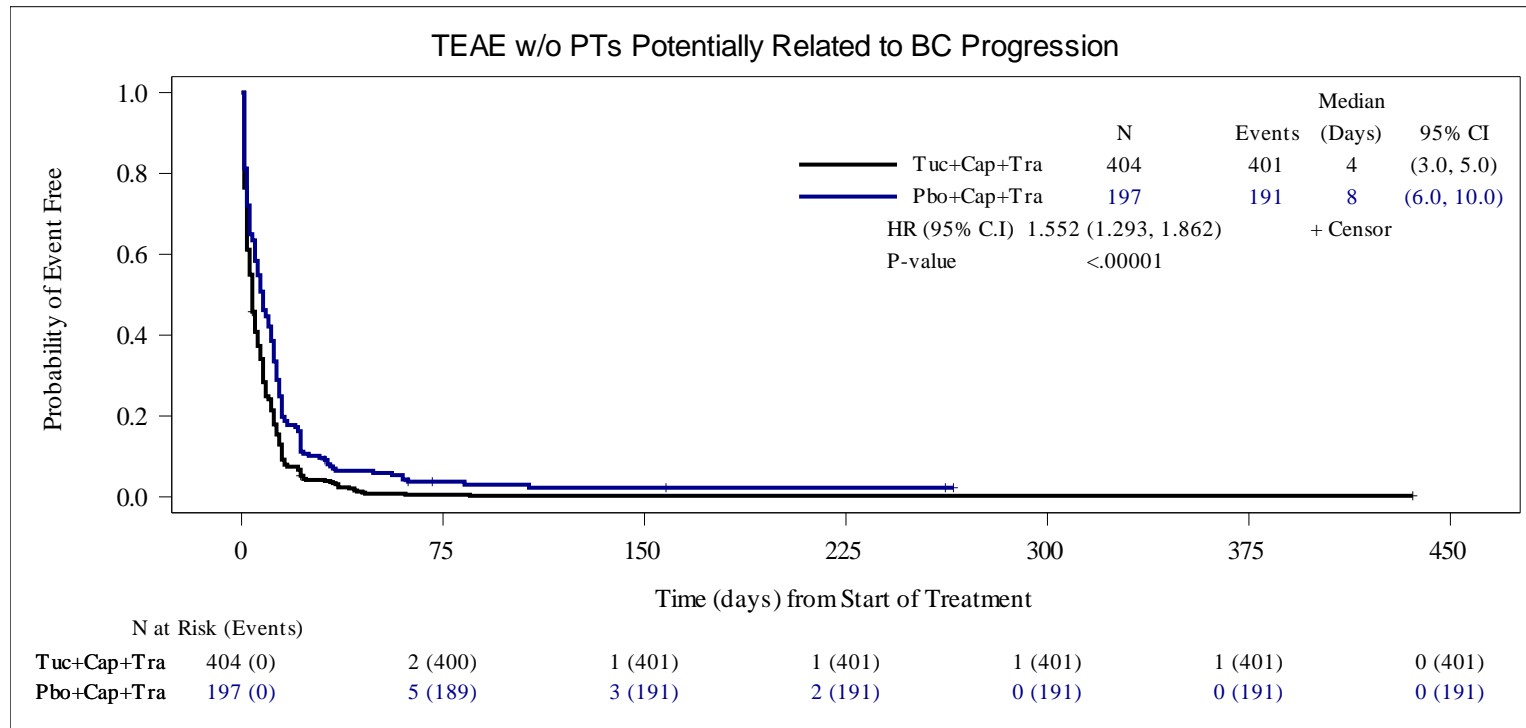
e. '+' means the observed time is from censored subjects.

Snapshot date: 10SEP2020, data cutoff date: 29MAY2020.

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_may2020_dco_1943\v01\outputs\tlfs\pgms\t-ae-km-overall-sens-safs.sas Output:
t02-04-02-ae-km-overall-sens-safs.rtf (14DEC20:17:13) Data: adsl, adae, adttesaf

Seagen Protocol ONT-380-206

Figure 2.5.2 Kaplan-Meier Estimate of Time to First Onset of Treatment-Emergent Adverse Events (Sensitivity Analysis) Safety Analysis Set



HR is computed from the Cox proportional hazards model using stratification factors (Presence or history of brain metastases: Yes/No, ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization. When the number of subjects with at least one event was ≤ 30 , an unstratified Cox model was run.

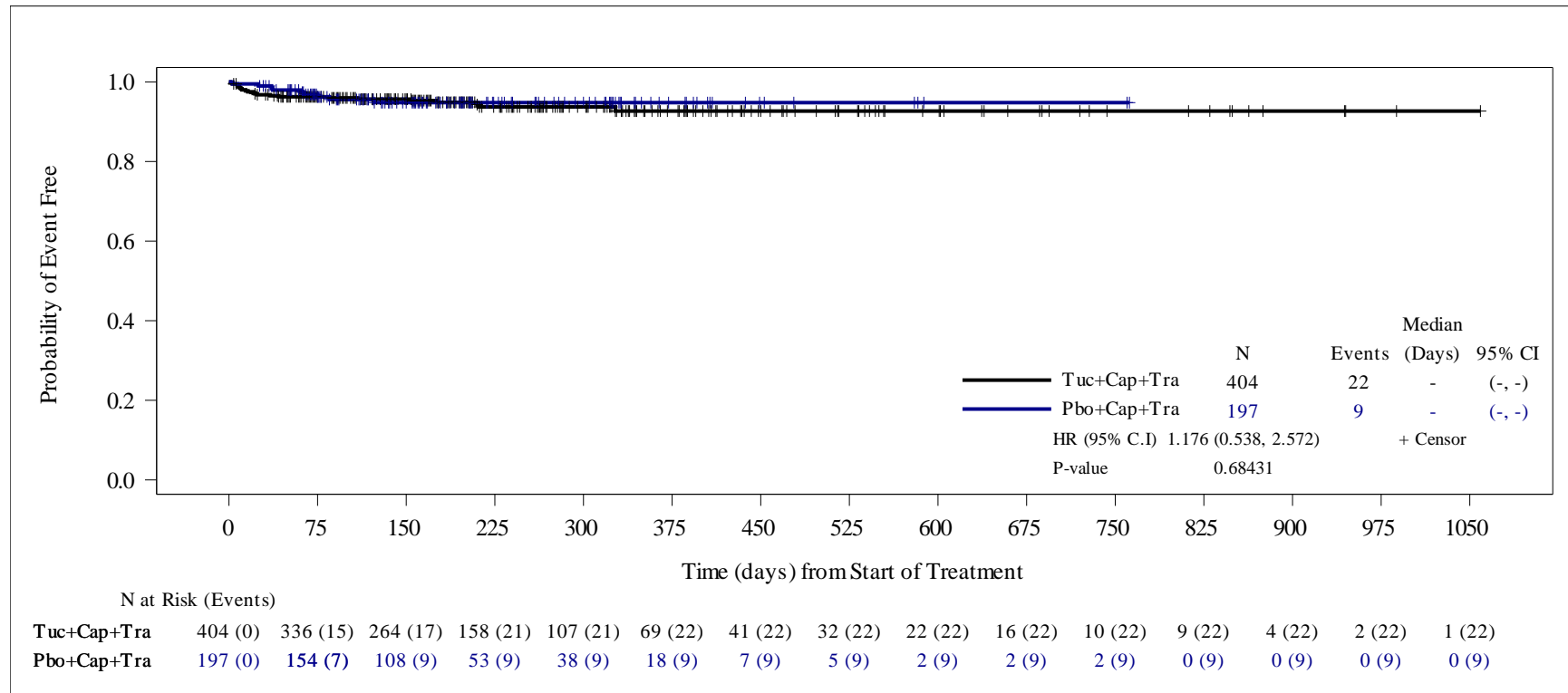
Two-sided p-value calculated from Cox proportional hazards model .

Snapshot date: 10SEP2020, data cutoff date: 29MAY2020.

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_may2020_dco_1943\v01\outputs\tlfs\pgms\ae-km-overall-sens-safs.sas Output: f02-05-02-ae-km-overall-sens-safs.rtf(14DEC20:17:09) Data: adsl, adae, adtesaf

Seattle Genetics Protocol ONT-380-206

**Figure 2.3.11 Kaplan-Meier Estimate of Time to First Onset of Adverse Events - Abdominal Distension
Safety Analysis Set**



HR is computed from the Cox proportional hazards model using stratification factors (Presence or history of brain metastases: Yes/No, ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization.

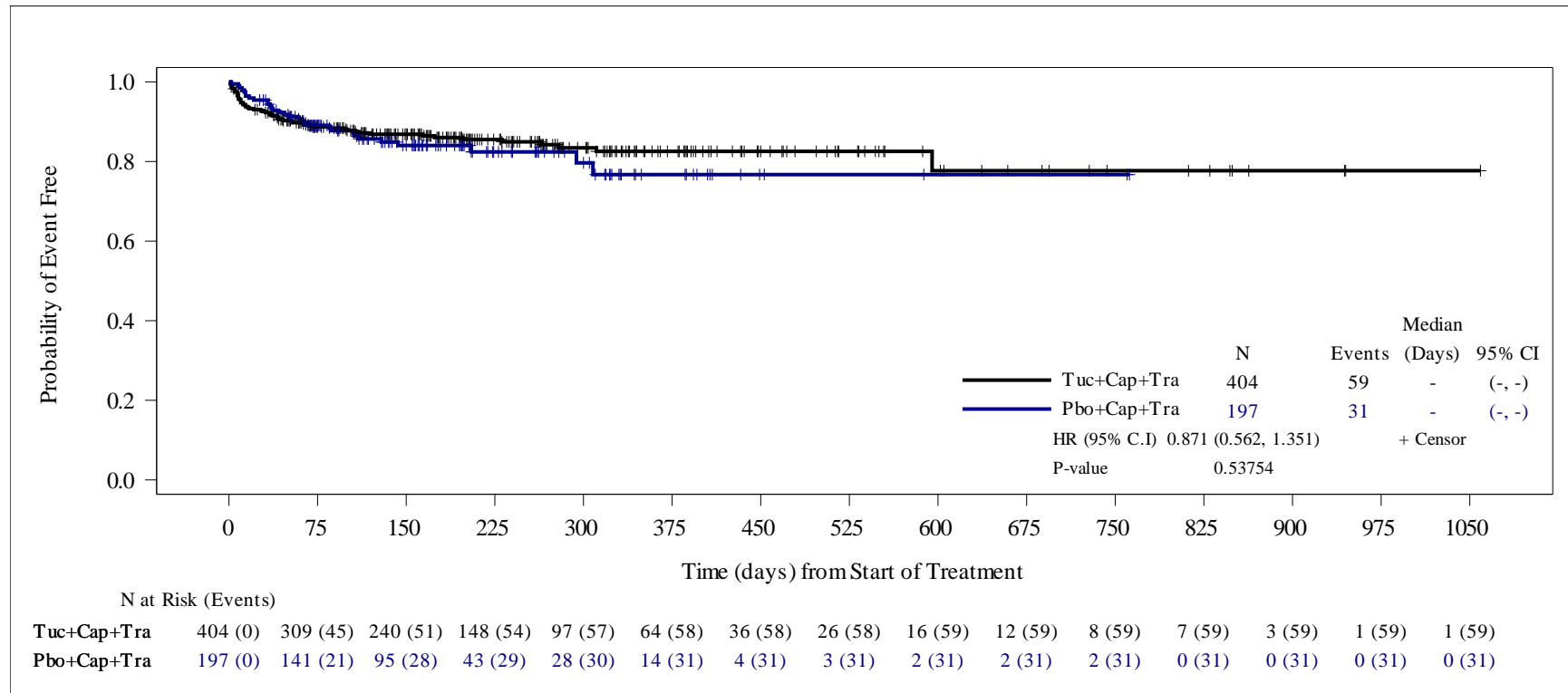
Two-sided p-value calculated from Cox proportional hazards model .

Data Snapshot: 14OCT2019, Data Cutoff Date: 04SEP2019

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_1753\v01\outputs\tlfs\pgms\f-ae-onset-gastro.sas Output: f-ae-km-gi-abd-safs.rtf(22APR20:14:20) Data: adsl, adae, adttesaf

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**Figure 2.3.6 Kaplan-Meier Estimate of Time to First Onset of Adverse Events - Abdominal Pain
Safety Analysis Set**



HR is computed from the Cox proportional hazards model using stratification factors (Presence or history of brain metastases: Yes/No, ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization.

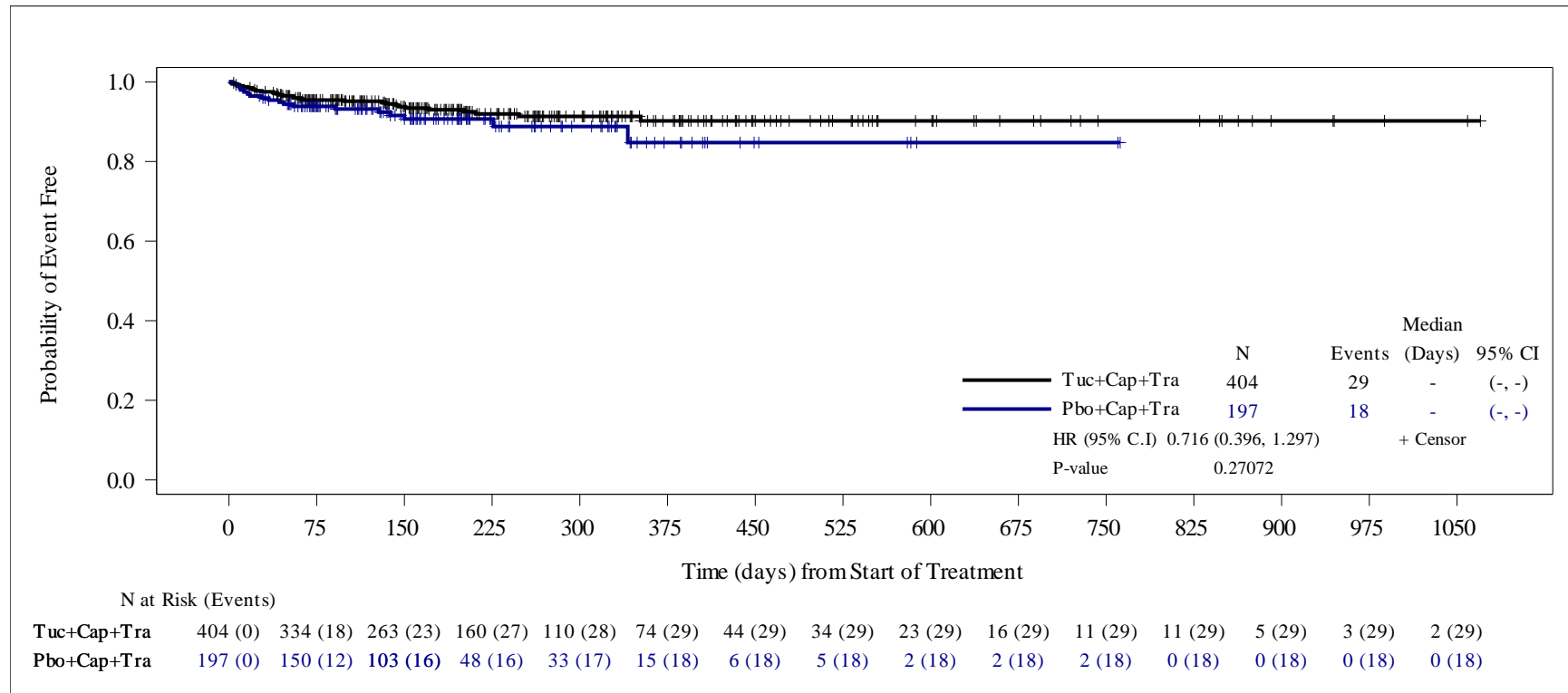
Two-sided p-value calculated from Cox proportional hazards model .

Data Snapshot: 14OCT2019, Data Cutoff Date: 04SEP2019

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_1753\v01\outputs\tlfs\pgms\f-ae-onset-gastro.sas Output: f-ae-km-gi-abp-safs.rtf(22APR20:14:20) Data: adsl, adae, adttesaf

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Figure 2.3.9 Kaplan-Meier Estimate of Time to First Onset of Adverse Events - Abdominal Pain Upper Safety Analysis Set



HR is computed from the Cox proportional hazards model using stratification factors (Presence or history of brain metastases: Yes/No, ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization.

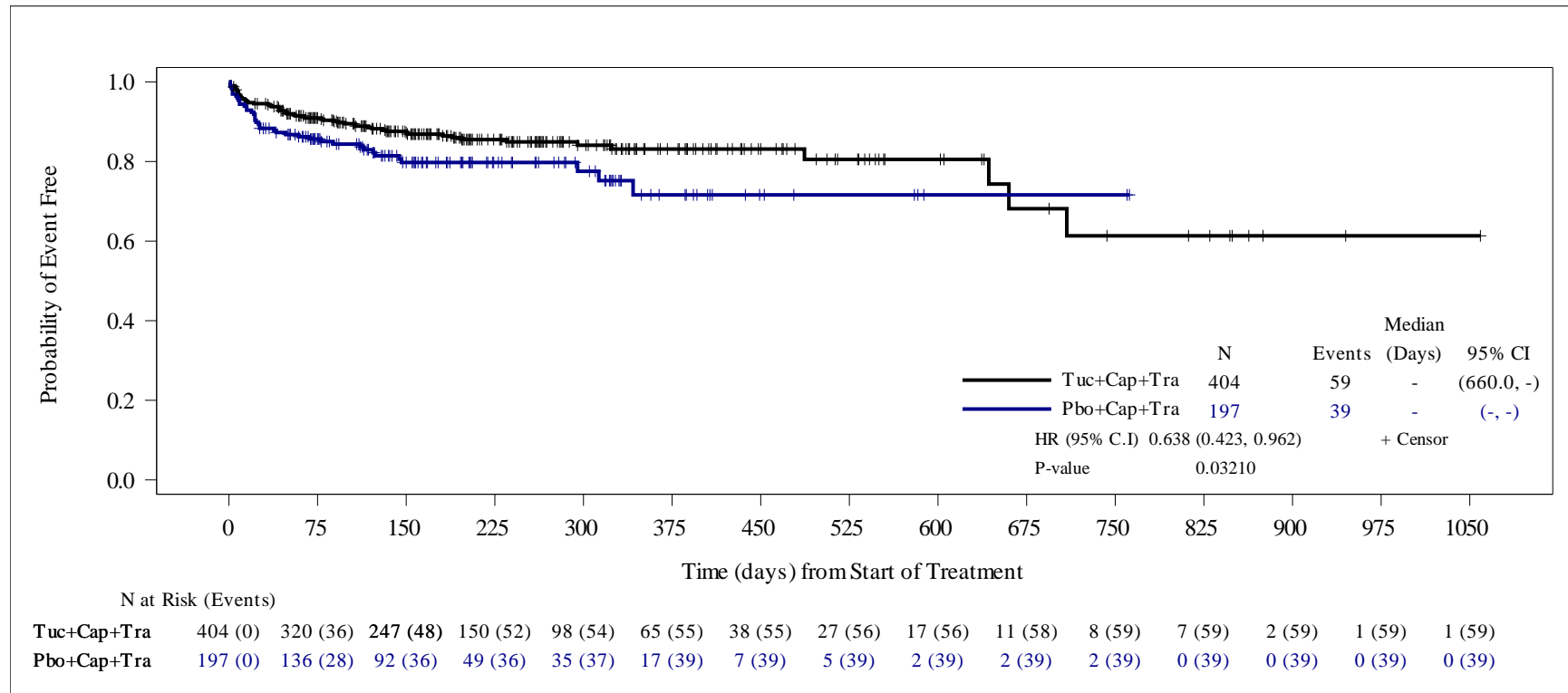
Two-sided p-value calculated from Cox proportional hazards model .

Data Snapshot: 14OCT2019, Data Cutoff Date: 04SEP2019

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_1753\v01\outputs\tlfs\pgms\f-ae-onset-gastro.sas Output: f-ae-km-gi-abu-safs.rtf(22APR20:14:20) Data: adsl, adae, adttesaf

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**Figure 2.3.7 Kaplan-Meier Estimate of Time to First Onset of Adverse Events - Constipation
Safety Analysis Set**



HR is computed from the Cox proportional hazards model using stratification factors (Presence or history of brain metastases: Yes/No, ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization.

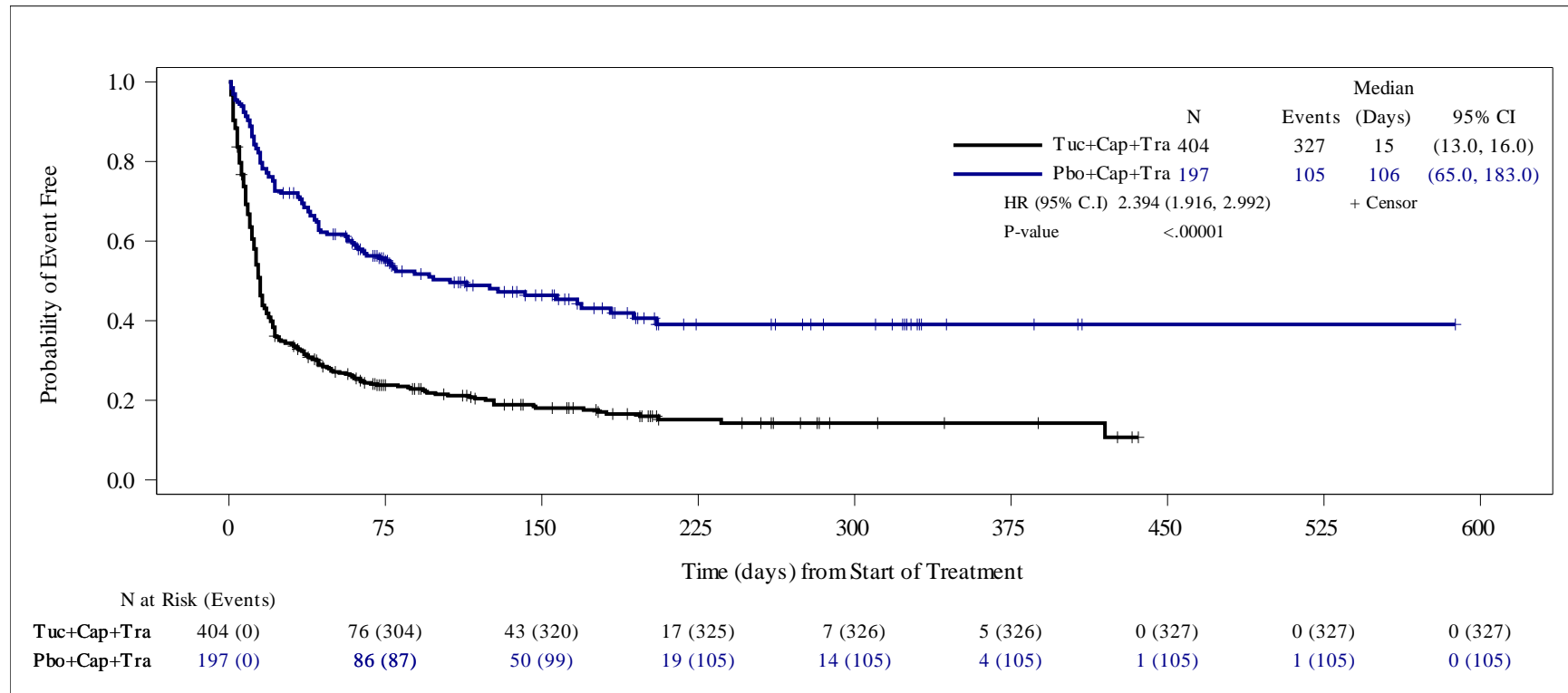
Two-sided p-value calculated from Cox proportional hazards model .

Data Snapshot: 14OCT2019, Data Cutoff Date: 04SEP2019

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_1753\v01\outputs\tlfs\pgms\f-ae-onset-gastro.sas Output: f-ae-km-gi-con-safs.rtf(22APR20:14:20) Data: adsl, adae, adttesaf

Seattle Genetics Protocol ONT-380-206

**Figure 2.3.2 Kaplan-Meier Estimate of Time to First Onset of Adverse Events - Diarrhoea
Safety Analysis Set**



HR is computed from the Cox proportional hazards model using stratification factors (Presence or history of brain metastases: Yes/No, ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization.

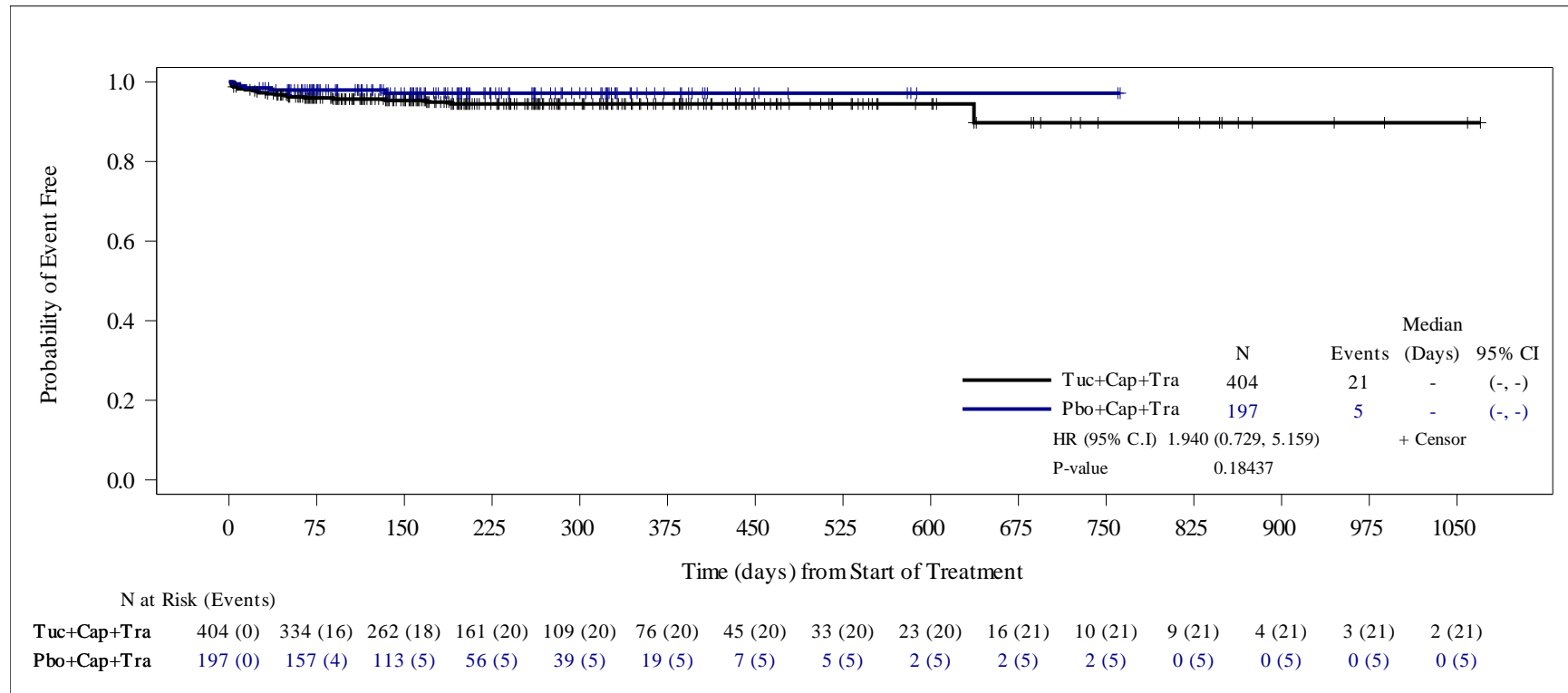
Two-sided p-value calculated from Cox proportional hazards model .

Data Snapshot: 14OCT2019, Data Cutoff Date: 04SEP2019

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_1753\v01\outputs\tlfs\pgms\f-ae-onset-gastro.sas Output: f-ae-km-gi-dia-safs.rtf(22APR20:14:20) Data: adsl, adae, adttesaf

Seattle Genetics Protocol ONT-380-206

**Figure 2.3.12 Kaplan-Meier Estimate of Time to First Onset of Adverse Events - Dry Mouth
Safety Analysis Set**



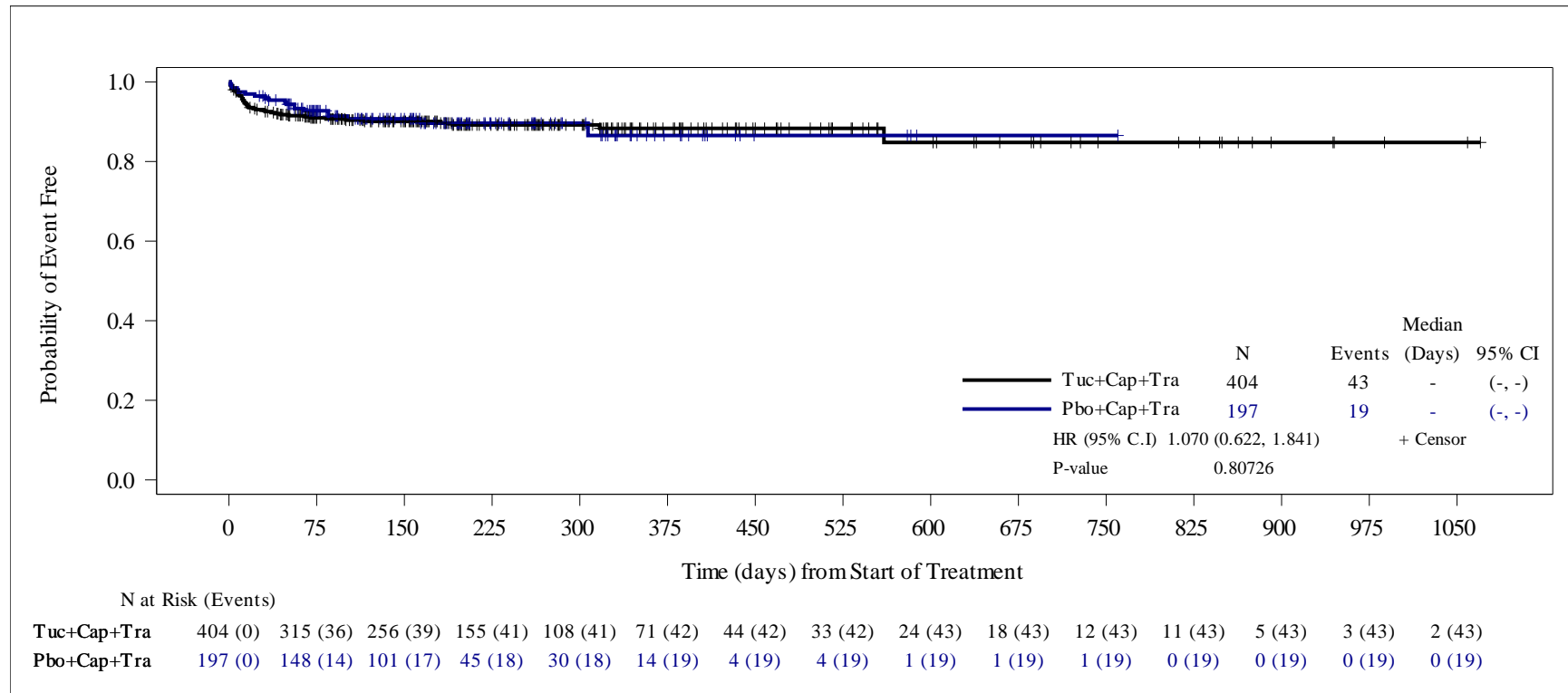
HR and two-sided p-value were computed from the unstratified Cox proportional hazards model.

Data Snapshot: 14OCT2019, Data Cutoff Date: 04SEP2019

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_1753\v01\outputs\tlfs\pgms\f-ae-onset-gastro.sas Output: f-ae-km-gi-drm-safs.rtf(19JUN20:11:02) Data: adsl, adae, adttesaf

Seattle Genetics Protocol ONT-380-206

**Figure 2.3.8 Kaplan-Meier Estimate of Time to First Onset of Adverse Events - Dyspepsia
Safety Analysis Set**



HR is computed from the Cox proportional hazards model using stratification factors (Presence or history of brain metastases: Yes/No, ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization.

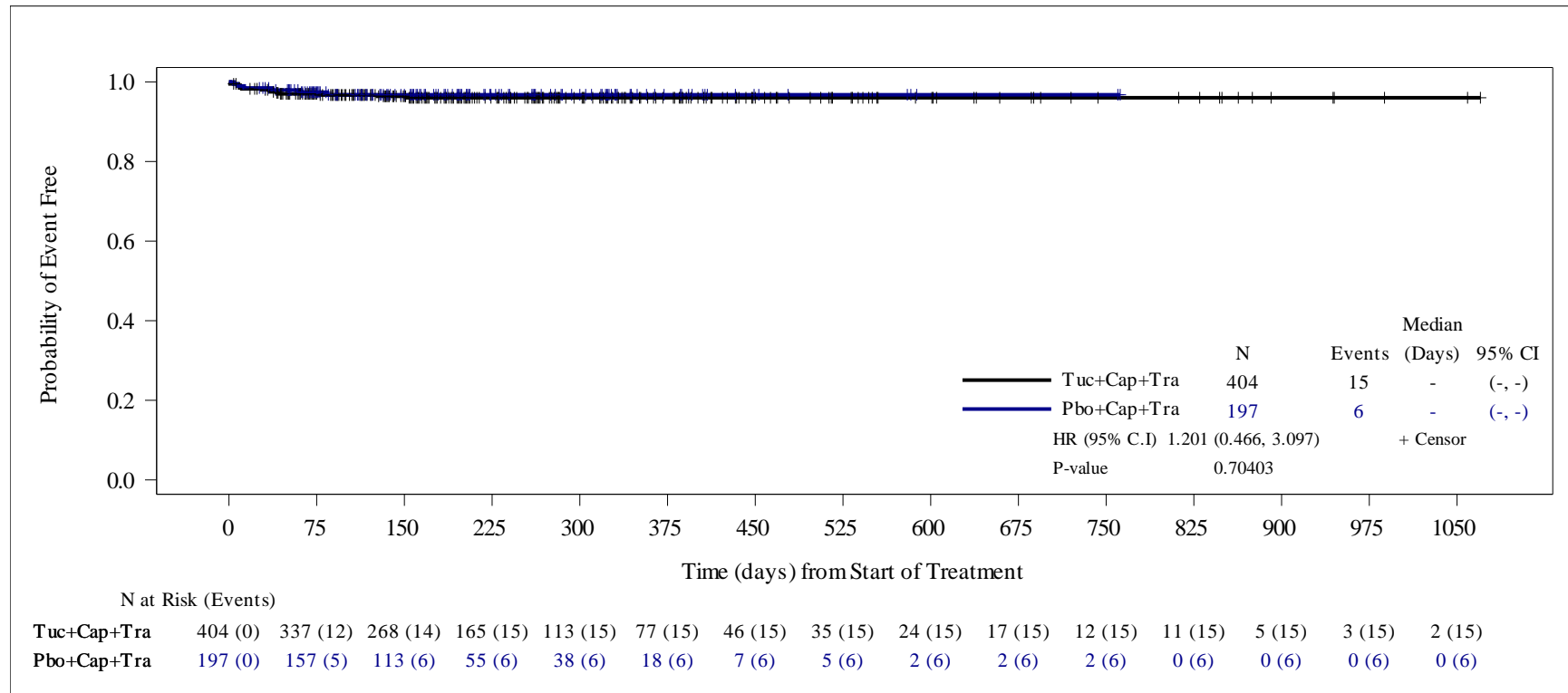
Two-sided p-value calculated from Cox proportional hazards model .

Data Snapshot: 14OCT2019, Data Cutoff Date: 04SEP2019

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_1753\v01\outputs\tlfs\pgms\f-ae-onset-gastro.sas Output: f-ae-km-gi-dys-safs.rtf(22APR20:14:20) Data: adsl, adae, adttesaf

Seattle Genetics Protocol ONT-380-206

**Figure 2.3.13 Kaplan-Meier Estimate of Time to First Onset of Adverse Events - Flatulence
Safety Analysis Set**



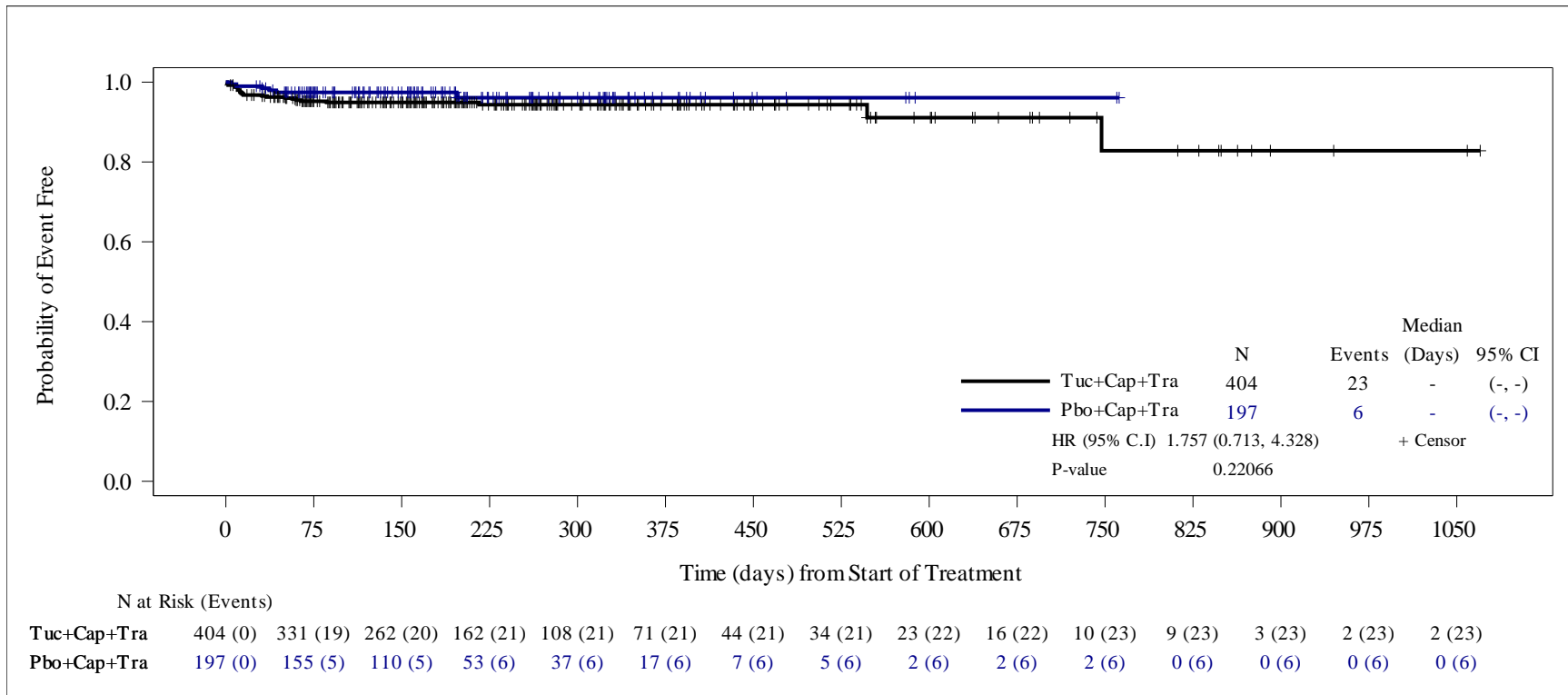
HR and two-sided p-value were computed from the unstratified Cox proportional hazards model.

Data Snapshot: 14OCT2019, Data Cutoff Date: 04SEP2019

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_1753\v01\outputs\tlfs\pgms\f-ae-onset-gastro.sas Output: f-ae-km-gi-ftu-safs.rtf(19JUN20:11:02) Data: adsl, adae, adttesaf

Seattle Genetics Protocol ONT-380-206

Figure 2.3.10 Kaplan-Meier Estimate of Time to First Onset of Adverse Events - Gastroesophageal Reflux Disease Safety Analysis Set



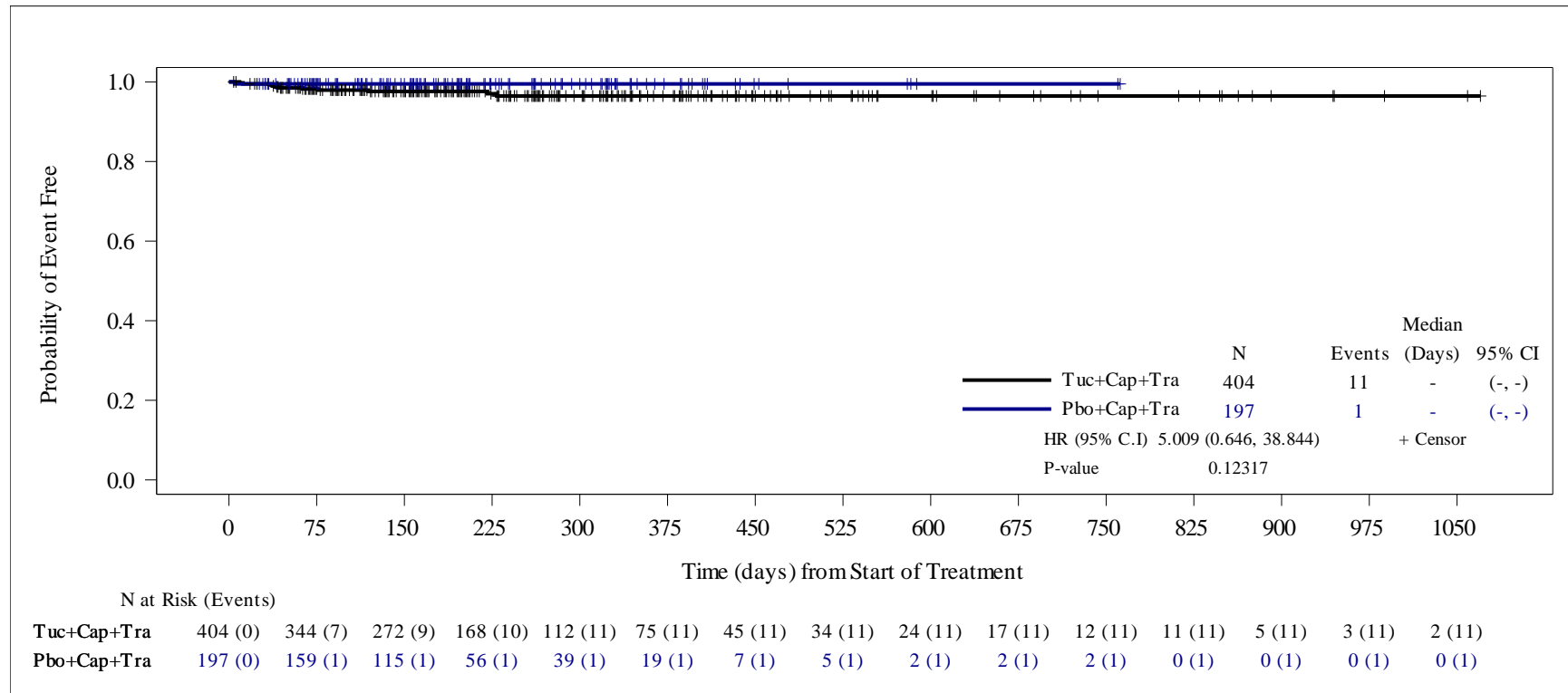
HR and two-sided p-value were computed from the unstratified Cox proportional hazards model.

Data Snapshot: 14OCT2019, Data Cutoff Date: 04SEP2019

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_1753\v01\outputs\tlfs\pgms\f-ae-onset-gastro.sas Output: f-ae-km-gi-grd-safs.rtf(19JUN20:11:02) Data: adsl, adae, adttesaf

Seattle Genetics Protocol ONT-380-206

**Figure 2.3.14 Kaplan-Meier Estimate of Time to First Onset of Adverse Events - Haemorrhoids
Safety Analysis Set**



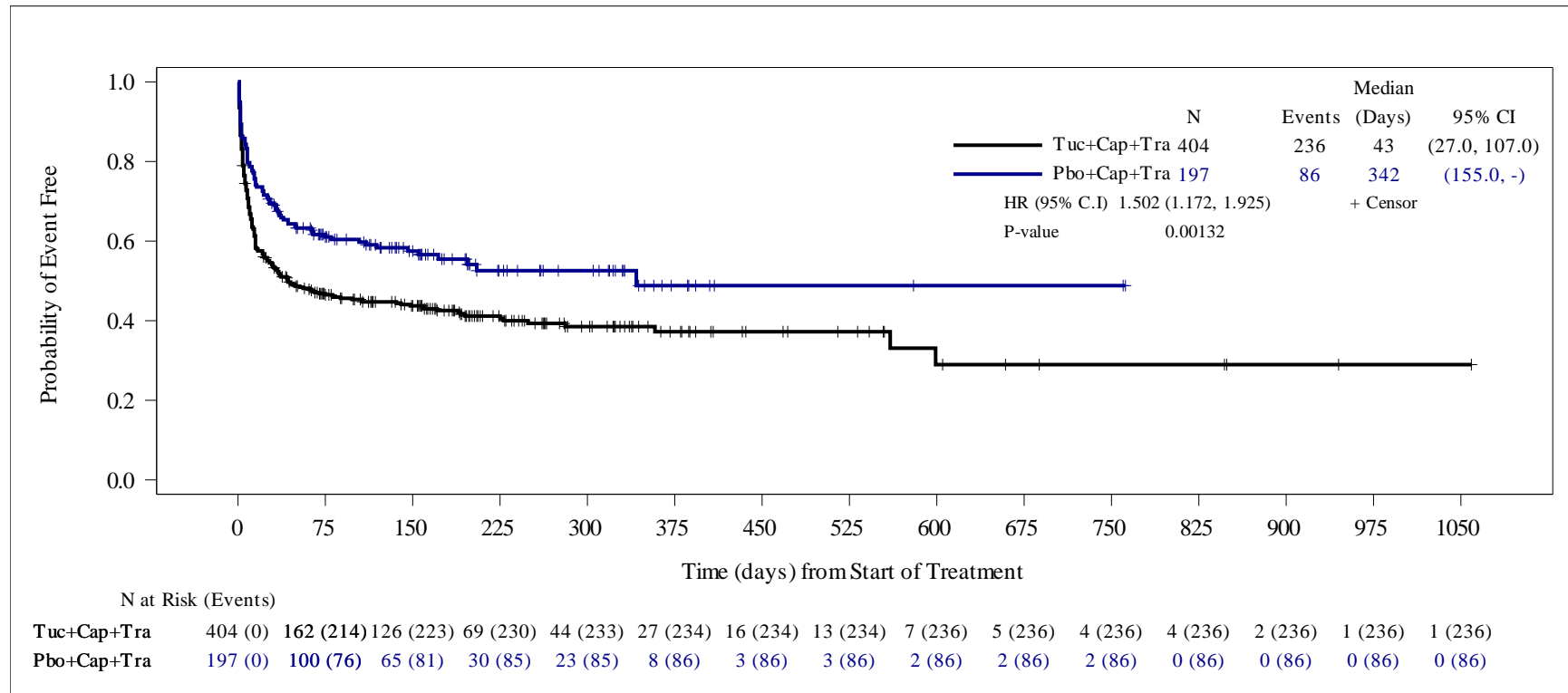
HR and two-sided p-value were computed from the unstratified Cox proportional hazards model.

Data Snapshot: 14OCT2019, Data Cutoff Date: 04SEP2019

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_1753\v01\outputs\tlfs\pgms\f-ae-onset-gastro.sas Output: f-ae-km-gi-hae-safs.rtf(19JUN20:11:02) Data: adsl, adae, adttesaf

Seattle Genetics Protocol ONT-380-206

**Figure 2.3.3 Kaplan-Meier Estimate of Time to First Onset of Adverse Events - Nausea
Safety Analysis Set**



HR is computed from the Cox proportional hazards model using stratification factors (Presence or history of brain metastases: Yes/No, ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization.

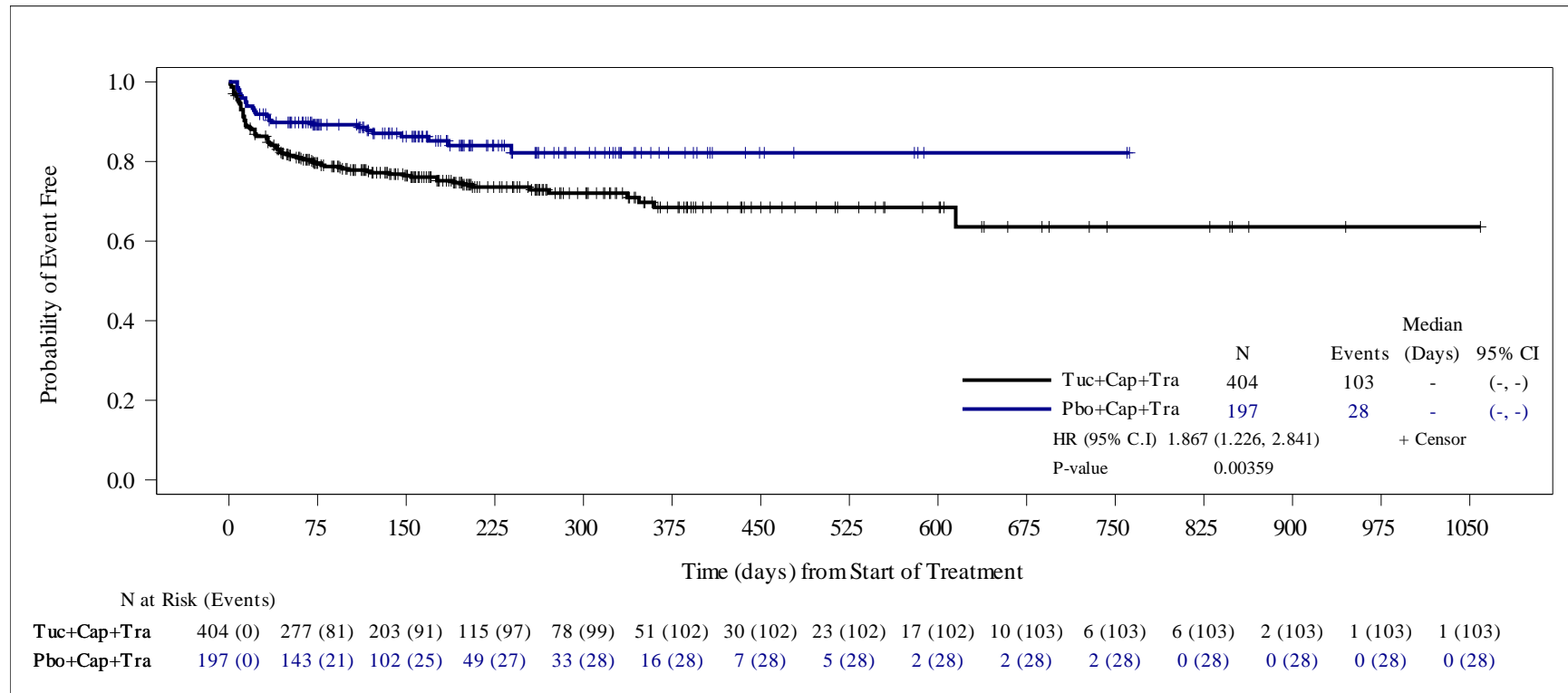
Two-sided p-value calculated from Cox proportional hazards model .

Data Snapshot: 14OCT2019, Data Cutoff Date: 04SEP2019

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_1753\v01\outputs\tlfs\pgms\f-ae-onset-gastro.sas Output: f-ae-km-gi-nau-safs.rtf(22APR20:14:20) Data: adsl, adae, adttesaf

Seattle Genetics Protocol ONT-380-206

Figure 2.3.5 Kaplan-Meier Estimate of Time to First Onset of Adverse Events - Stomatitis
Safety Analysis Set



HR is computed from the Cox proportional hazards model using stratification factors (Presence or history of brain metastases: Yes/No, ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization.

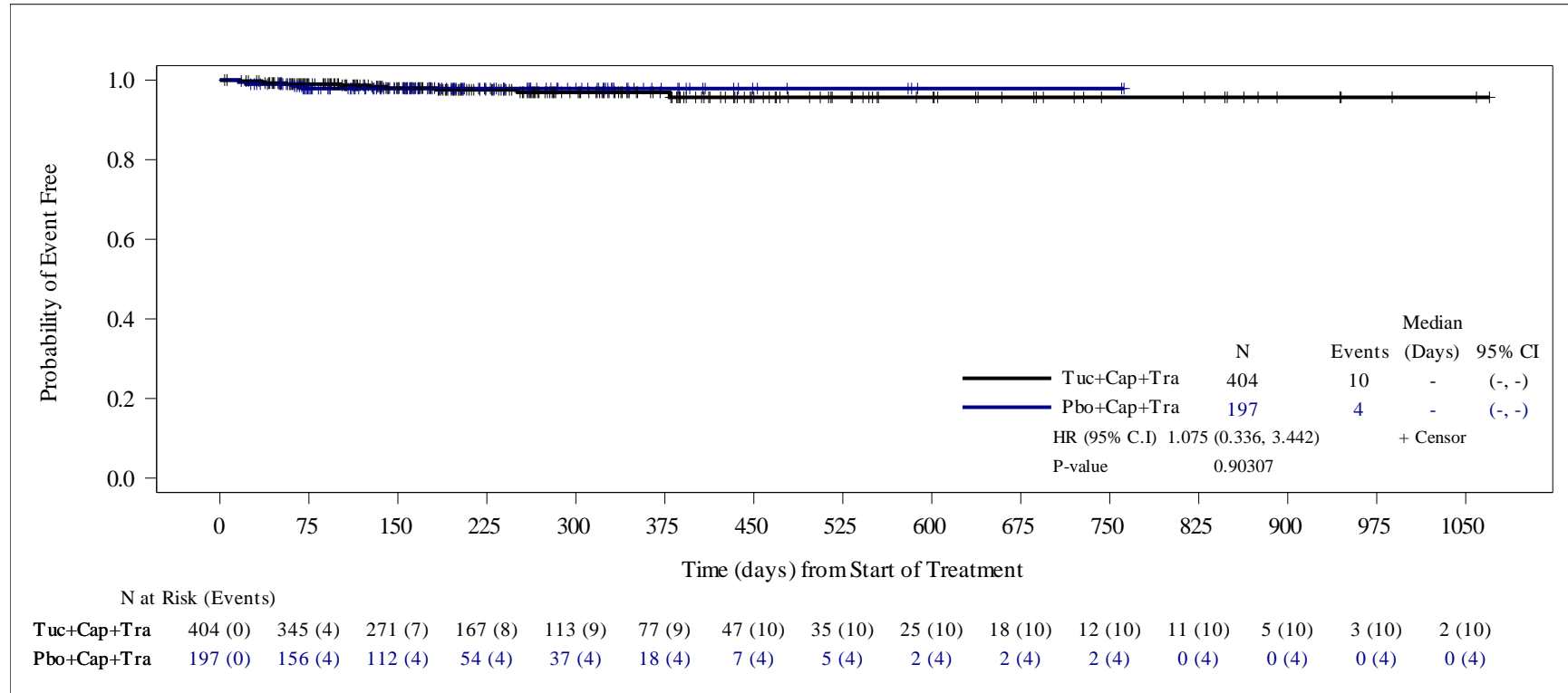
Two-sided p-value calculated from Cox proportional hazards model .

Data Snapshot: 14OCT2019, Data Cutoff Date: 04SEP2019

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_1753\v01\outputs\tlfs\pgms\f-ae-onset-gastro.sas Output: f-ae-km-gi-sto-safs.rtf(22APR20:14:20) Data: adsl, adae, adttesaf

Seattle Genetics Protocol ONT-380-206

Figure 2.3.15 Kaplan-Meier Estimate of Time to First Onset of Adverse Events - Mouth Ulceration
Safety Analysis Set



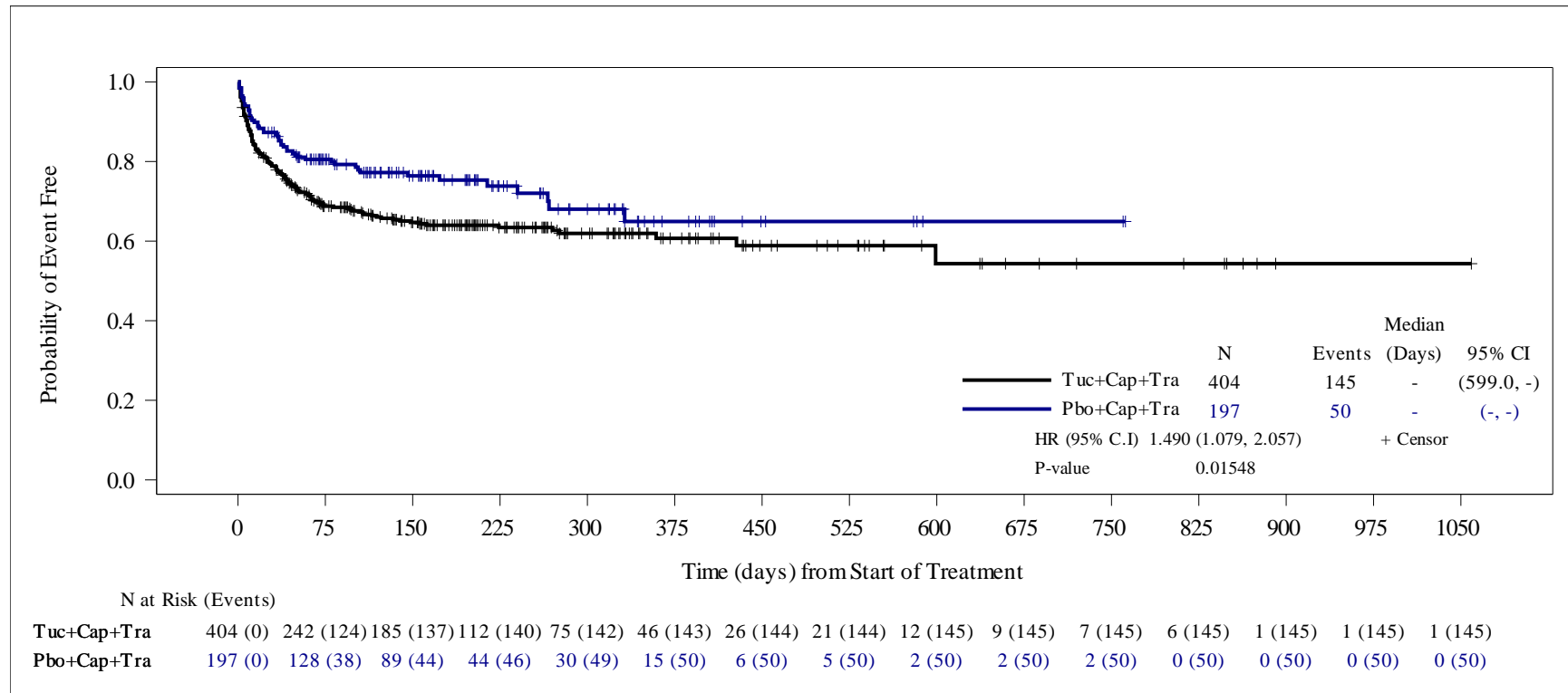
HR and two-sided p-value were computed from the unstratified Cox proportional hazards model.

Data Snapshot: 14OCT2019, Data Cutoff Date: 04SEP2019

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Seattle Genetics Protocol ONT-380-206

**Figure 2.3.4 Kaplan-Meier Estimate of Time to First Onset of Adverse Events - Vomiting
Safety Analysis Set**



HR is computed from the Cox proportional hazards model using stratification factors (Presence or history of brain metastases: Yes/No, ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization.

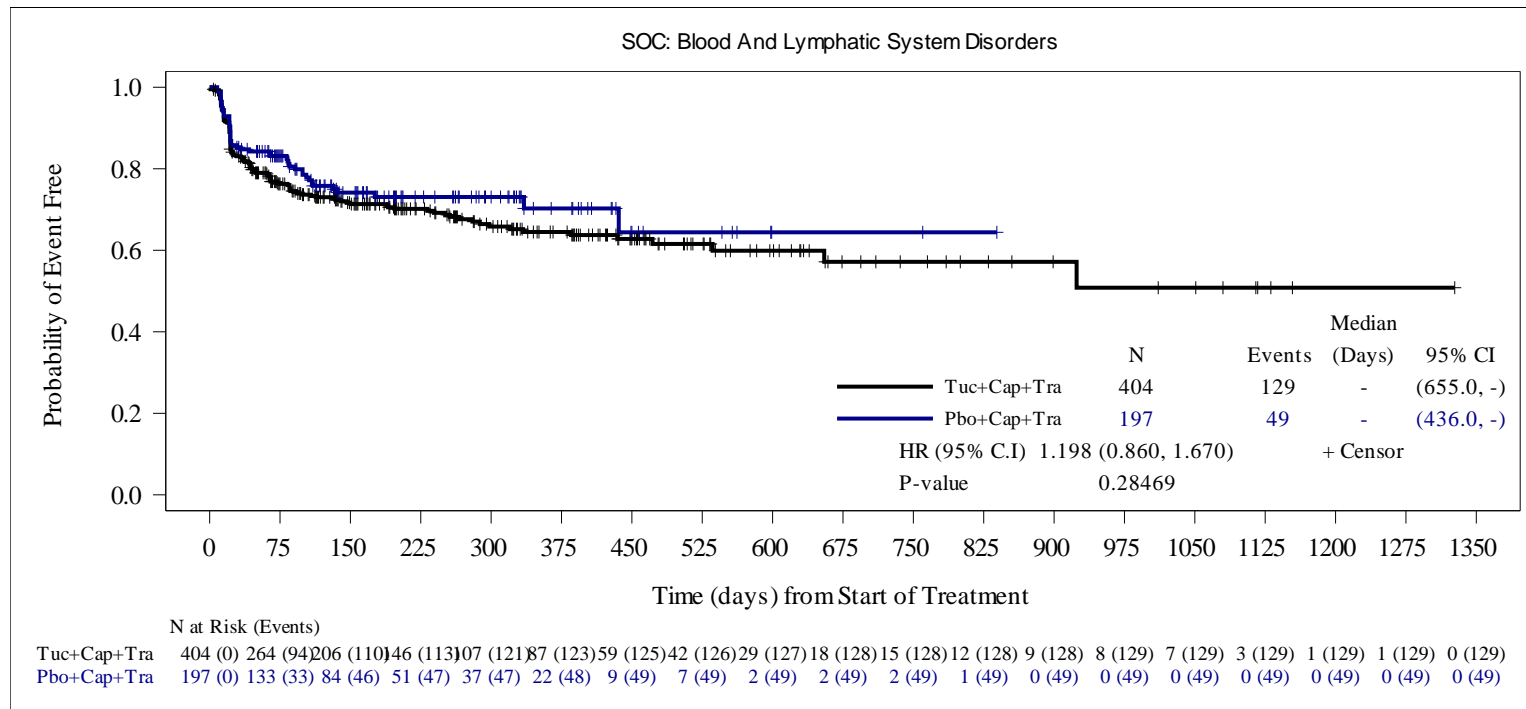
Two-sided p-value calculated from Cox proportional hazards model .

Data Snapshot: 14OCT2019, Data Cutoff Date: 04SEP2019

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_1753\v01\outputs\tlfs\pgms\f-ae-onset-gastro.sas Output: f-ae-km-gi-vom-safs.rtf(22APR20:14:20) Data: adsl, adae, adttesaf

Seagen Protocol ONT-380-206

**Figure 2.7.1 Kaplan-Meier Estimate of Time to First Onset of Treatment-Emergent Adverse Events by System Organ Class and Preferred Term
Safety Analysis Set**



HR is computed from the Cox proportional hazards model using stratification factors (Presence or history of brain metastases: Yes/No, ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization. When the number of subjects with at least one event was ≤ 30 , an unstratified Cox model was run.

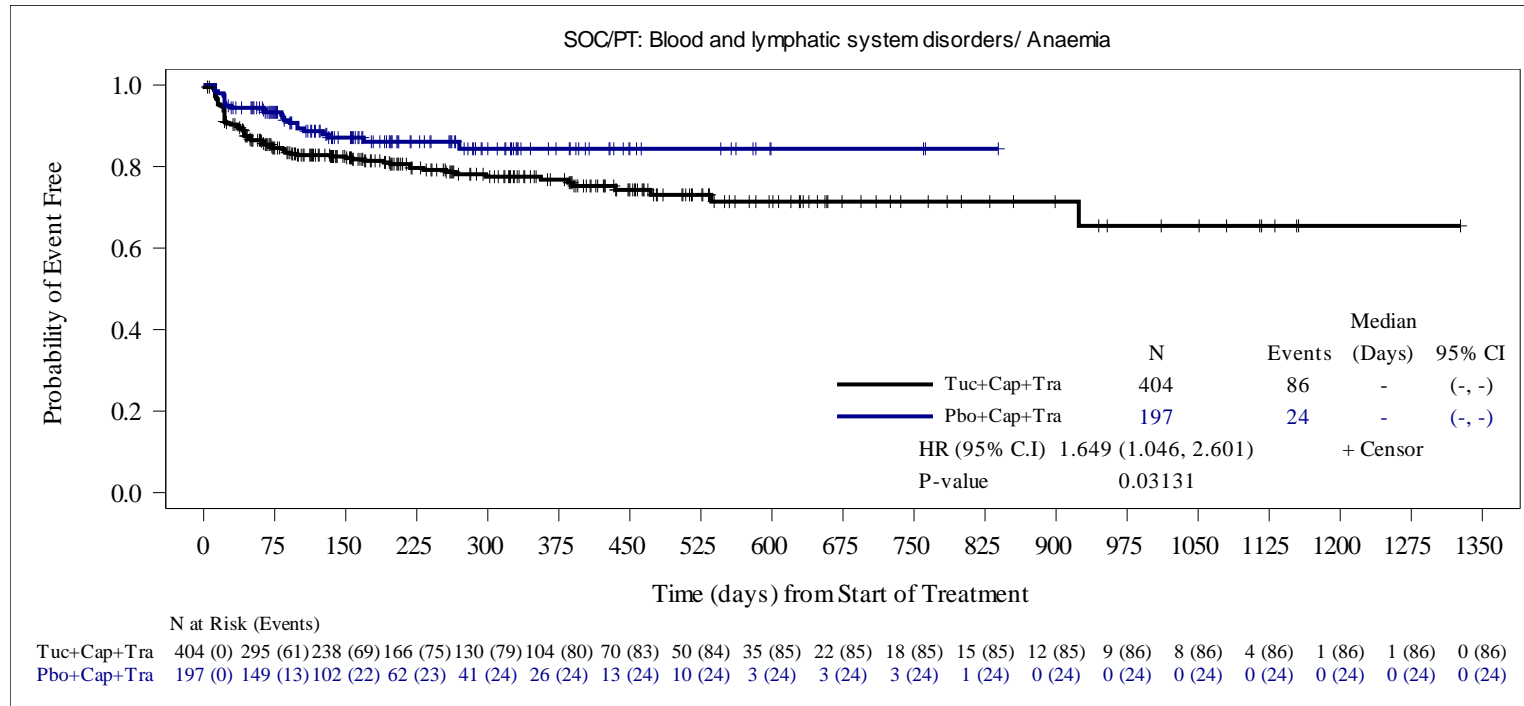
Two-sided p-value calculated from Cox proportional hazards model .

Snapshot date: 10SEP2020, data cutoff date: 29MAY2020.

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_may2020_dco_1943\v01\outputs\tlfs\pgms\f-ae-km-socpt-safs.sas Output: f02-07-01-ae-km-socpt-safs.rtf(14DEC20:17:09) Data: adsl, adae, adttesaf

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**Figure 2.7.1 Kaplan-Meier Estimate of Time to First Onset of Treatment-Emergent Adverse Events by System Organ Class and Preferred Term
Safety Analysis Set**



HR is computed from the Cox proportional hazards model using stratification factors (Presence or history of brain metastases: Yes/No, ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization. When the number of subjects with at least one event was ≤ 30 , an unstratified Cox model was run.

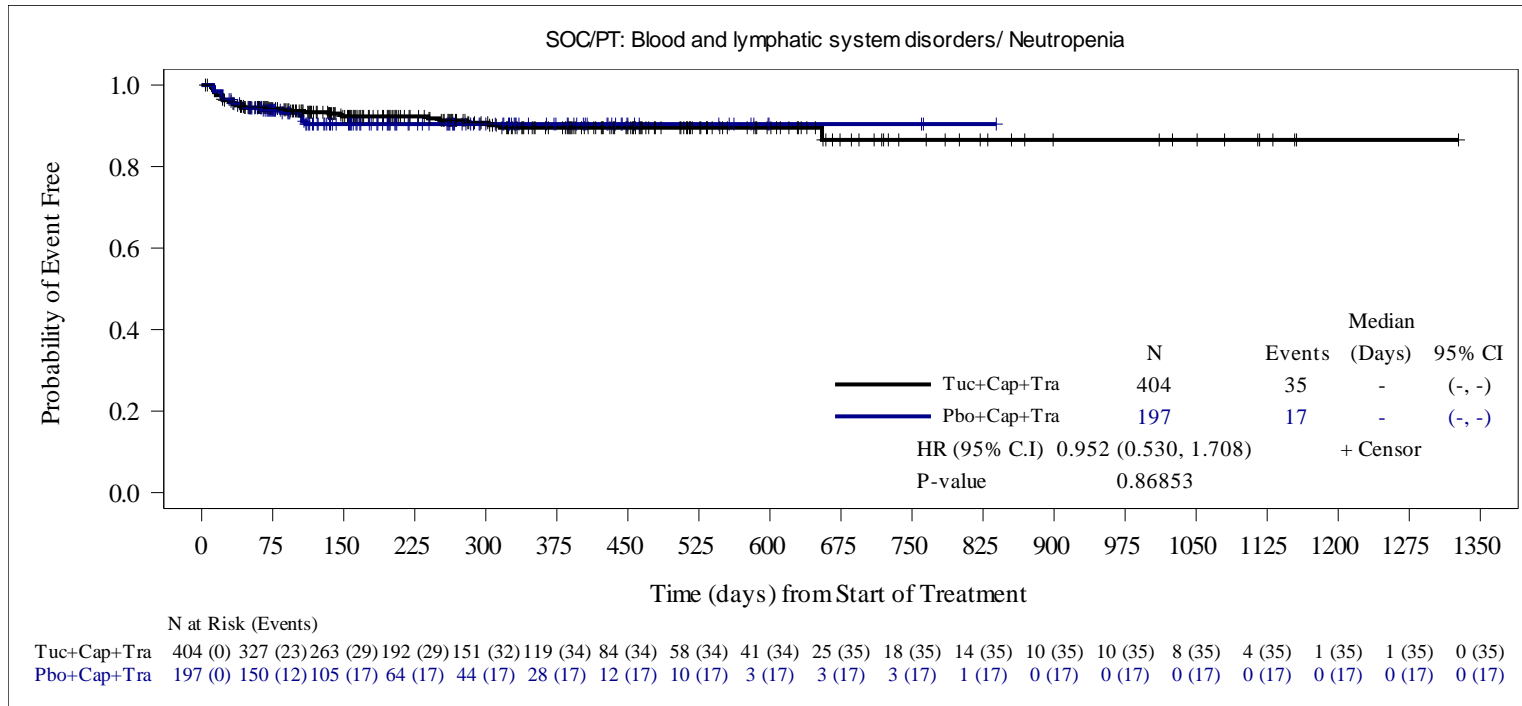
Two-sided p-value calculated from Cox proportional hazards model .

Snapshot date: 10SEP2020, data cutoff date: 29MAY2020.

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_may2020_dco_1943\01\outputs\tlfs\pgms\ae-km-socpt-safs.sas Output:
f02-07-01-ae-km-socpt-safs.rtf(14DEC20:17:09) Data: adsl, adae, adttesaf

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**Figure 2.7.1 Kaplan-Meier Estimate of Time to First Onset of Treatment-Emergent Adverse Events by System Organ Class and Preferred Term
Safety Analysis Set**



HR is computed from the Cox proportional hazards model using stratification factors (Presence or history of brain metastases: Yes/No, ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization. When the number of subjects with at least one event was ≤ 30 , an unstratified Cox model was run.

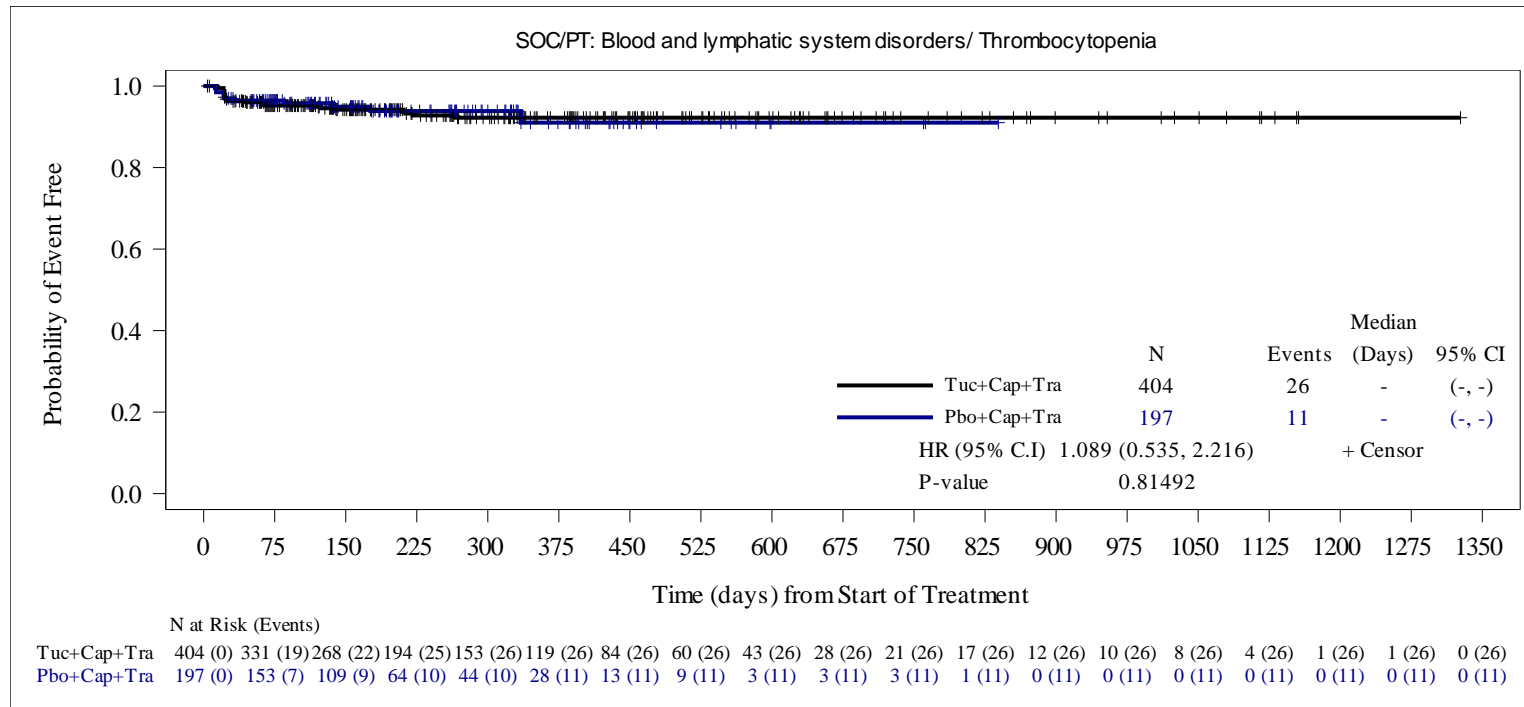
Two-sided p-value calculated from Cox proportional hazards model .

Snapshot date: 10SEP2020, data cutoff date: 29MAY2020.

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f02-07-01-ae-km-socpt-safs.rtf(14DEC20:17:09) Data: adsl, adae, adttesaf

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**Figure 2.7.1 Kaplan-Meier Estimate of Time to First Onset of Treatment-Emergent Adverse Events by System Organ Class and Preferred Term
Safety Analysis Set**



HR is computed from the Cox proportional hazards model using stratification factors (Presence or history of brain metastases: Yes/No, ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization. When the number of subjects with at least one event was ≤ 30 , an unstratified Cox model was run.

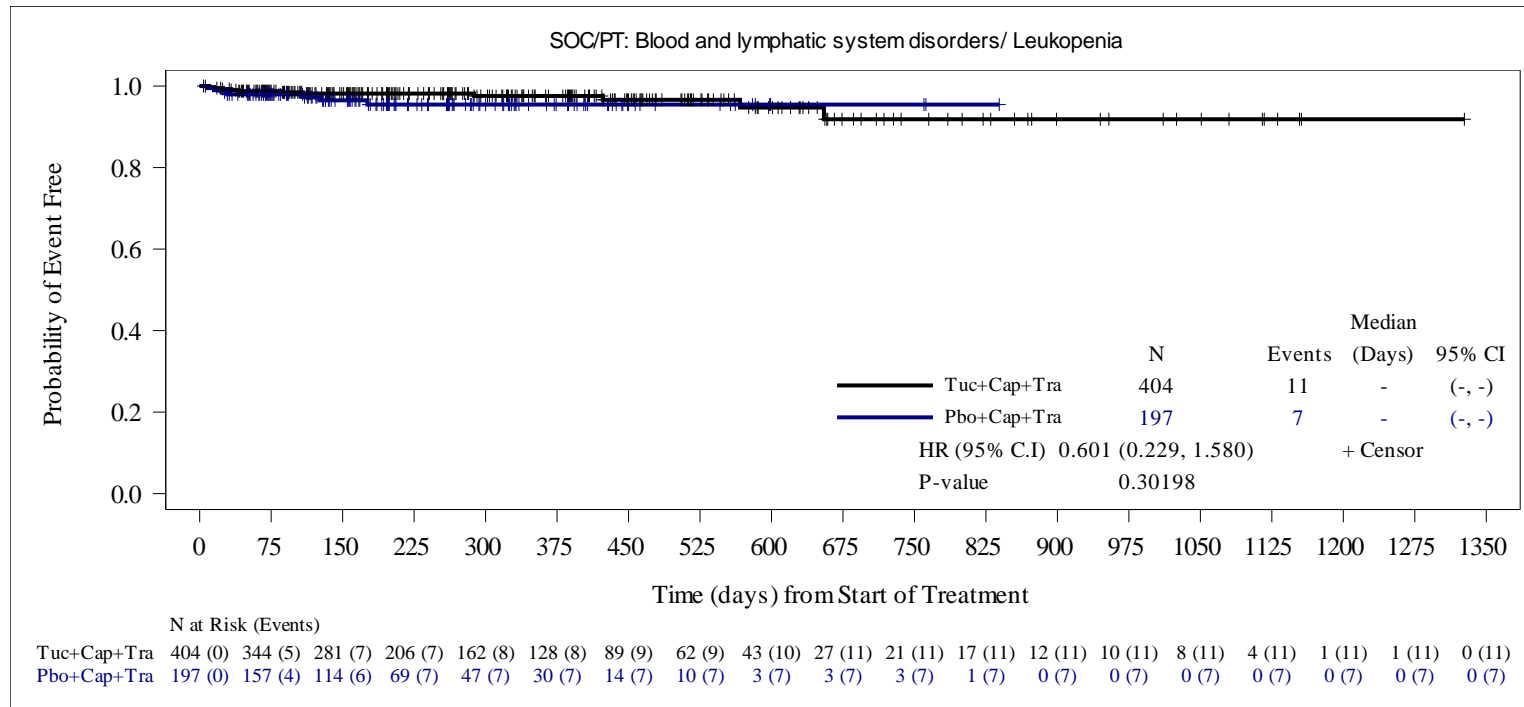
Two-sided p-value calculated from Cox proportional hazards model .

Snapshot date: 10SEP2020, data cutoff date: 29MAY2020.

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**Figure 2.7.1 Kaplan-Meier Estimate of Time to First Onset of Treatment-Emergent Adverse Events by System Organ Class and Preferred Term
Safety Analysis Set**



HR is computed from the Cox proportional hazards model using stratification factors (Presence or history of brain metastases: Yes/No, ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization. When the number of subjects with at least one event was ≤ 30 , an unstratified Cox model was run.

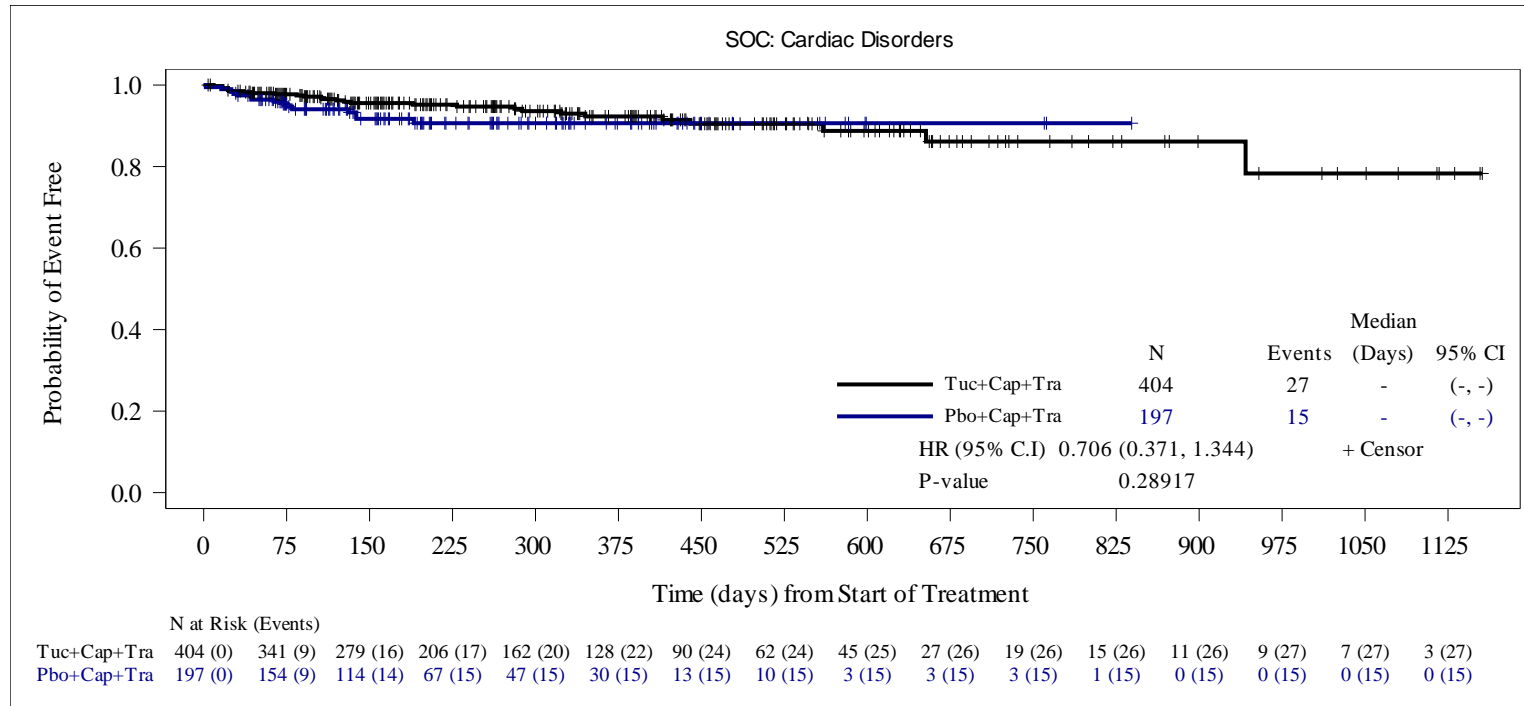
Two-sided p-value calculated from Cox proportional hazards model .

Snapshot date: 10SEP2020, data cutoff date: 29MAY2020.

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_may2020_dco_1943\v01\outputs\tlfs\pgms\f-ae-km-socpt-safs.sas Output: f02-07-01-ae-km-socpt-safs.rtf(14DEC20:17:09) Data: adsl, adae, adttesaf

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**Figure 2.7.1 Kaplan-Meier Estimate of Time to First Onset of Treatment-Emergent Adverse Events by System Organ Class and Preferred Term
Safety Analysis Set**



HR is computed from the Cox proportional hazards model using stratification factors (Presence or history of brain metastases: Yes/No, ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization. When the number of subjects with at least one event was ≤ 30 , an unstratified Cox model was run.

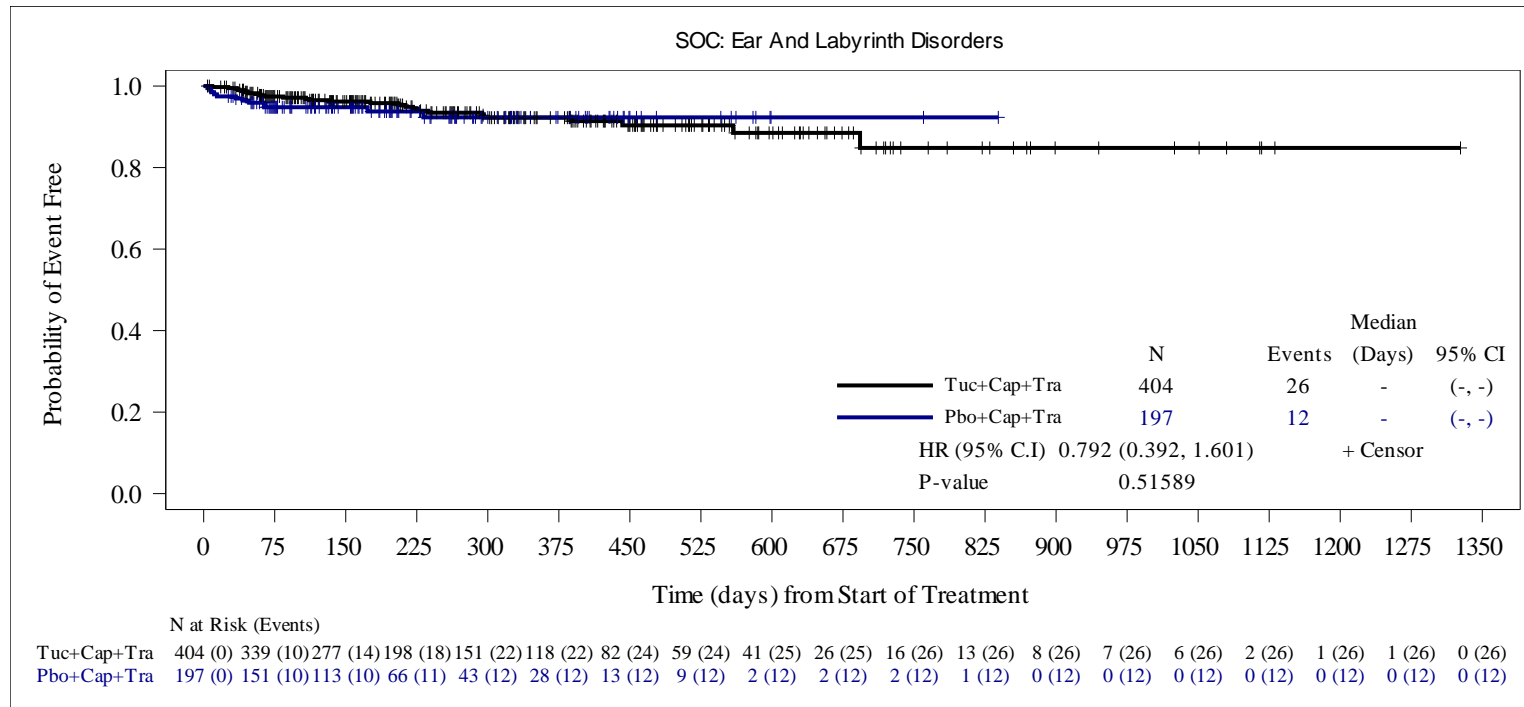
Two-sided p-value calculated from Cox proportional hazards model .

Snapshot date: 10SEP2020, data cutoff date: 29MAY2020.

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**Figure 2.7.1 Kaplan-Meier Estimate of Time to First Onset of Treatment-Emergent Adverse Events by System Organ Class and Preferred Term
Safety Analysis Set**



HR is computed from the Cox proportional hazards model using stratification factors (Presence or history of brain metastases: Yes/No, ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization. When the number of subjects with at least one event was ≤ 30 , an unstratified Cox model was run.

Two-sided p-value calculated from Cox proportional hazards model .

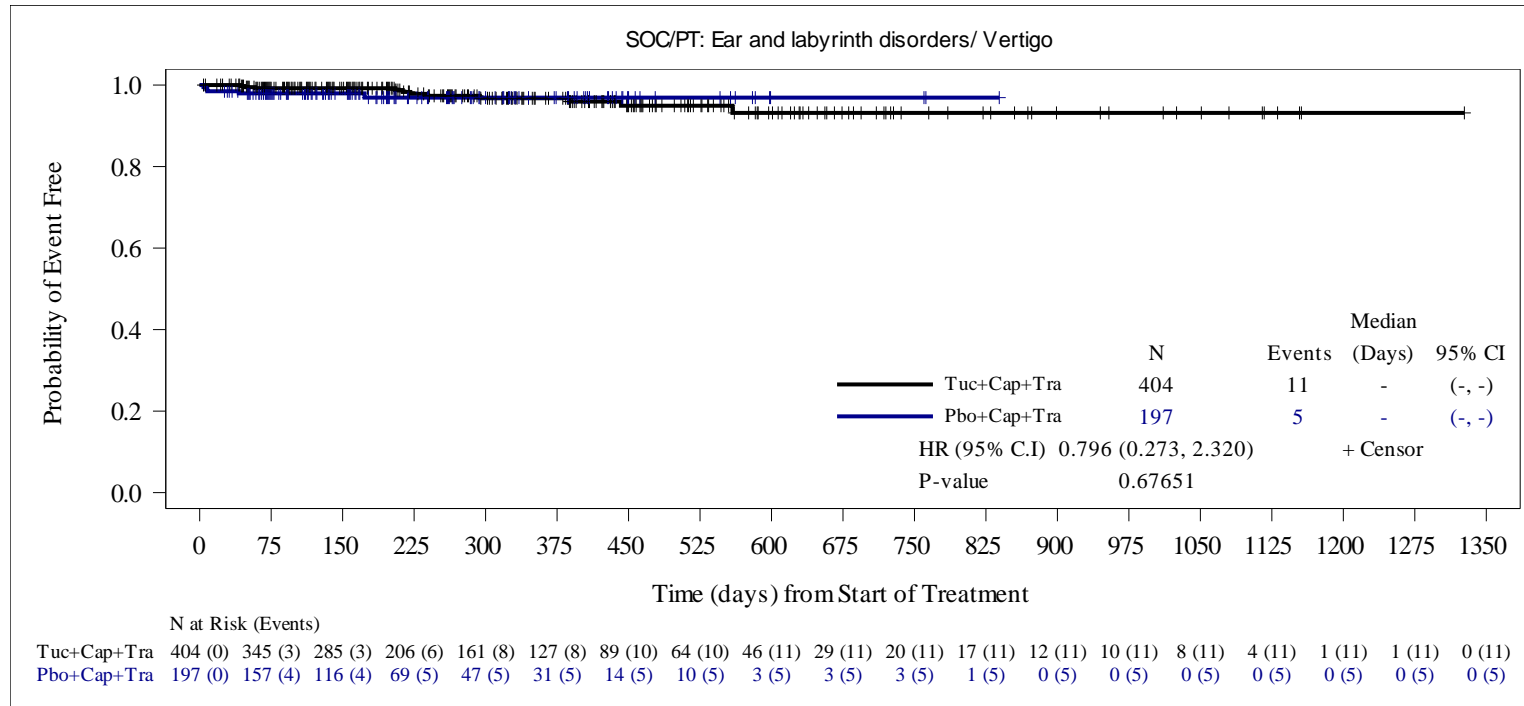
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f02-07-01-ae-km-socpt-safs.rtf(14DEC20:17:09) Data: adsl, adae, adttesaf

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**Figure 2.7.1 Kaplan-Meier Estimate of Time to First Onset of Treatment-Emergent Adverse Events by System Organ Class and Preferred Term
Safety Analysis Set**



HR is computed from the Cox proportional hazards model using stratification factors (Presence or history of brain metastases: Yes/No, ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization. When the number of subjects with at least one event was ≤ 30 , an unstratified Cox model was run.

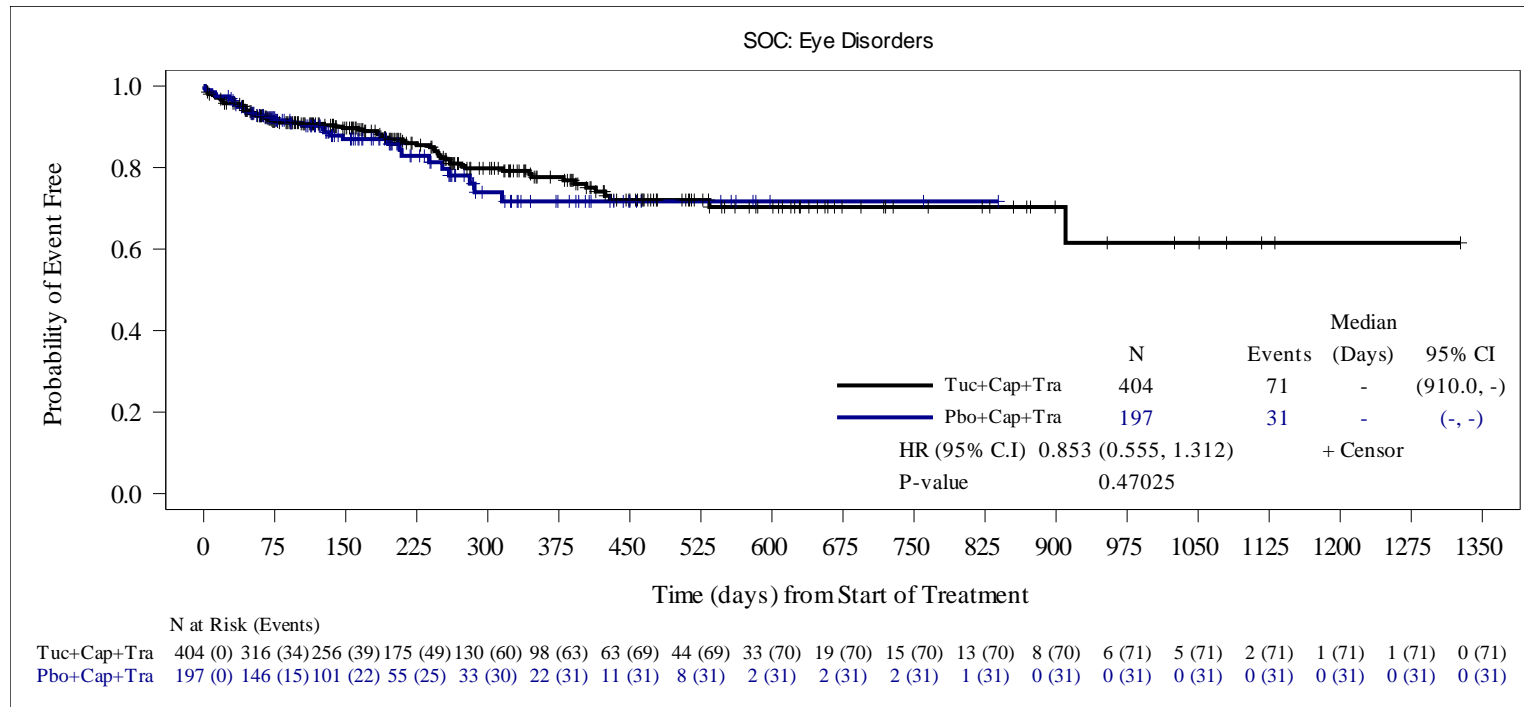
Two-sided p-value calculated from Cox proportional hazards model .

Snapshot date: 10SEP2020, data cutoff date: 29MAY2020.

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**Figure 2.7.1 Kaplan-Meier Estimate of Time to First Onset of Treatment-Emergent Adverse Events by System Organ Class and Preferred Term
Safety Analysis Set**



HR is computed from the Cox proportional hazards model using stratification factors (Presence or history of brain metastases: Yes/No, ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization. When the number of subjects with at least one event was ≤ 30 , an unstratified Cox model was run.

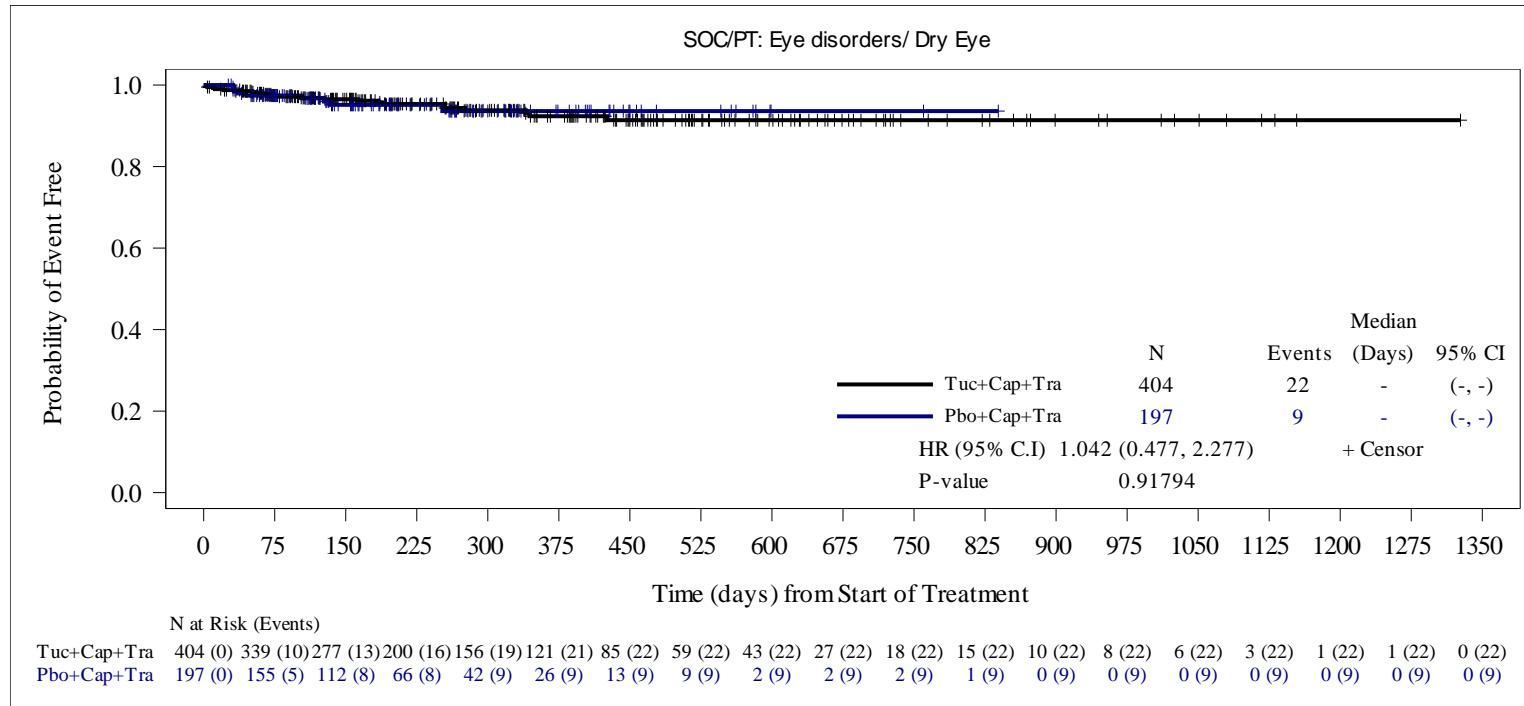
Two-sided p-value calculated from Cox proportional hazards model .

Snapshot date: 10SEP2020, data cutoff date: 29MAY2020.

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f02-07-01-ae-km-socpt-safs.rtf(14DEC20:17:09) Data: adsl, adae, adttesaf

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**Figure 2.7.1 Kaplan-Meier Estimate of Time to First Onset of Treatment-Emergent Adverse Events by System Organ Class and Preferred Term
Safety Analysis Set**



HR is computed from the Cox proportional hazards model using stratification factors (Presence or history of brain metastases: Yes/No, ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization. When the number of subjects with at least one event was ≤ 30 , an unstratified Cox model was run.

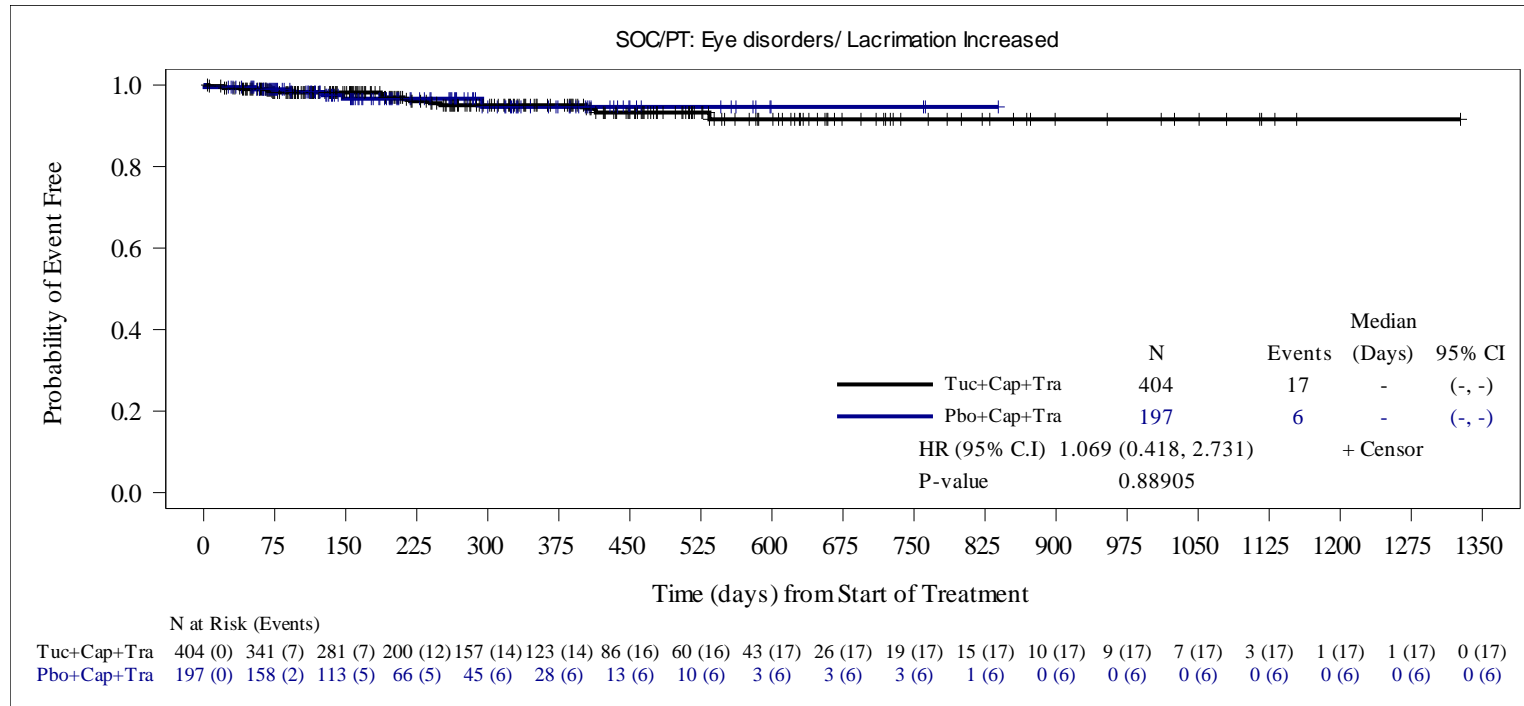
Two-sided p-value calculated from Cox proportional hazards model .

Snapshot date: 10SEP2020, data cutoff date: 29MAY2020.

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_may2020_dco_1943\v01\outputs\tlfs\pgms\f-ae-km-socpt-safs.sas Output: f02-07-01-ae-km-socpt-safs.rtf(14DEC20:17:09) Data: adsl, adae, adttesaf

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**Figure 2.7.1 Kaplan-Meier Estimate of Time to First Onset of Treatment-Emergent Adverse Events by System Organ Class and Preferred Term
Safety Analysis Set**



HR is computed from the Cox proportional hazards model using stratification factors (Presence or history of brain metastases: Yes/No, ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization. When the number of subjects with at least one event was ≤ 30 , an unstratified Cox model was run.

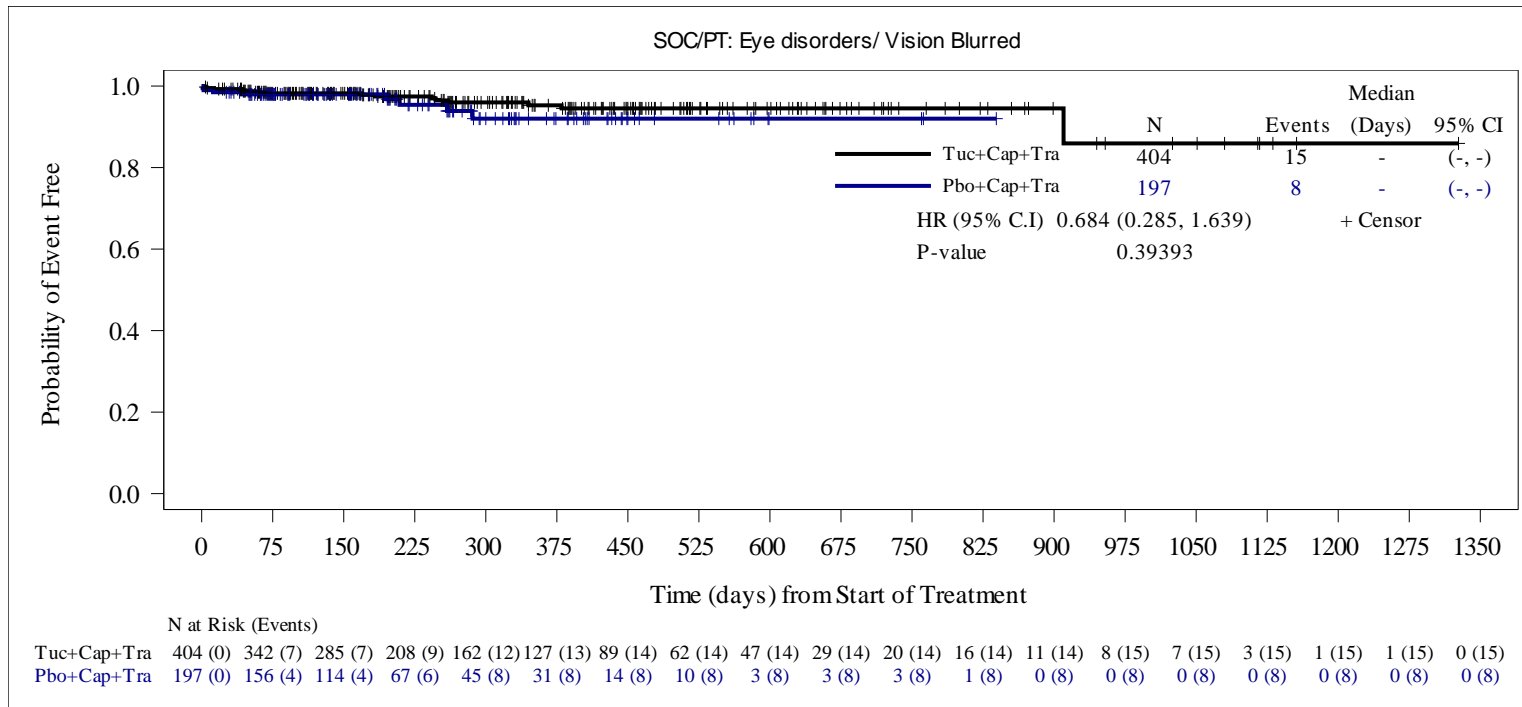
Two-sided p-value calculated from Cox proportional hazards model .

Snapshot date: 10SEP2020, data cutoff date: 29MAY2020.

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_may2020_dco_1943\v01\outputs\tlfs\pgms\ae-km-socpt-safs.sas Output:
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**Figure 2.7.1 Kaplan-Meier Estimate of Time to First Onset of Treatment-Emergent Adverse Events by System Organ Class and Preferred Term
Safety Analysis Set**



HR is computed from the Cox proportional hazards model using stratification factors (Presence or history of brain metastases: Yes/No, ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization. When the number of subjects with at least one event was ≤ 30 , an unstratified Cox model was run.

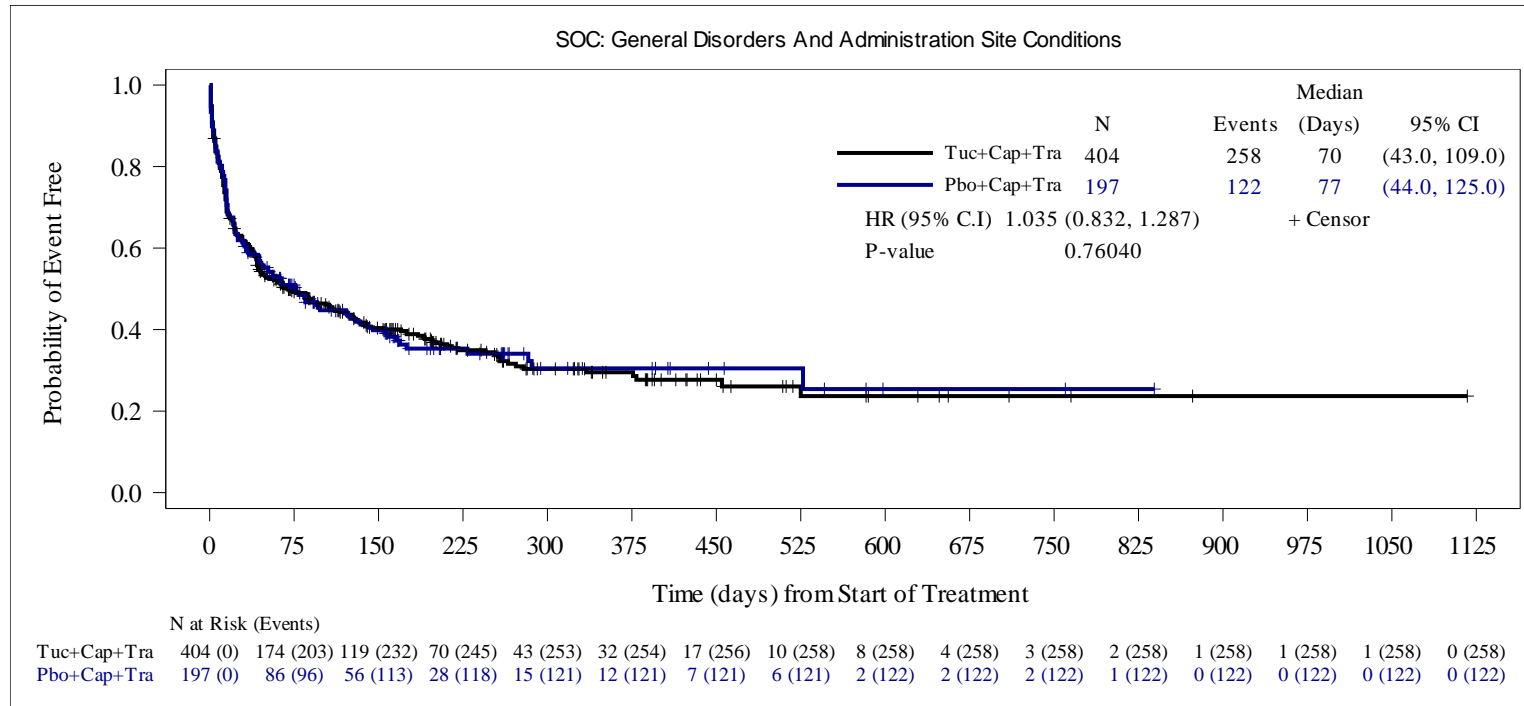
Two-sided p-value calculated from Cox proportional hazards model .

Snapshot date: 10SEP2020, data cutoff date: 29MAY2020.

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**Figure 2.7.1 Kaplan-Meier Estimate of Time to First Onset of Treatment-Emergent Adverse Events by System Organ Class and Preferred Term
Safety Analysis Set**



HR is computed from the Cox proportional hazards model using stratification factors (Presence or history of brain metastases: Yes/No, ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization. When the number of subjects with at least one event was ≤ 30 , an unstratified Cox model was run.

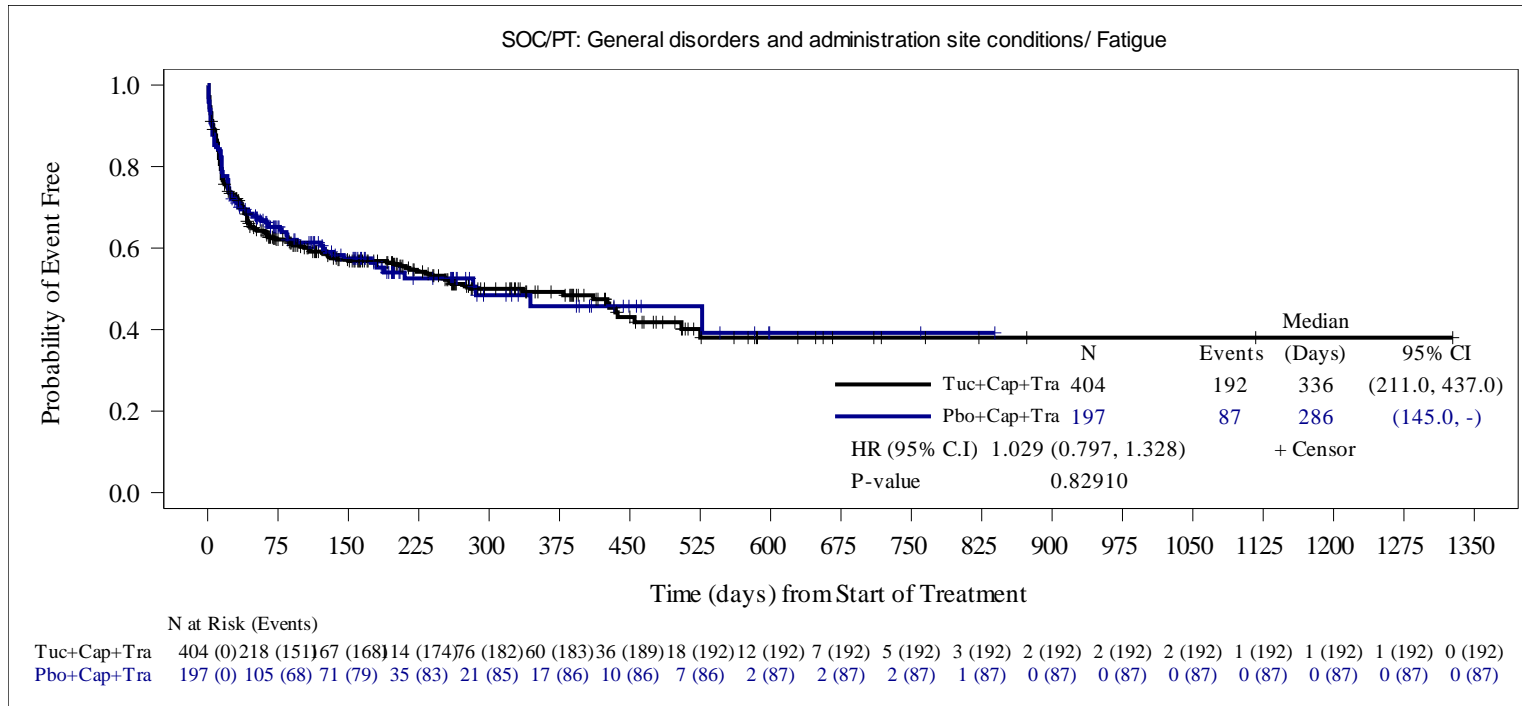
Two-sided p-value calculated from Cox proportional hazards model .

Snapshot date: 10SEP2020, data cutoff date: 29MAY2020.

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**Figure 2.7.1 Kaplan-Meier Estimate of Time to First Onset of Treatment-Emergent Adverse Events by System Organ Class and Preferred Term
Safety Analysis Set**



HR is computed from the Cox proportional hazards model using stratification factors (Presence or history of brain metastases: Yes/No, ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization. When the number of subjects with at least one event was ≤ 30 , an unstratified Cox model was run.

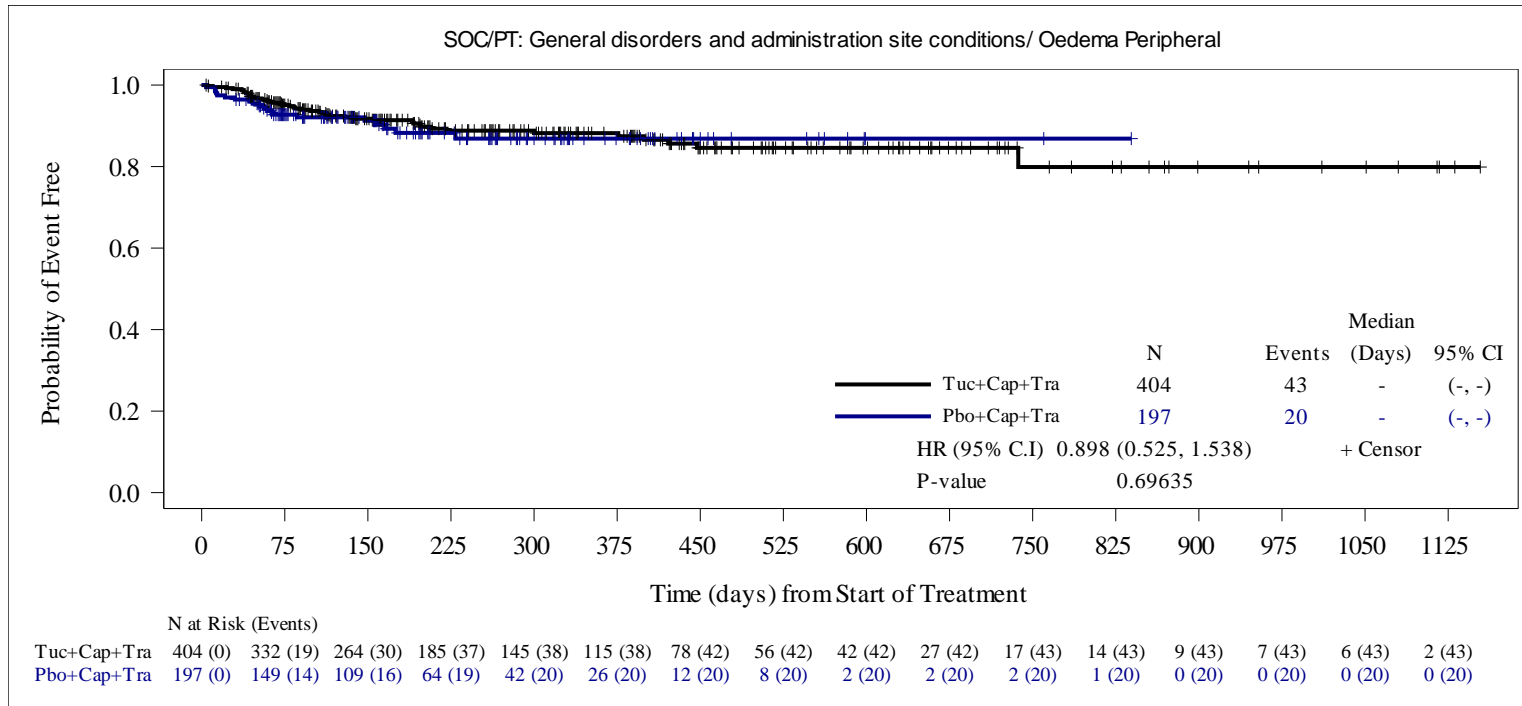
Two-sided p-value calculated from Cox proportional hazards model .

Snapshot date: 10SEP2020, data cutoff date: 29MAY2020.

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f02-07-01-ae-km-socpt-safs.rtf(14DEC20:17:09) Data: adsl, adae, adttesaf

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**Figure 2.7.1 Kaplan-Meier Estimate of Time to First Onset of Treatment-Emergent Adverse Events by System Organ Class and Preferred Term
Safety Analysis Set**



HR is computed from the Cox proportional hazards model using stratification factors (Presence or history of brain metastases: Yes/No, ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization. When the number of subjects with at least one event was ≤ 30 , an unstratified Cox model was run.

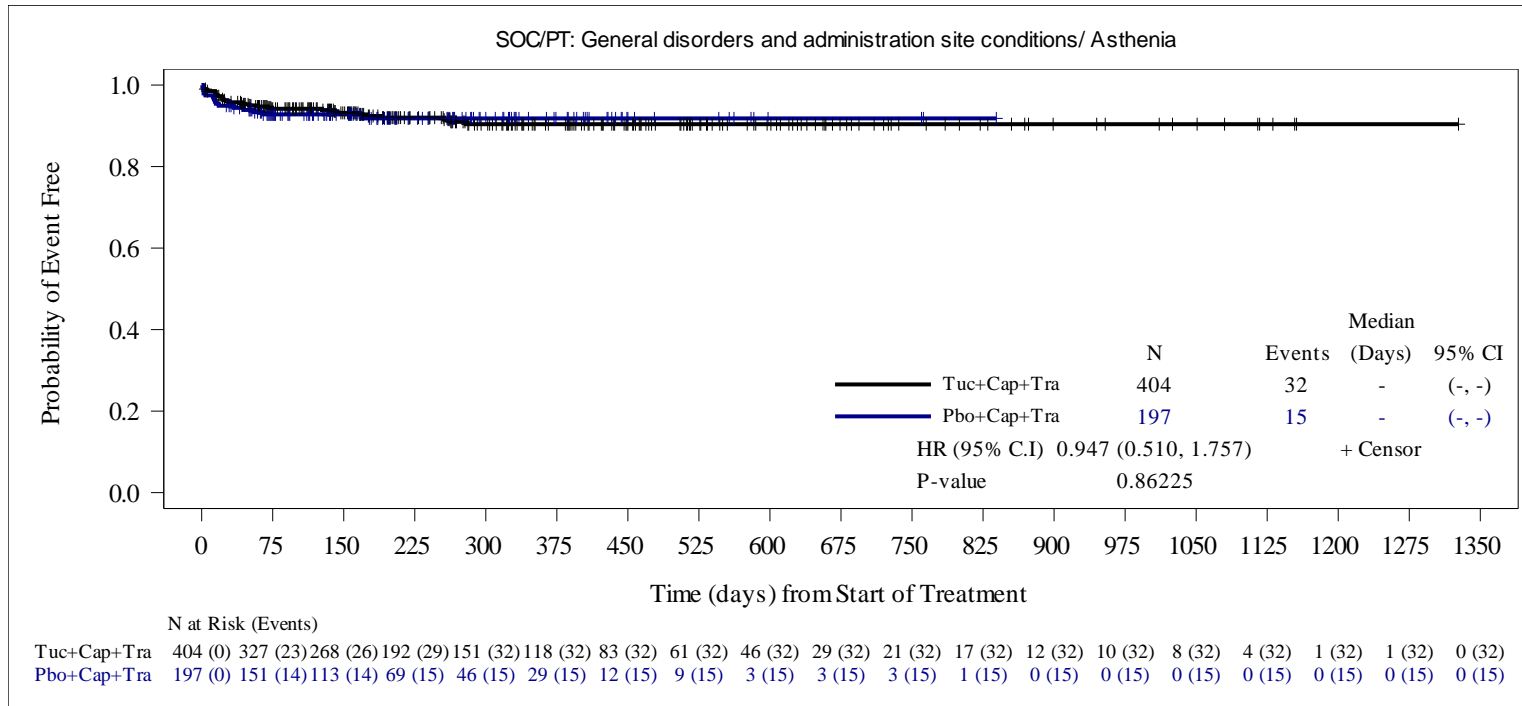
Two-sided p-value calculated from Cox proportional hazards model .

Snapshot date: 10SEP2020, data cutoff date: 29MAY2020.

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f02-07-01-ae-km-socpt-safs.rtf(14DEC20:17:09) Data: adsl, adae, adttesaf

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**Figure 2.7.1 Kaplan-Meier Estimate of Time to First Onset of Treatment-Emergent Adverse Events by System Organ Class and Preferred Term
Safety Analysis Set**



HR is computed from the Cox proportional hazards model using stratification factors (Presence or history of brain metastases: Yes/No, ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization. When the number of subjects with at least one event was ≤ 30 , an unstratified Cox model was run.

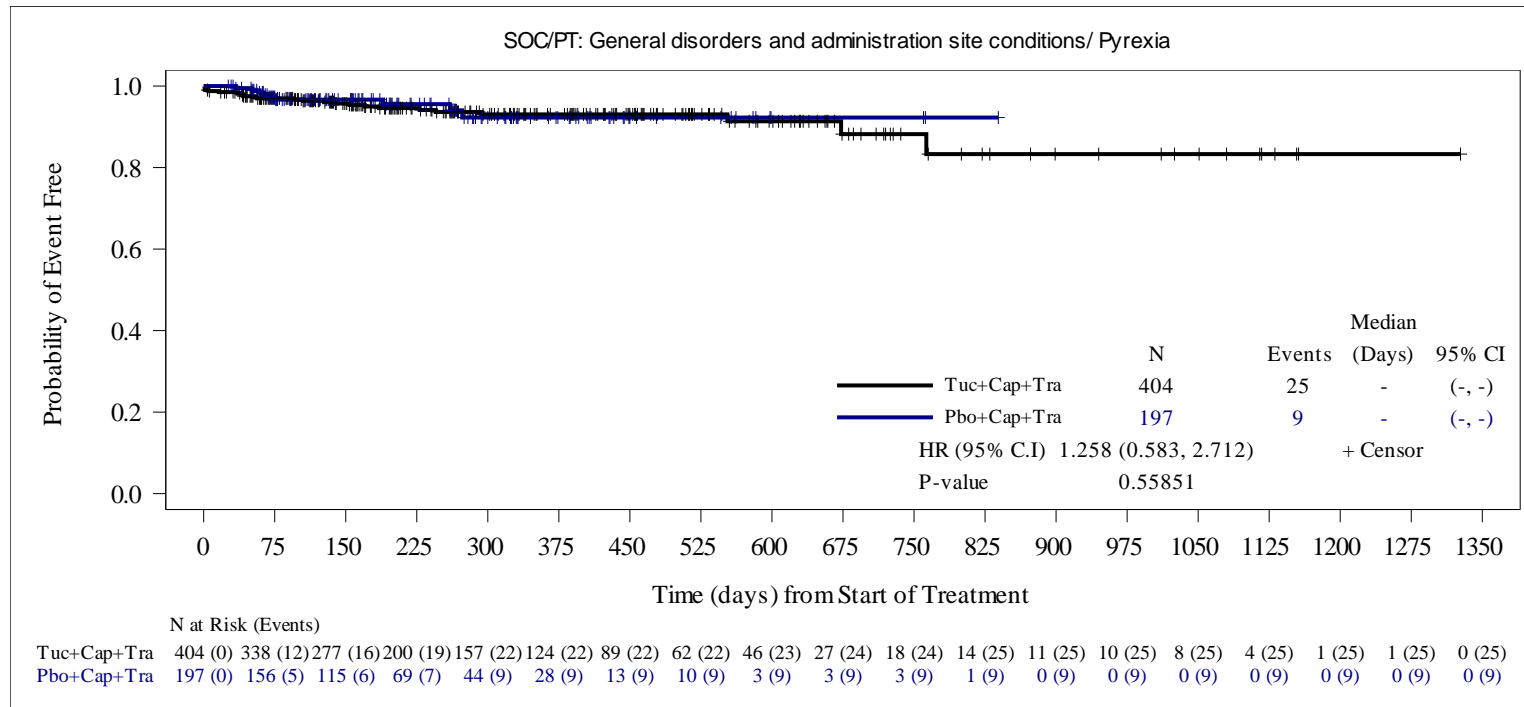
Two-sided p-value calculated from Cox proportional hazards model .

Snapshot date: 10SEP2020, data cutoff date: 29MAY2020.

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**Figure 2.7.1 Kaplan-Meier Estimate of Time to First Onset of Treatment-Emergent Adverse Events by System Organ Class and Preferred Term
Safety Analysis Set**



HR is computed from the Cox proportional hazards model using stratification factors (Presence or history of brain metastases: Yes/No, ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization. When the number of subjects with at least one event was ≤ 30 , an unstratified Cox model was run.

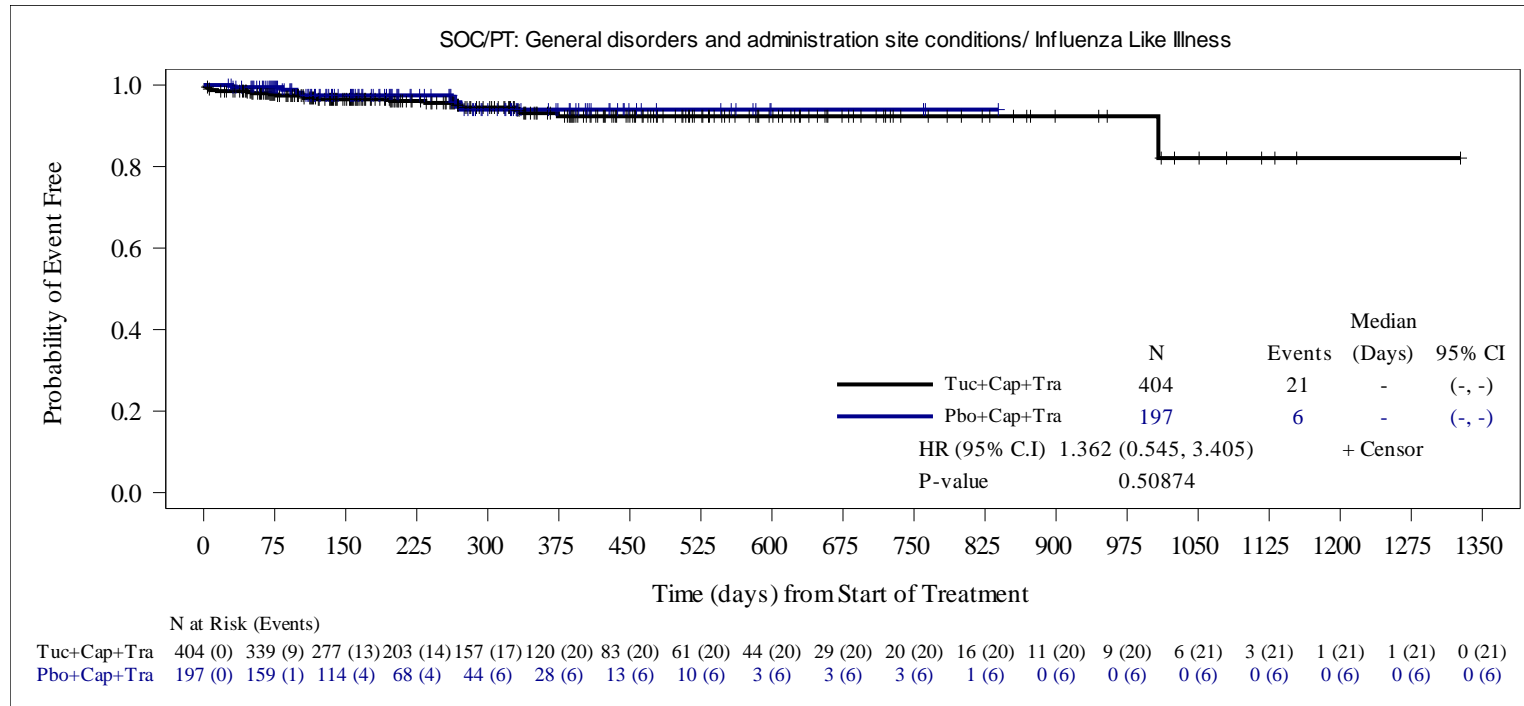
Two-sided p-value calculated from Cox proportional hazards model .

Snapshot date: 10SEP2020, data cutoff date: 29MAY2020.

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_may2020_dco_1943\v01\outputs\tlfs\pgms\f-ae-km-socpt-safs.sas Output:
f02-07-01-ae-km-socpt-safs.rtf(14DEC20:17:09) Data: adsl, adae, adttesaf

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**Figure 2.7.1 Kaplan-Meier Estimate of Time to First Onset of Treatment-Emergent Adverse Events by System Organ Class and Preferred Term
Safety Analysis Set**



HR is computed from the Cox proportional hazards model using stratification factors (Presence or history of brain metastases: Yes/No, ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization. When the number of subjects with at least one event was ≤ 30 , an unstratified Cox model was run.

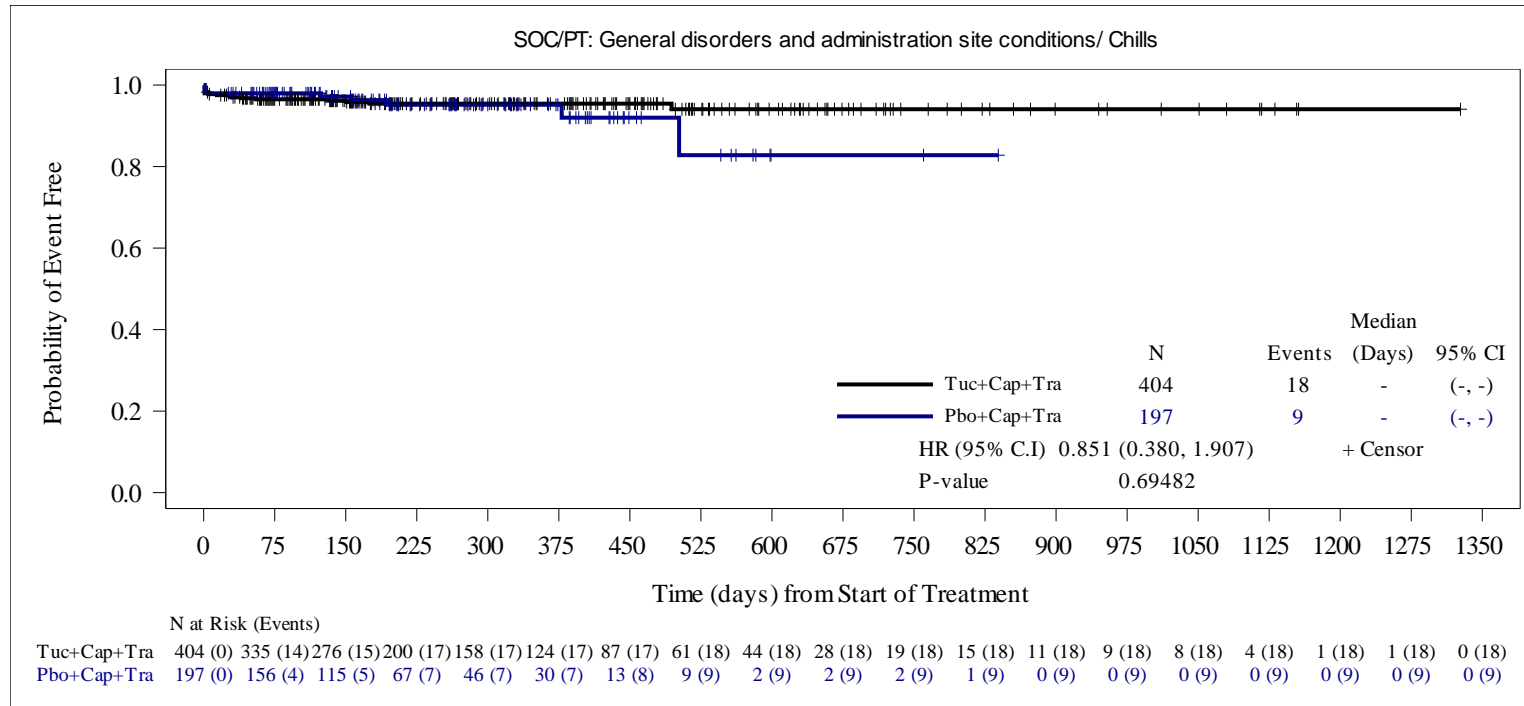
Two-sided p-value calculated from Cox proportional hazards model .

Snapshot date: 10SEP2020, data cutoff date: 29MAY2020.

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f02-07-01-ae-km-socpt-safs.rtf(14DEC20:17:09) Data: adsl, adae, adttesaf

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**Figure 2.7.1 Kaplan-Meier Estimate of Time to First Onset of Treatment-Emergent Adverse Events by System Organ Class and Preferred Term
Safety Analysis Set**



HR is computed from the Cox proportional hazards model using stratification factors (Presence or history of brain metastases: Yes/No, ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization. When the number of subjects with at least one event was ≤ 30 , an unstratified Cox model was run.

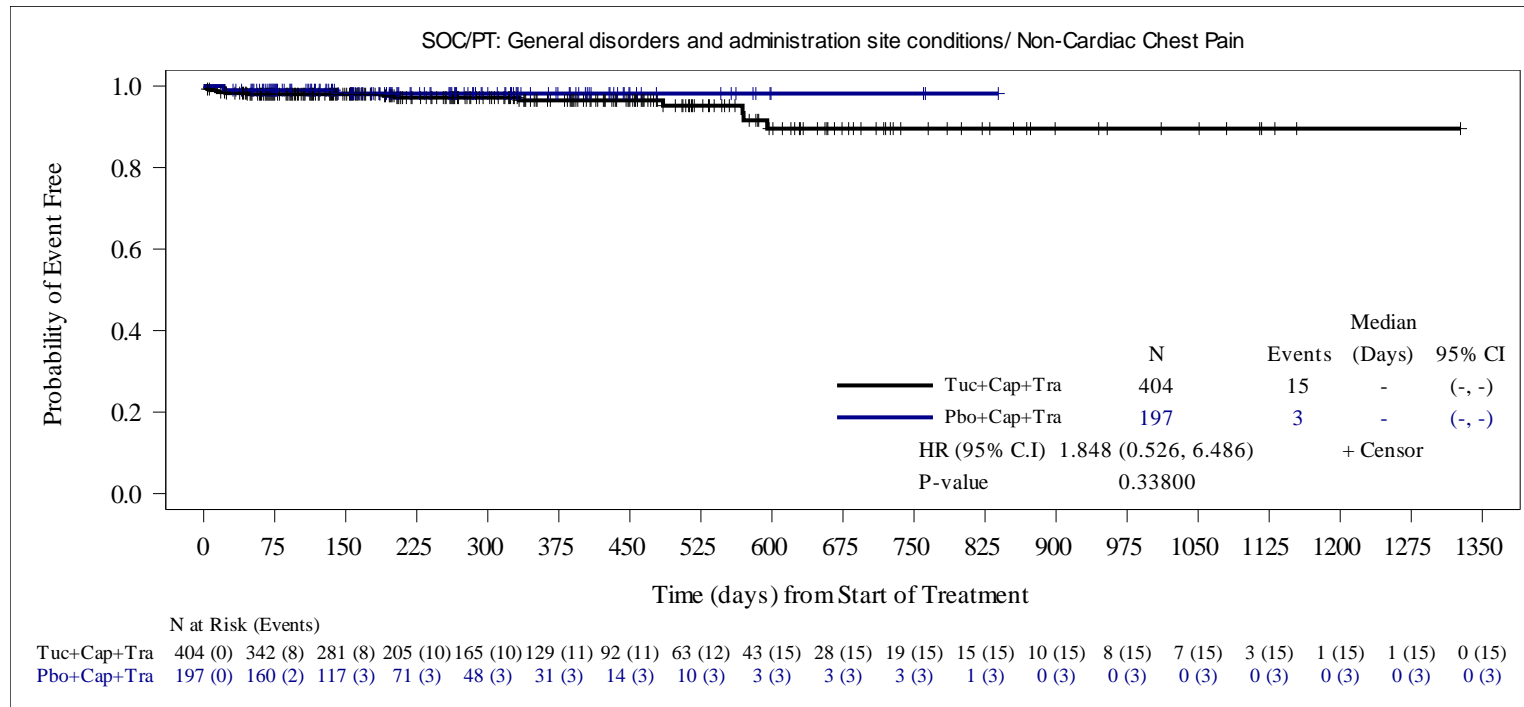
Two-sided p-value calculated from Cox proportional hazards model .

Snapshot date: 10SEP2020, data cutoff date: 29MAY2020.

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f02-07-01-ae-km-socpt-safs.rtf(14DEC20:17:09) Data: adsl, adae, adttesaf

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**Figure 2.7.1 Kaplan-Meier Estimate of Time to First Onset of Treatment-Emergent Adverse Events by System Organ Class and Preferred Term
Term
Safety Analysis Set**



HR is computed from the Cox proportional hazards model using stratification factors (Presence or history of brain metastases: Yes/No, ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization. When the number of subjects with at least one event was ≤ 30 , an unstratified Cox model was run.

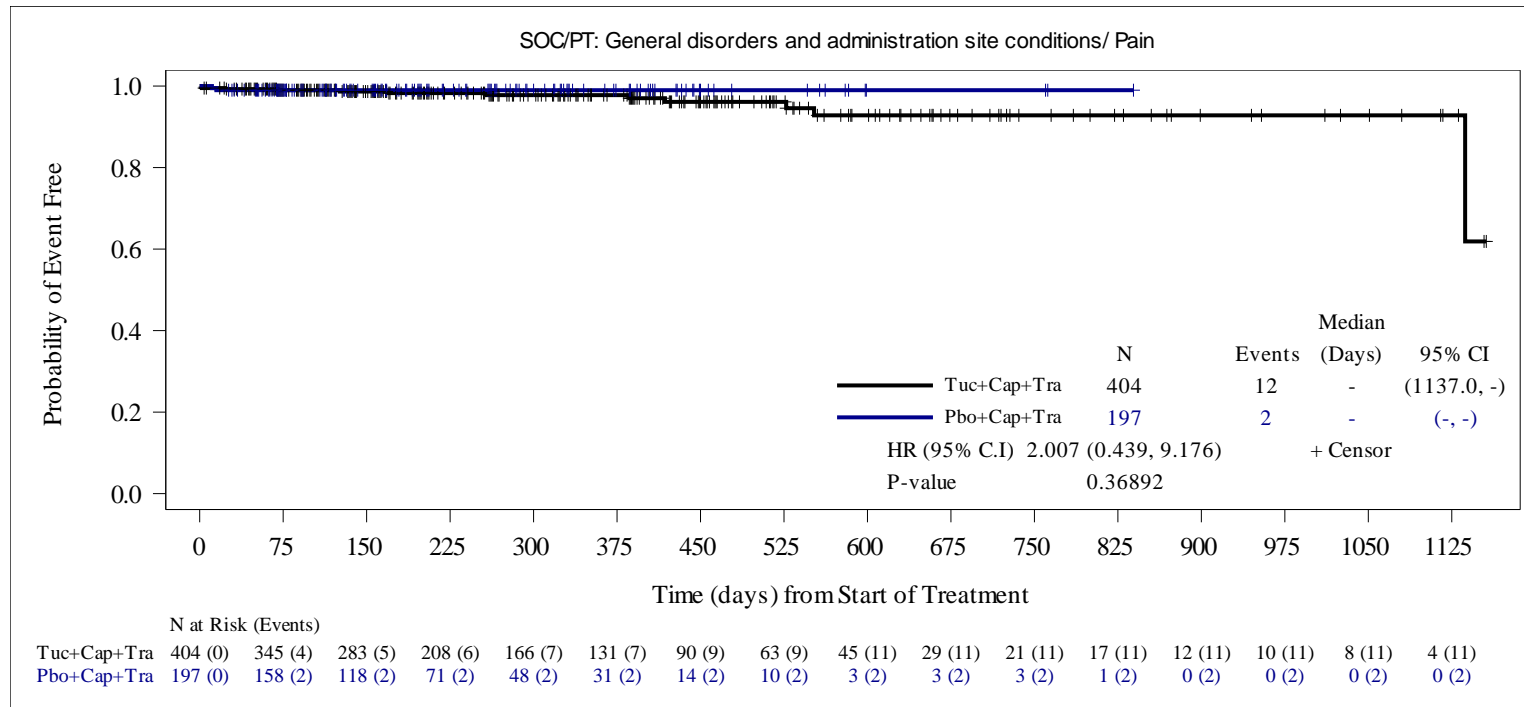
Two-sided p-value calculated from Cox proportional hazards model .

Snapshot date: 10SEP2020, data cutoff date: 29MAY2020.

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**Figure 2.7.1 Kaplan-Meier Estimate of Time to First Onset of Treatment-Emergent Adverse Events by System Organ Class and Preferred Term
Safety Analysis Set**



HR is computed from the Cox proportional hazards model using stratification factors (Presence or history of brain metastases: Yes/No, ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization. When the number of subjects with at least one event was ≤ 30 , an unstratified Cox model was run.

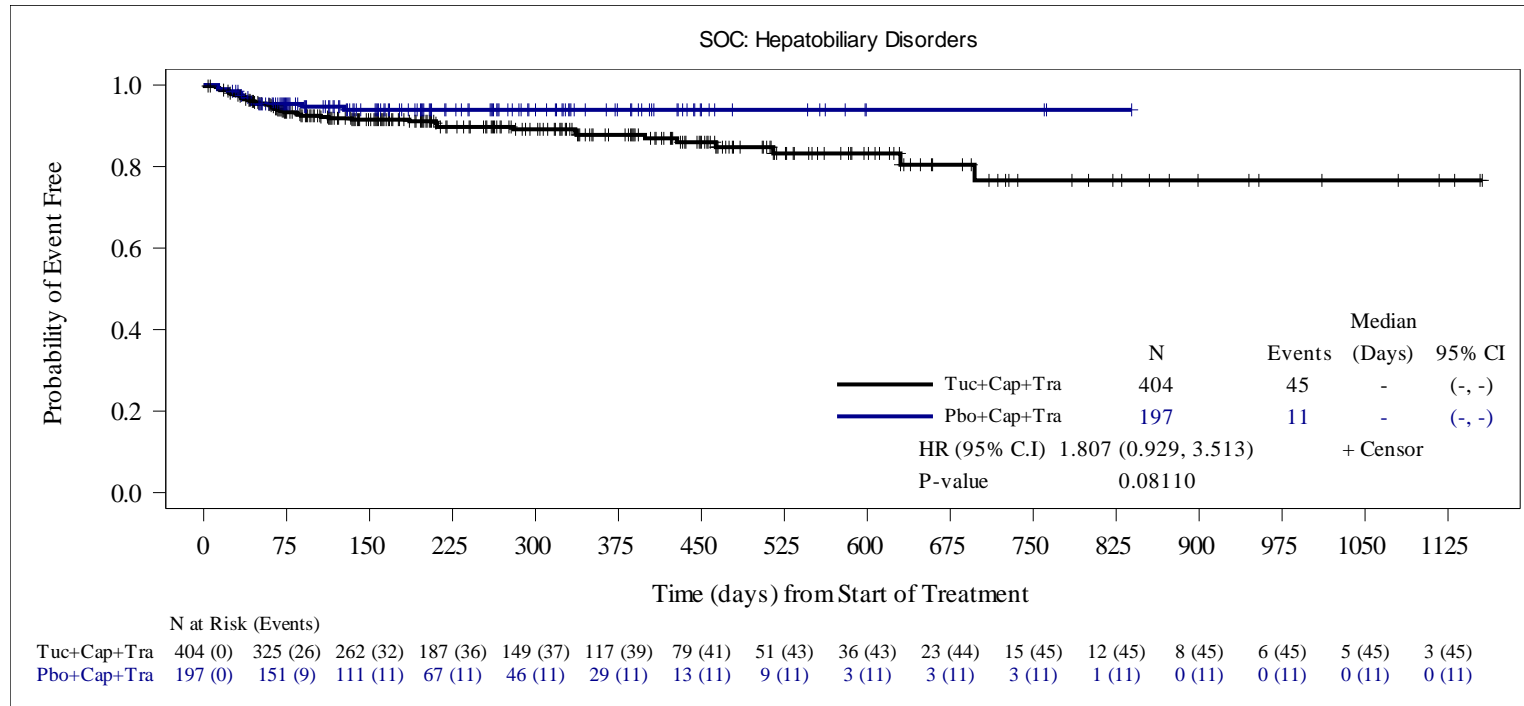
Two-sided p-value calculated from Cox proportional hazards model .

Snapshot date: 10SEP2020, data cutoff date: 29MAY2020.

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Seagen Protocol ONT-380-206

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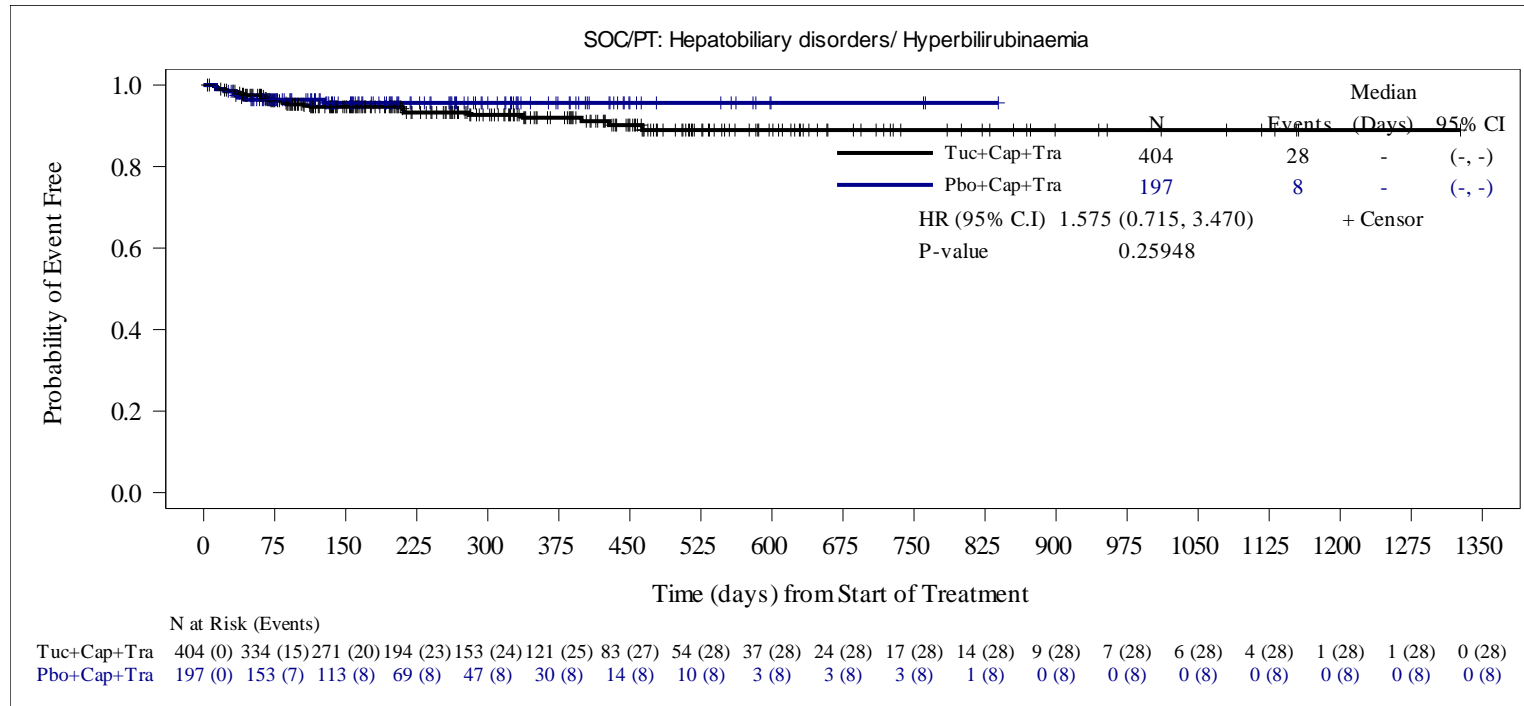
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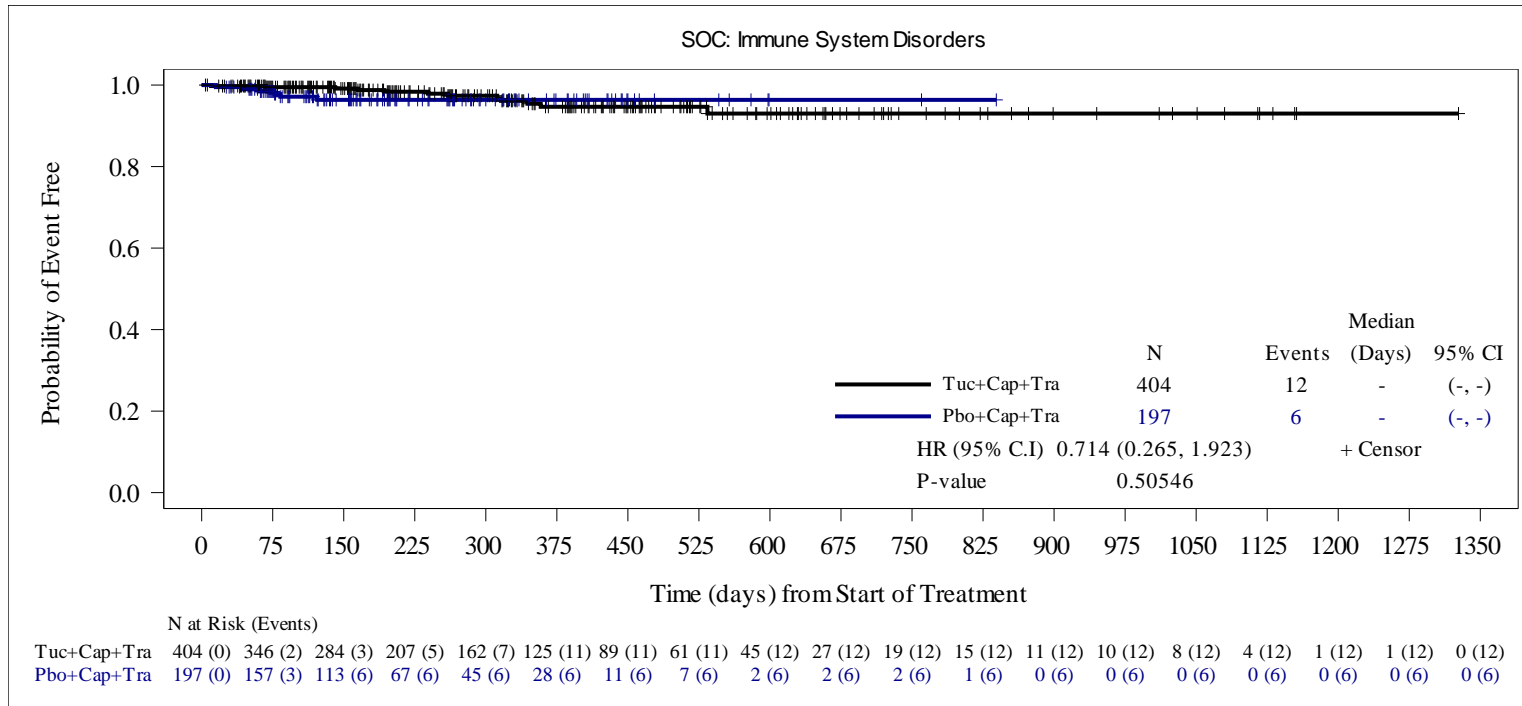
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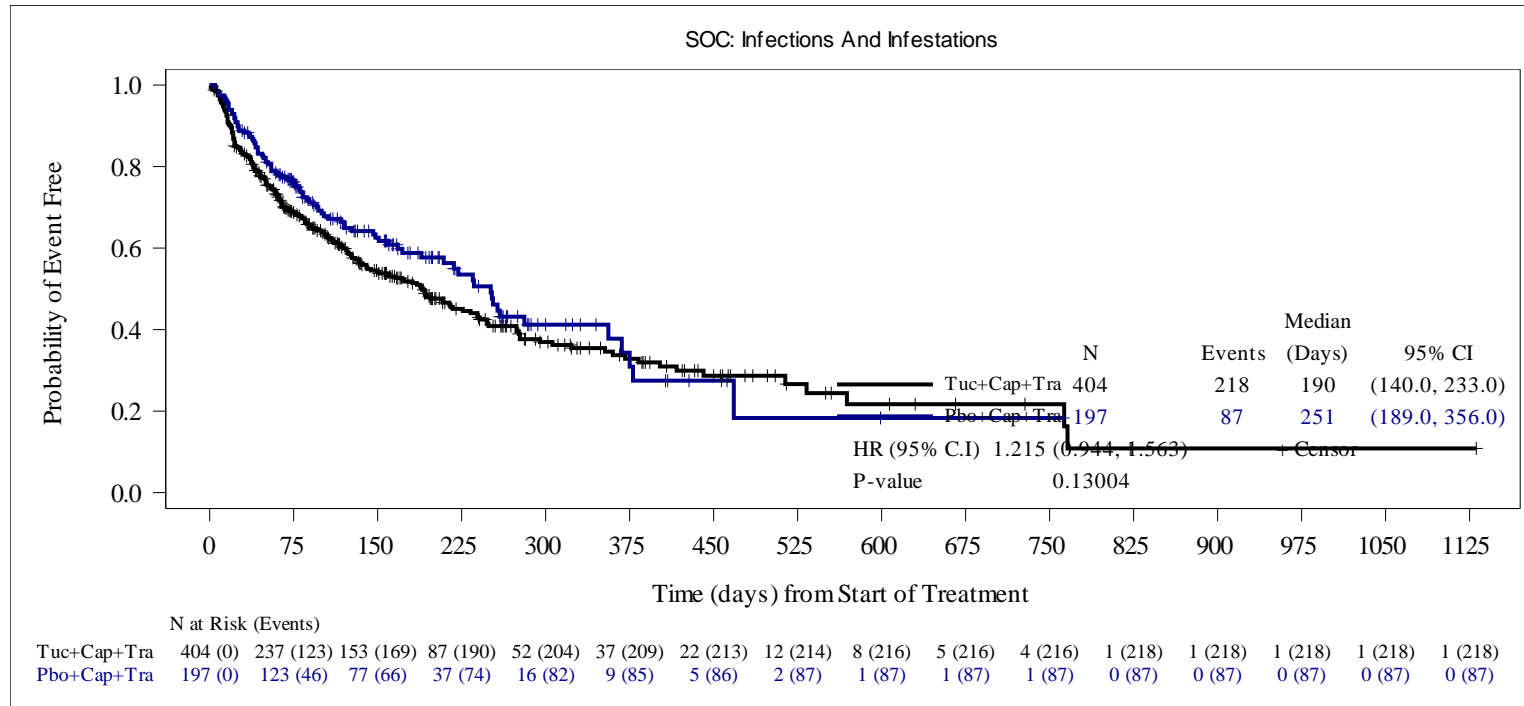
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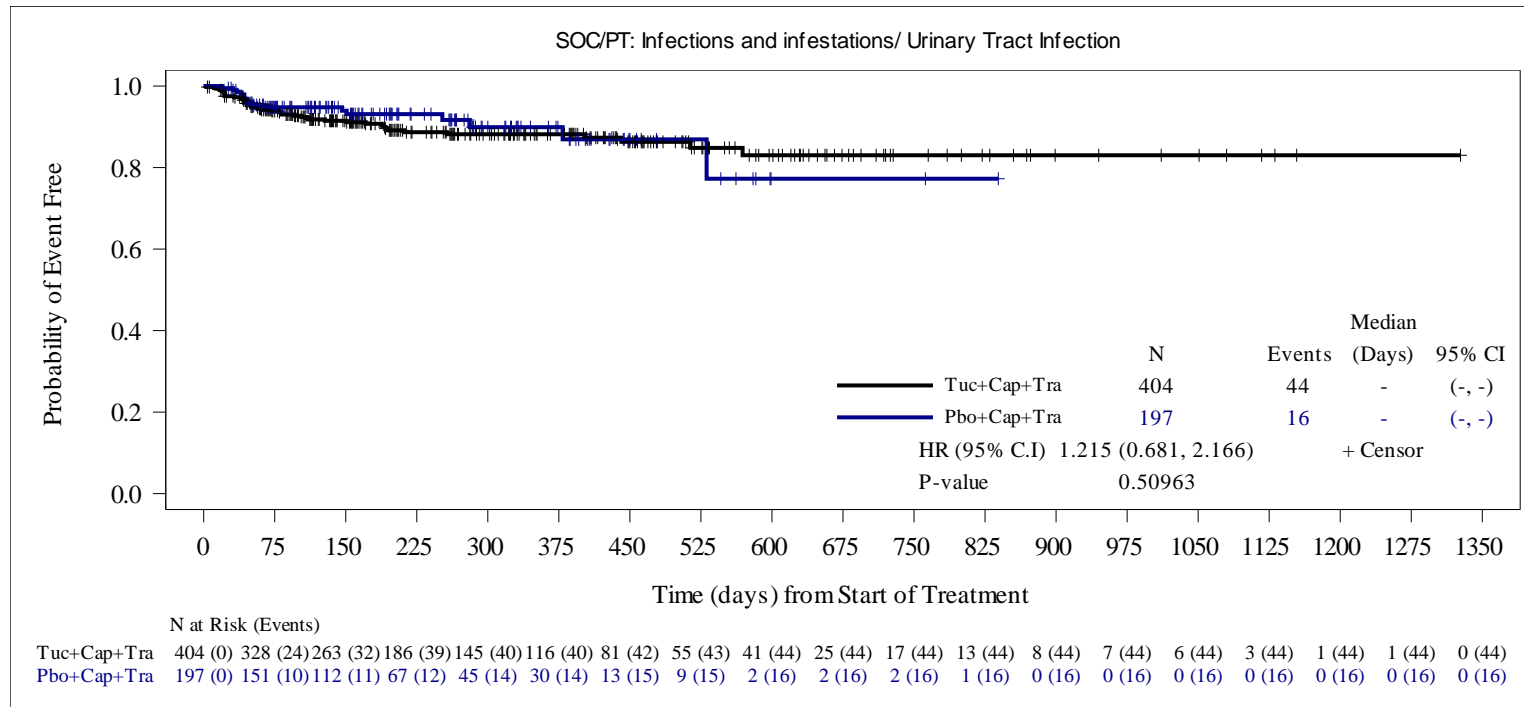
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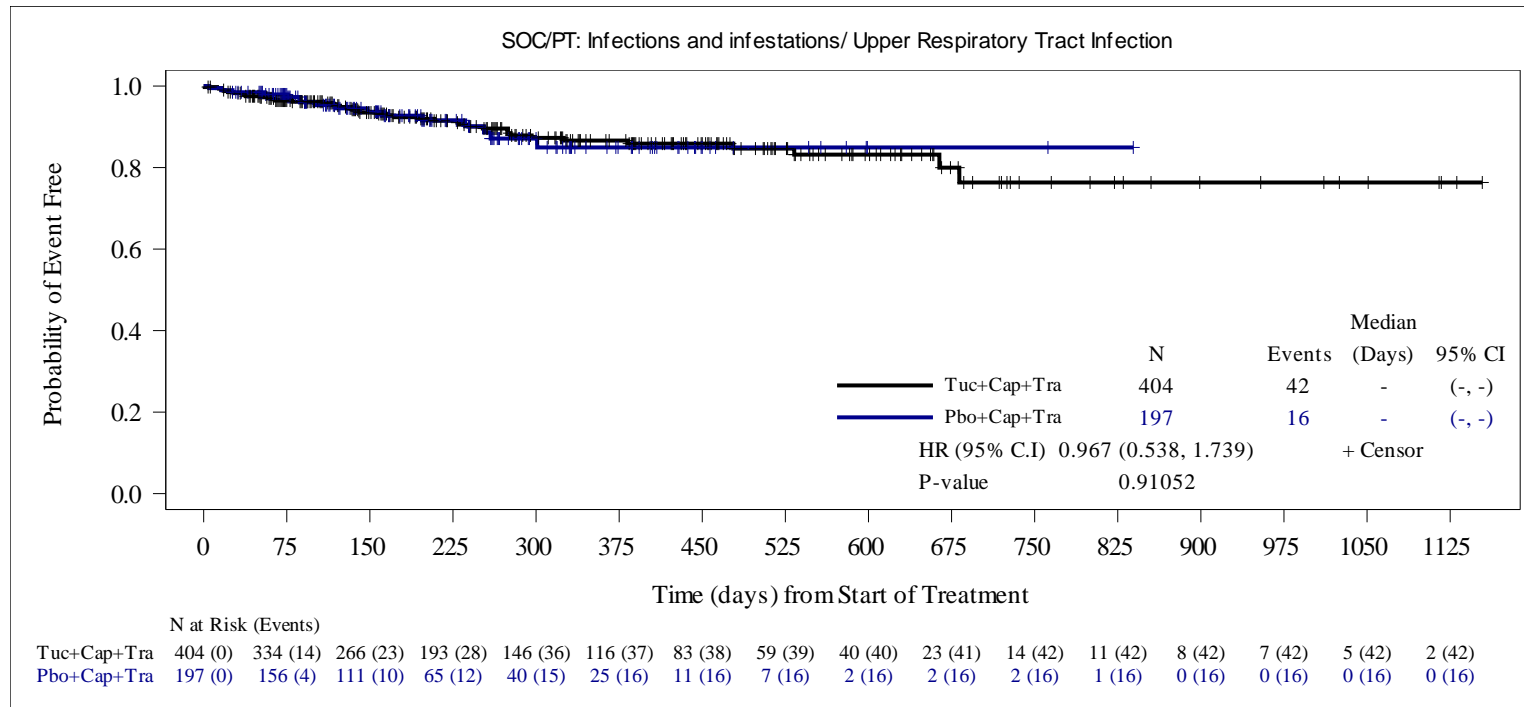
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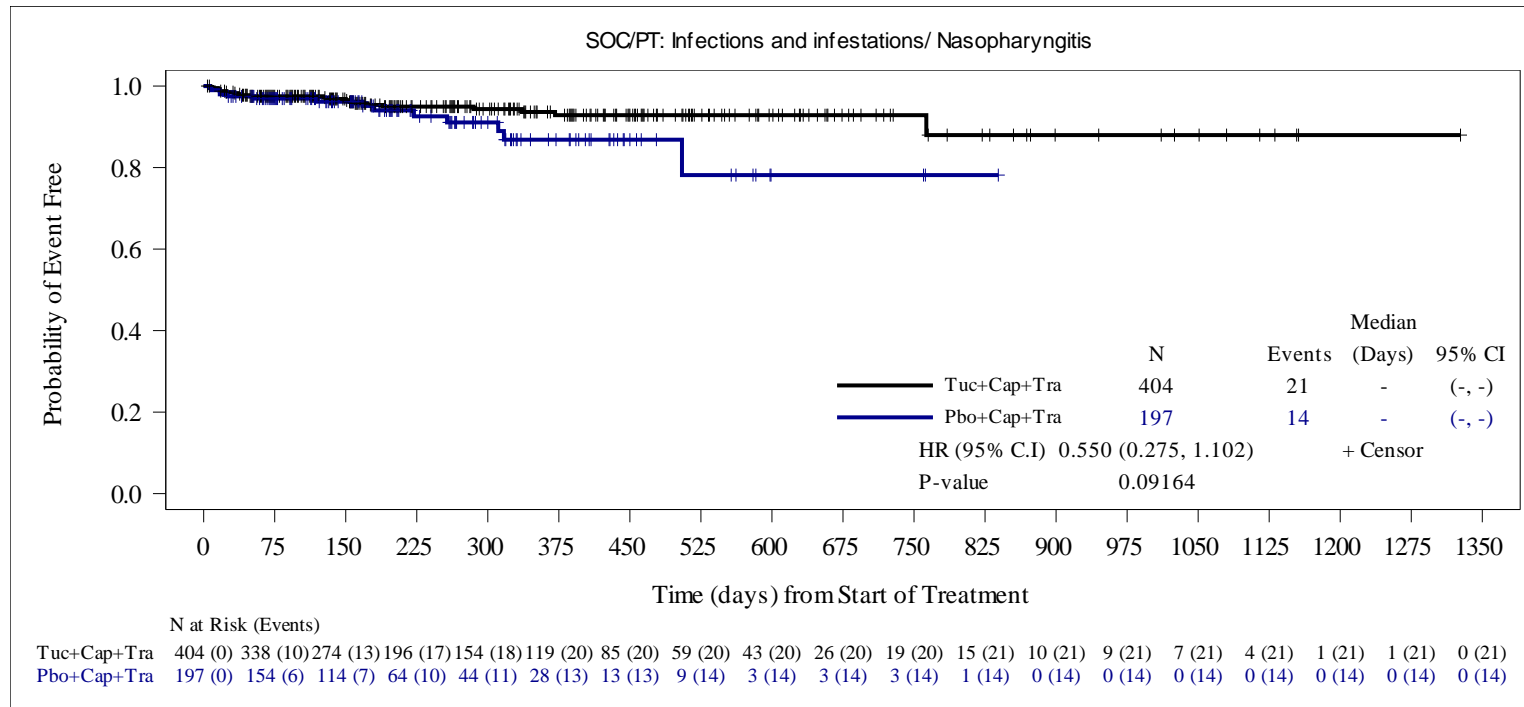
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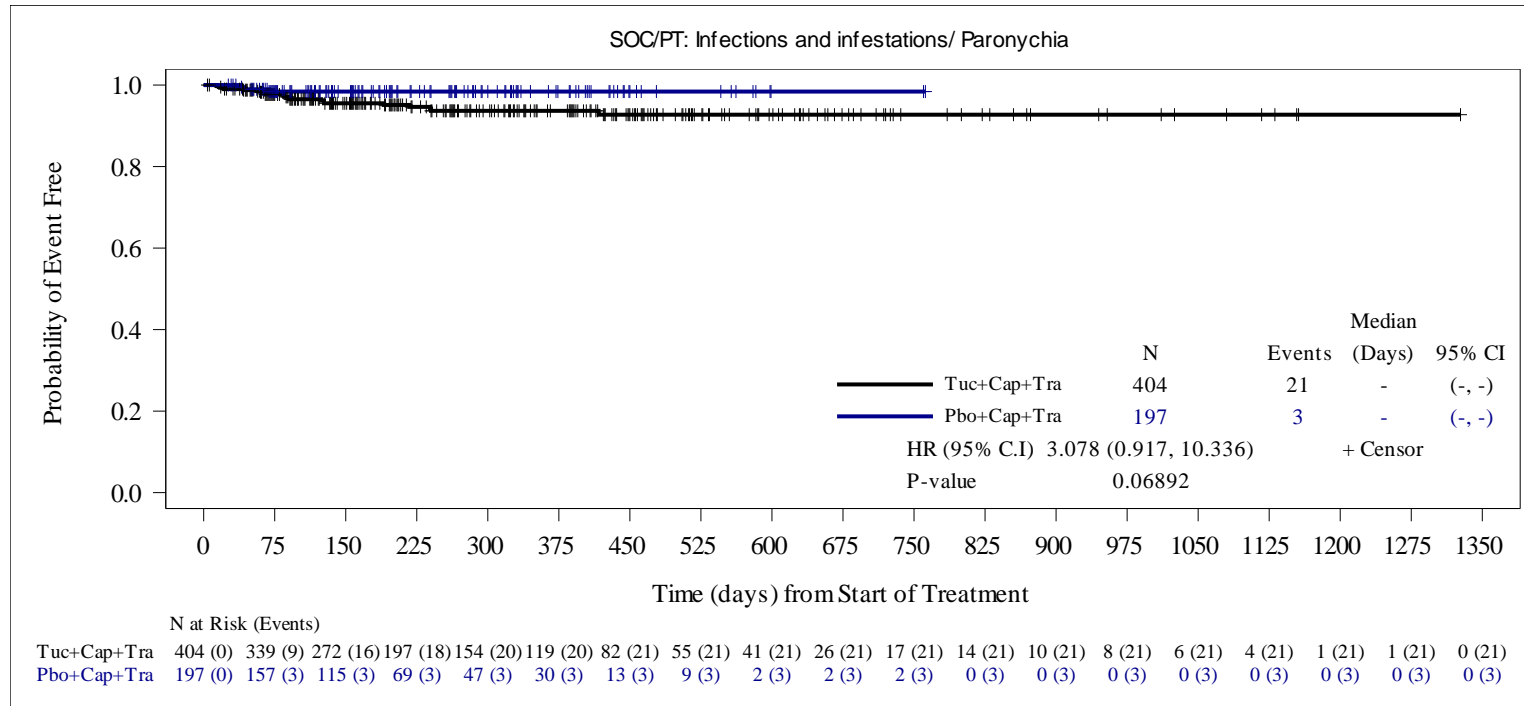
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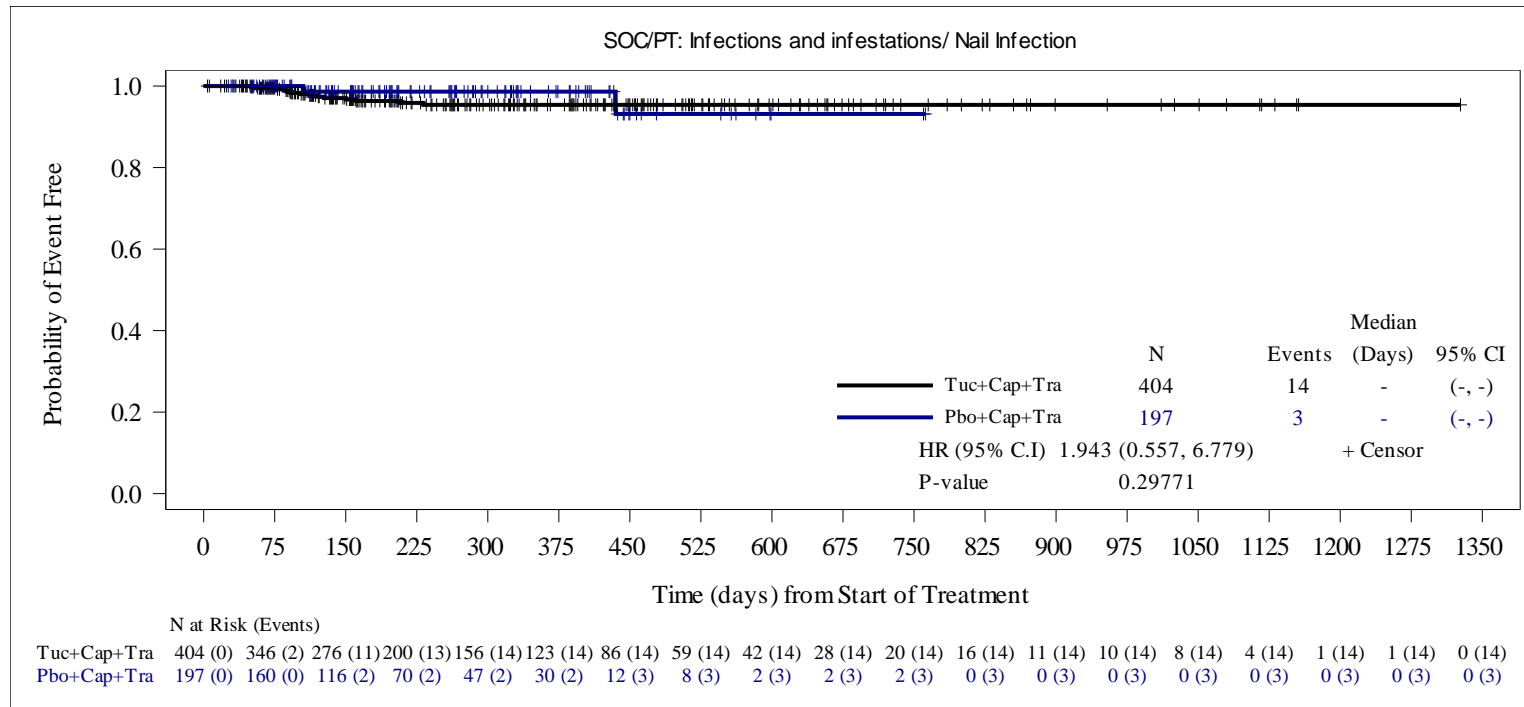
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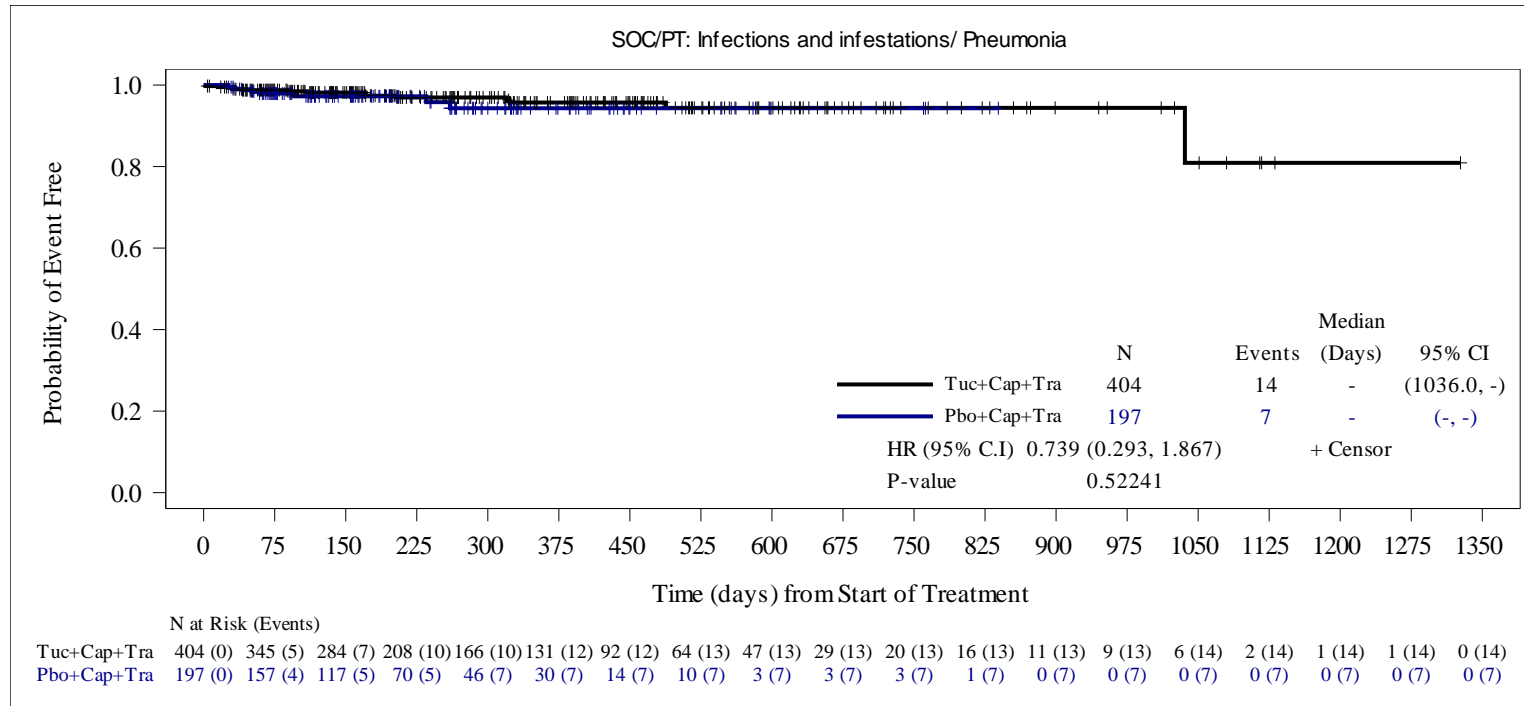
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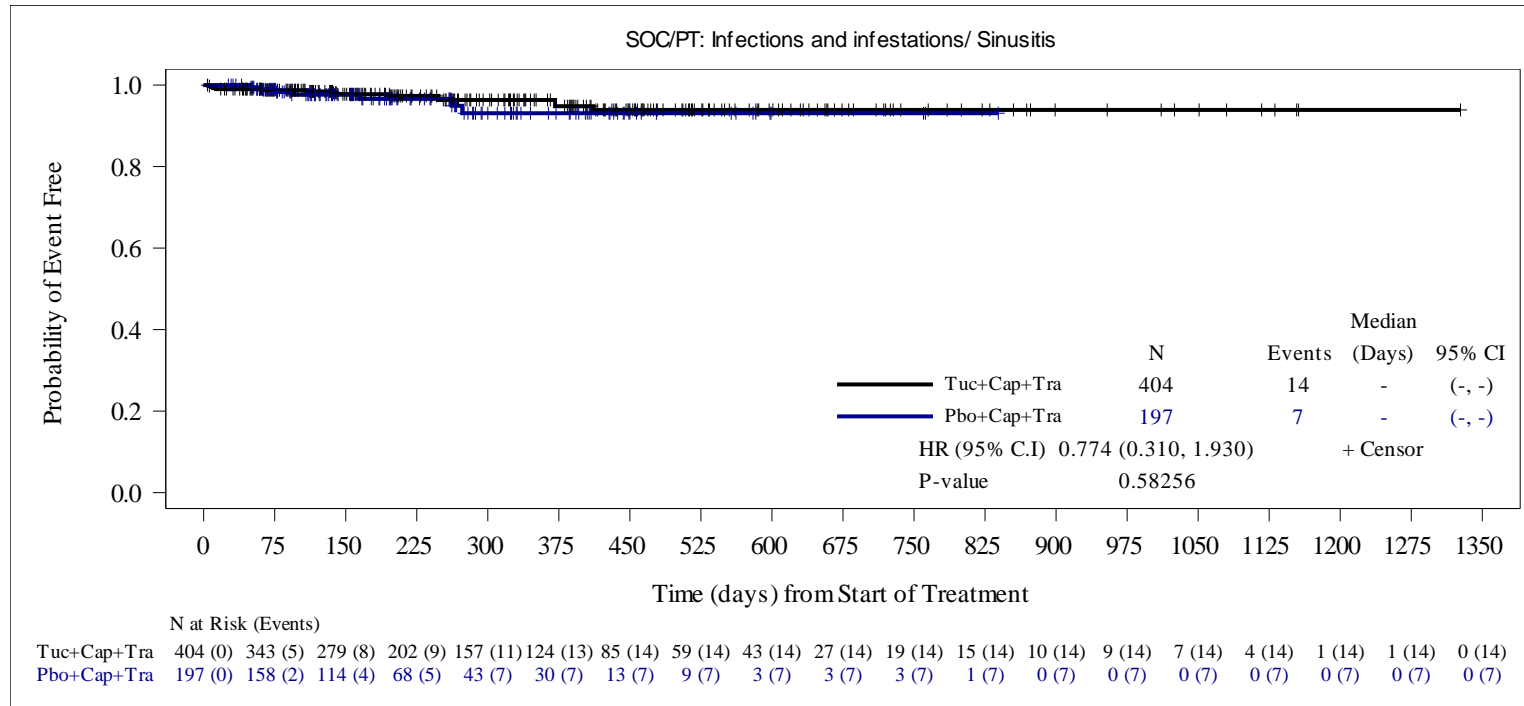
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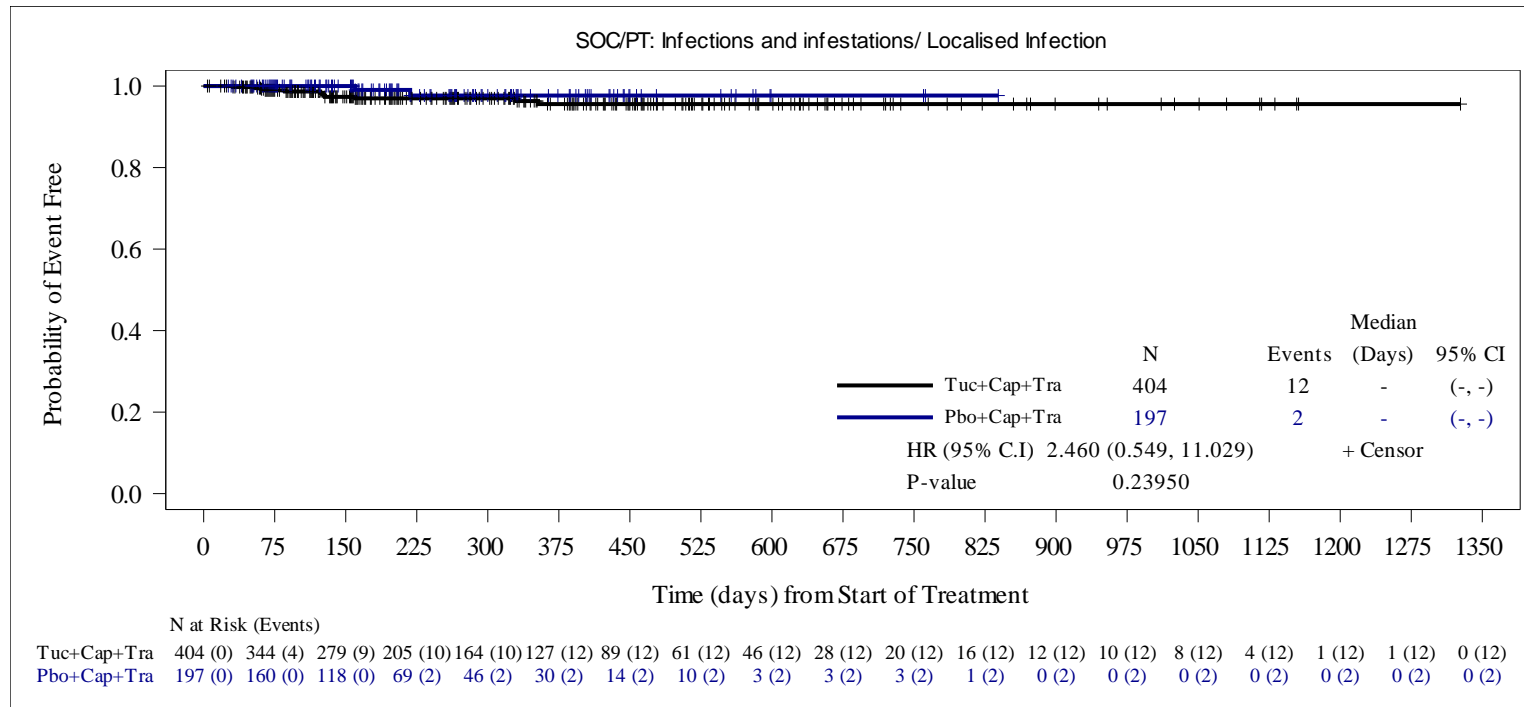
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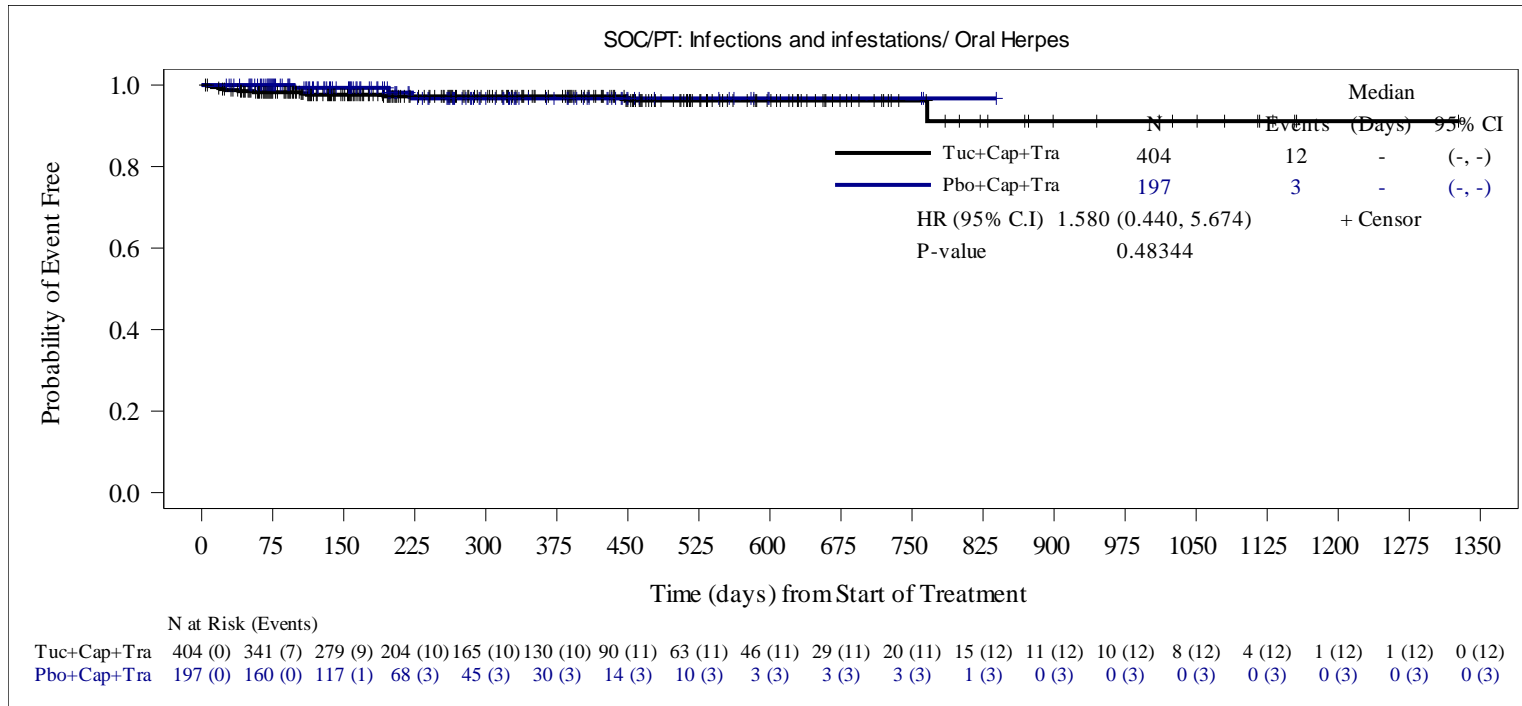
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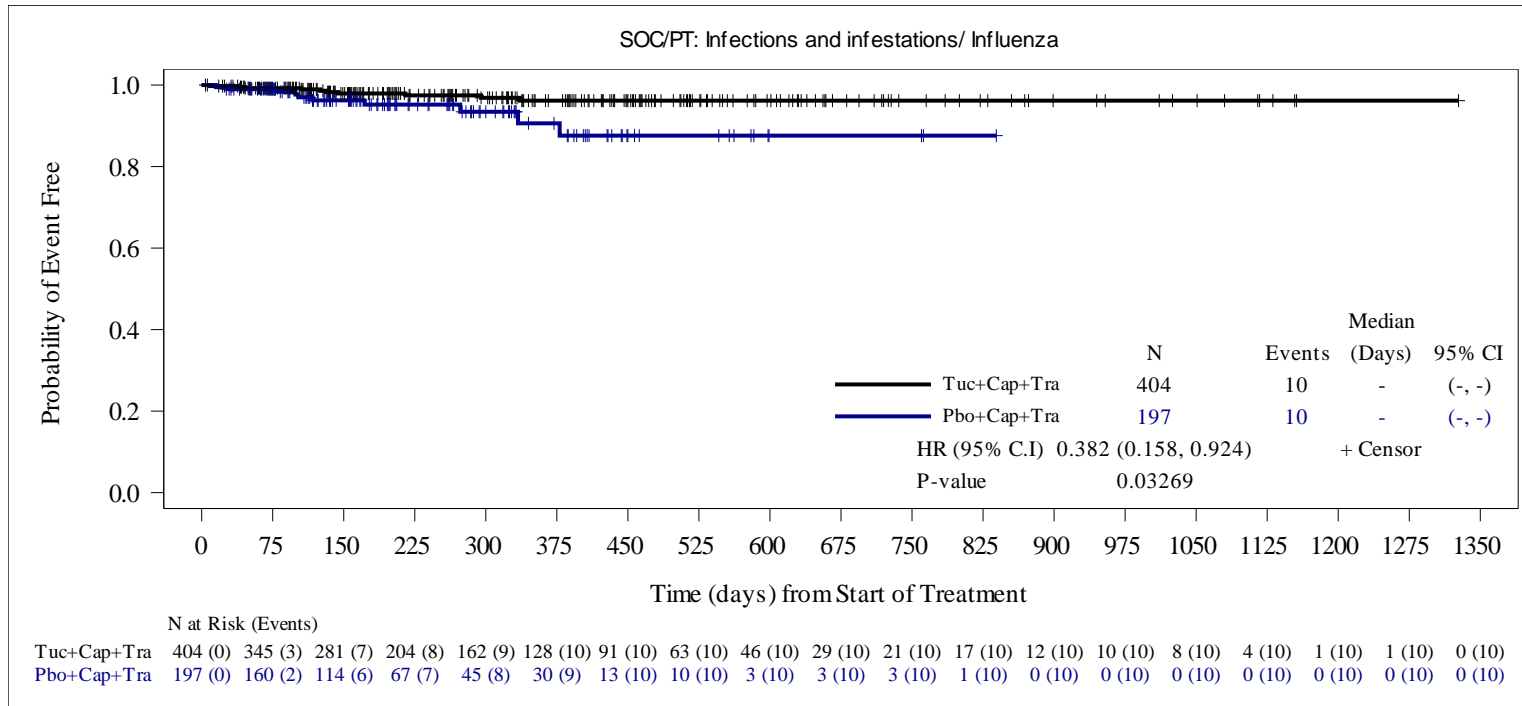
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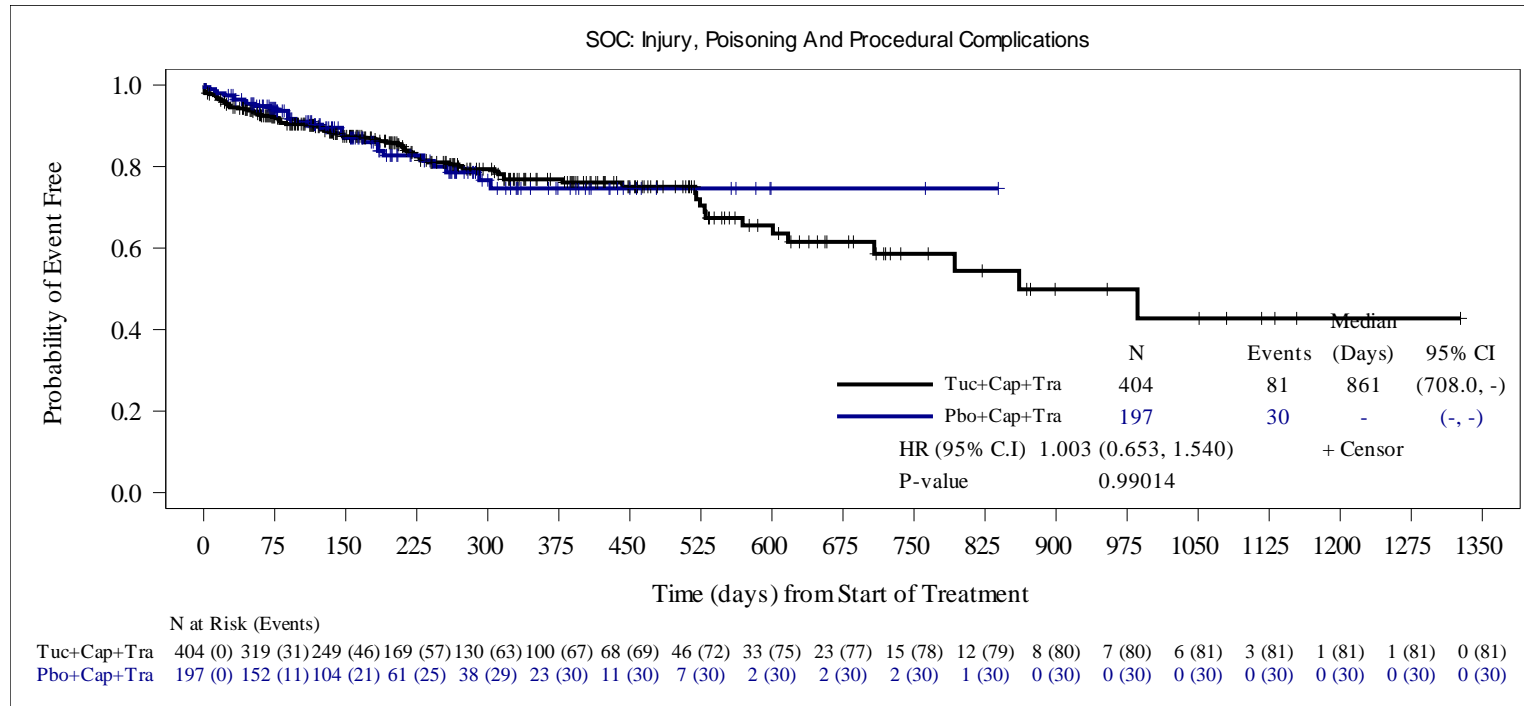
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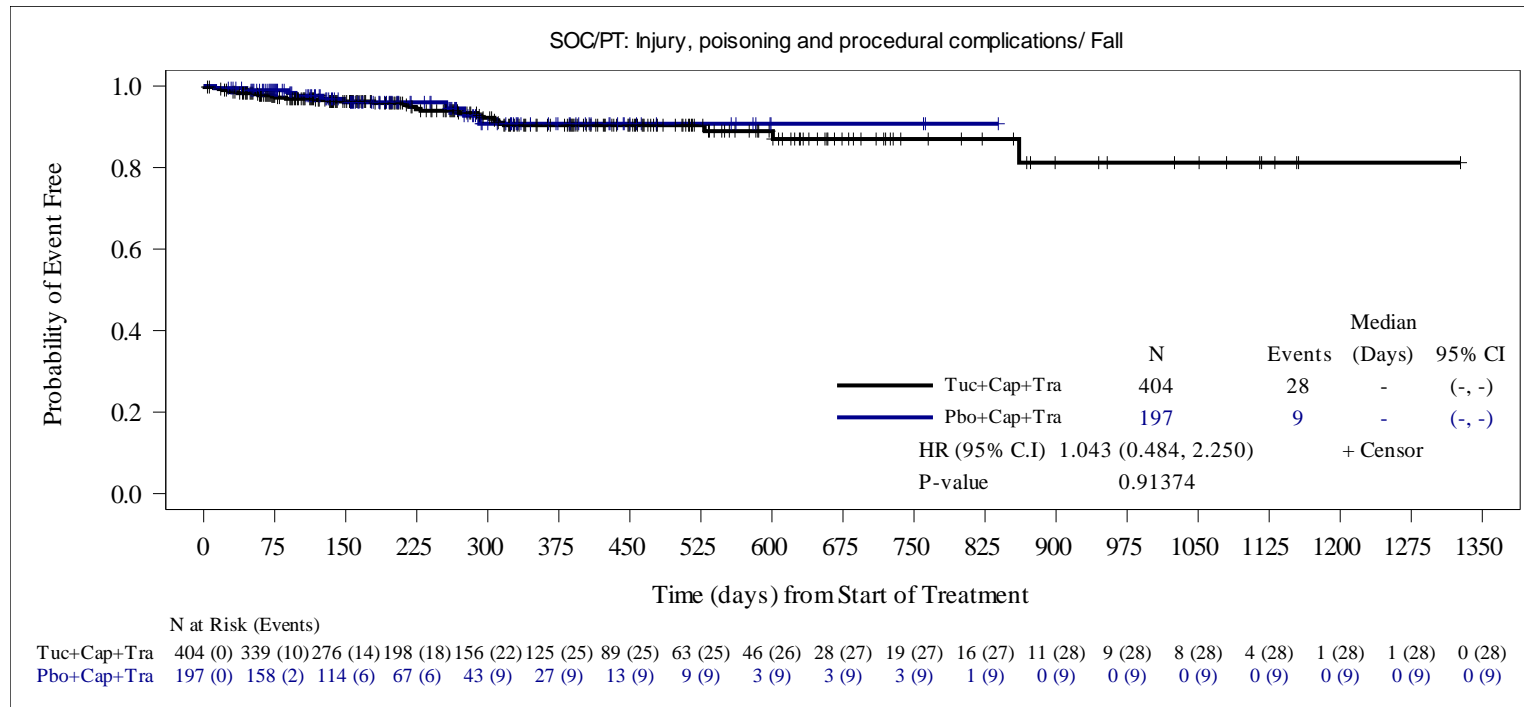
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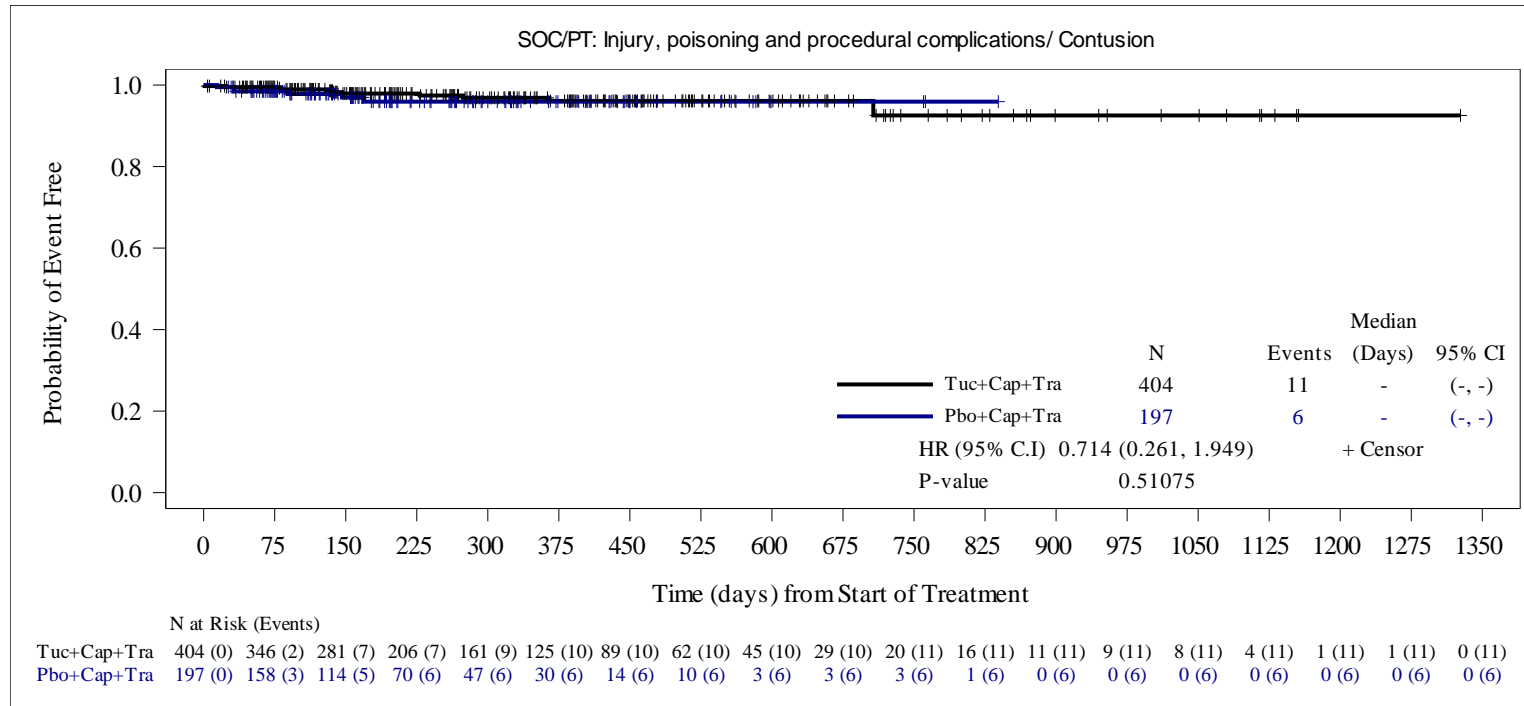
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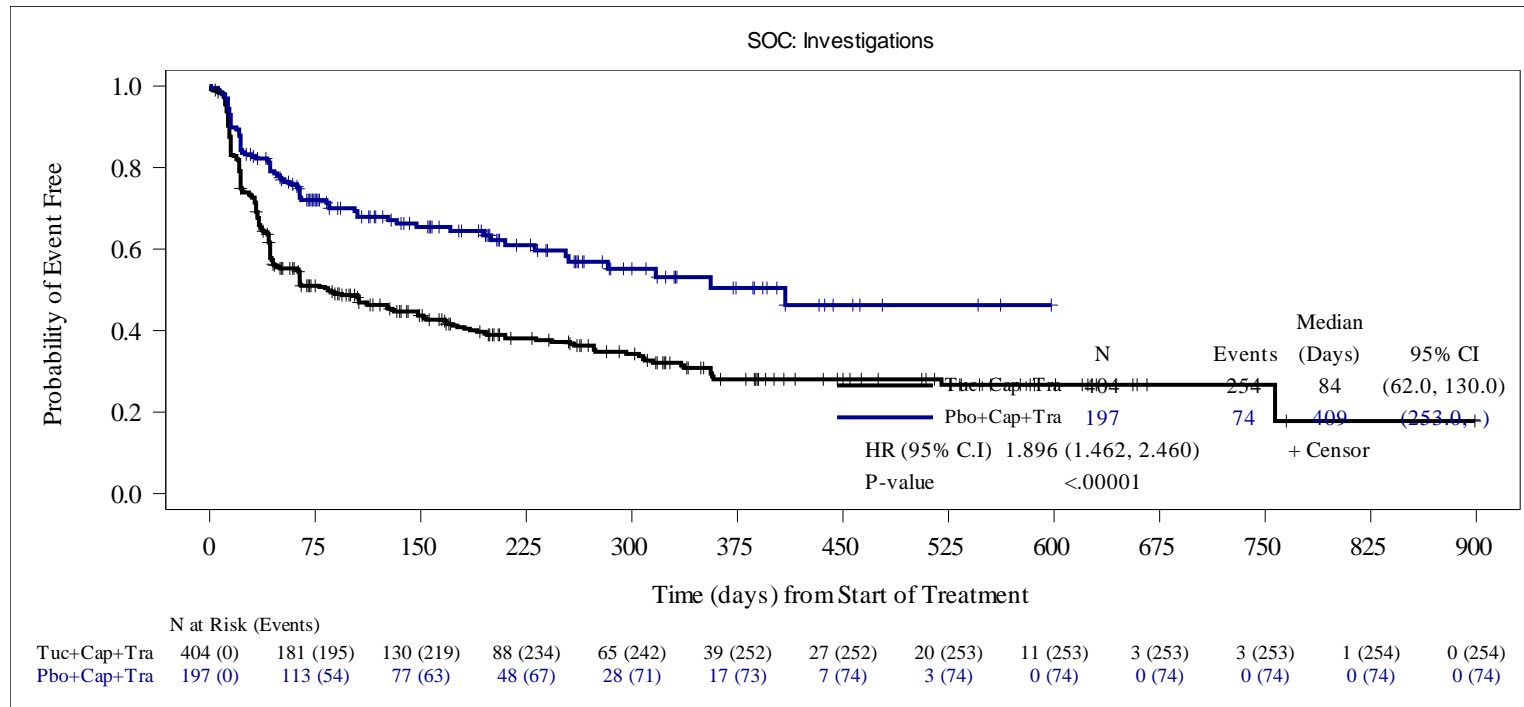
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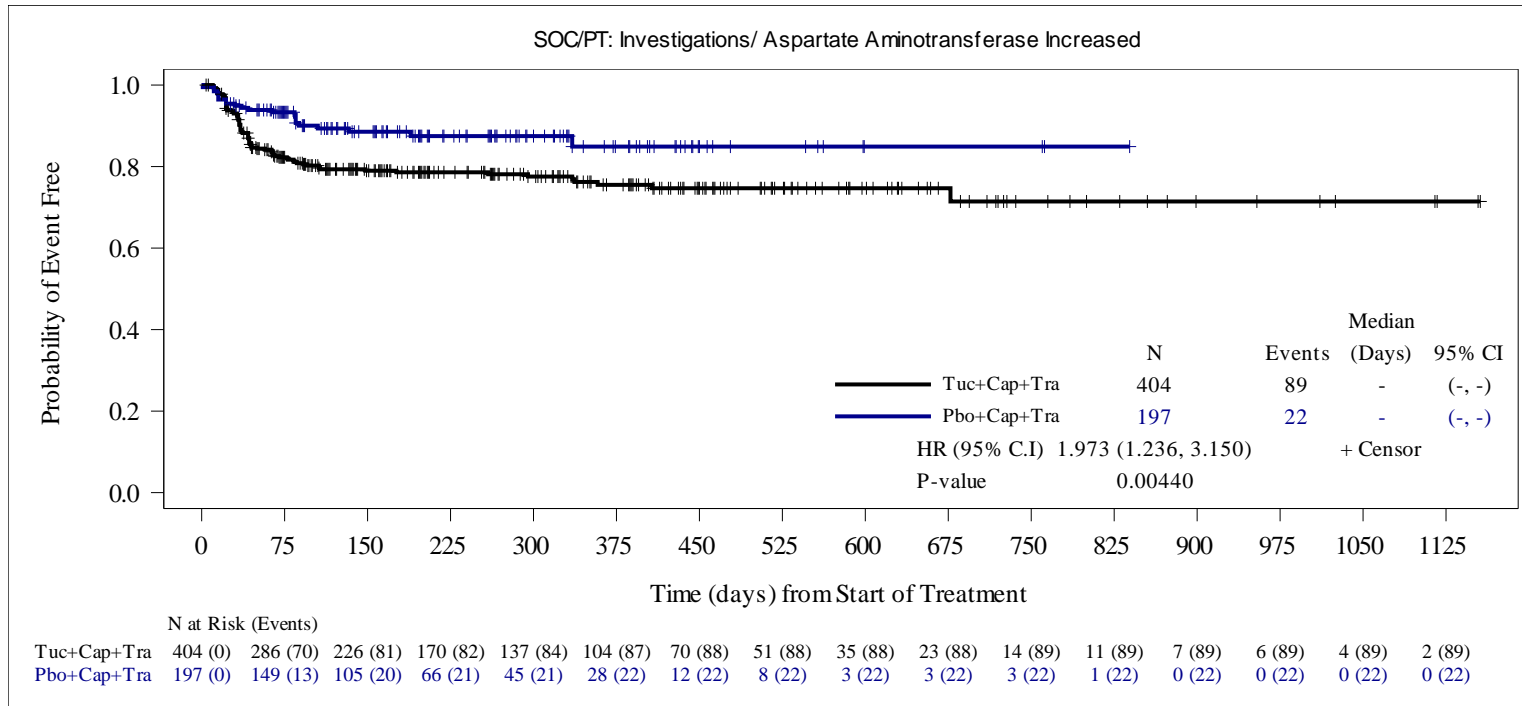
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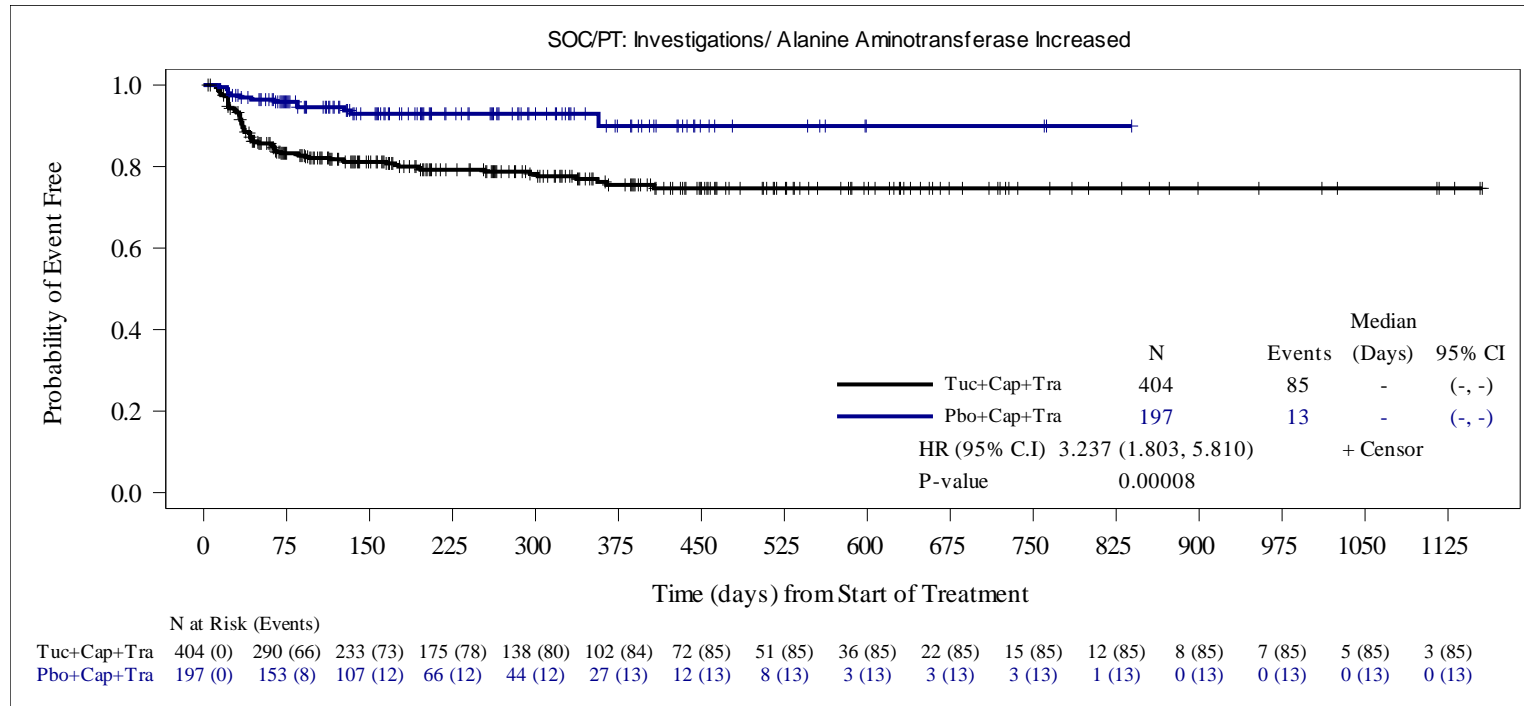
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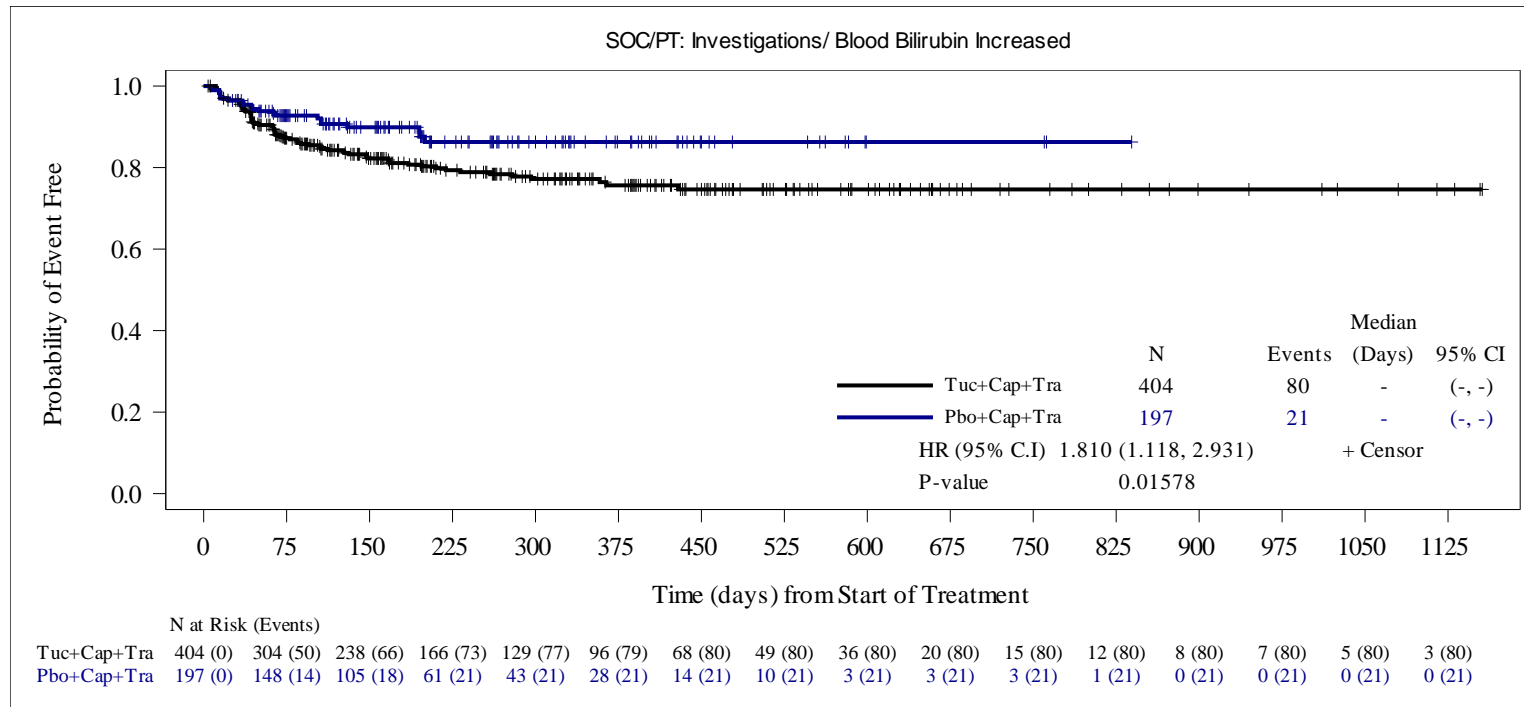
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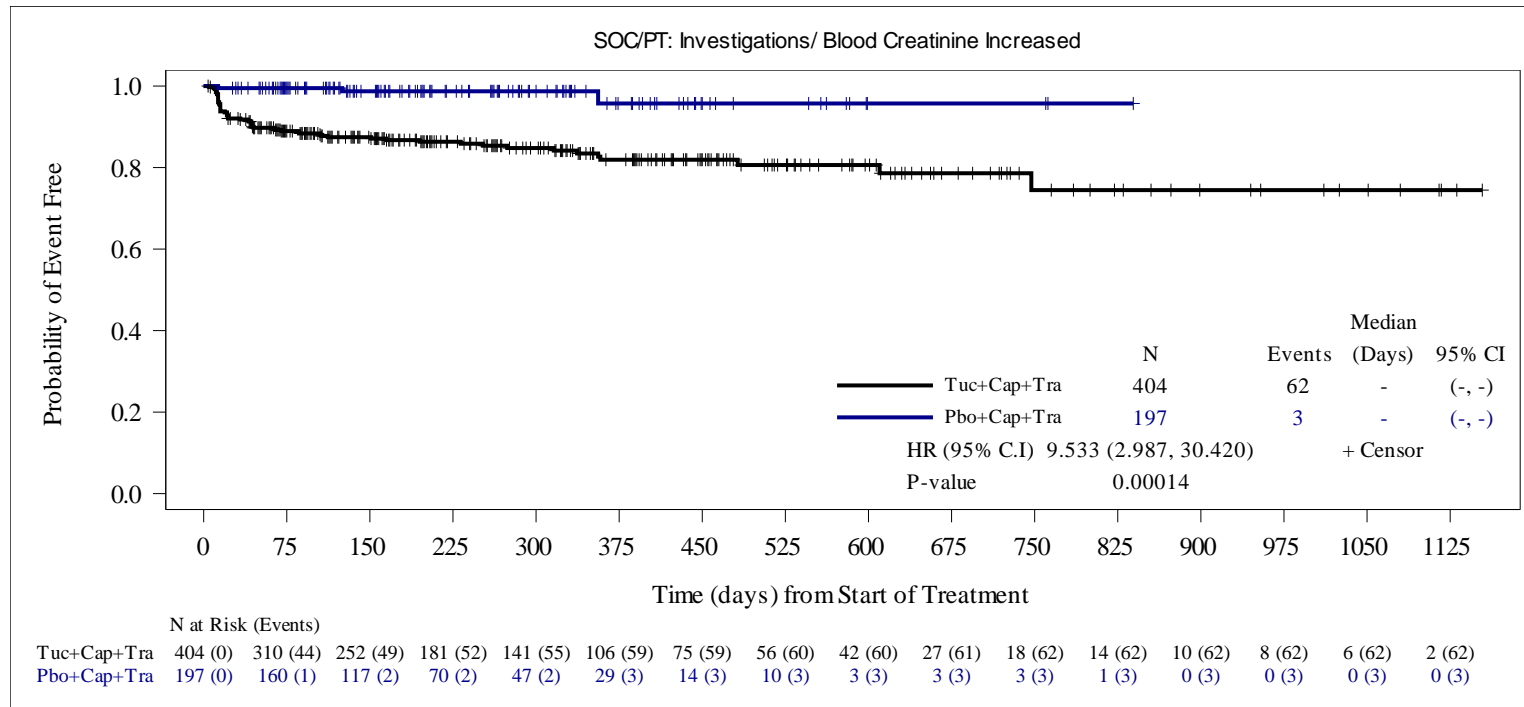
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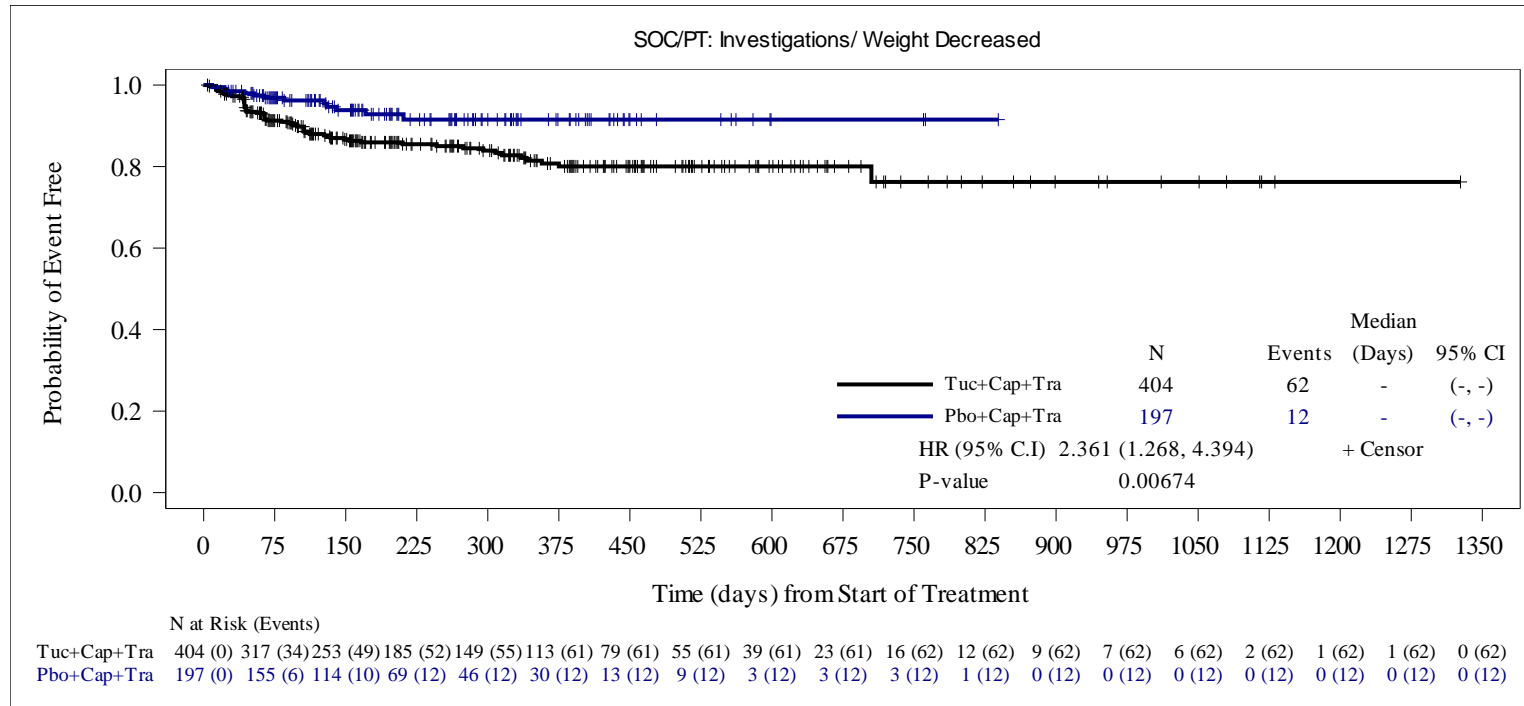
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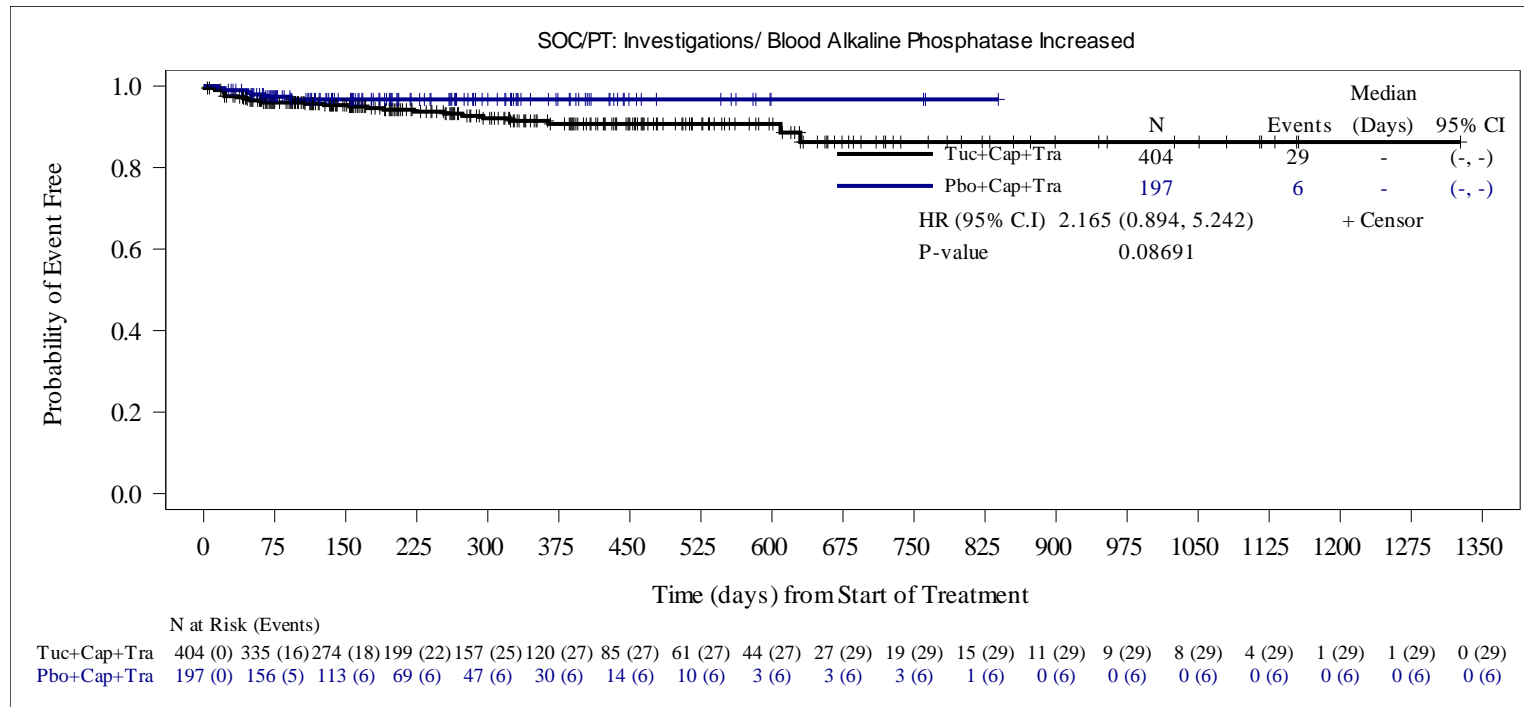
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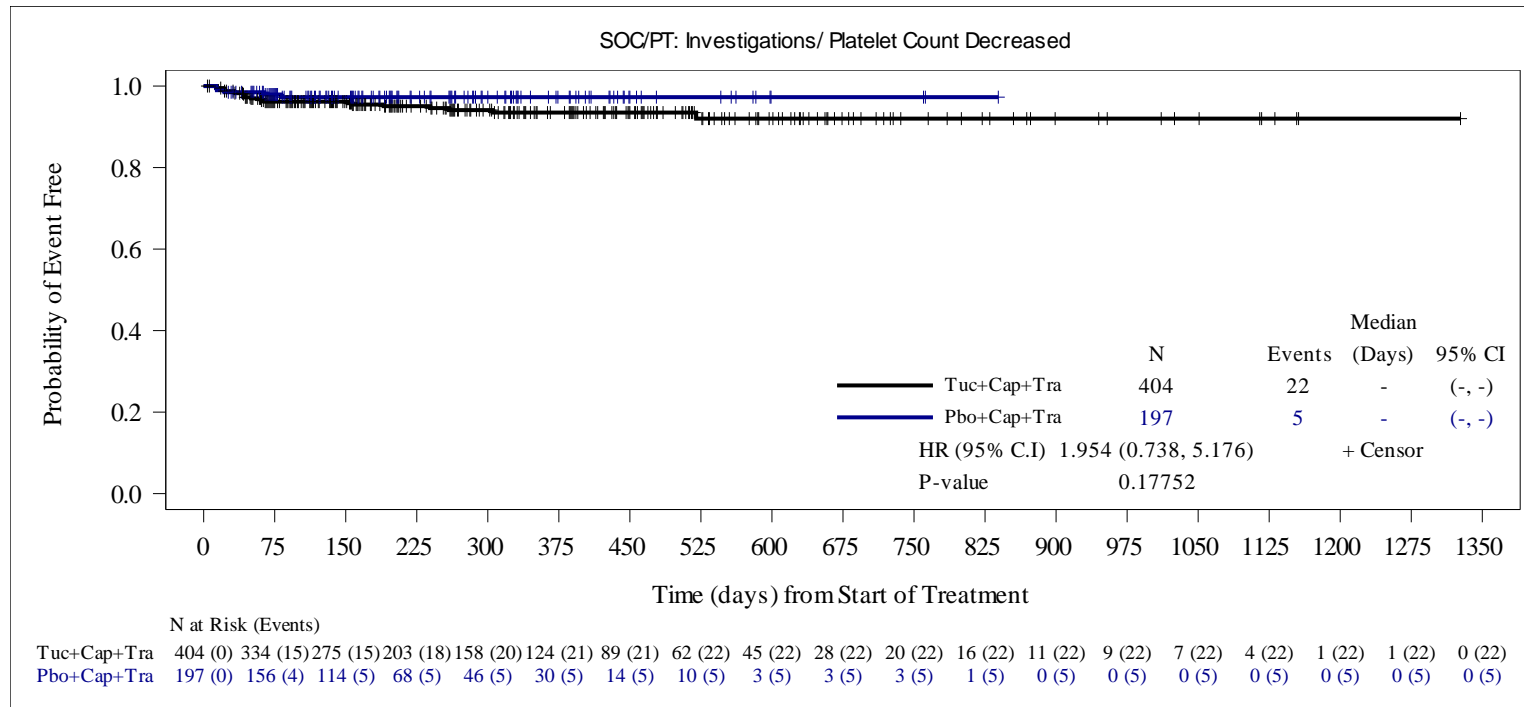
Two-sided p-value calculated from Cox proportional hazards model .

Snapshot date: 10SEP2020, data cutoff date: 29MAY2020.

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Seagen Protocol ONT-380-206

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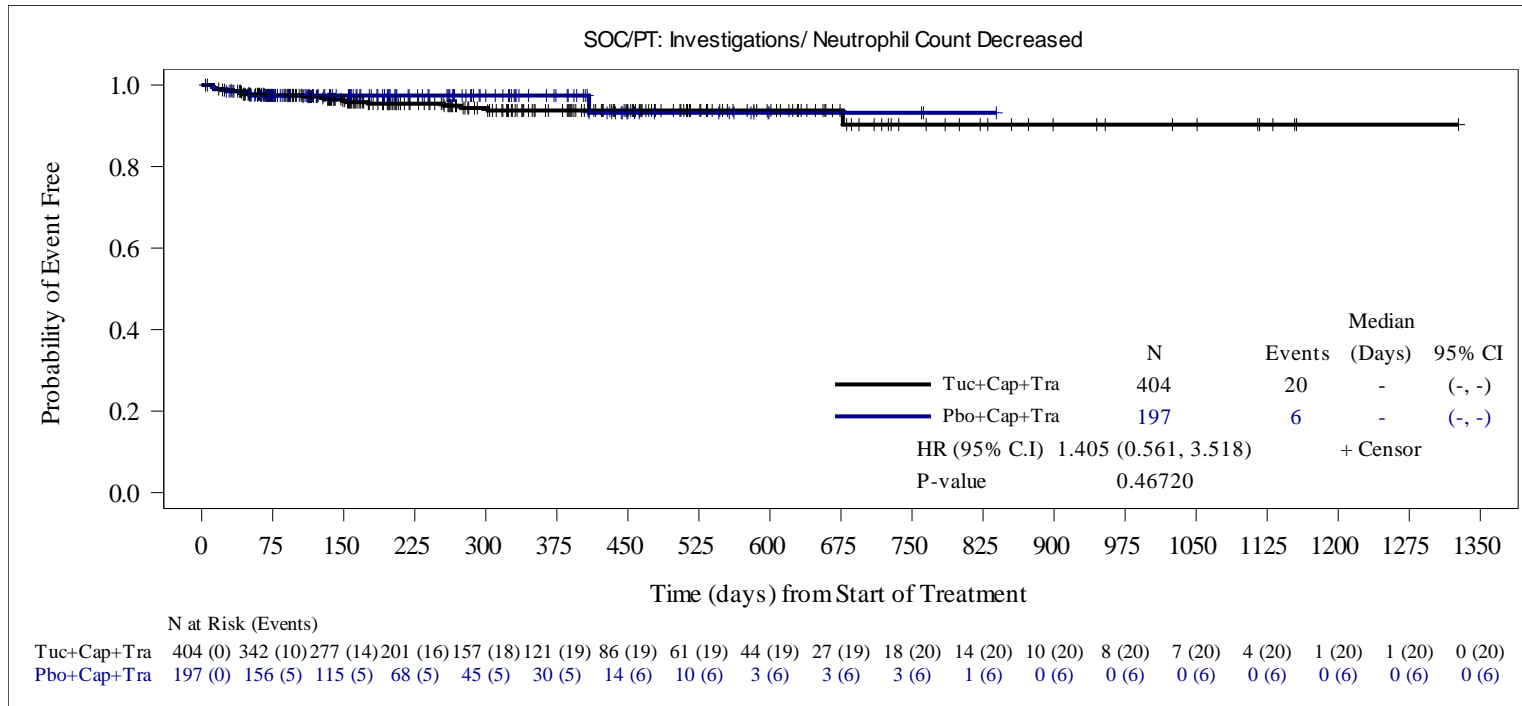
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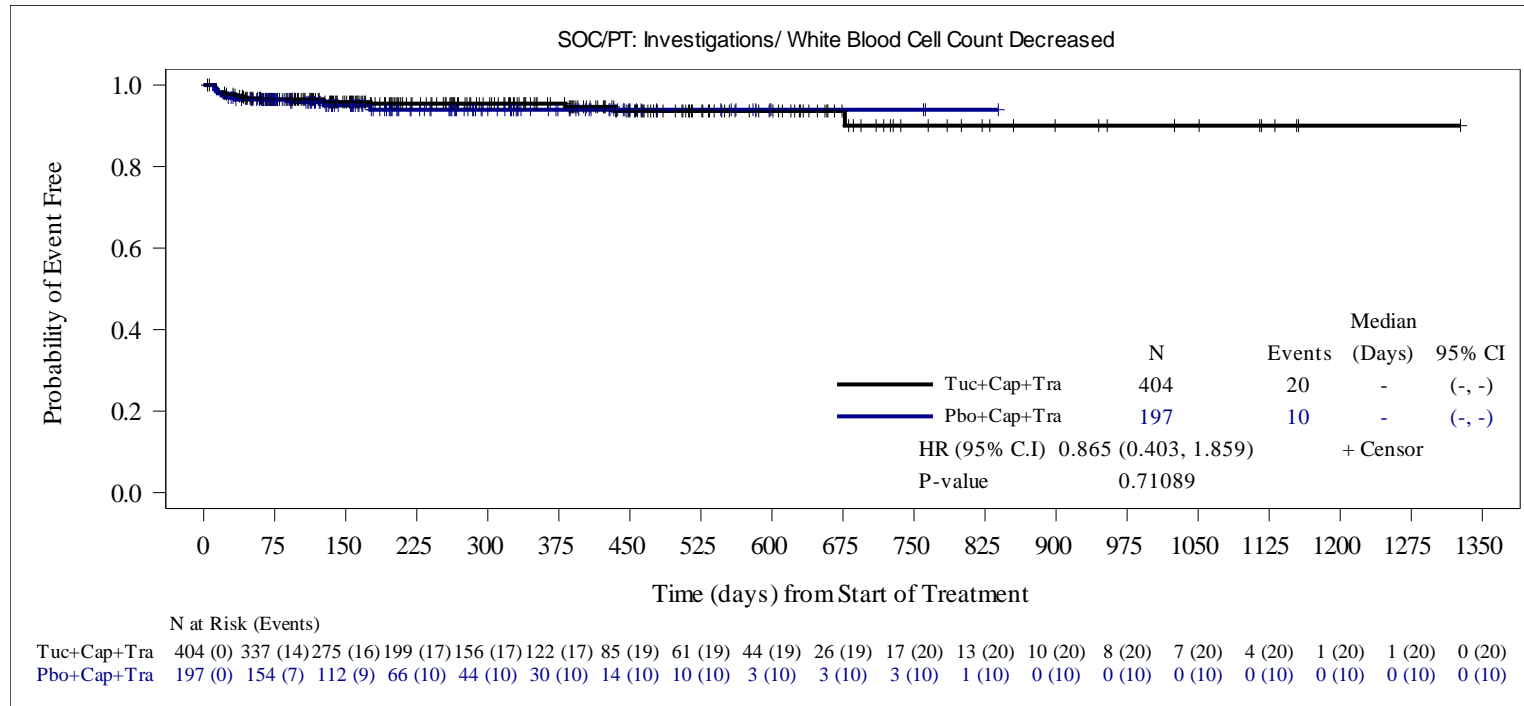
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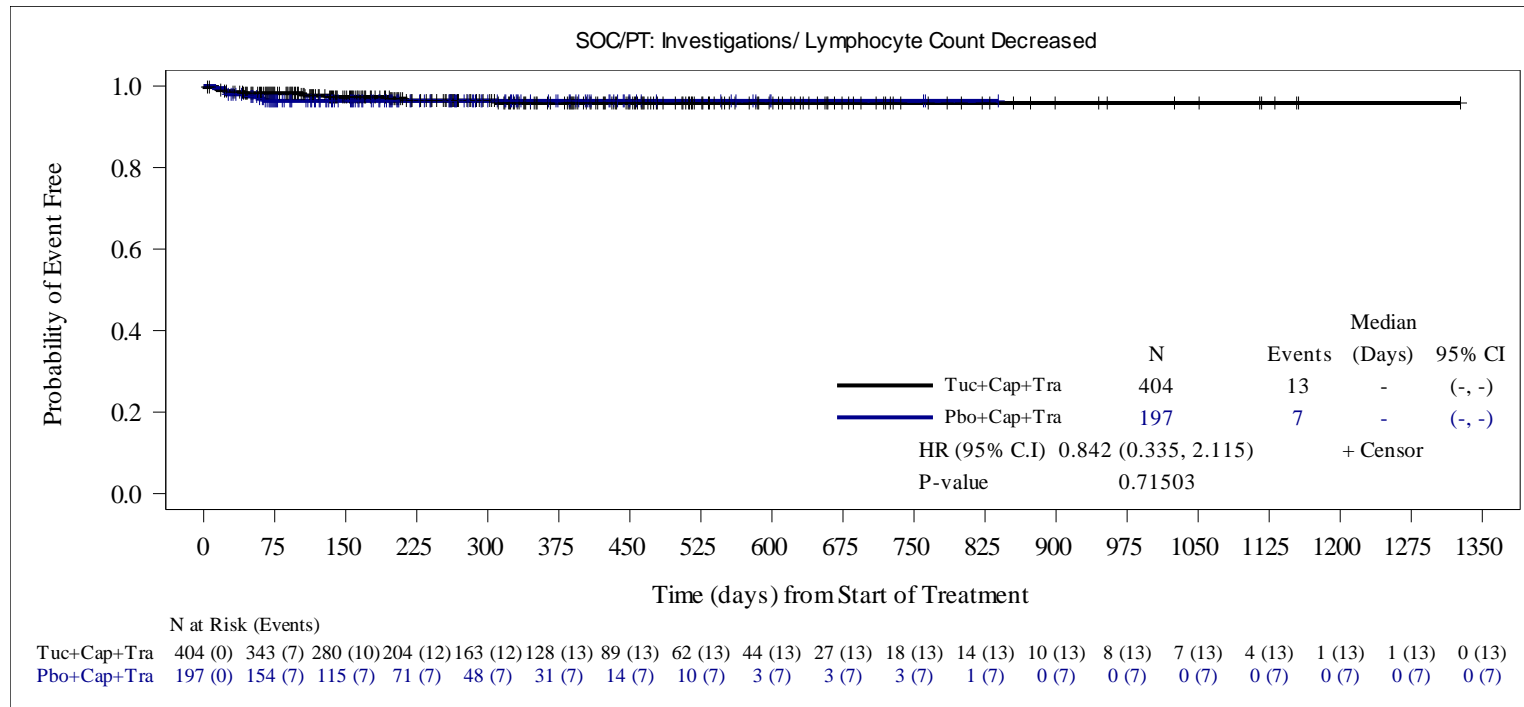
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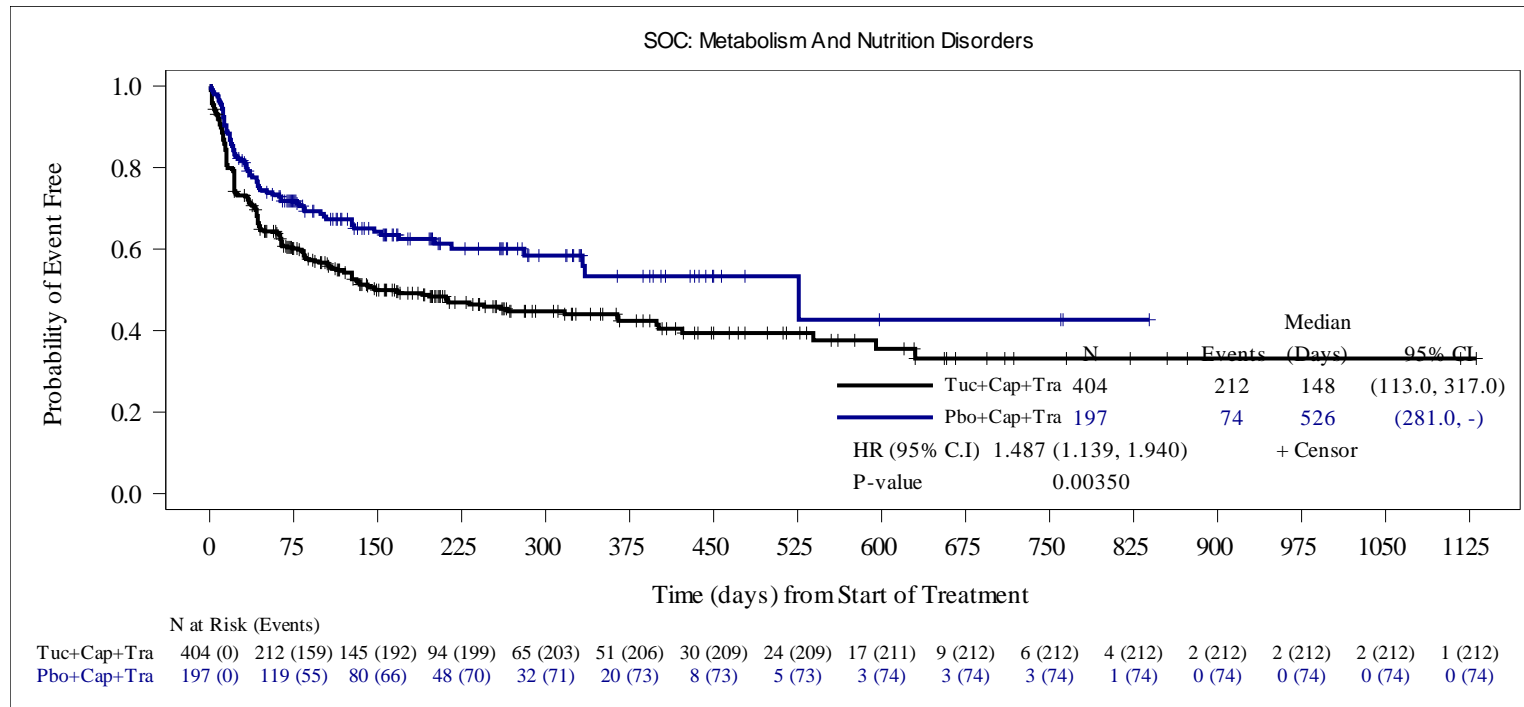
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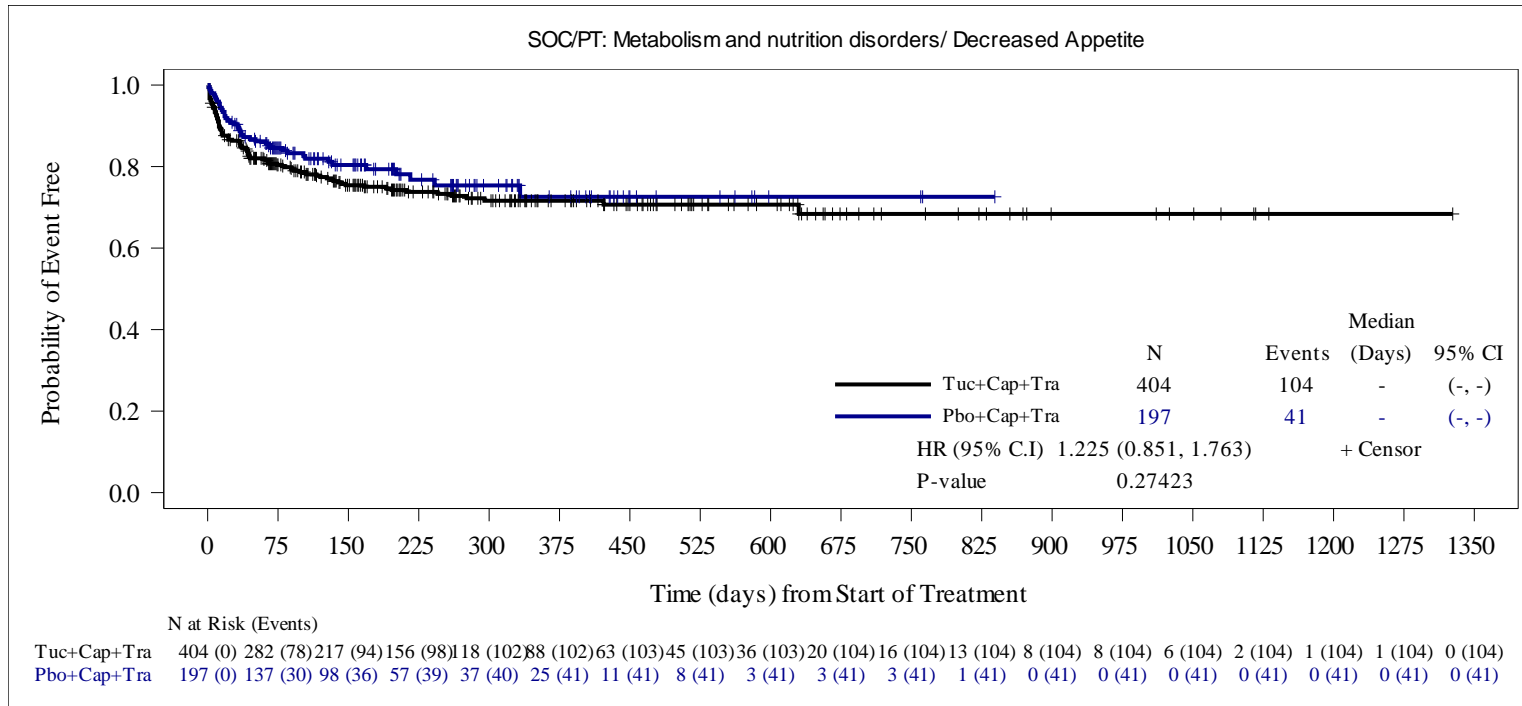
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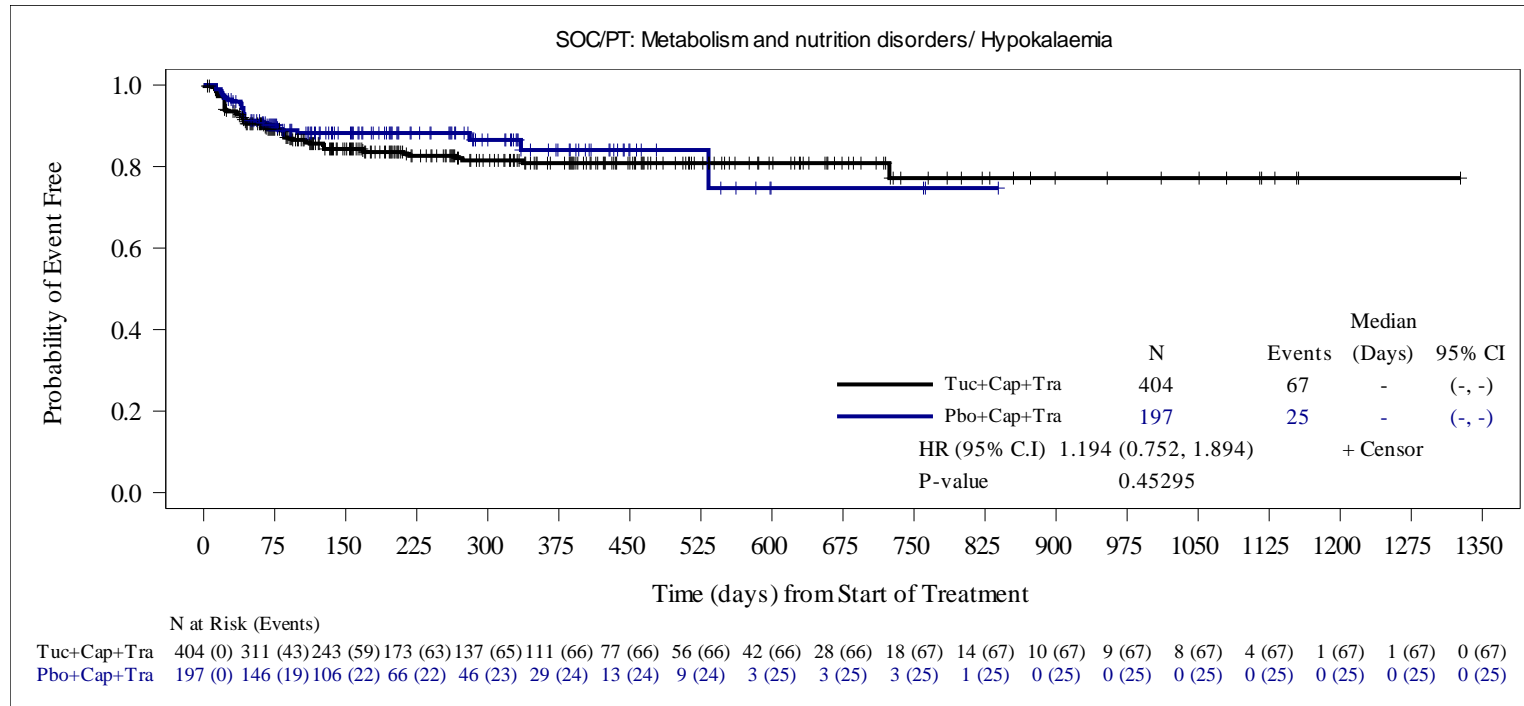
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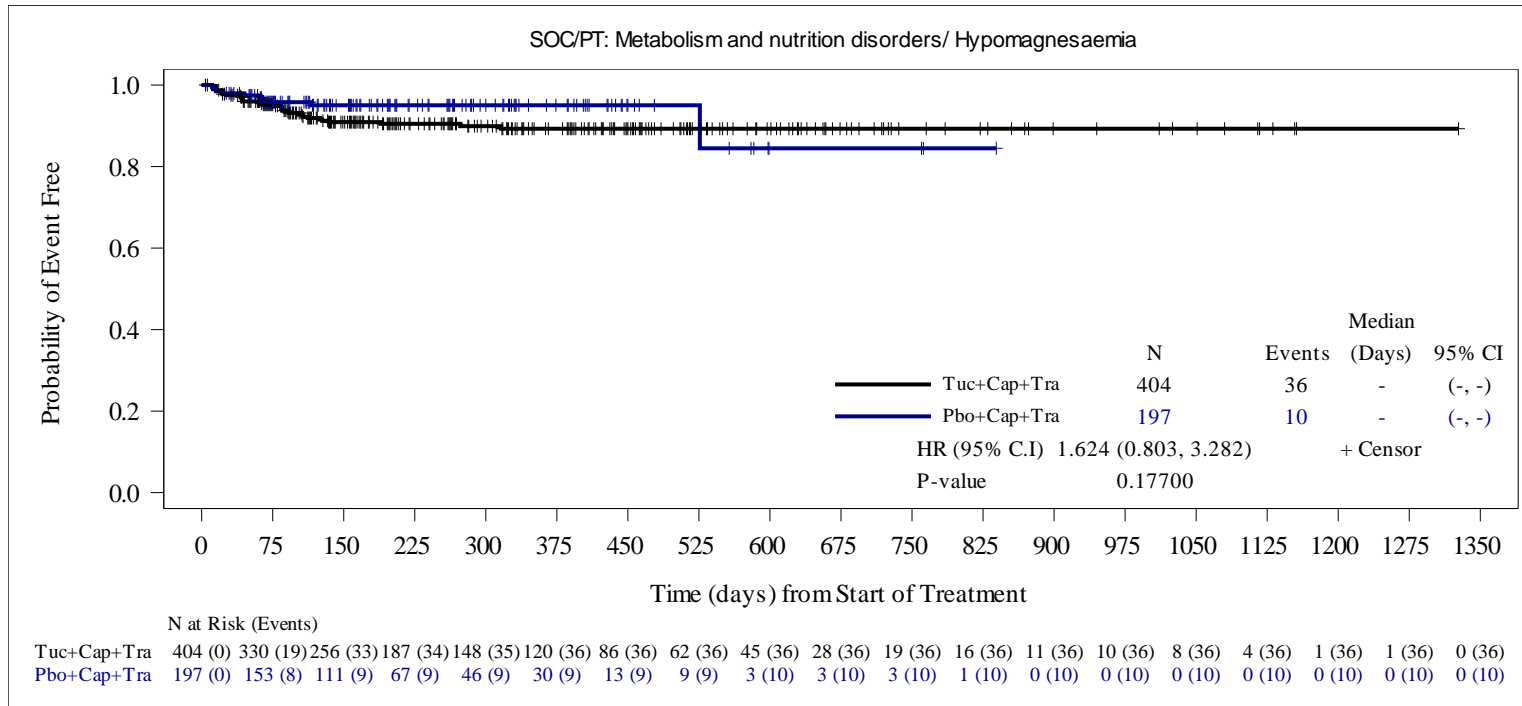
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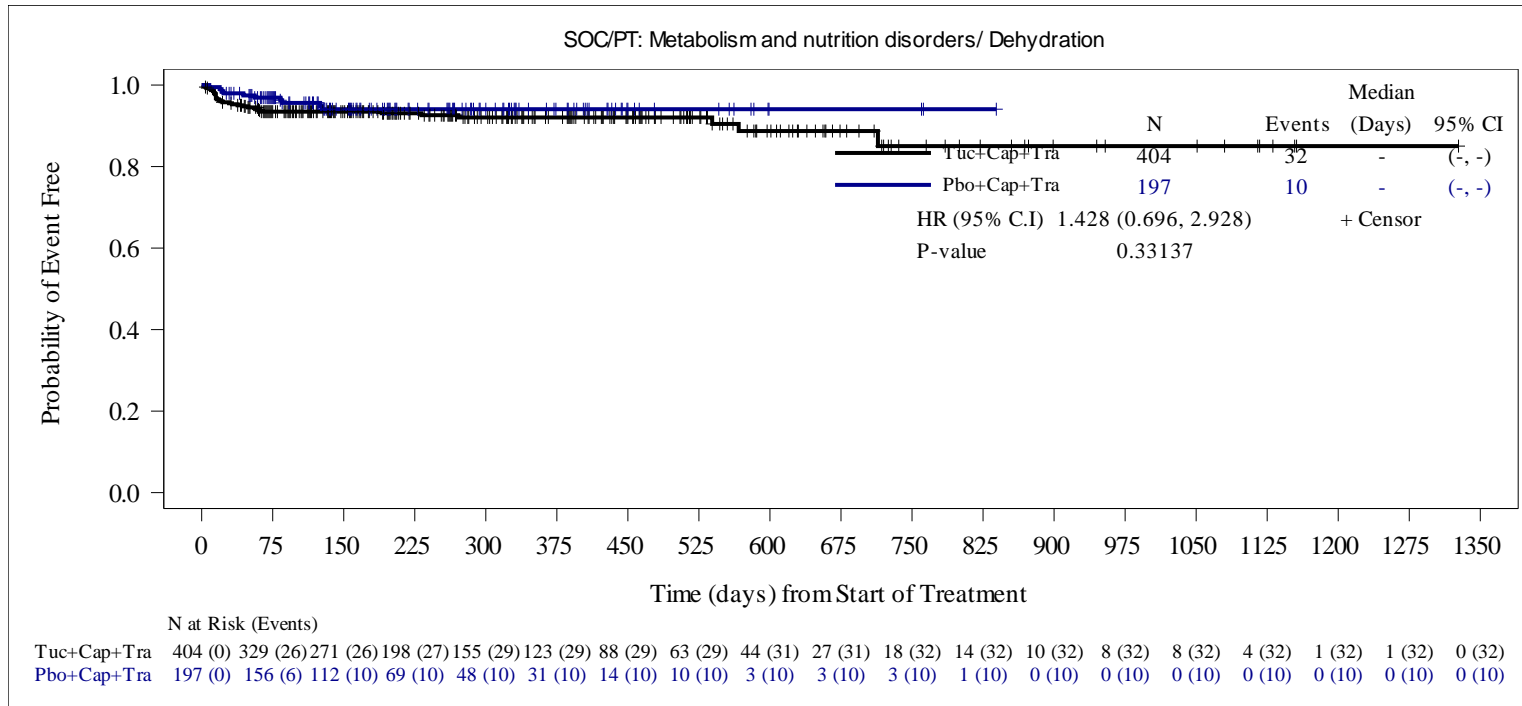
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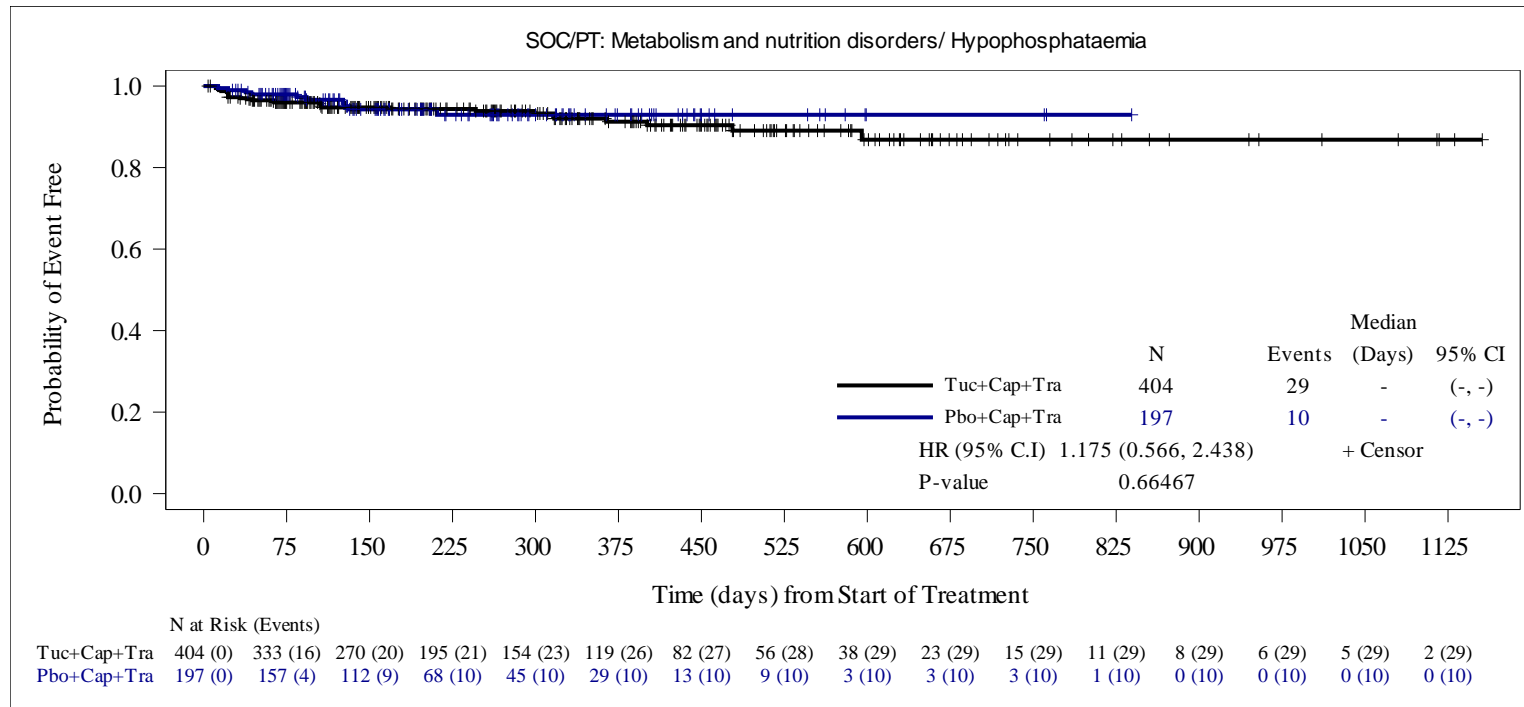
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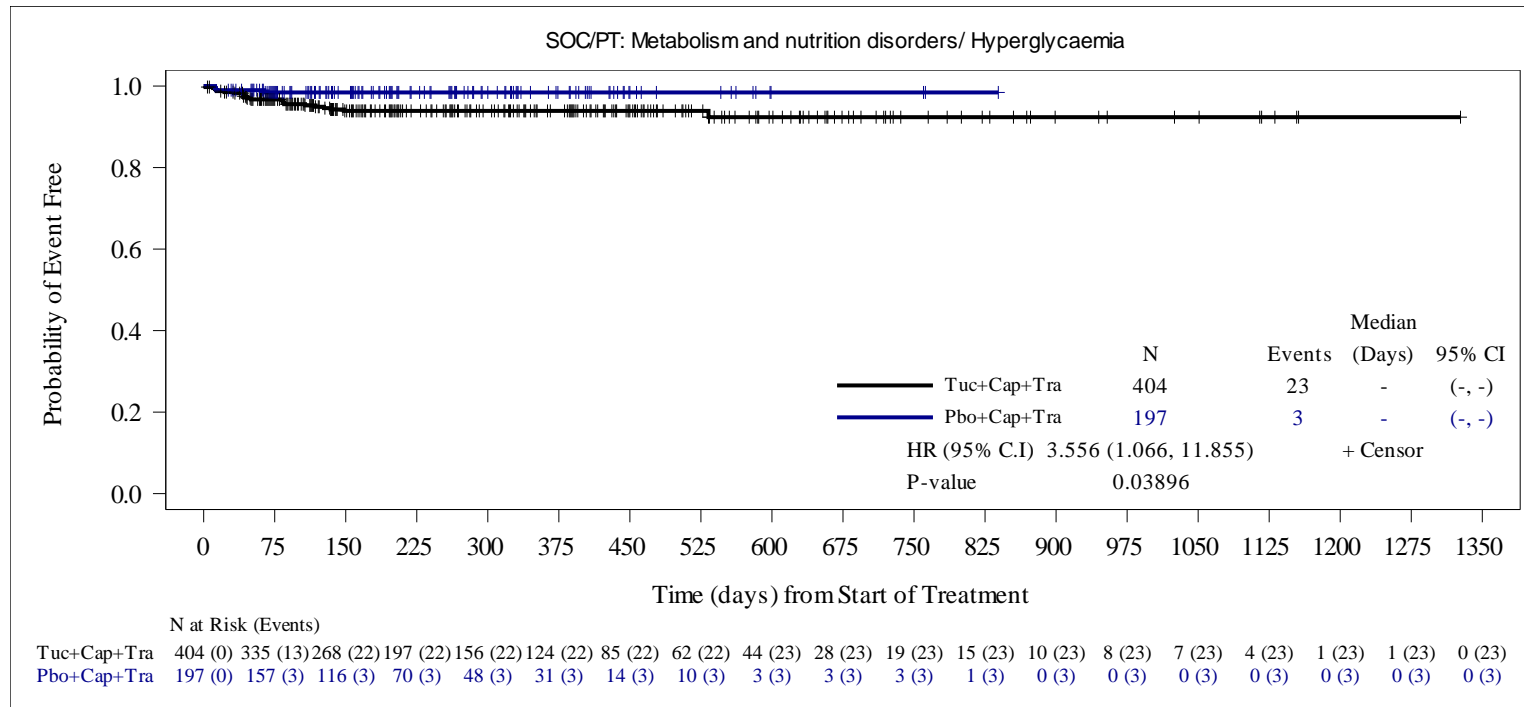
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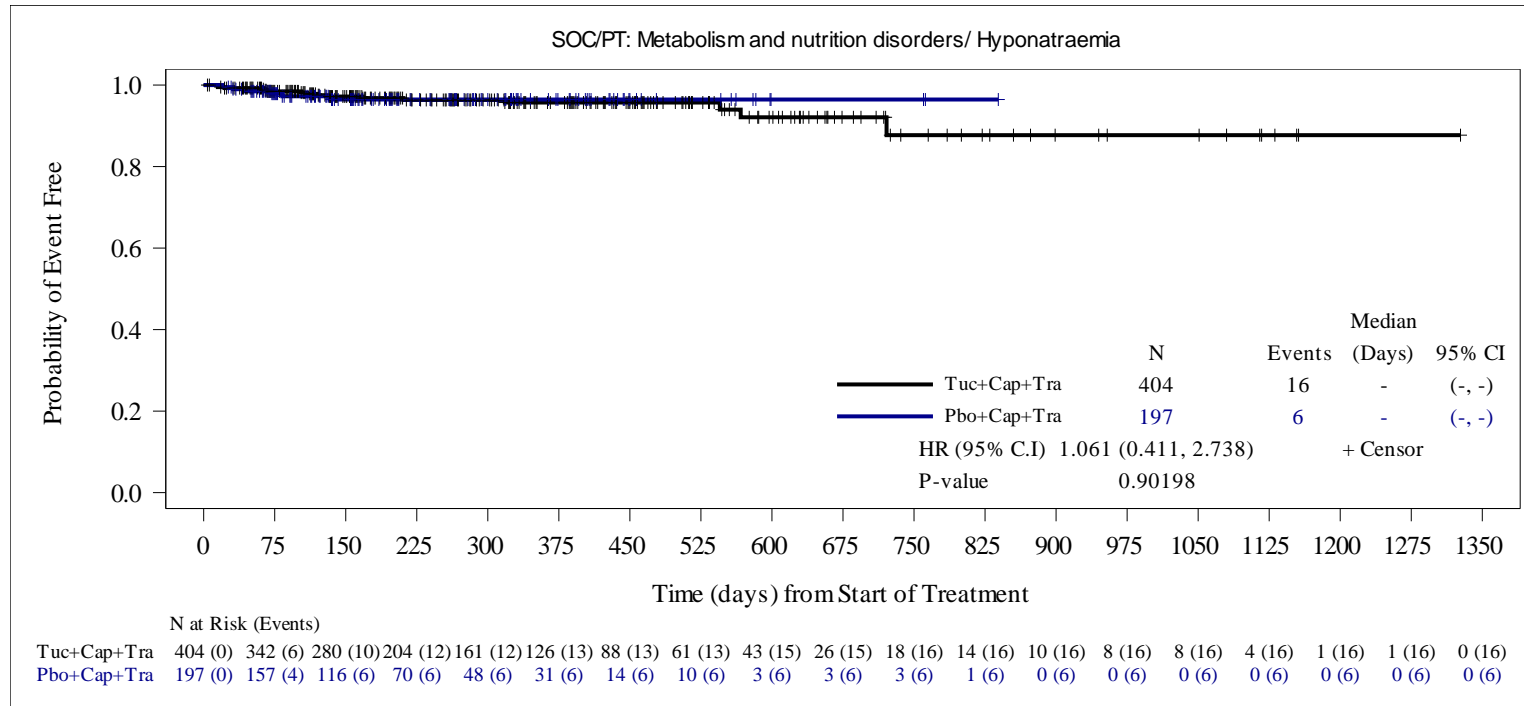
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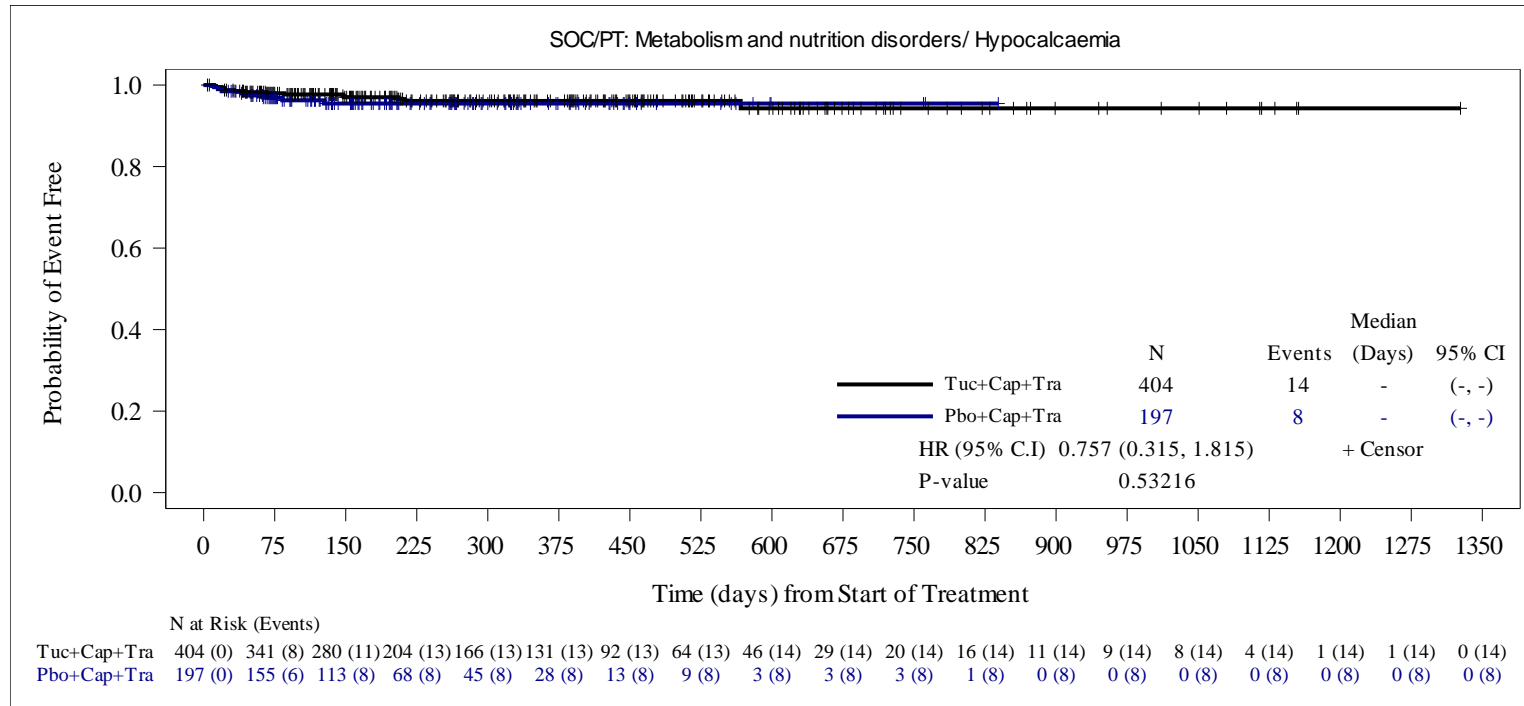
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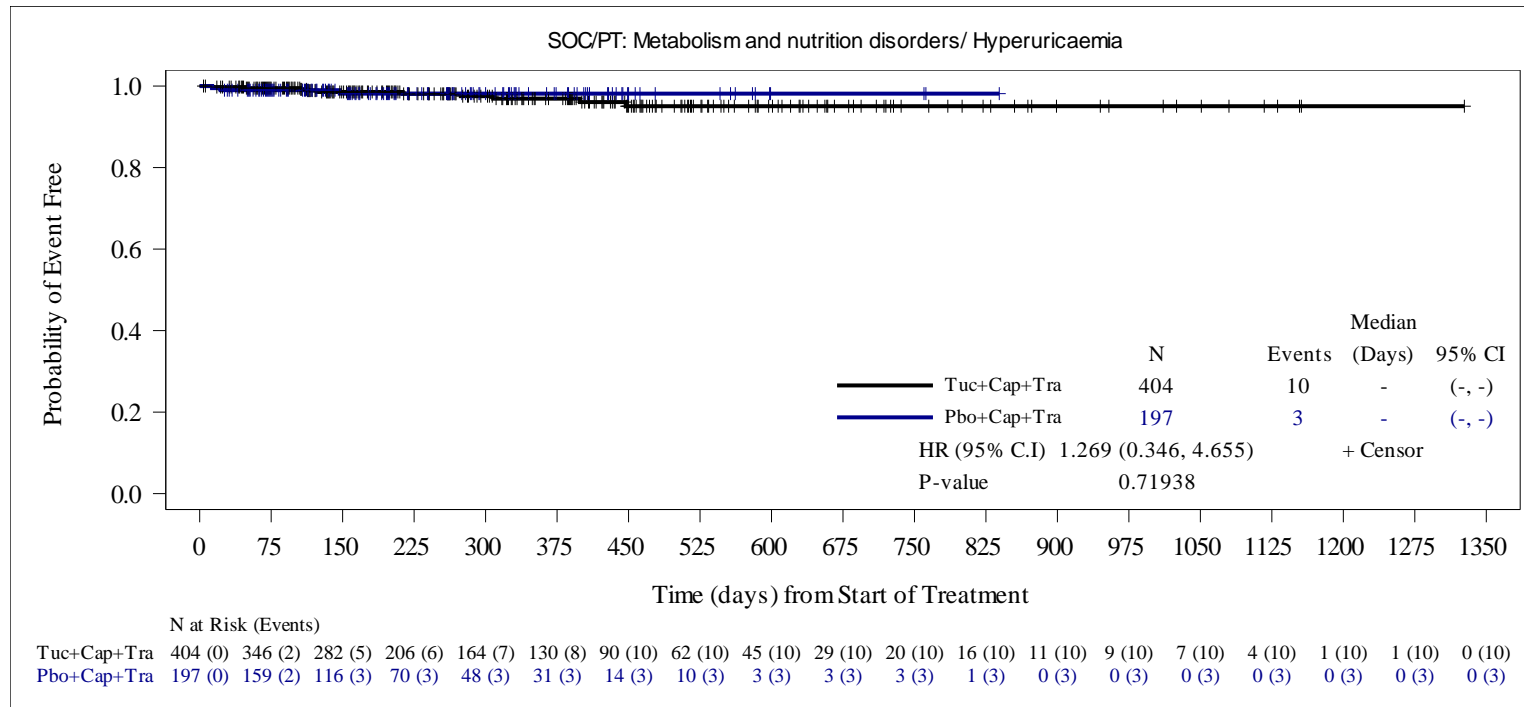
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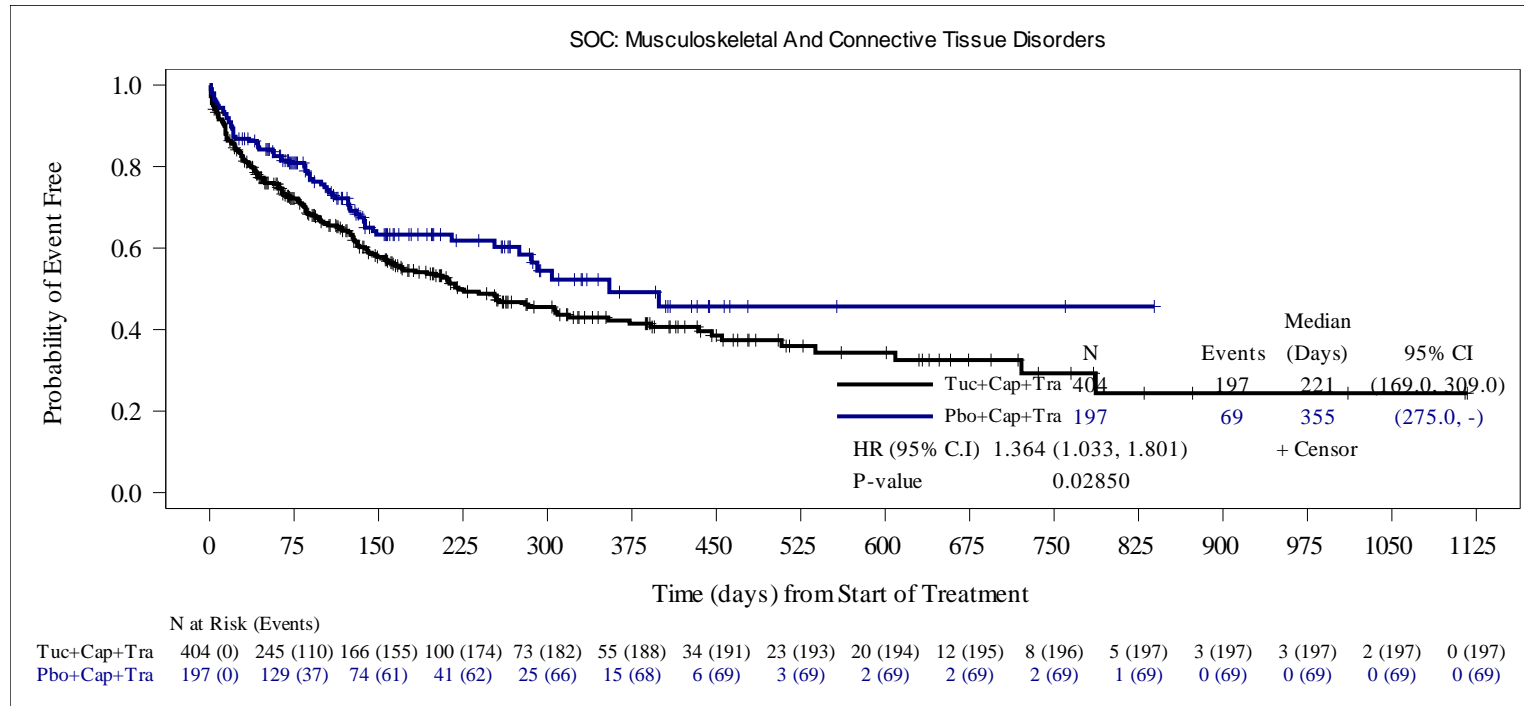
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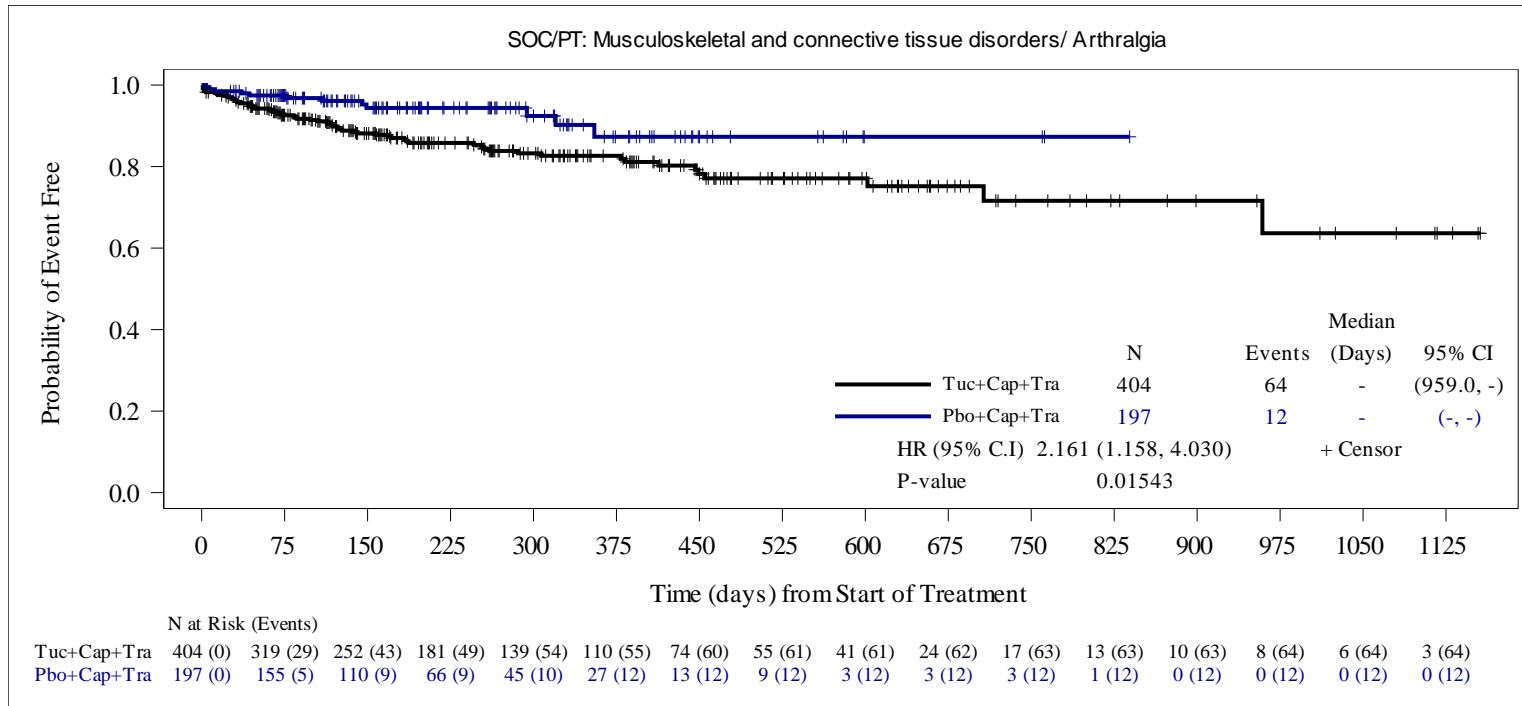
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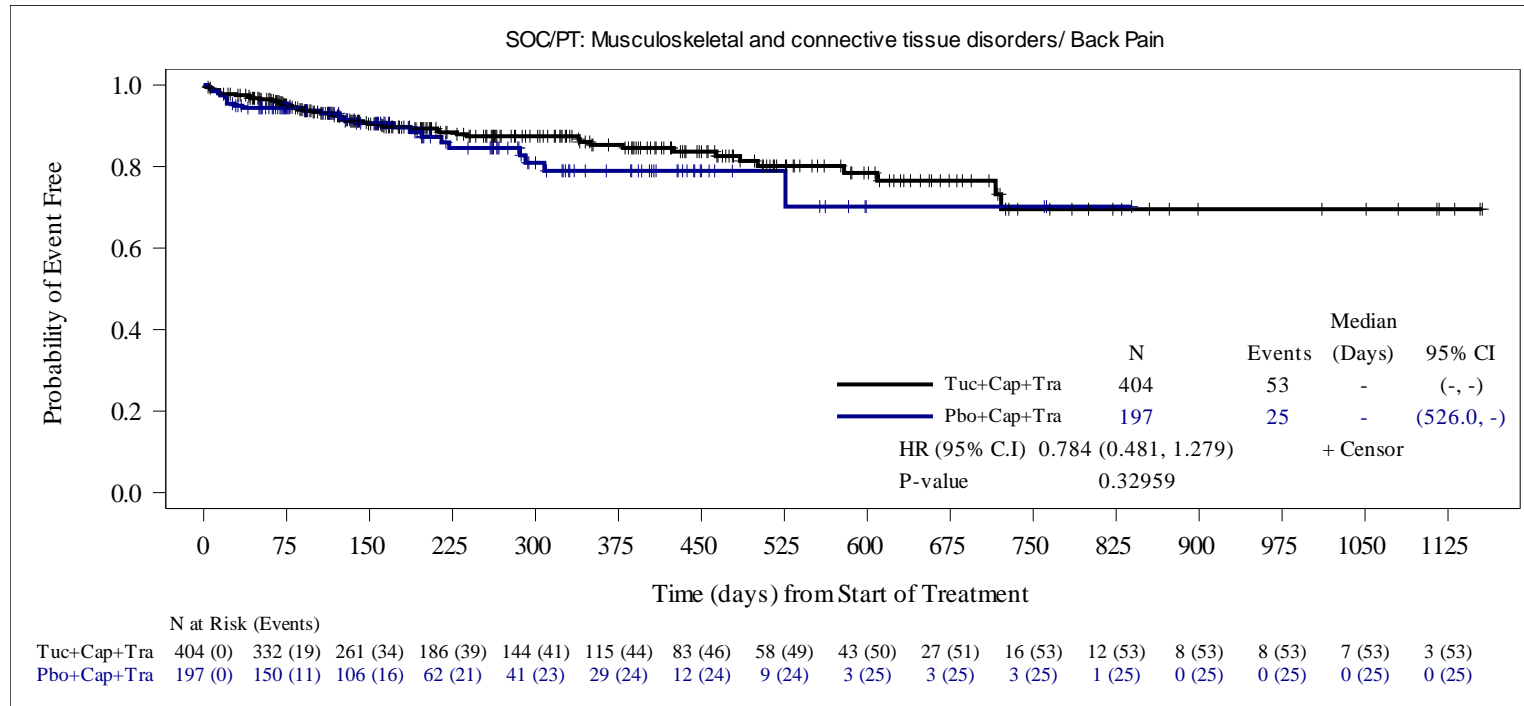
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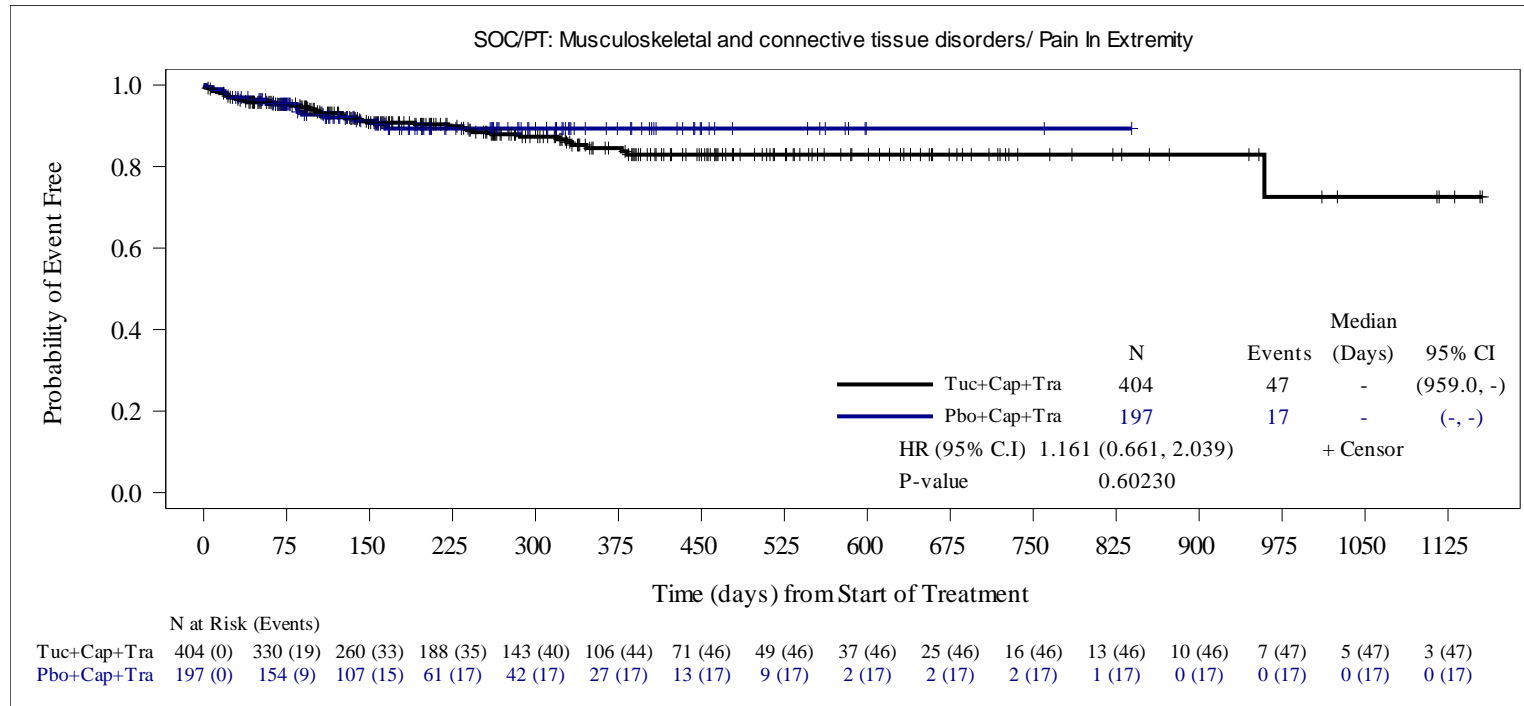
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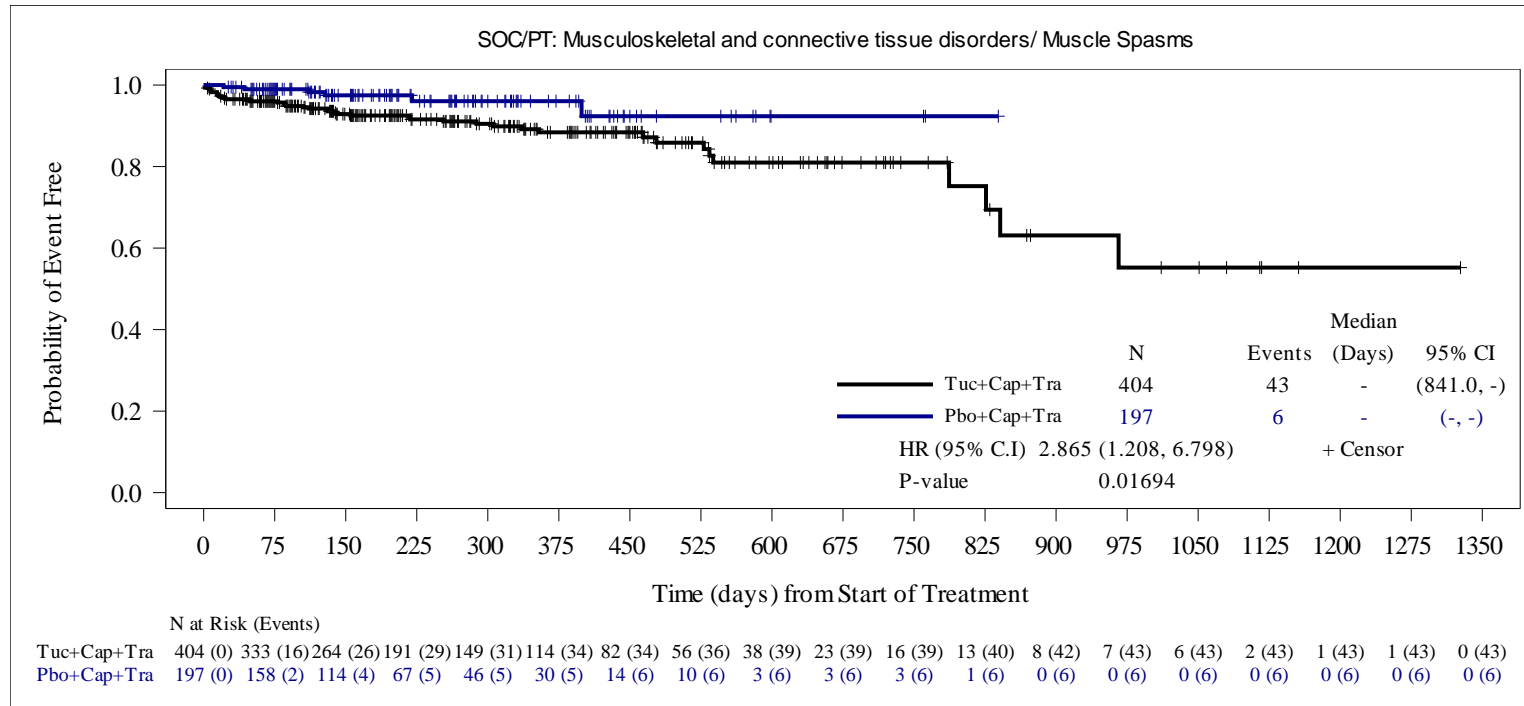
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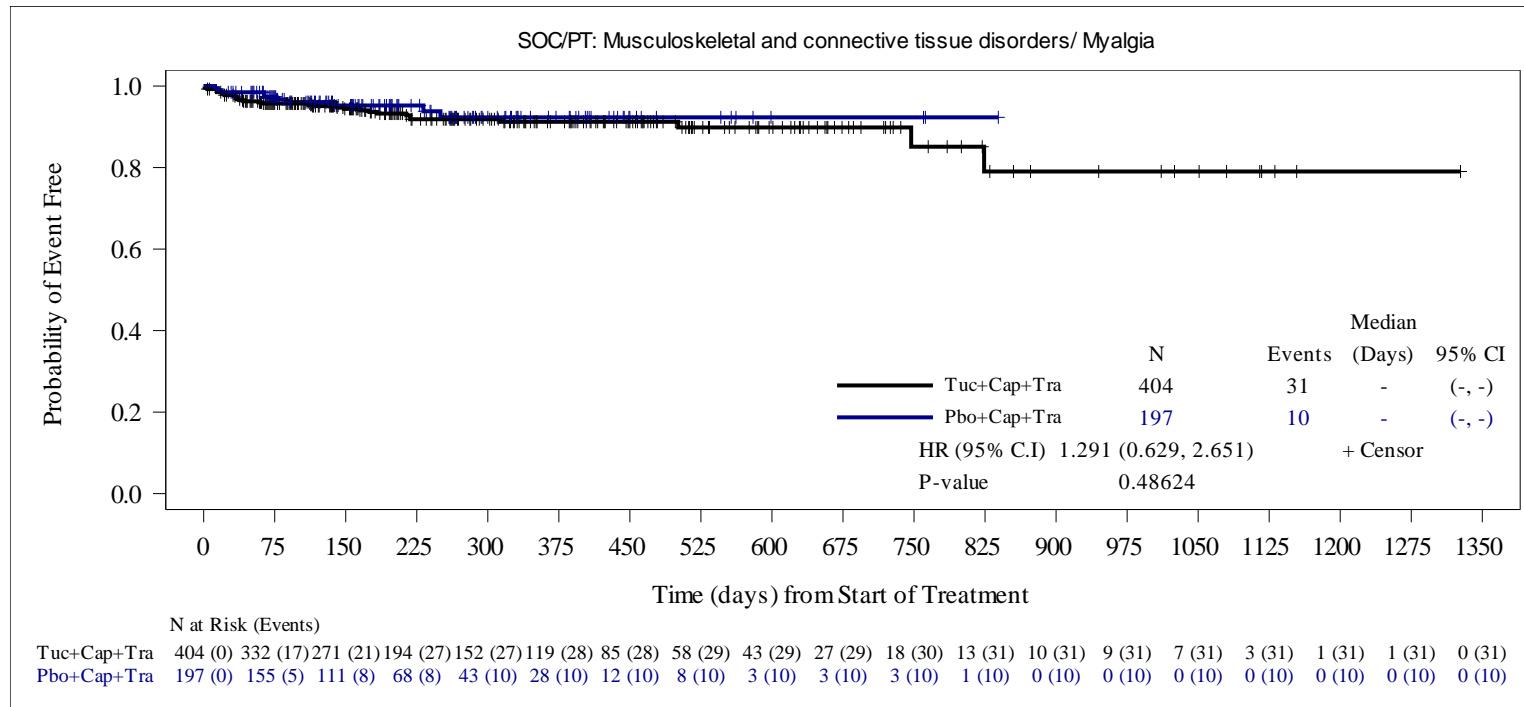
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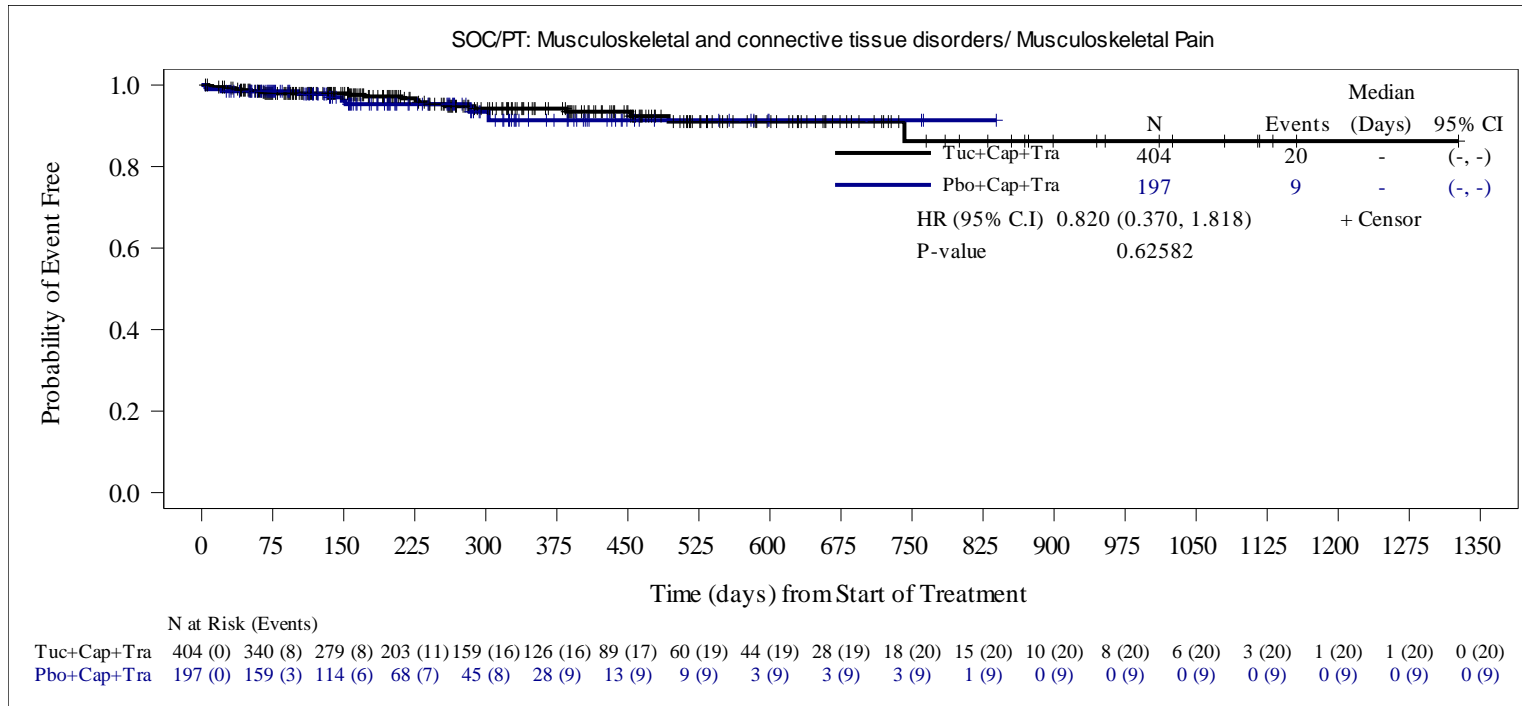
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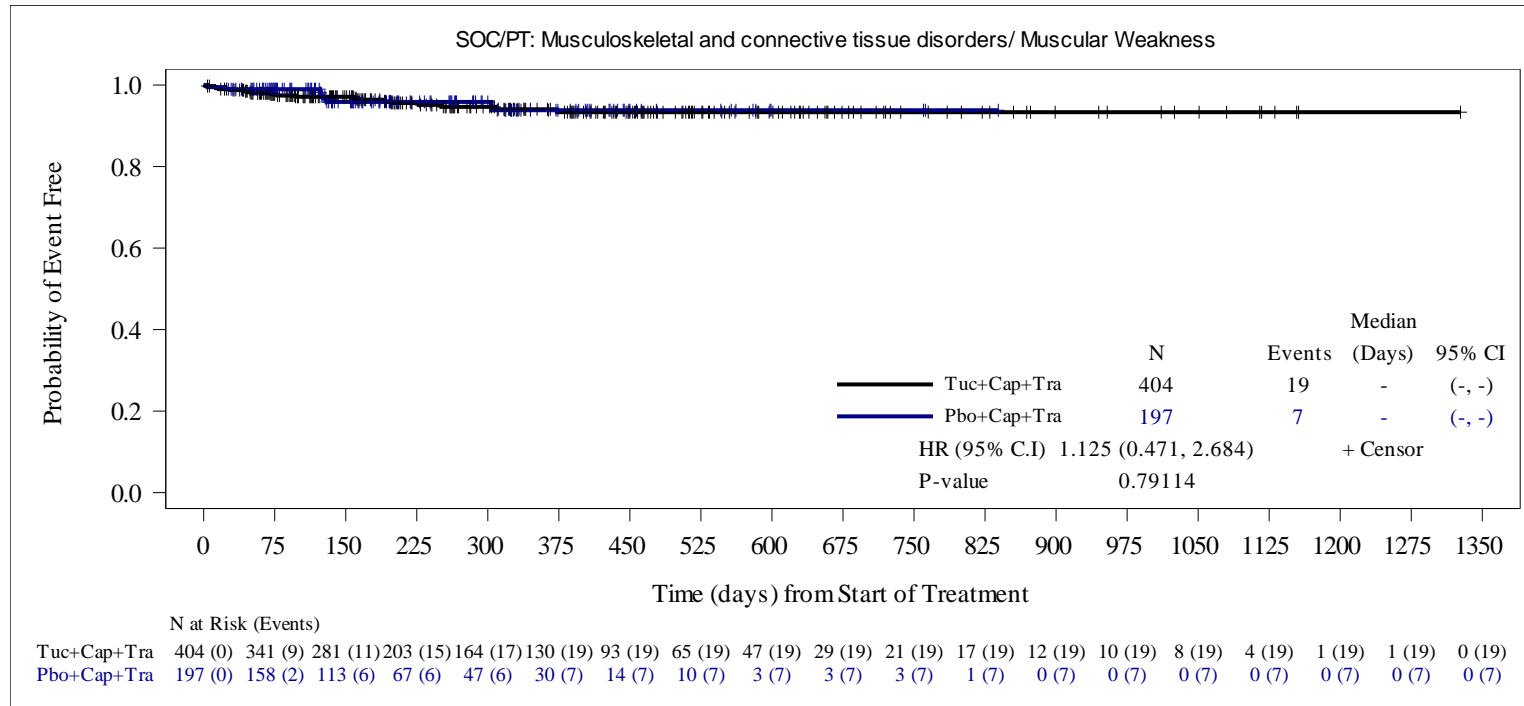
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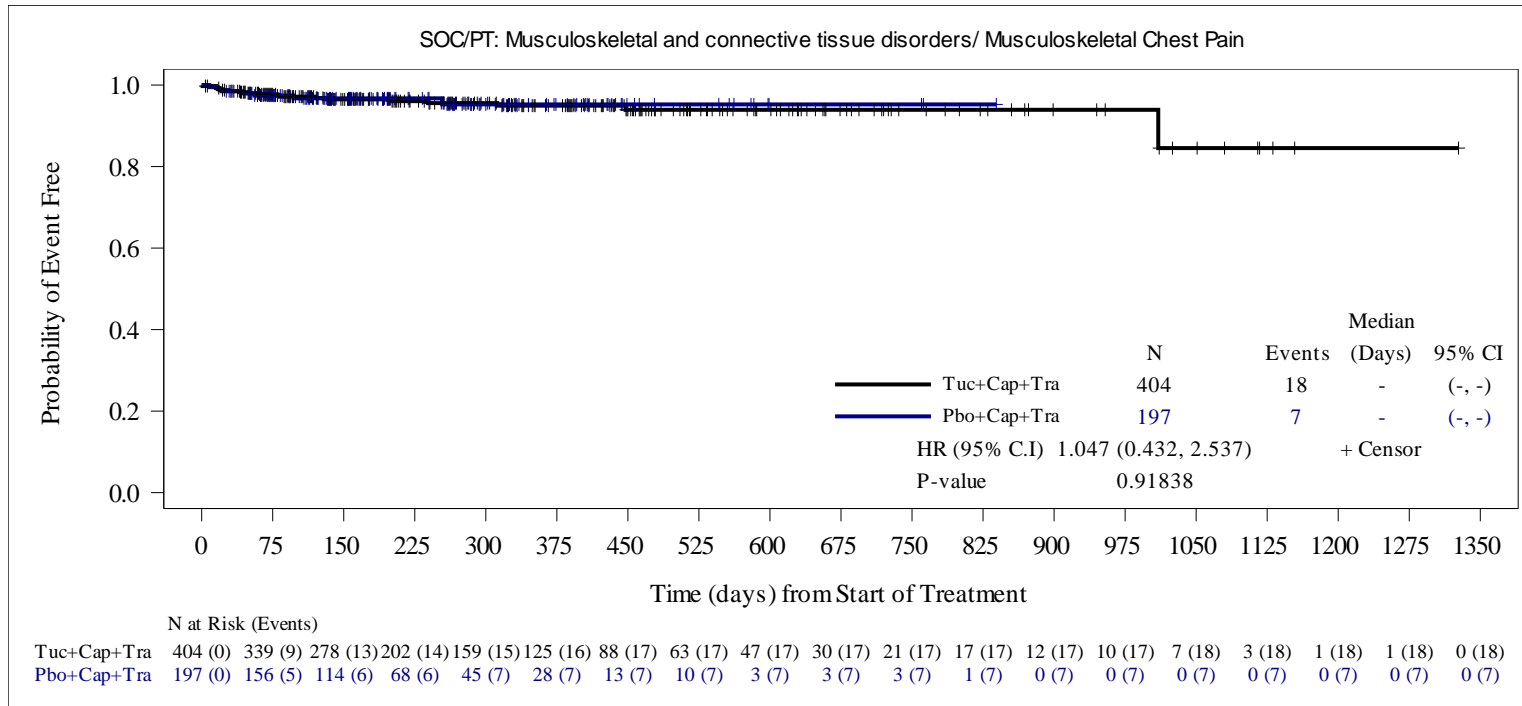
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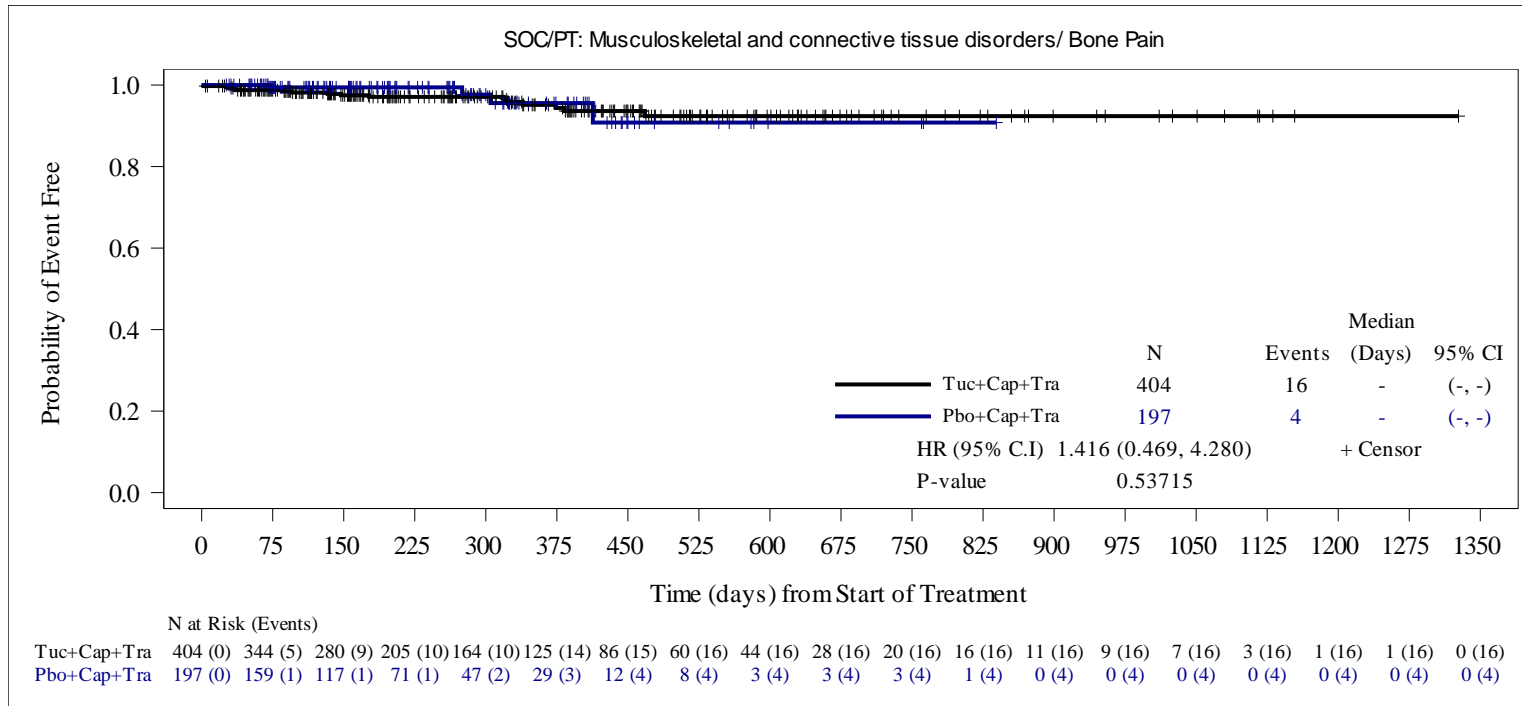
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Seagen Protocol ONT-380-206

**Figure 2.7.1 Kaplan-Meier Estimate of Time to First Onset of Treatment-Emergent Adverse Events by System Organ Class and Preferred Term
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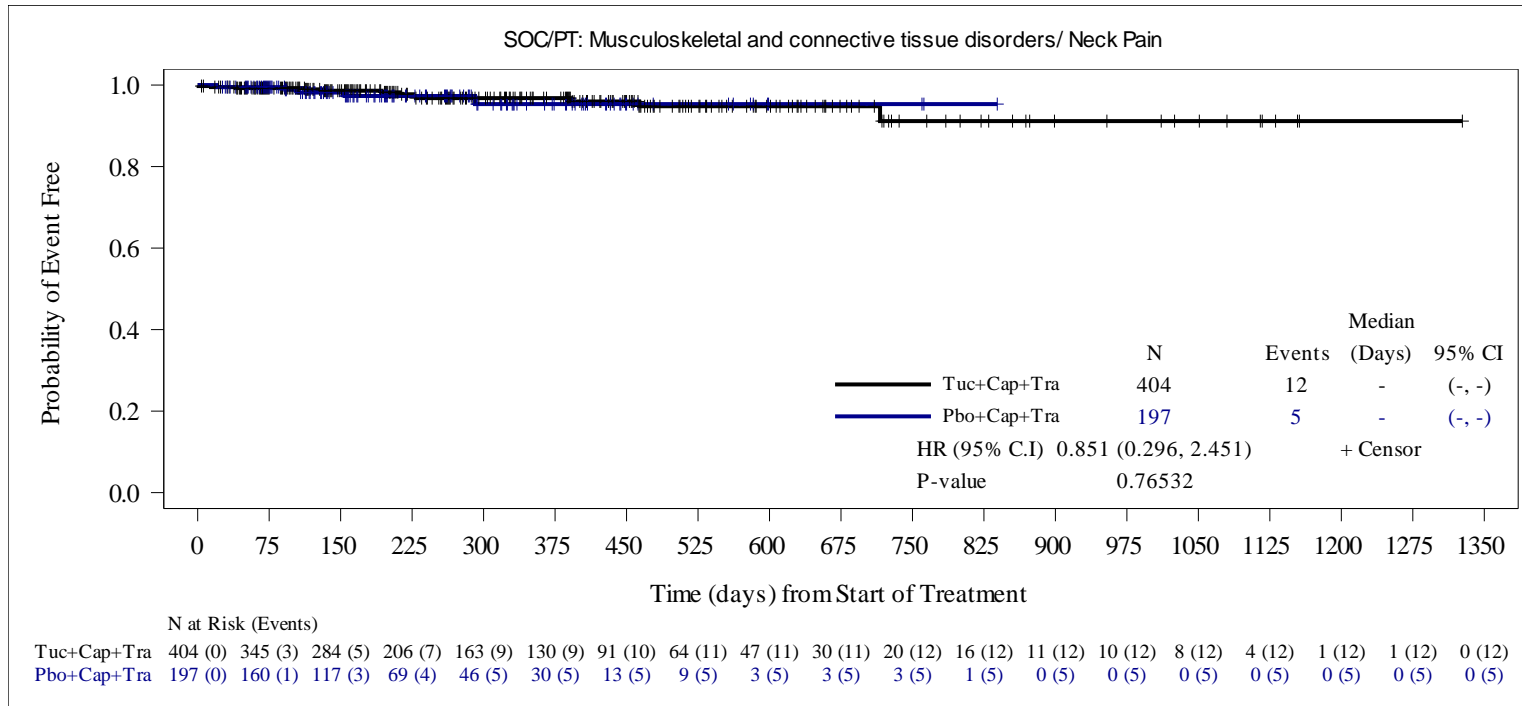
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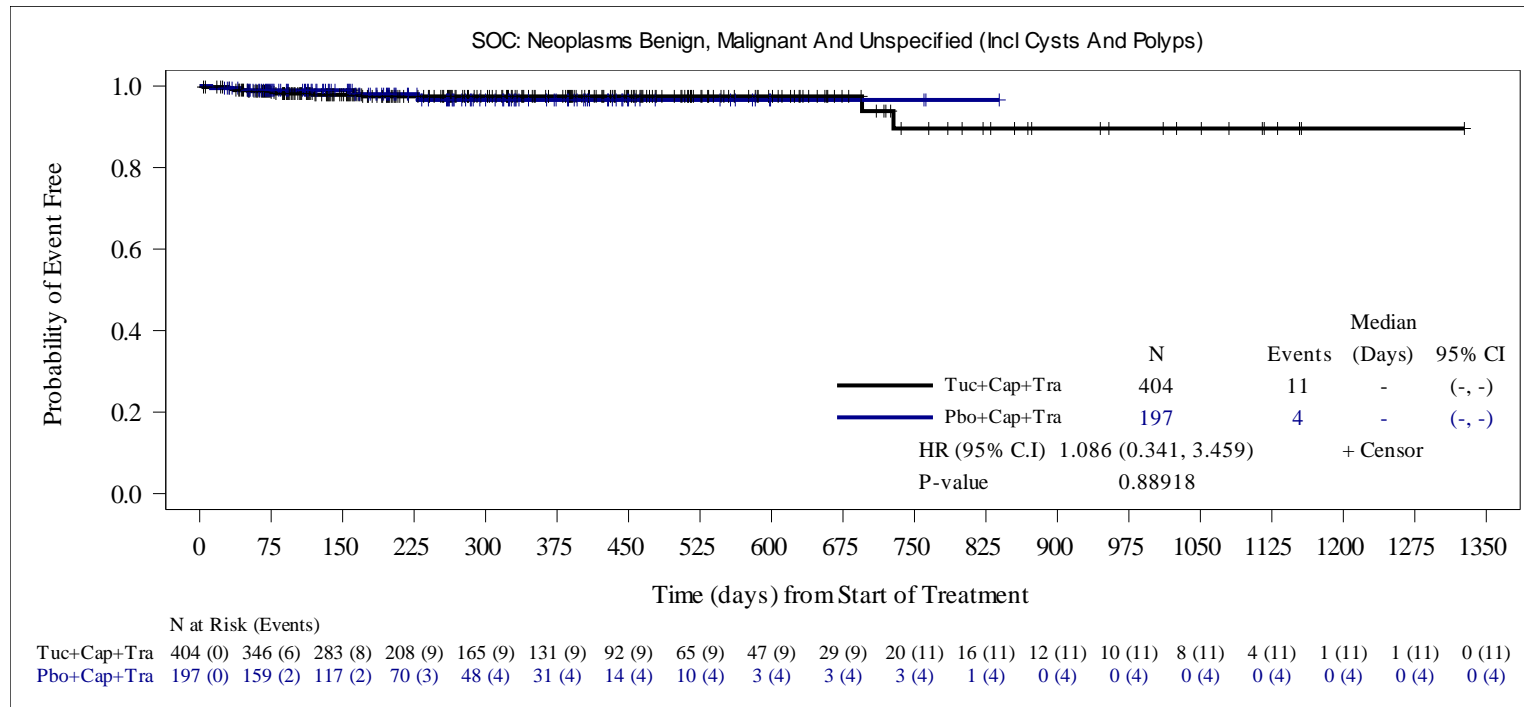
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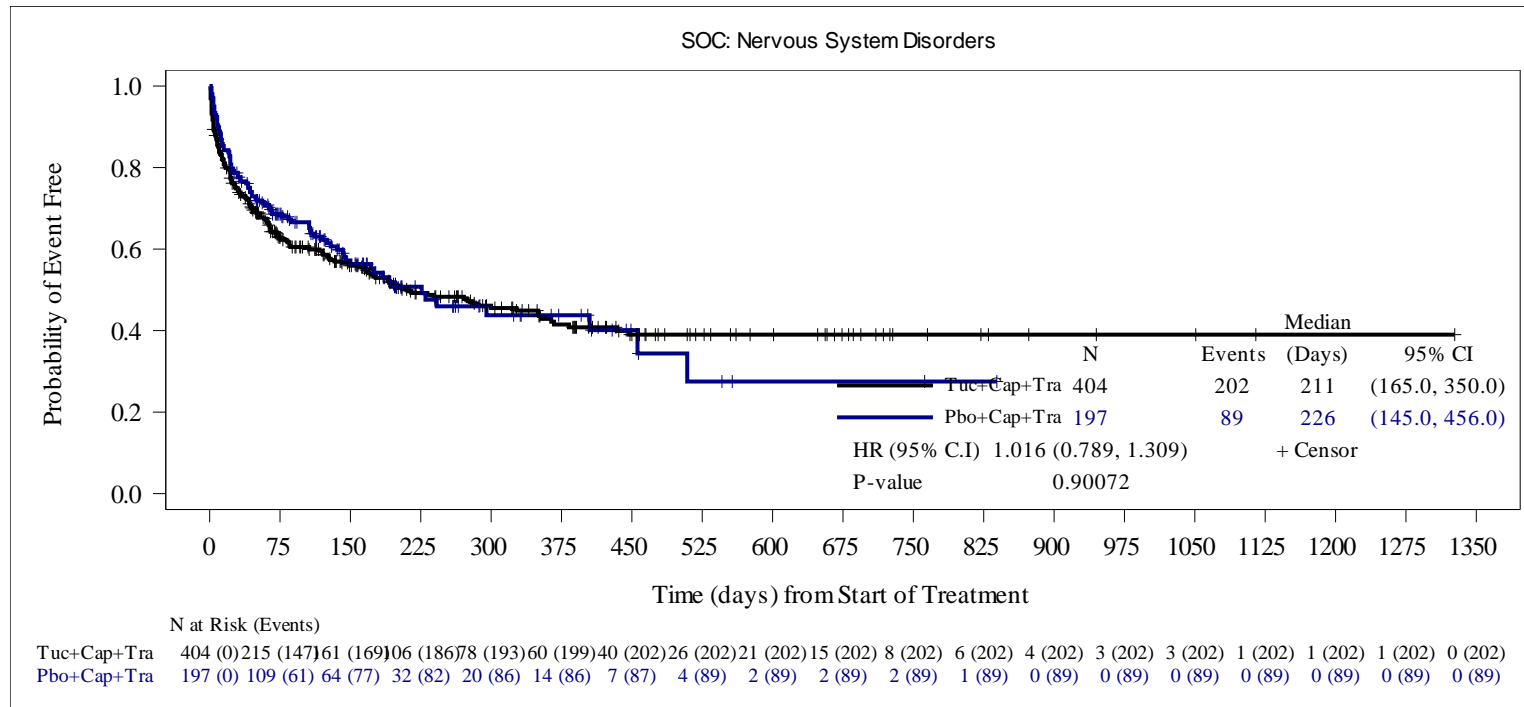
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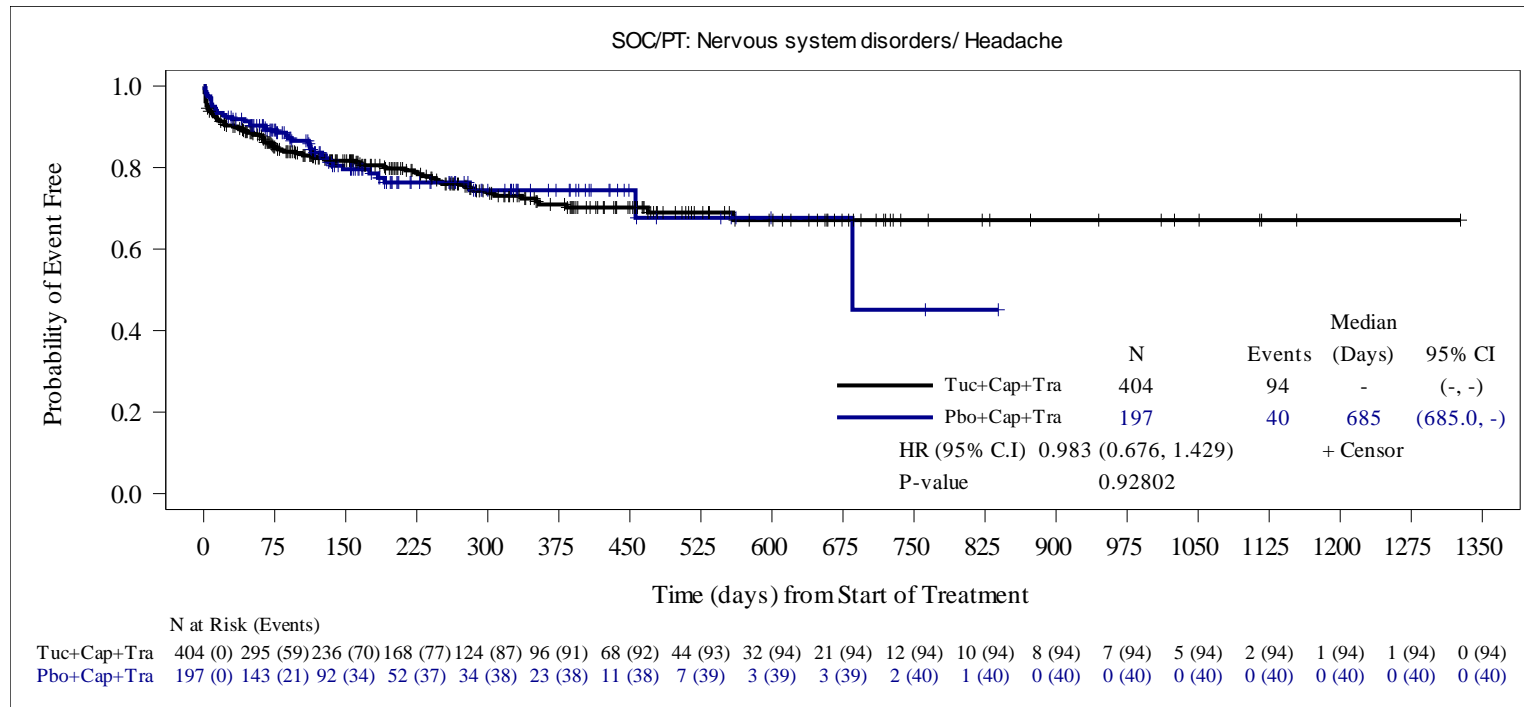
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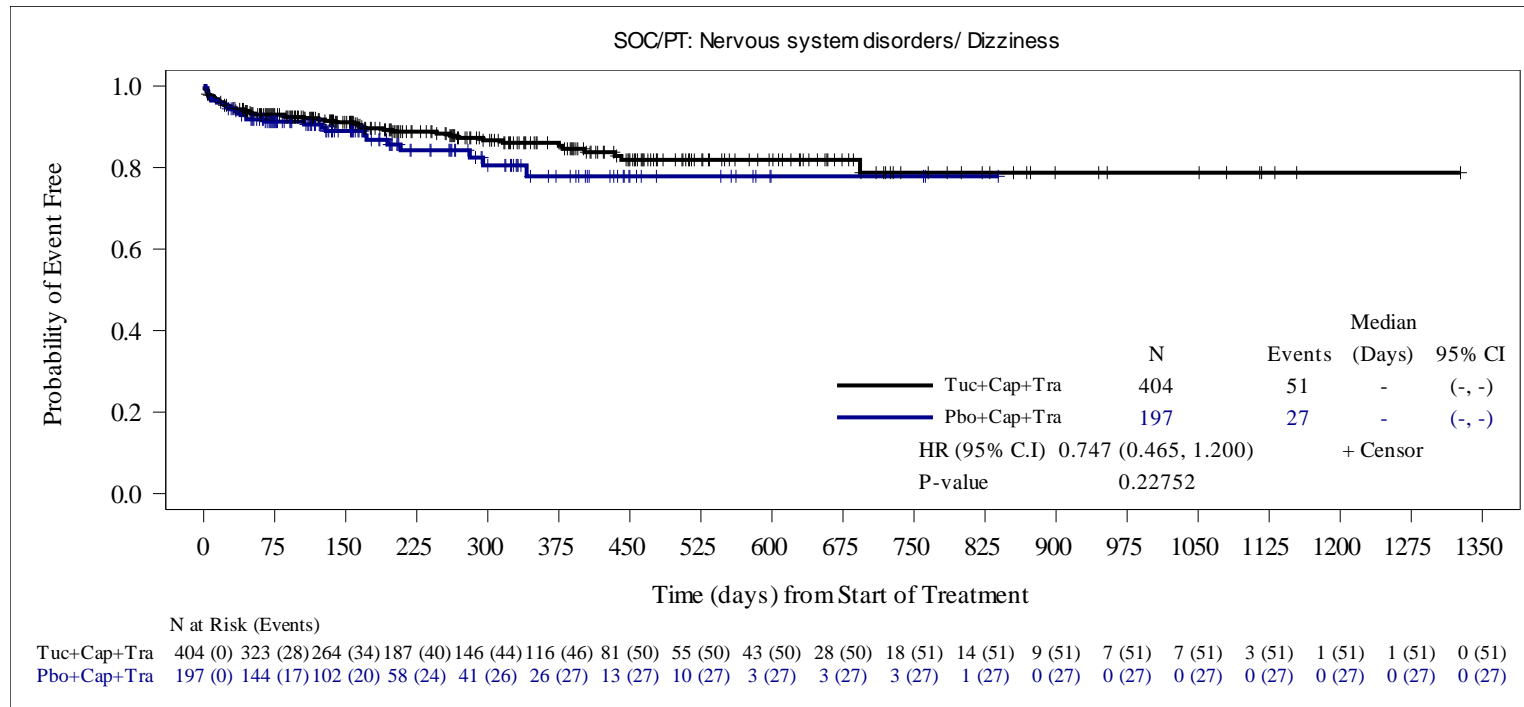
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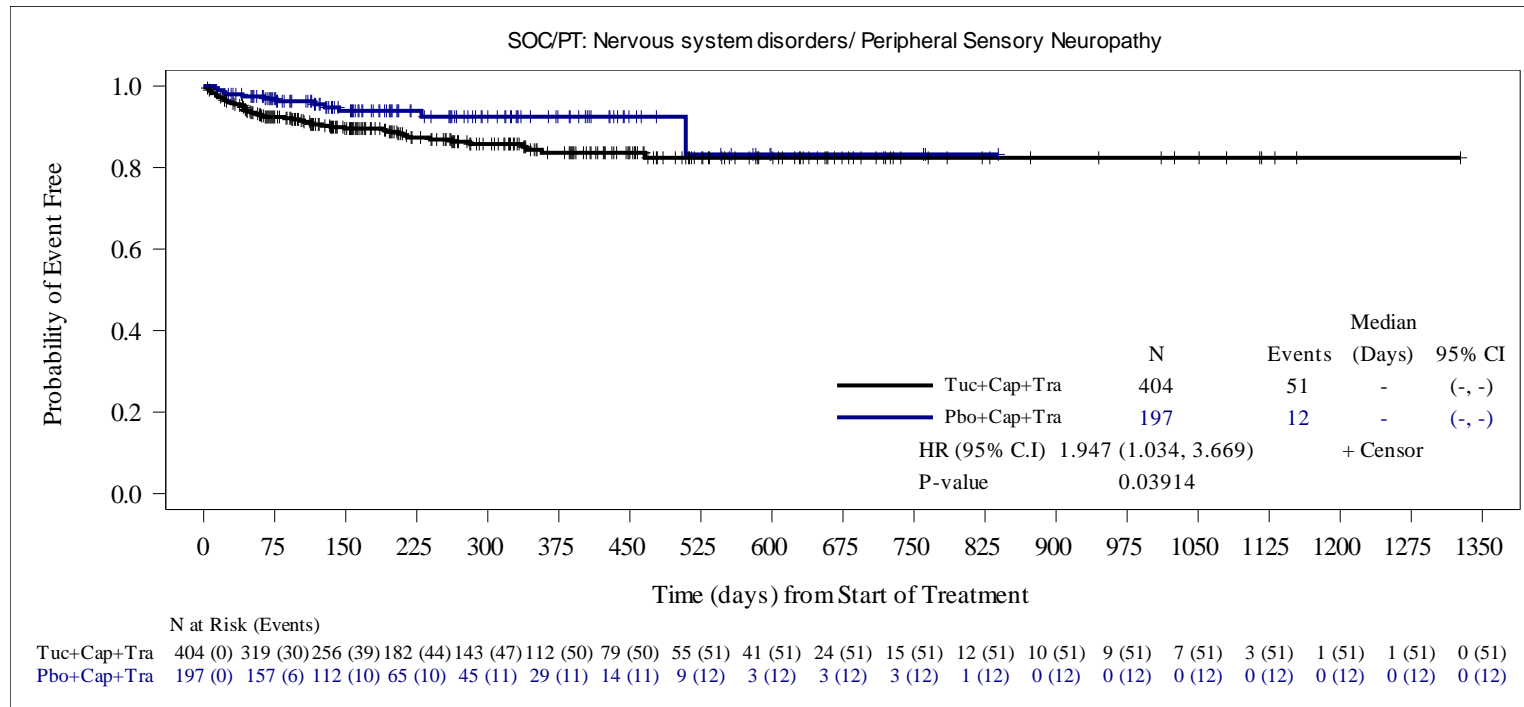
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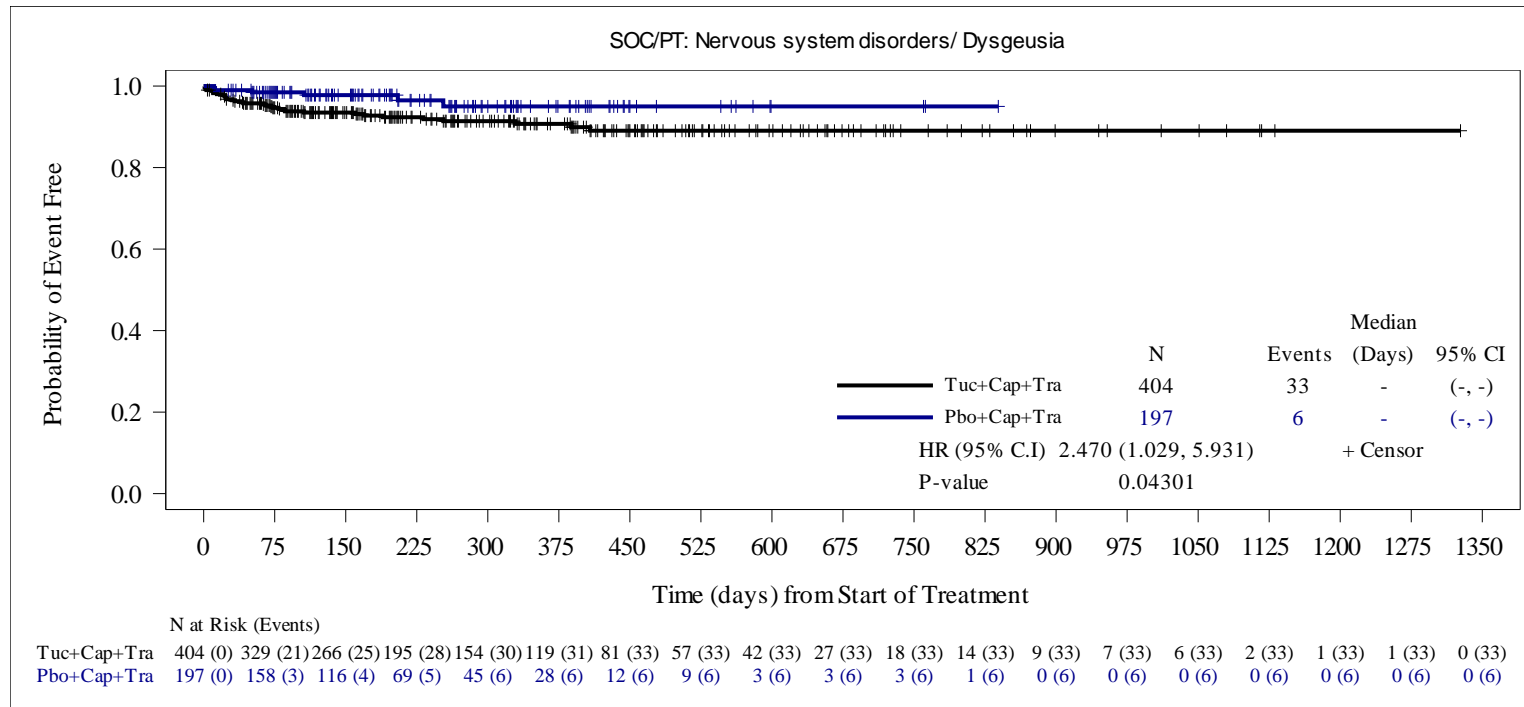
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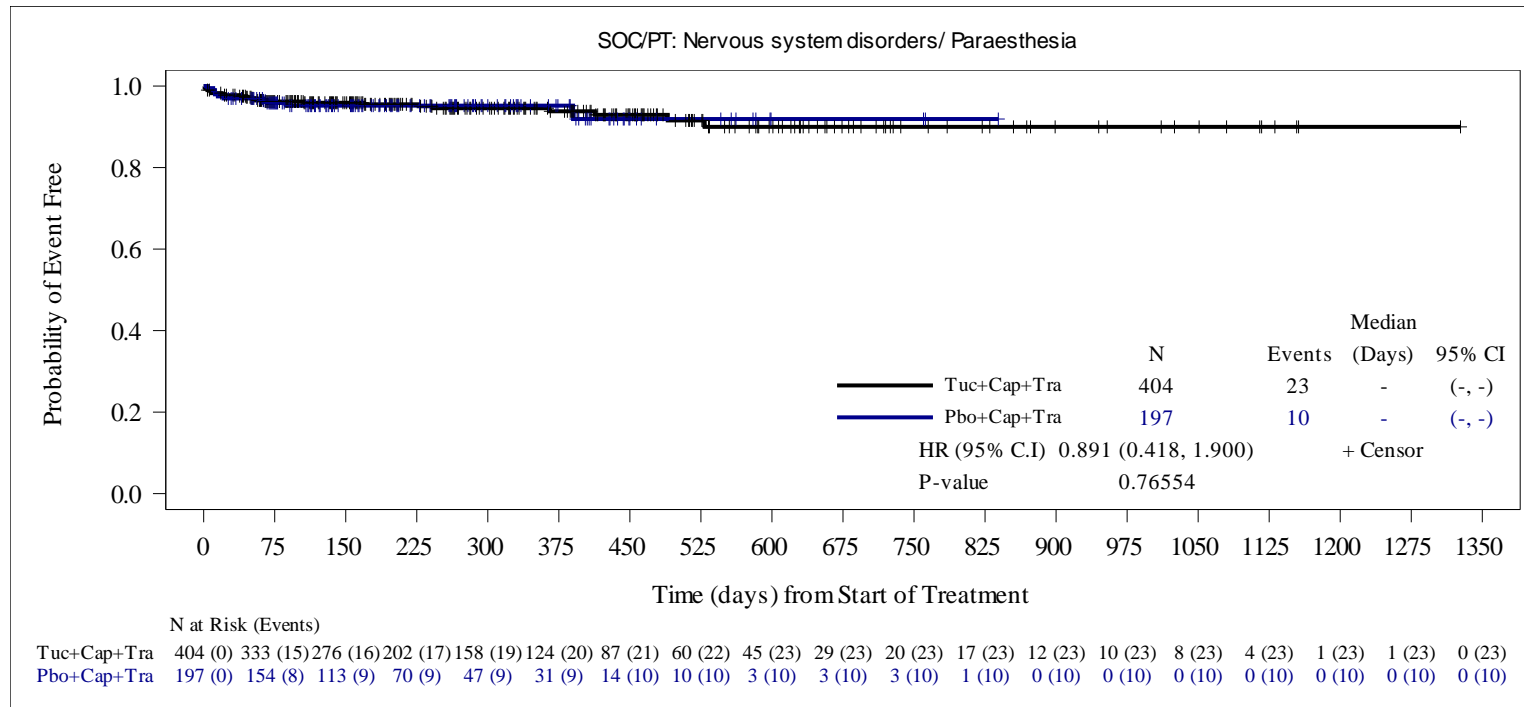
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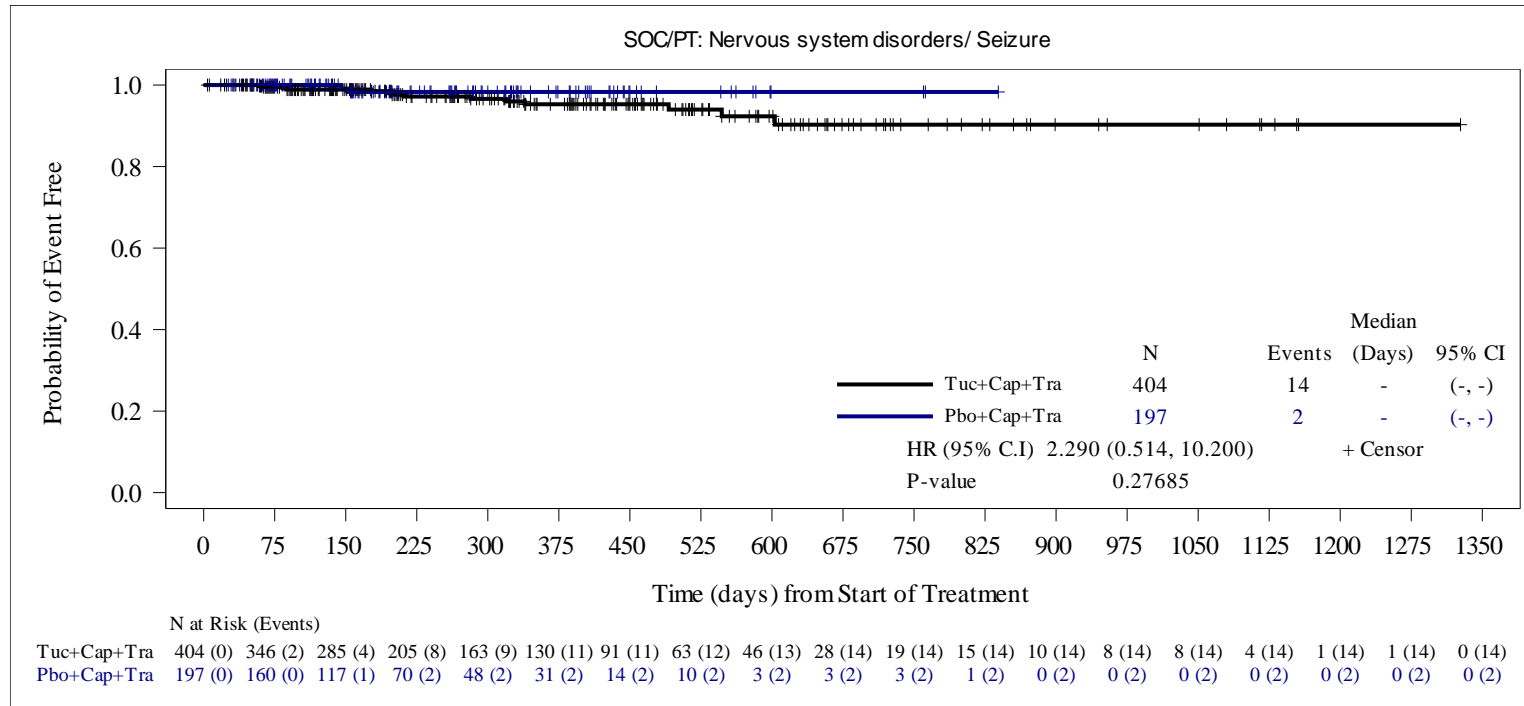
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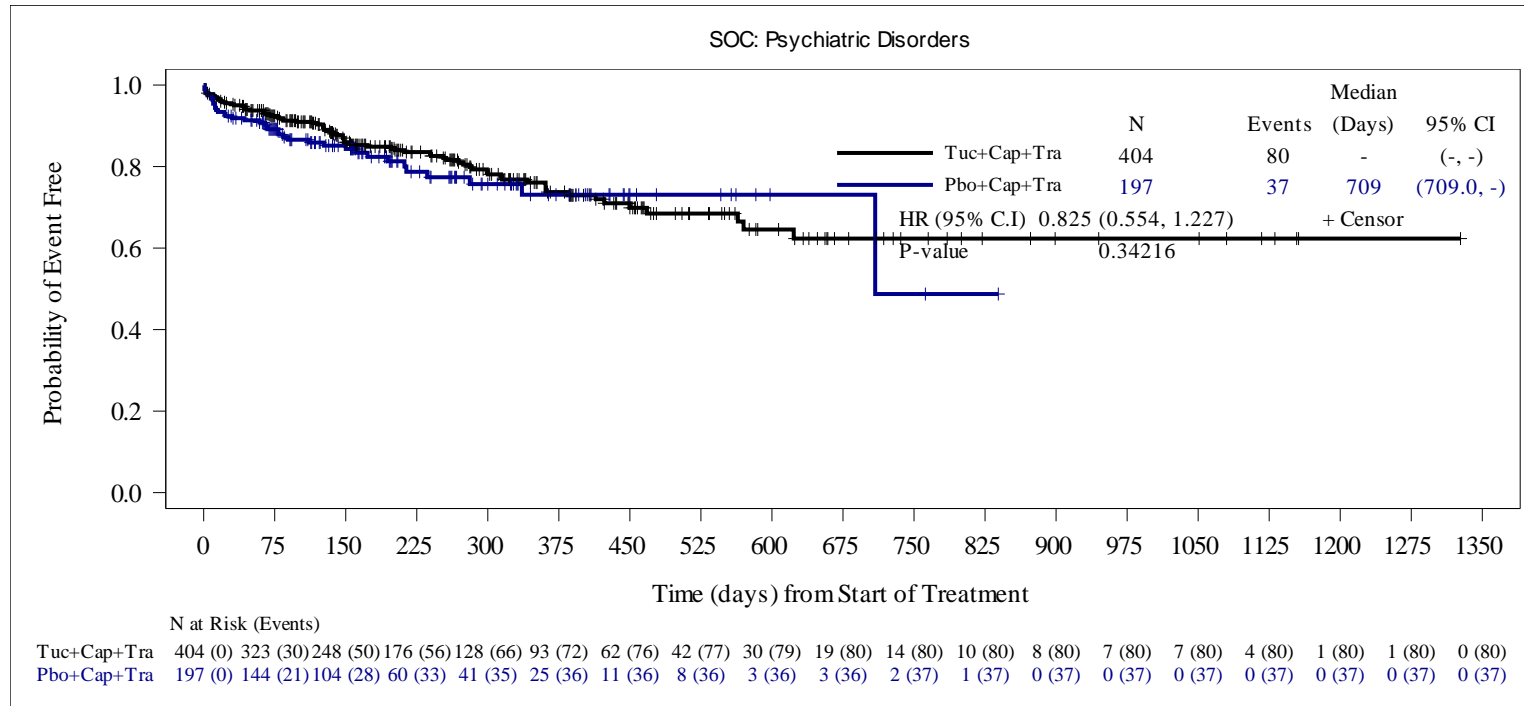
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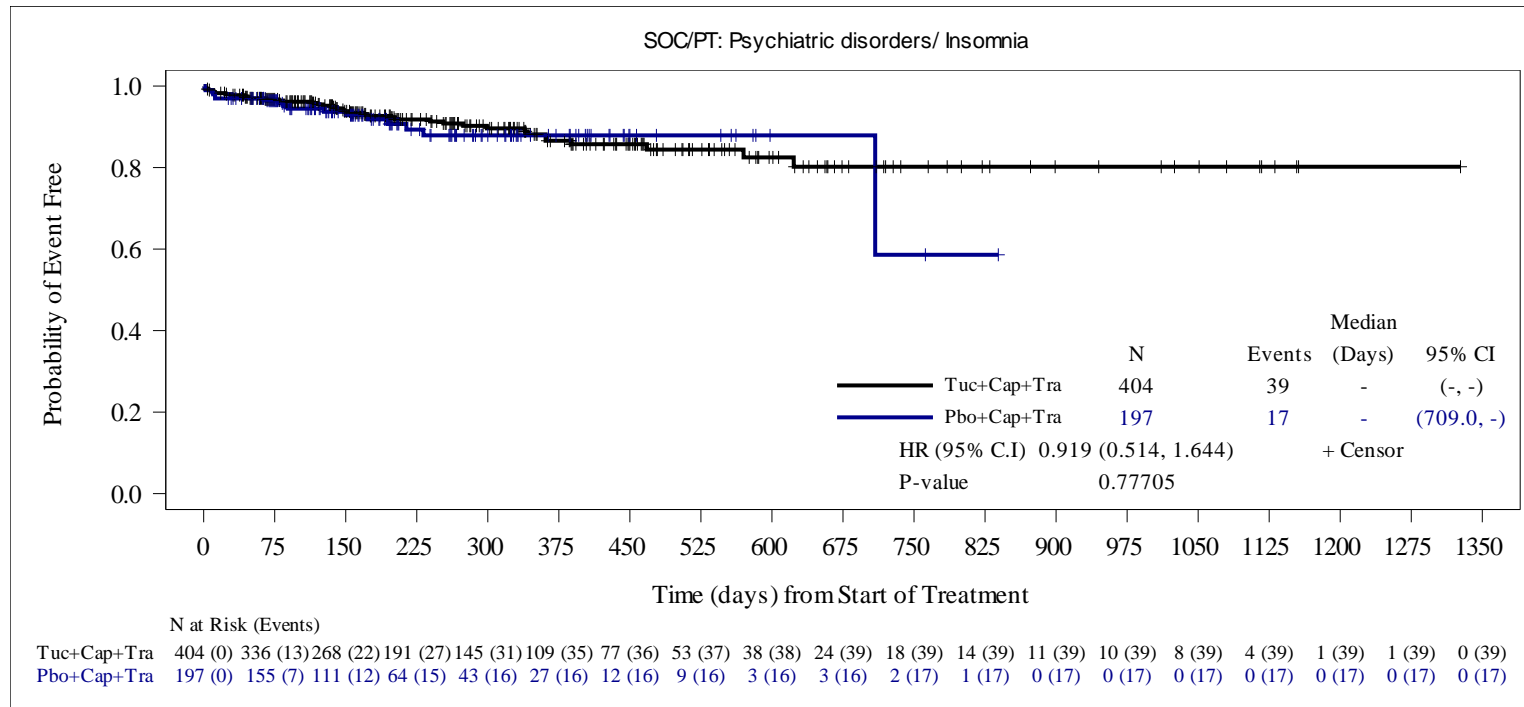
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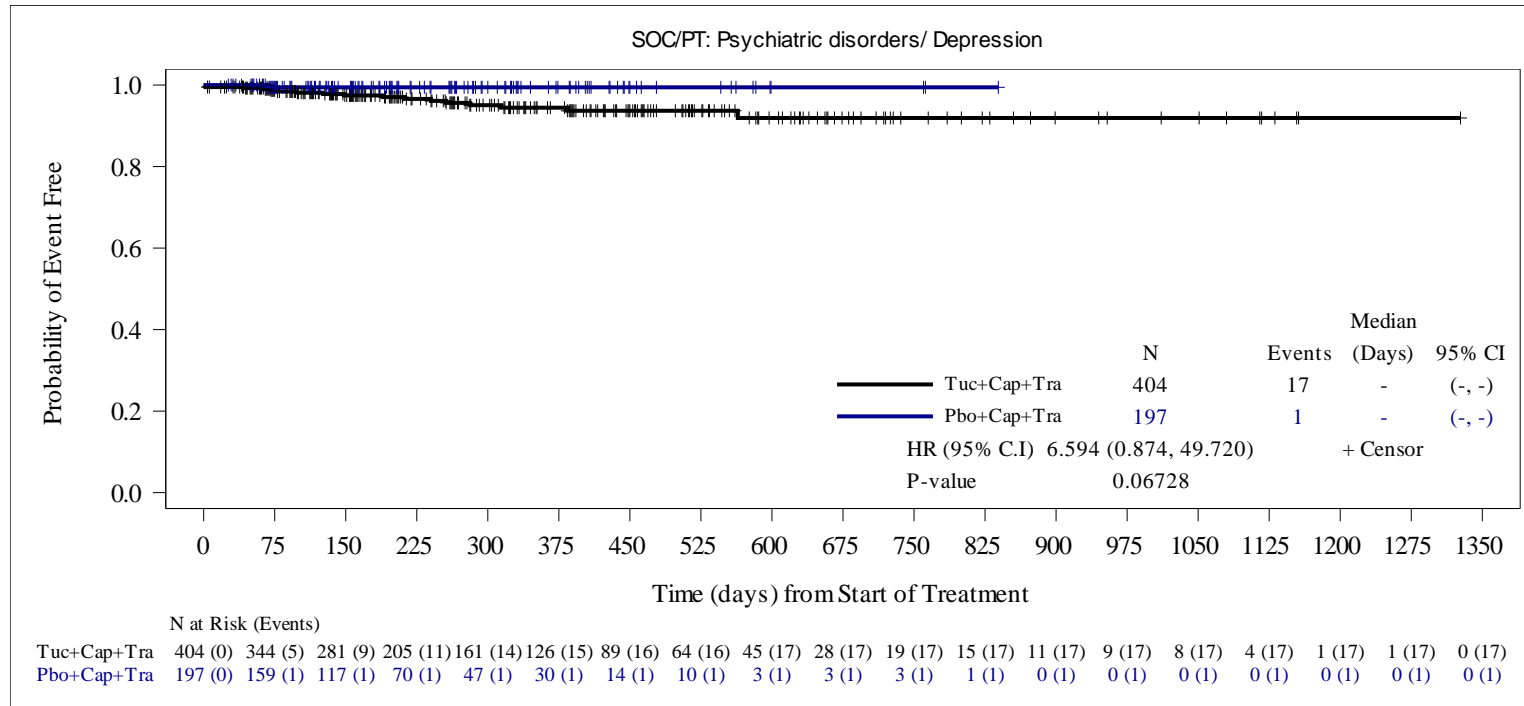
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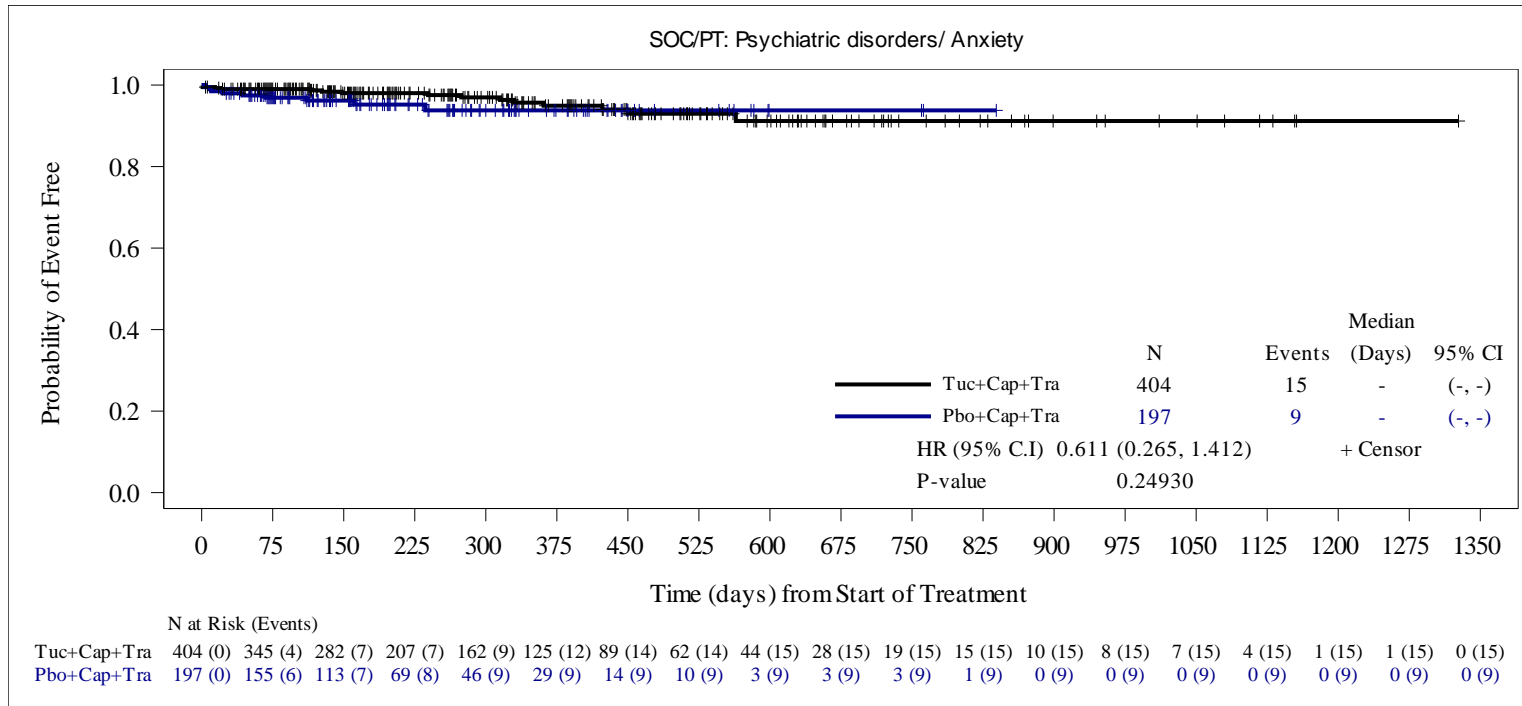
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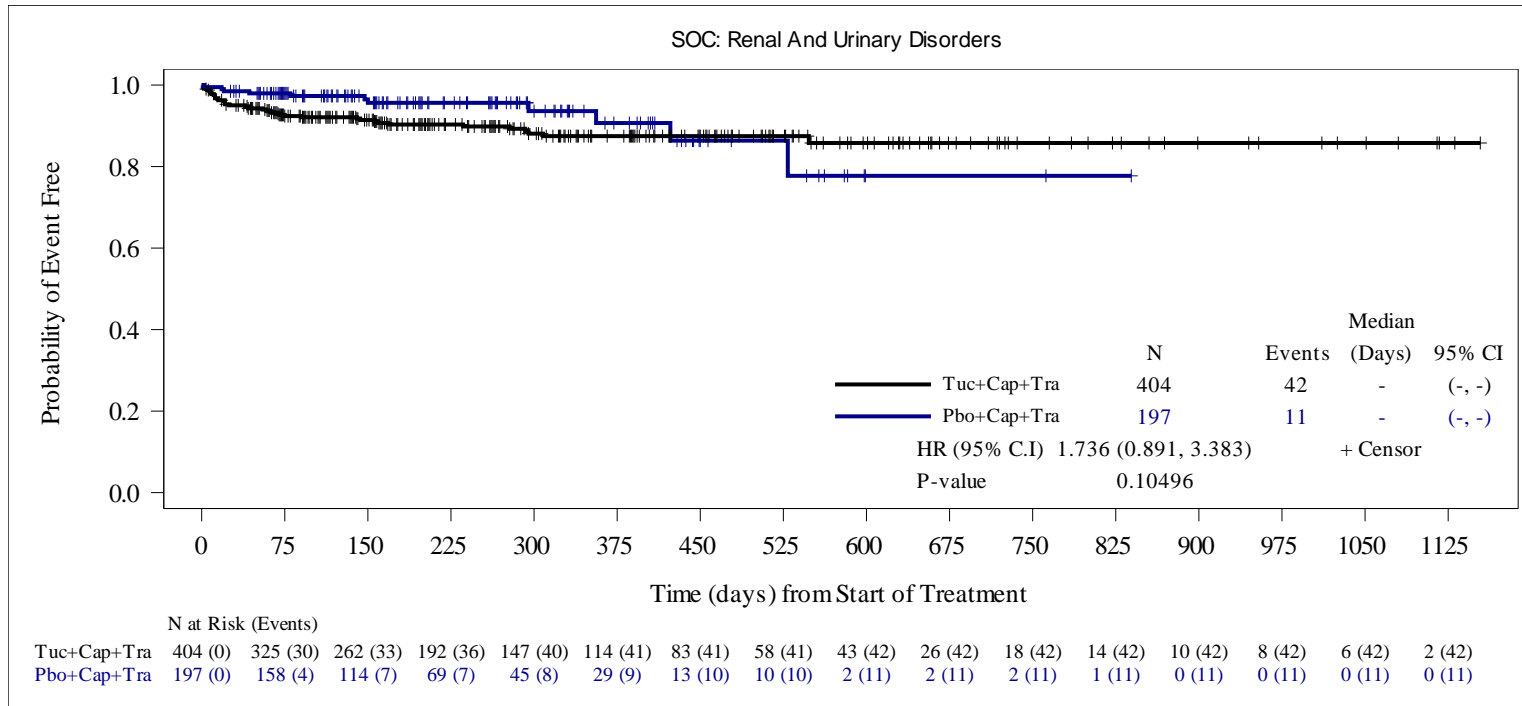
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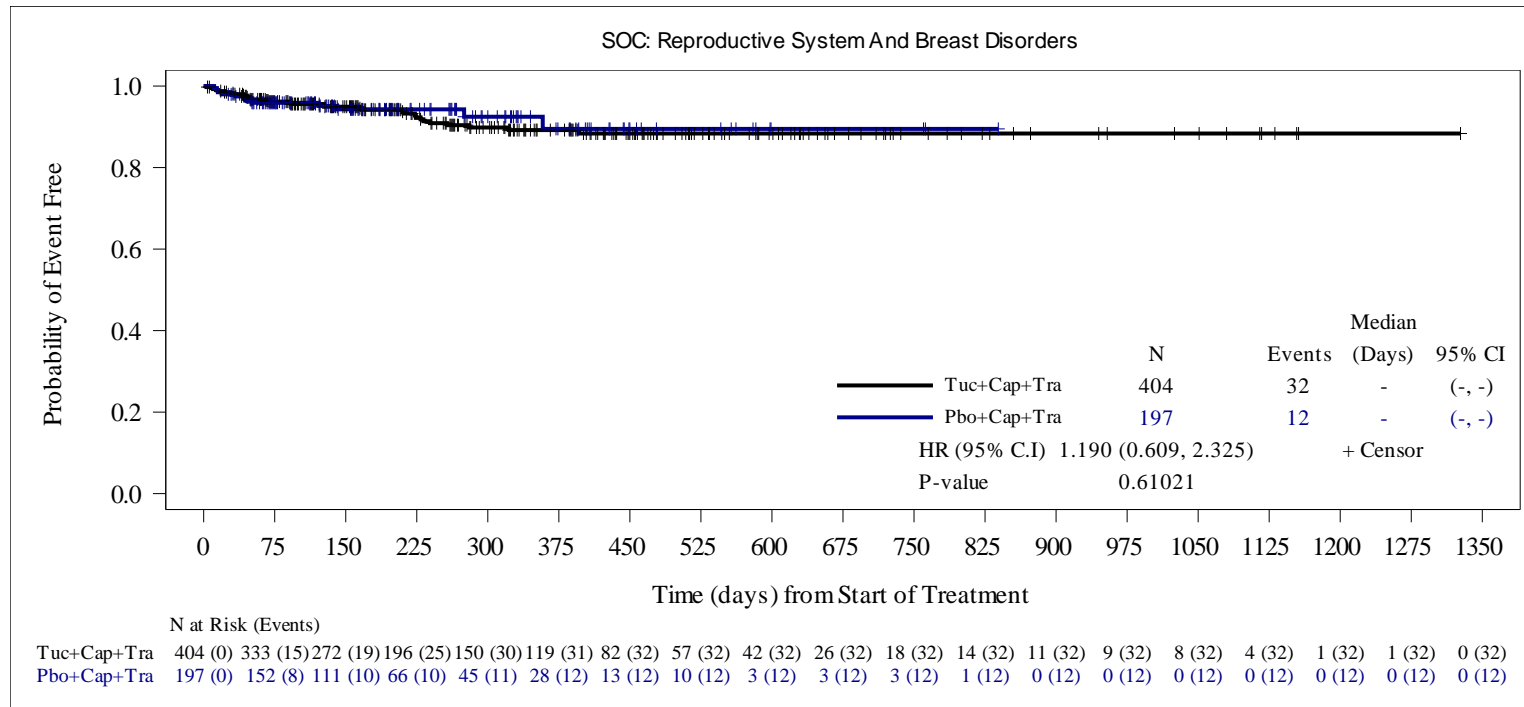
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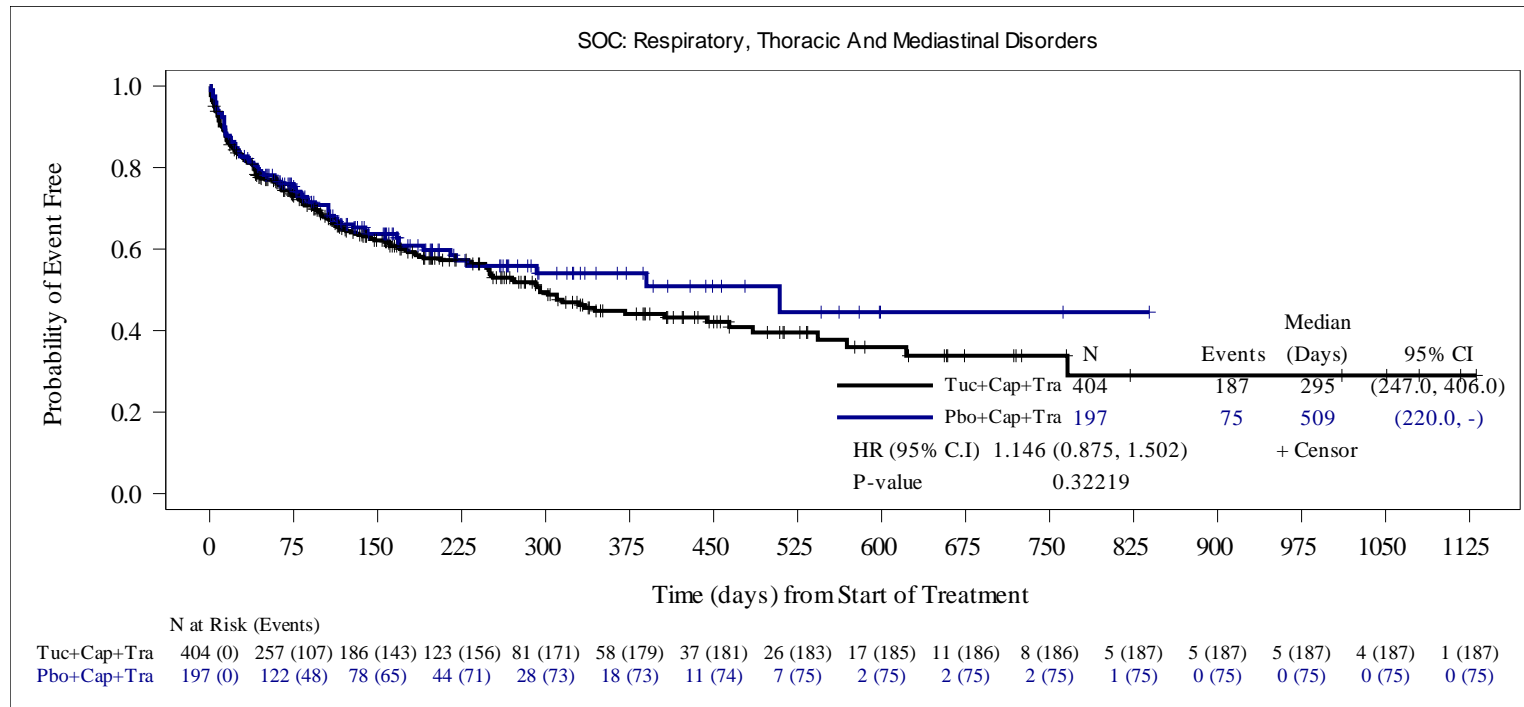
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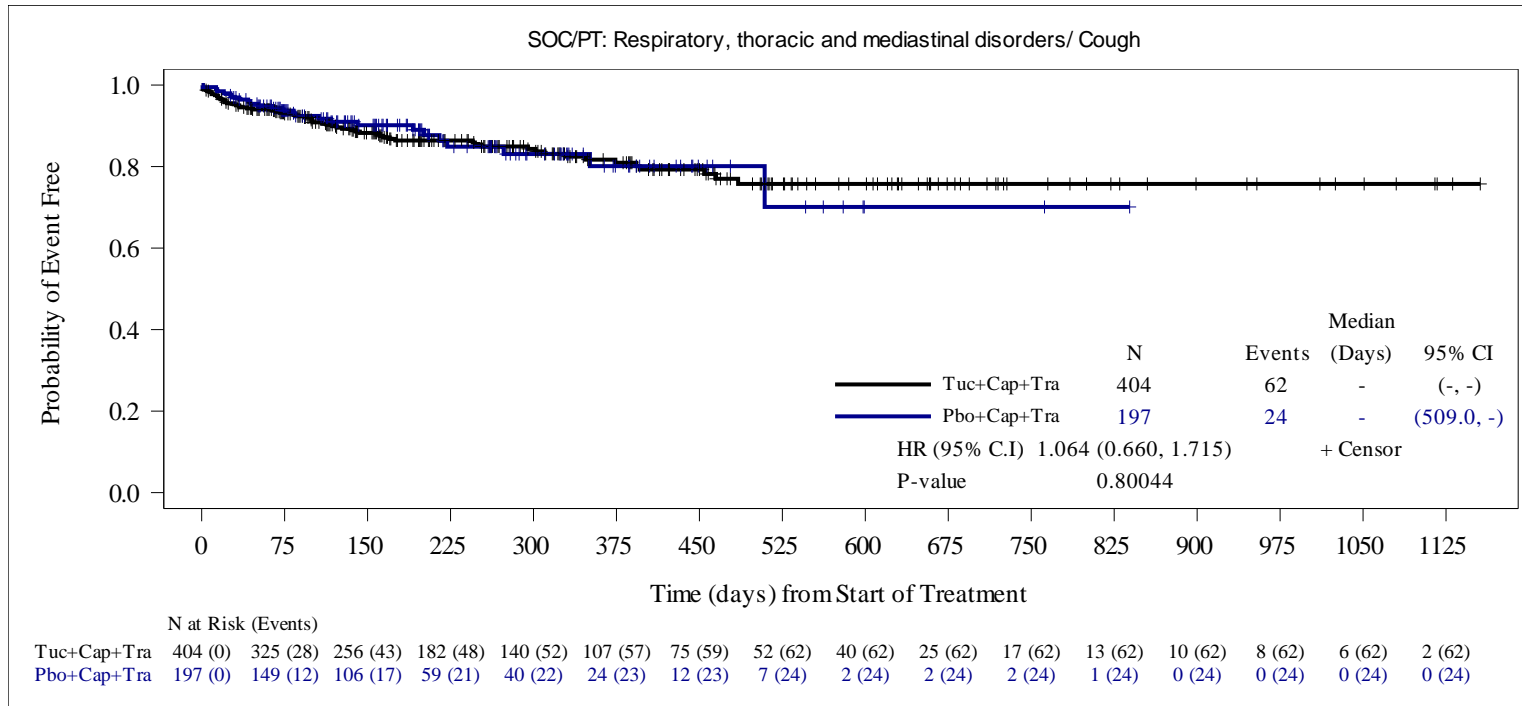
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Seagen Protocol ONT-380-206

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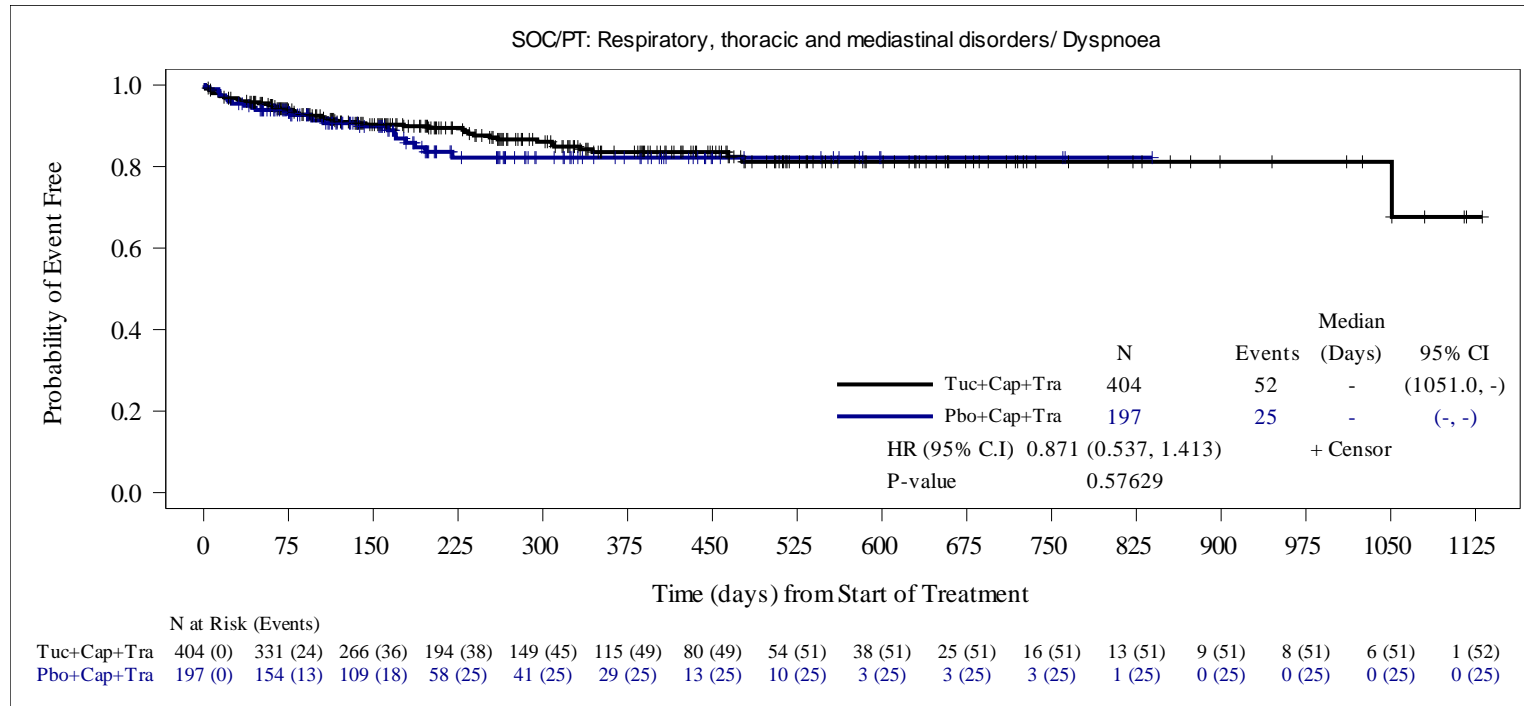
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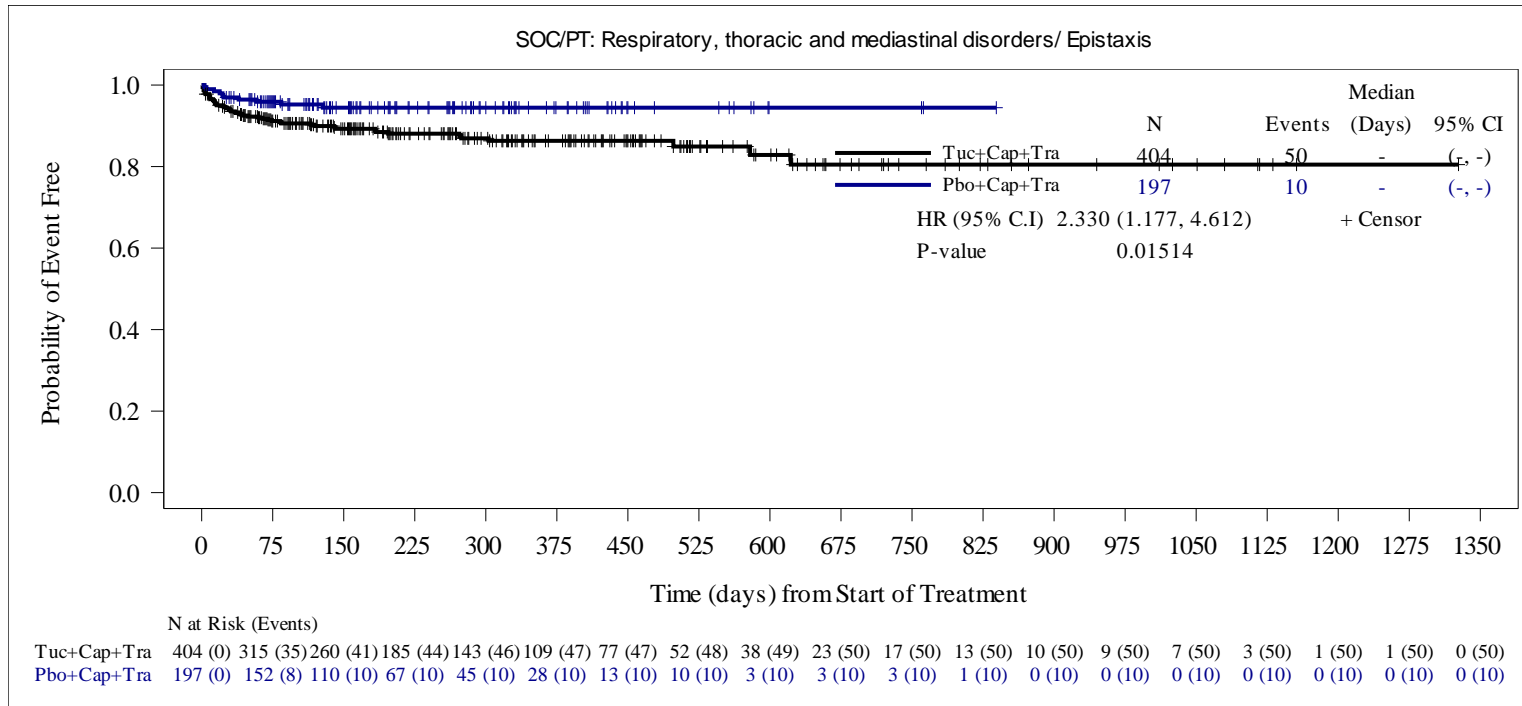
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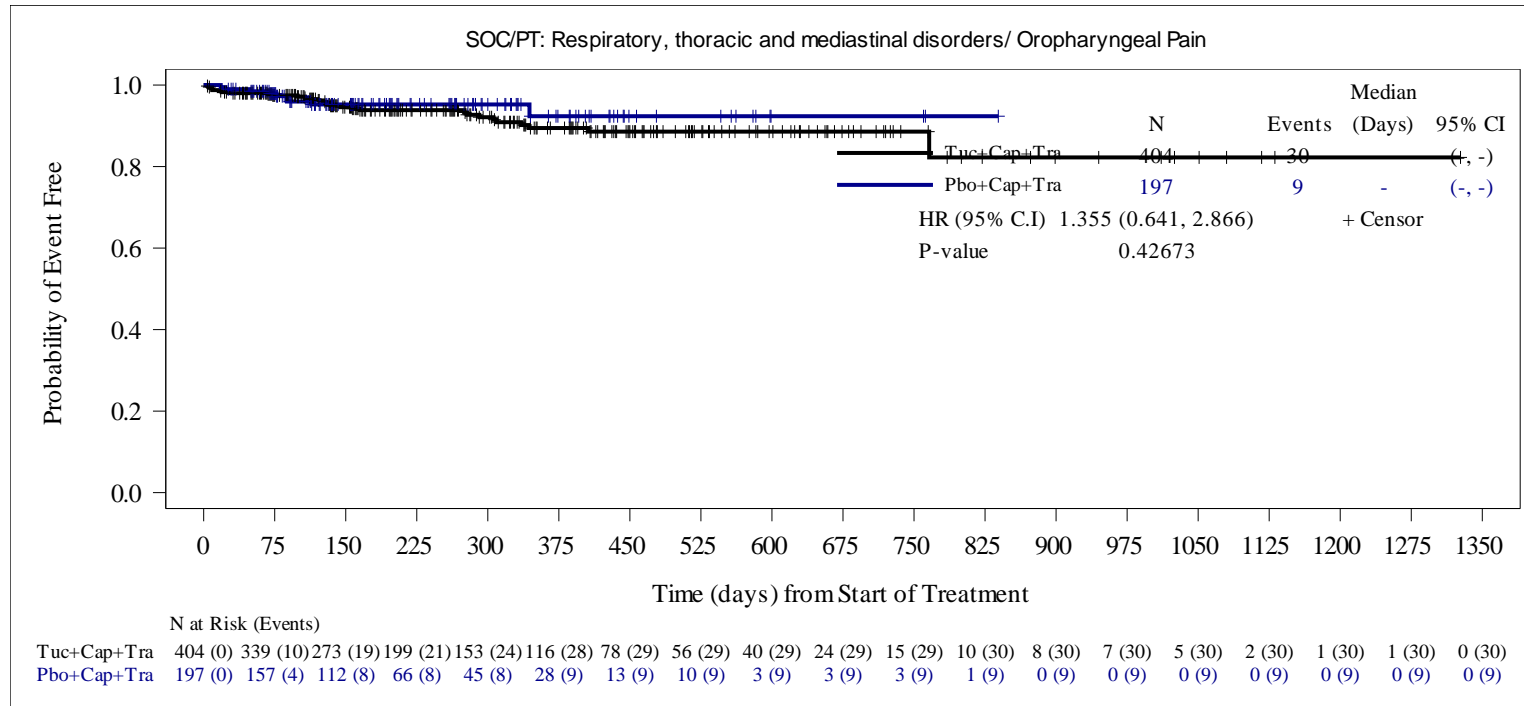
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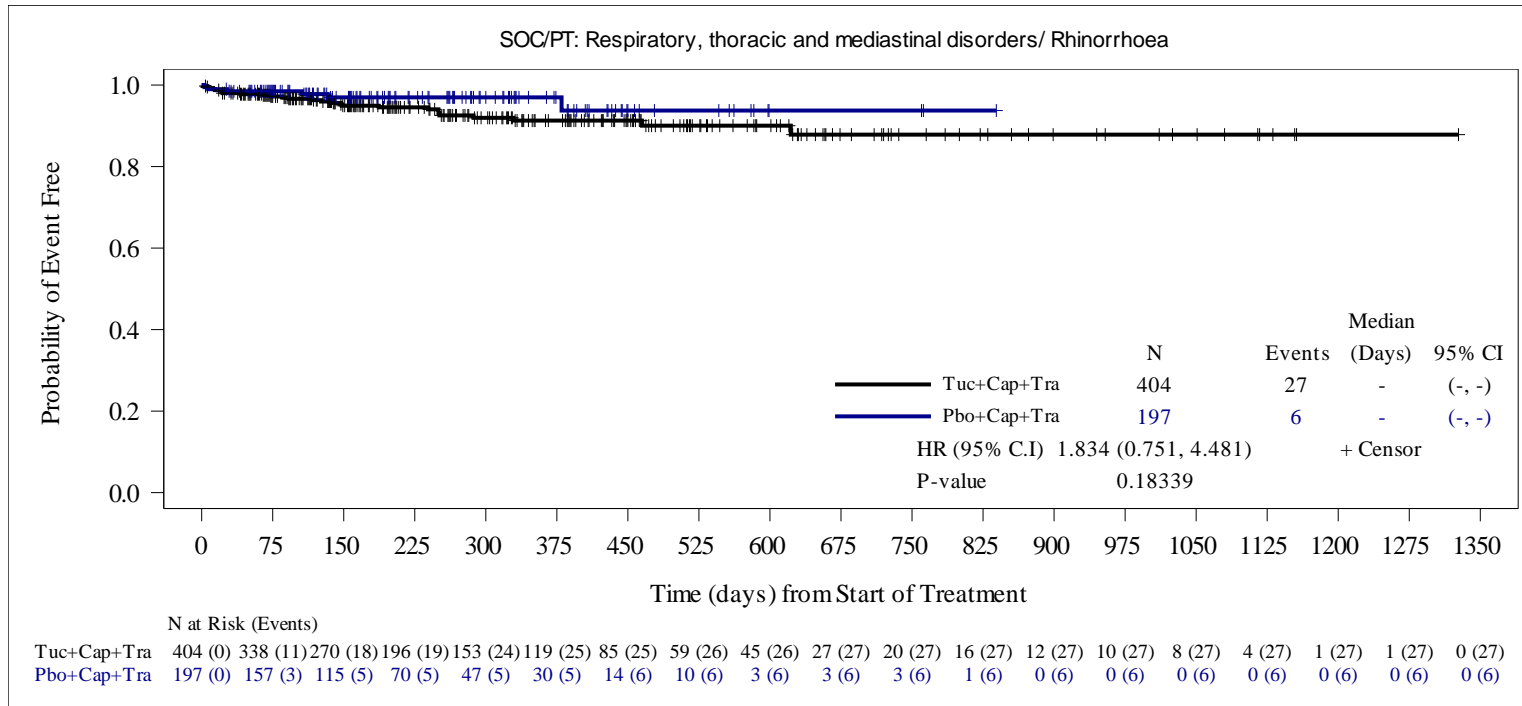
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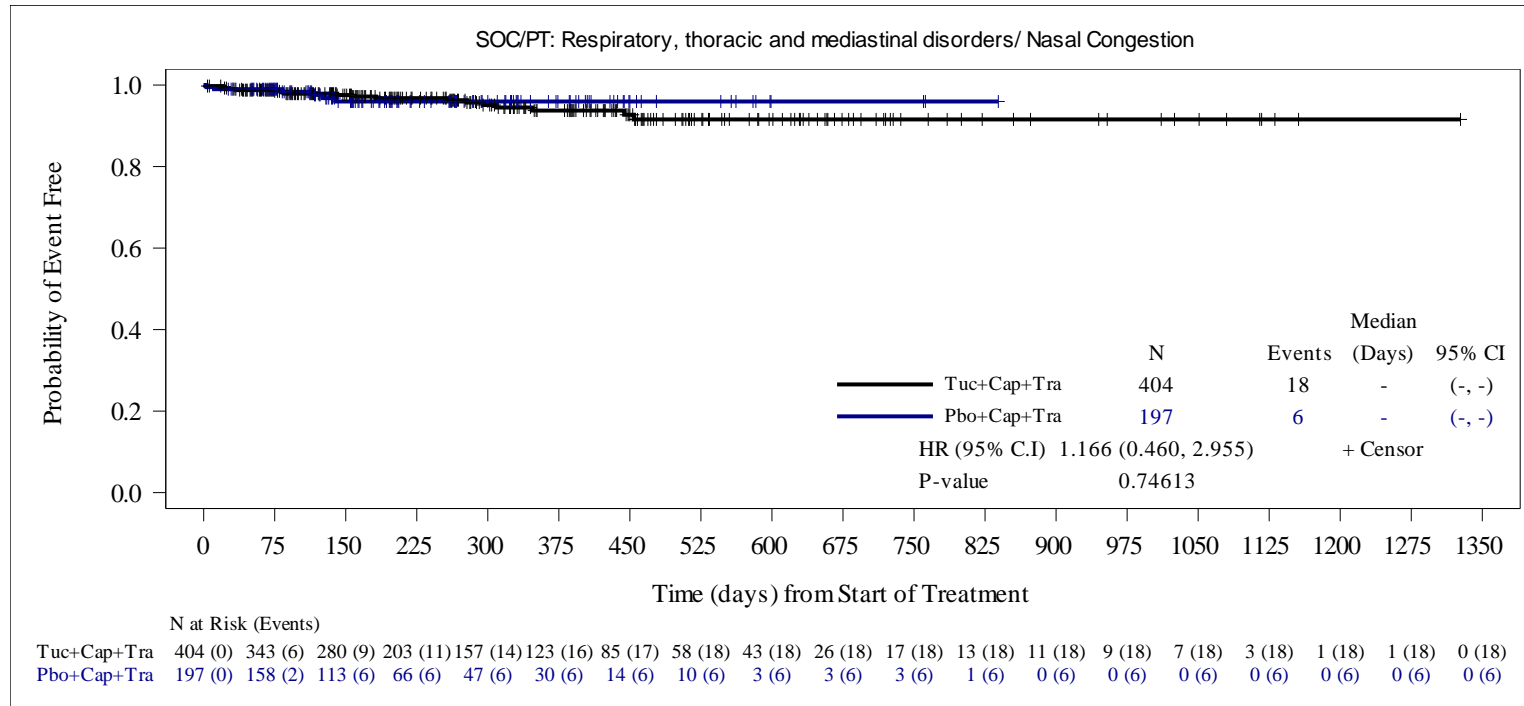
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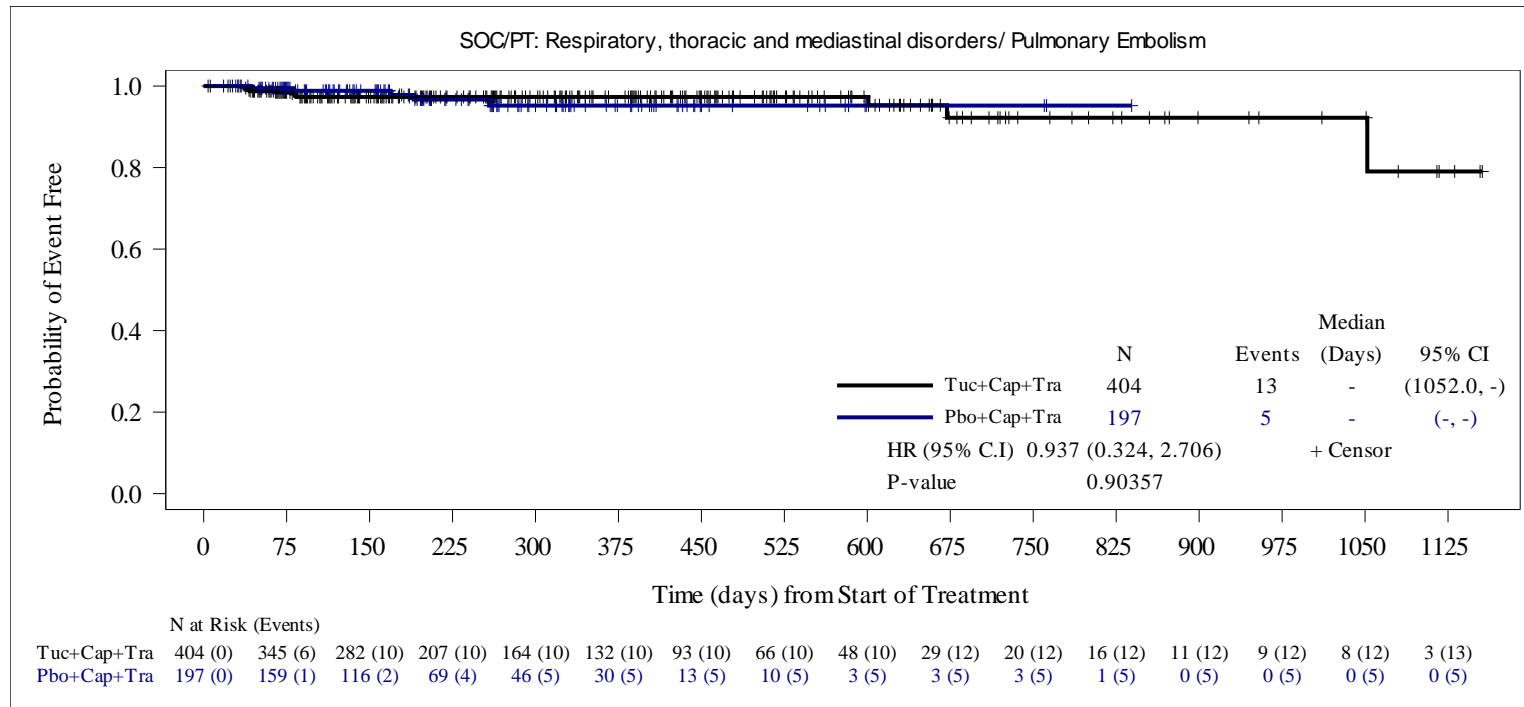
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HR is computed from the Cox proportional hazards model using stratification factors (Presence or history of brain metastases: Yes/No, ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization. When the number of subjects with at least one event was ≤ 30 , an unstratified Cox model was run.

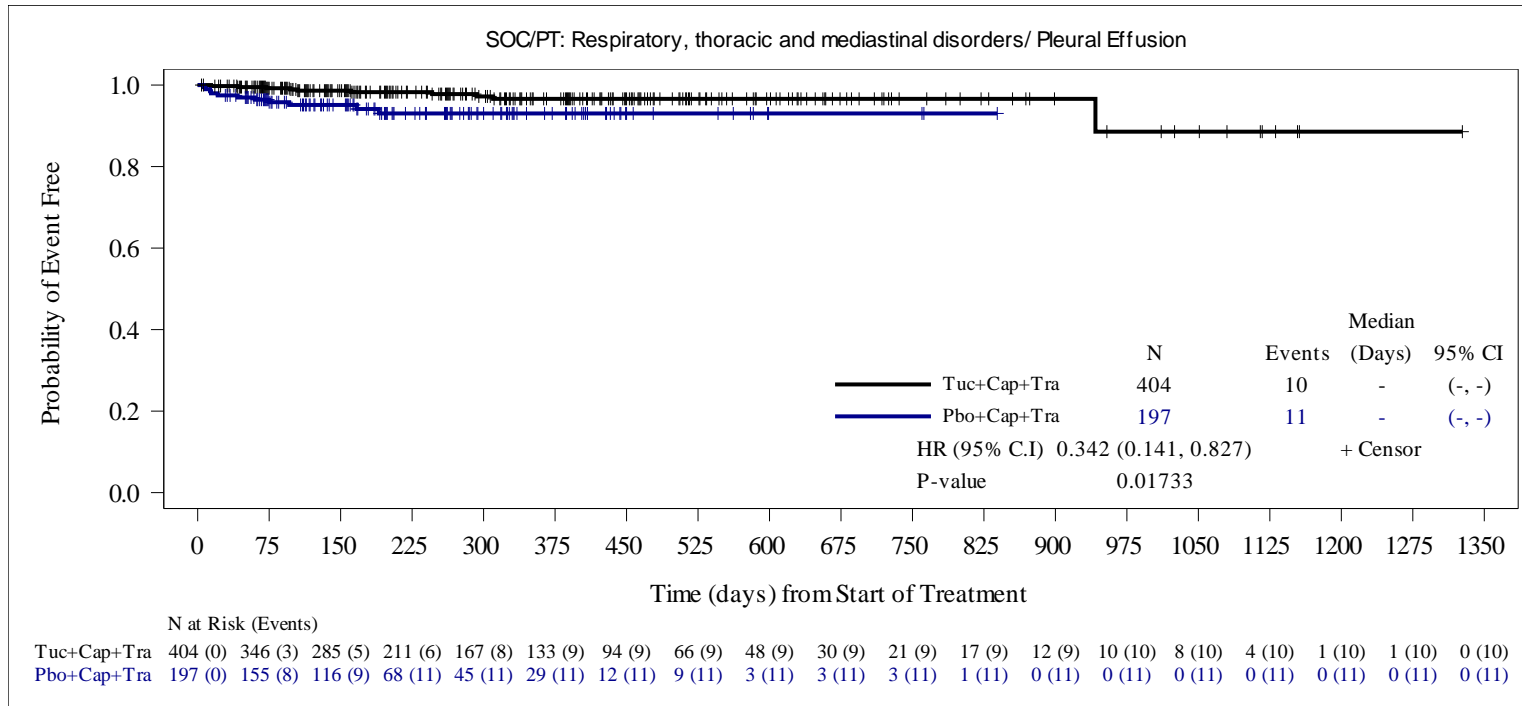
Two-sided p-value calculated from Cox proportional hazards model .

Snapshot date: 10SEP2020, data cutoff date: 29MAY2020.

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**Figure 2.7.1 Kaplan-Meier Estimate of Time to First Onset of Treatment-Emergent Adverse Events by System Organ Class and Preferred Term
Safety Analysis Set**



HR is computed from the Cox proportional hazards model using stratification factors (Presence or history of brain metastases: Yes/No, ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization. When the number of subjects with at least one event was ≤ 30 , an unstratified Cox model was run.

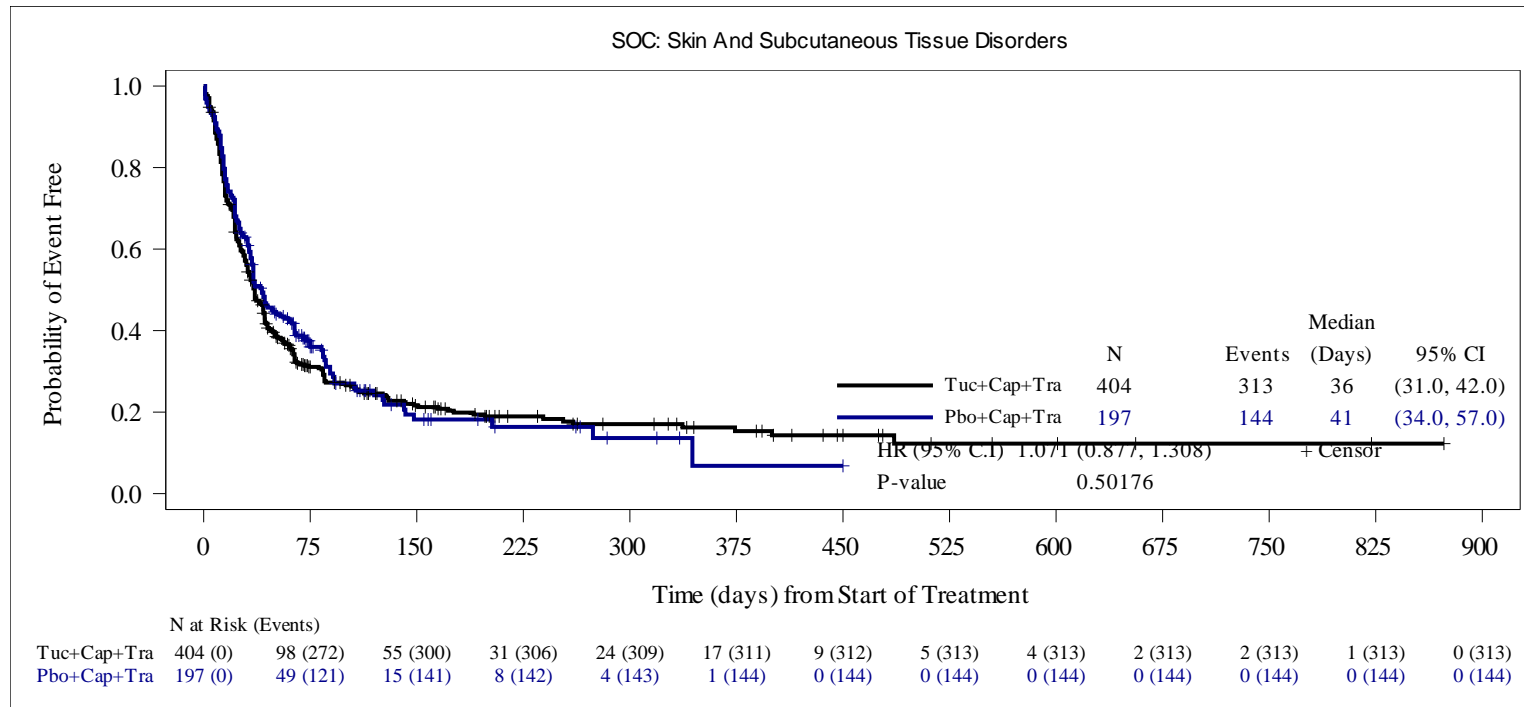
Two-sided p-value calculated from Cox proportional hazards model .

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f02-07-01-ae-km-socpt-safs.rtf(14DEC20:17:09) Data: adsl, adae, adttesaf

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**Figure 2.7.1 Kaplan-Meier Estimate of Time to First Onset of Treatment-Emergent Adverse Events by System Organ Class and Preferred Term
Safety Analysis Set**



HR is computed from the Cox proportional hazards model using stratification factors (Presence or history of brain metastases: Yes/No, ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization. When the number of subjects with at least one event was ≤ 30 , an unstratified Cox model was run.

Two-sided p-value calculated from Cox proportional hazards model .

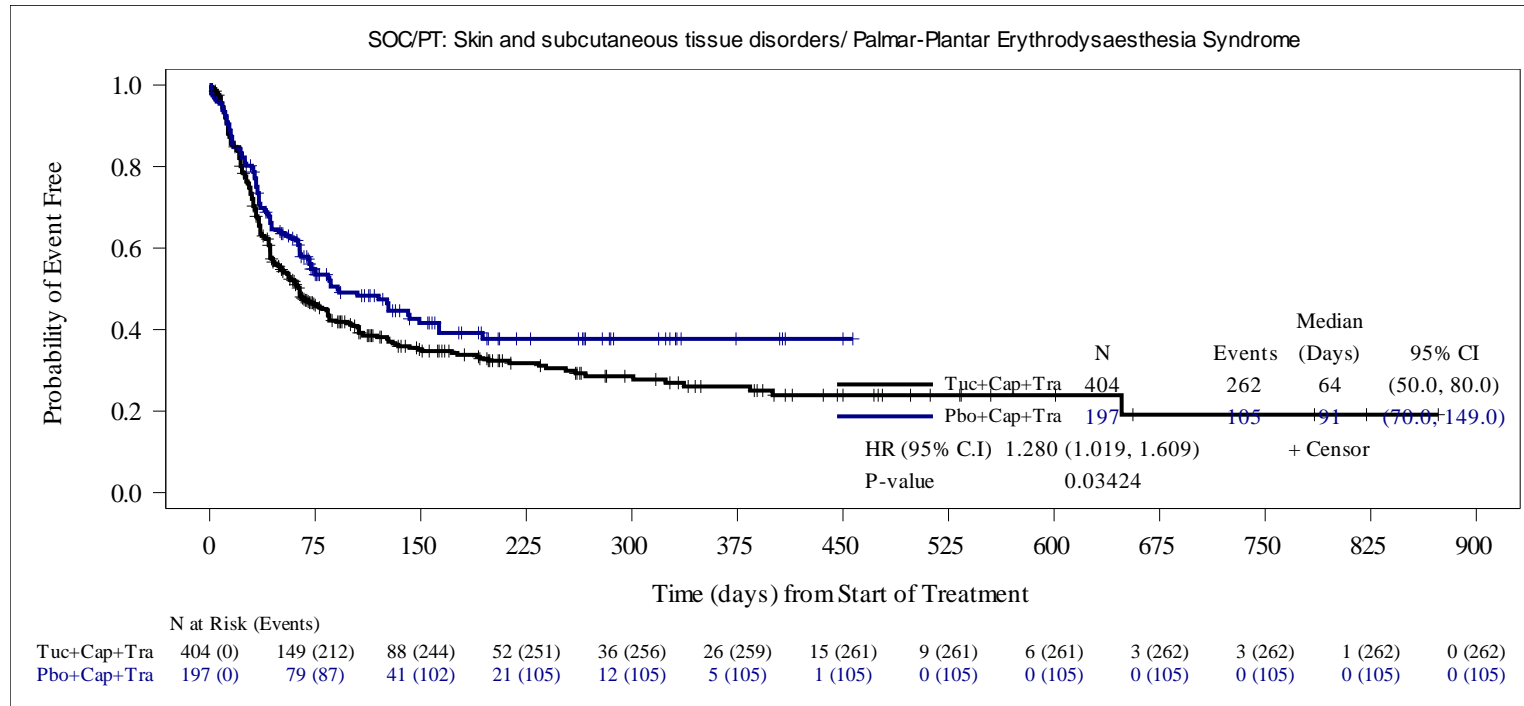
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**Figure 2.7.1 Kaplan-Meier Estimate of Time to First Onset of Treatment-Emergent Adverse Events by System Organ Class and Preferred Term
Safety Analysis Set**



HR is computed from the Cox proportional hazards model using stratification factors (Presence or history of brain metastases: Yes/No, ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization. When the number of subjects with at least one event was ≤ 30 , an unstratified Cox model was run.

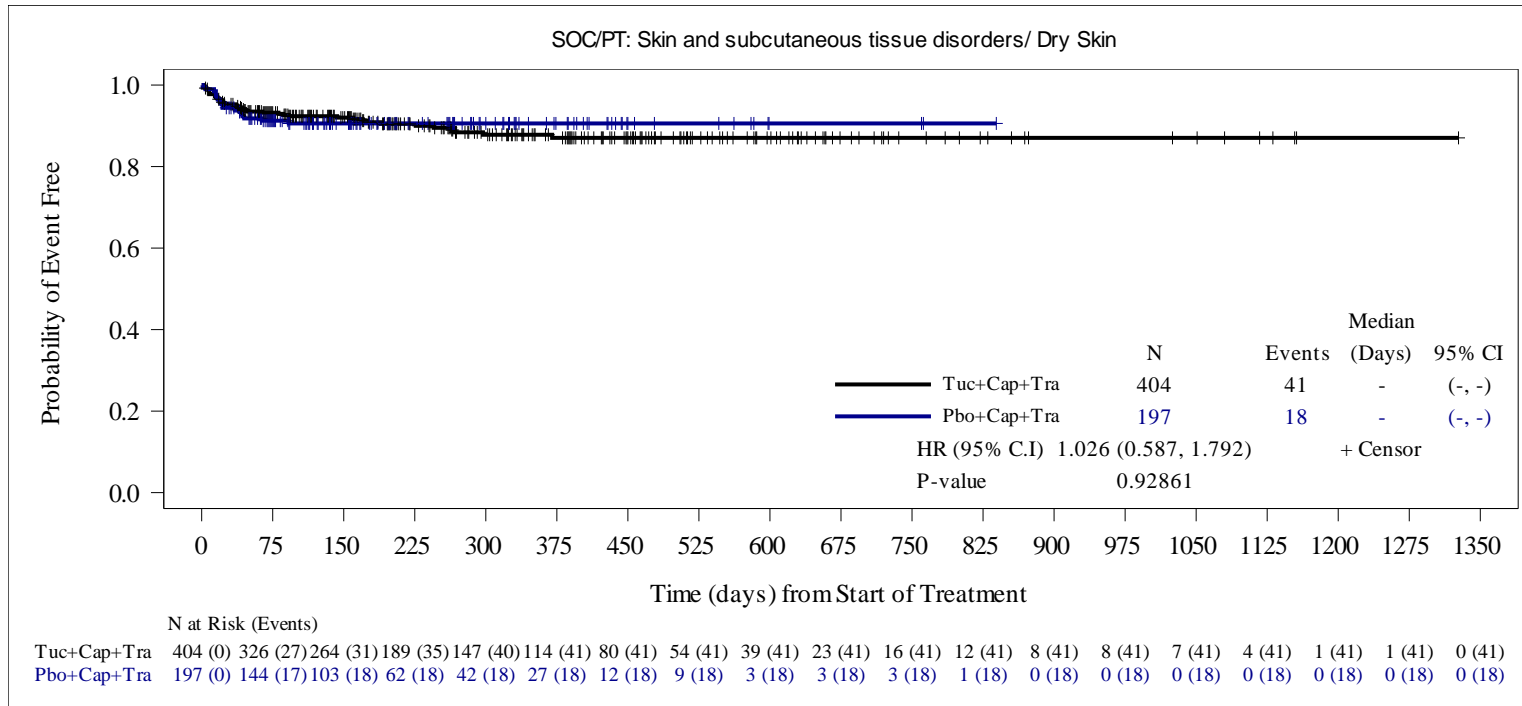
Two-sided p-value calculated from Cox proportional hazards model .

Snapshot date: 10SEP2020, data cutoff date: 29MAY2020.

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**Figure 2.7.1 Kaplan-Meier Estimate of Time to First Onset of Treatment-Emergent Adverse Events by System Organ Class and Preferred Term
Safety Analysis Set**



HR is computed from the Cox proportional hazards model using stratification factors (Presence or history of brain metastases: Yes/No, ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization. When the number of subjects with at least one event was ≤ 30 , an unstratified Cox model was run.

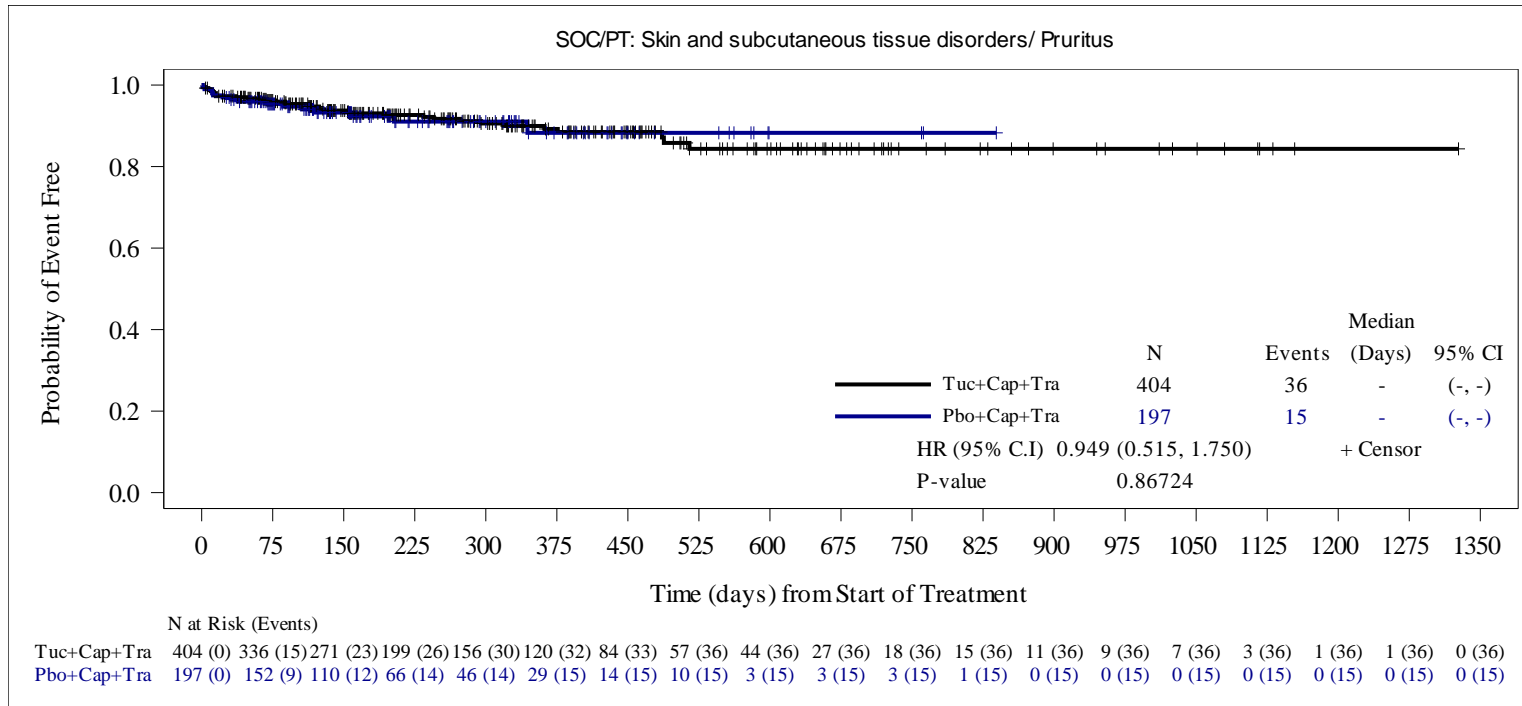
Two-sided p-value calculated from Cox proportional hazards model .

Snapshot date: 10SEP2020, data cutoff date: 29MAY2020.

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f02-07-01-ae-km-socpt-safs.rtf(14DEC20:17:09) Data: adsl, adae, adttesaf

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**Figure 2.7.1 Kaplan-Meier Estimate of Time to First Onset of Treatment-Emergent Adverse Events by System Organ Class and Preferred Term
Safety Analysis Set**



HR is computed from the Cox proportional hazards model using stratification factors (Presence or history of brain metastases: Yes/No, ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization. When the number of subjects with at least one event was ≤ 30 , an unstratified Cox model was run.

Two-sided p-value calculated from Cox proportional hazards model .

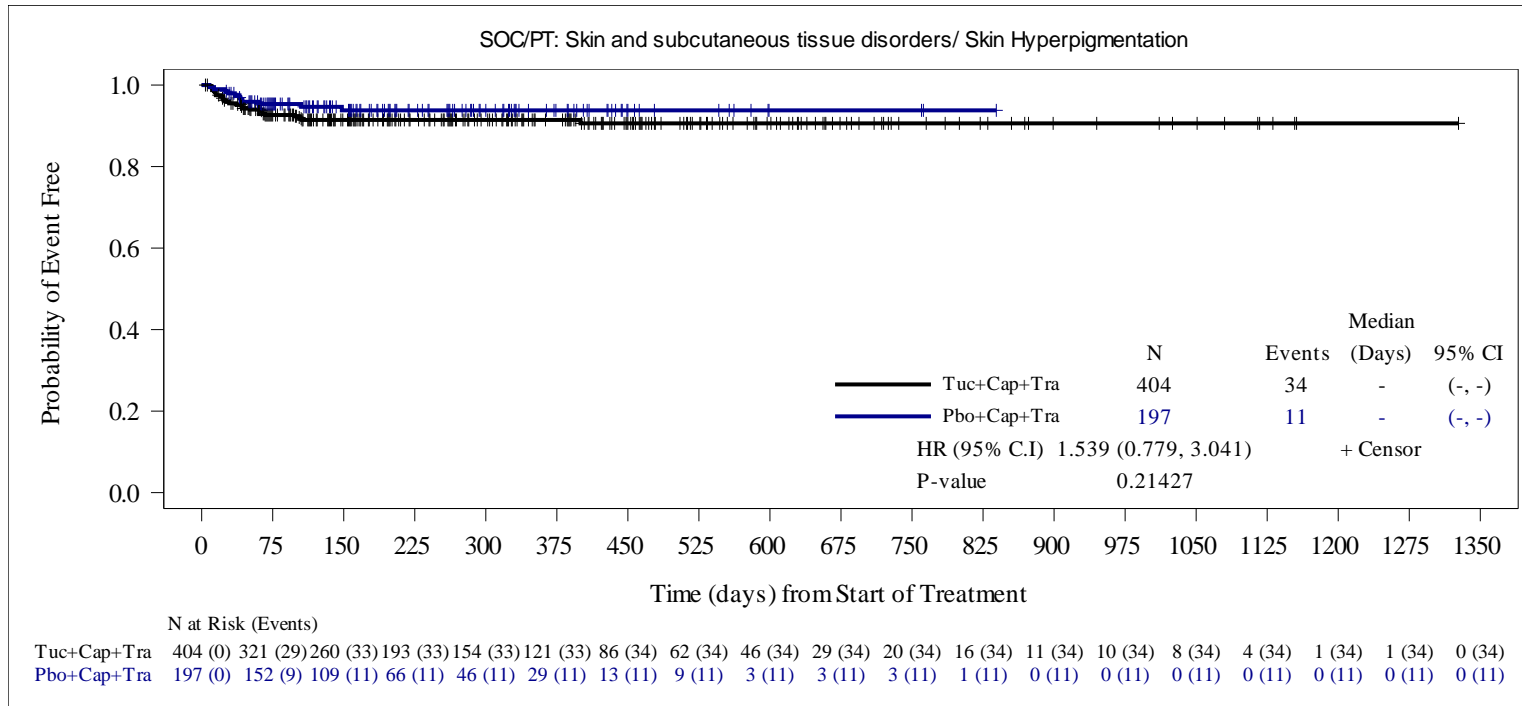
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**Figure 2.7.1 Kaplan-Meier Estimate of Time to First Onset of Treatment-Emergent Adverse Events by System Organ Class and Preferred Term
Safety Analysis Set**



HR is computed from the Cox proportional hazards model using stratification factors (Presence or history of brain metastases: Yes/No, ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization. When the number of subjects with at least one event was ≤ 30 , an unstratified Cox model was run.

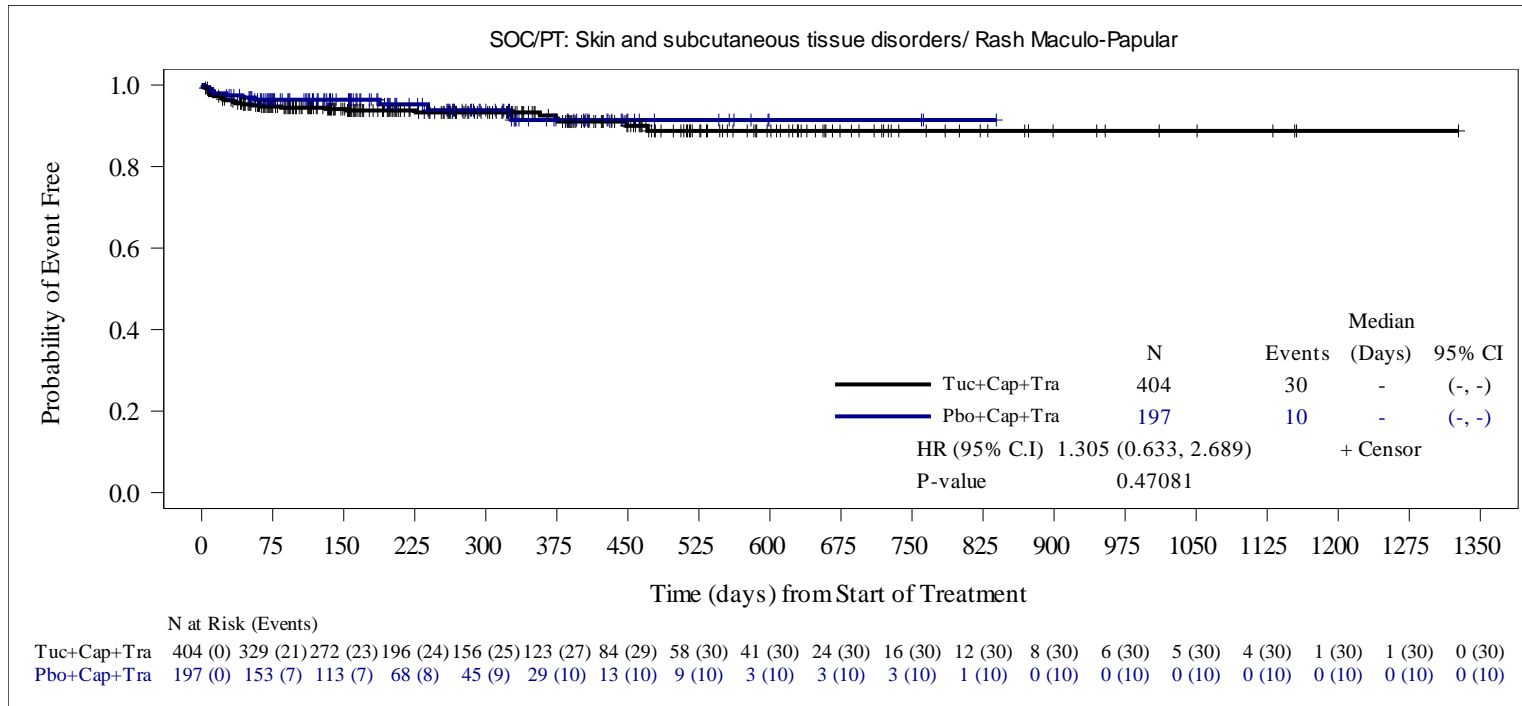
Two-sided p-value calculated from Cox proportional hazards model .

Snapshot date: 10SEP2020, data cutoff date: 29MAY2020.

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f02-07-01-ae-km-socpt-safs.rtf(14DEC20:17:09) Data: adsl, adae, adttesaf

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HR is computed from the Cox proportional hazards model using stratification factors (Presence or history of brain metastases: Yes/No, ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization. When the number of subjects with at least one event was ≤ 30 , an unstratified Cox model was run.

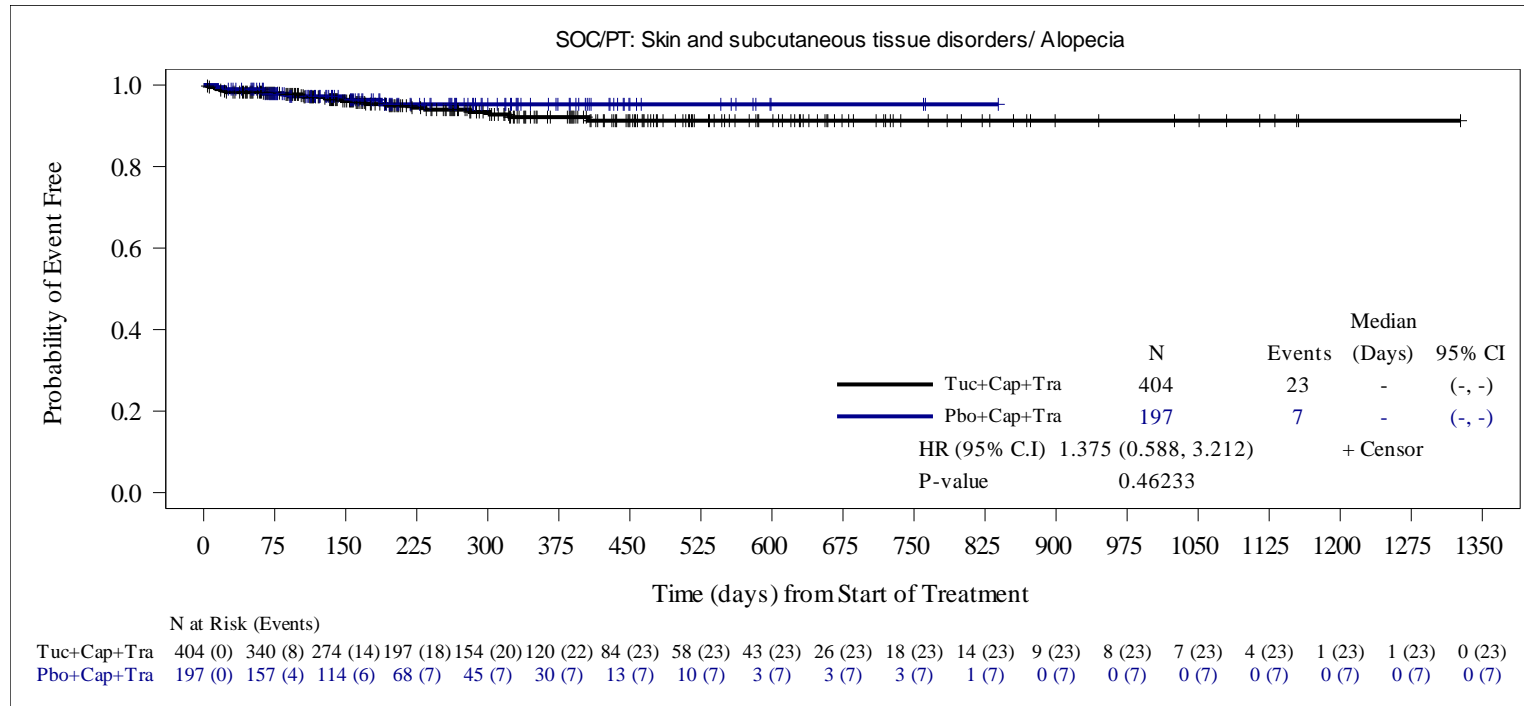
Two-sided p-value calculated from Cox proportional hazards model .

Snapshot date: 10SEP2020, data cutoff date: 29MAY2020.

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Two-sided p-value calculated from Cox proportional hazards model .

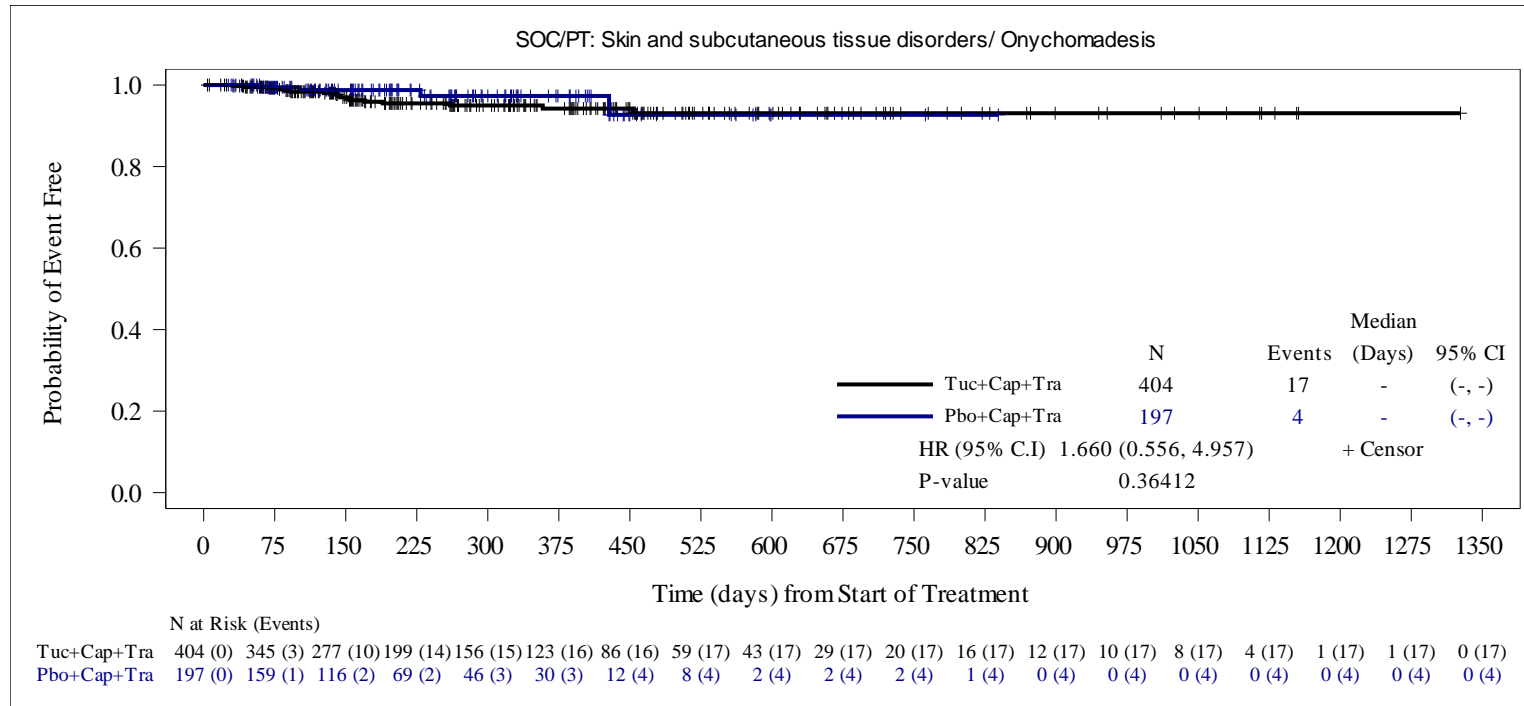
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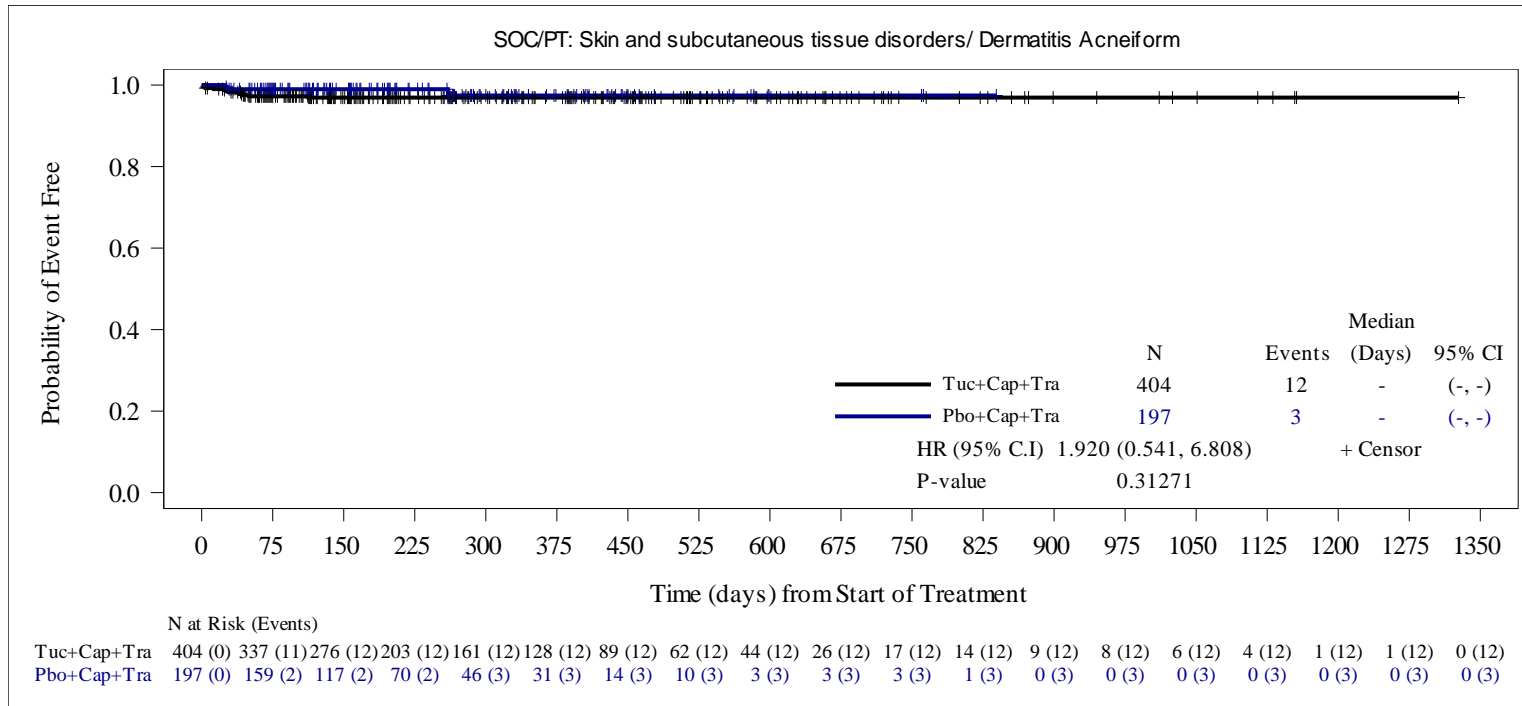
Two-sided p-value calculated from Cox proportional hazards model .

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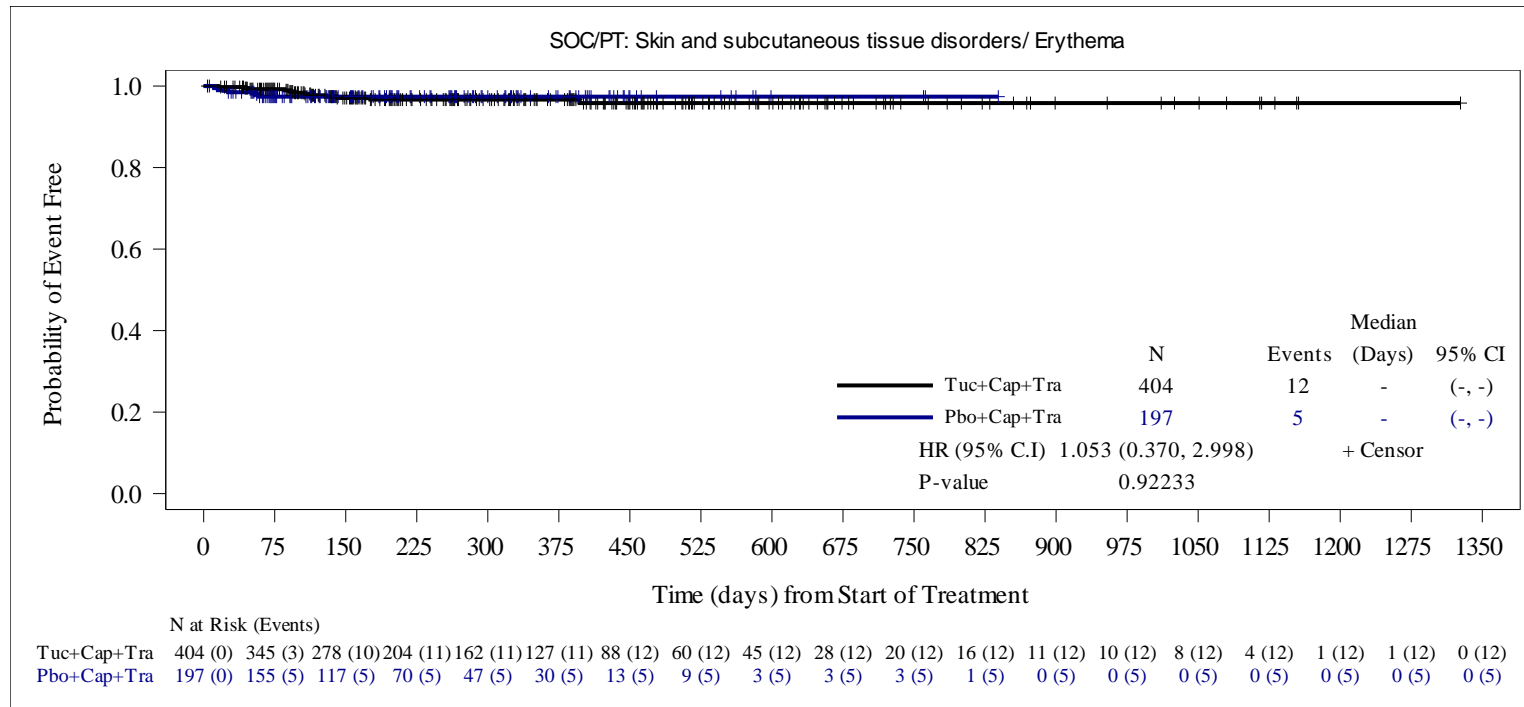
Two-sided p-value calculated from Cox proportional hazards model .

Snapshot date: 10SEP2020, data cutoff date: 29MAY2020.

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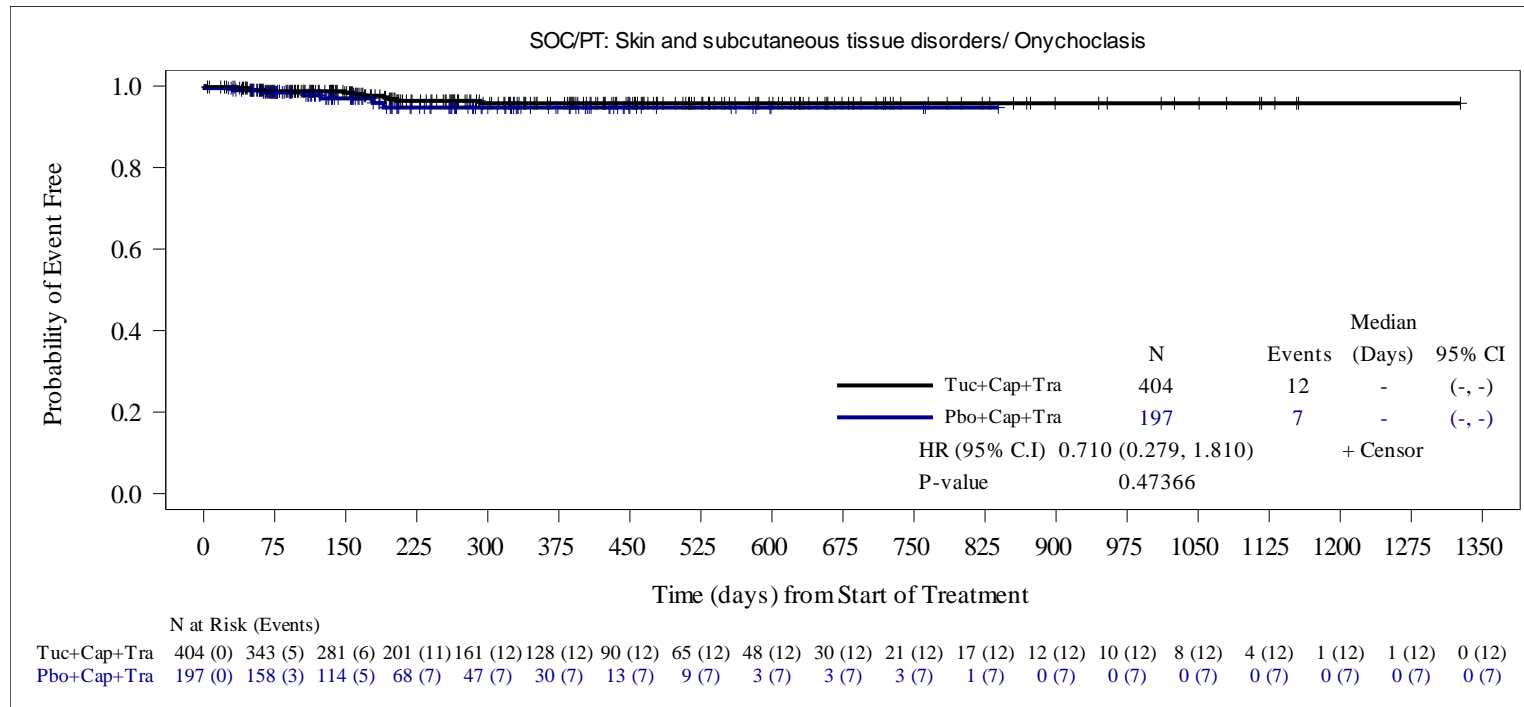
Two-sided p-value calculated from Cox proportional hazards model .

Snapshot date: 10SEP2020, data cutoff date: 29MAY2020.

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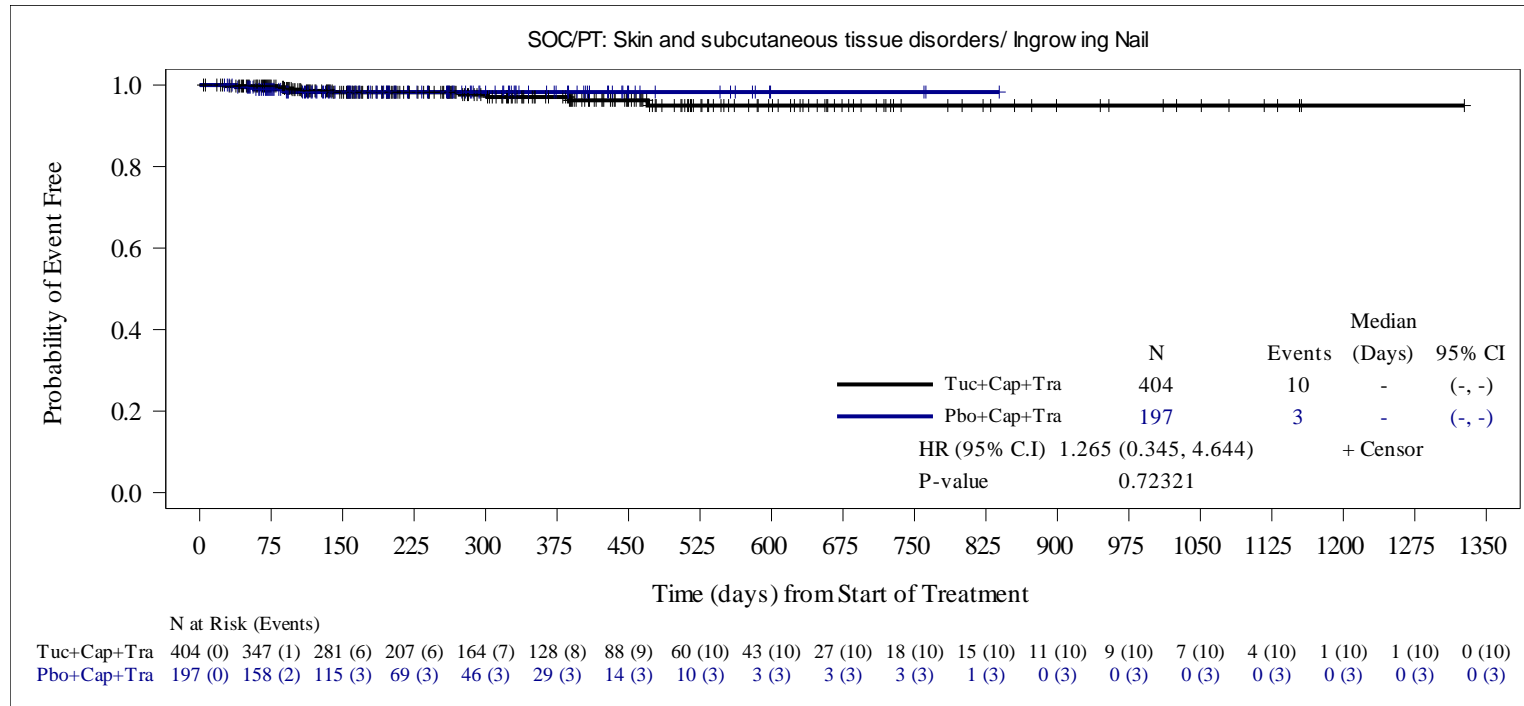
Two-sided p-value calculated from Cox proportional hazards model .

Snapshot date: 10SEP2020, data cutoff date: 29MAY2020.

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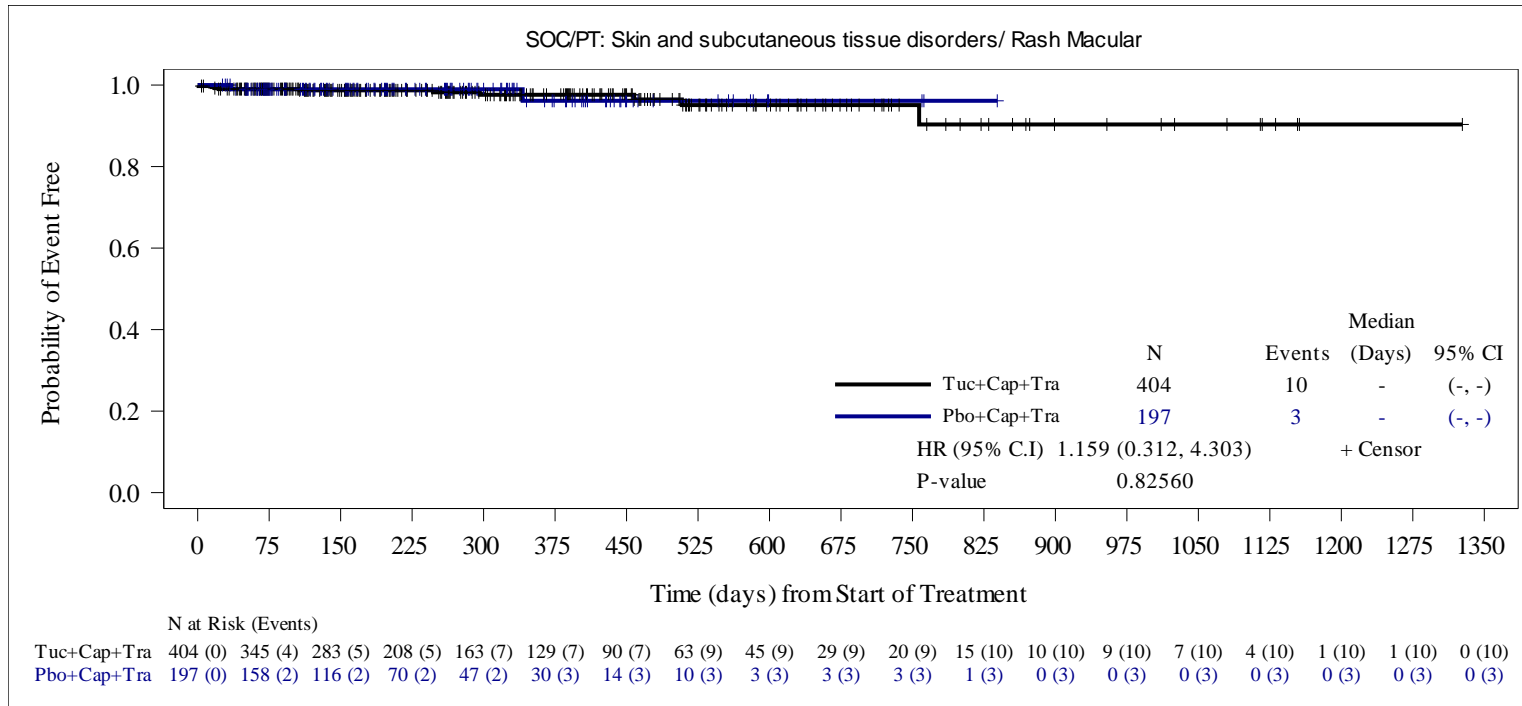
Two-sided p-value calculated from Cox proportional hazards model .

Snapshot date: 10SEP2020, data cutoff date: 29MAY2020.

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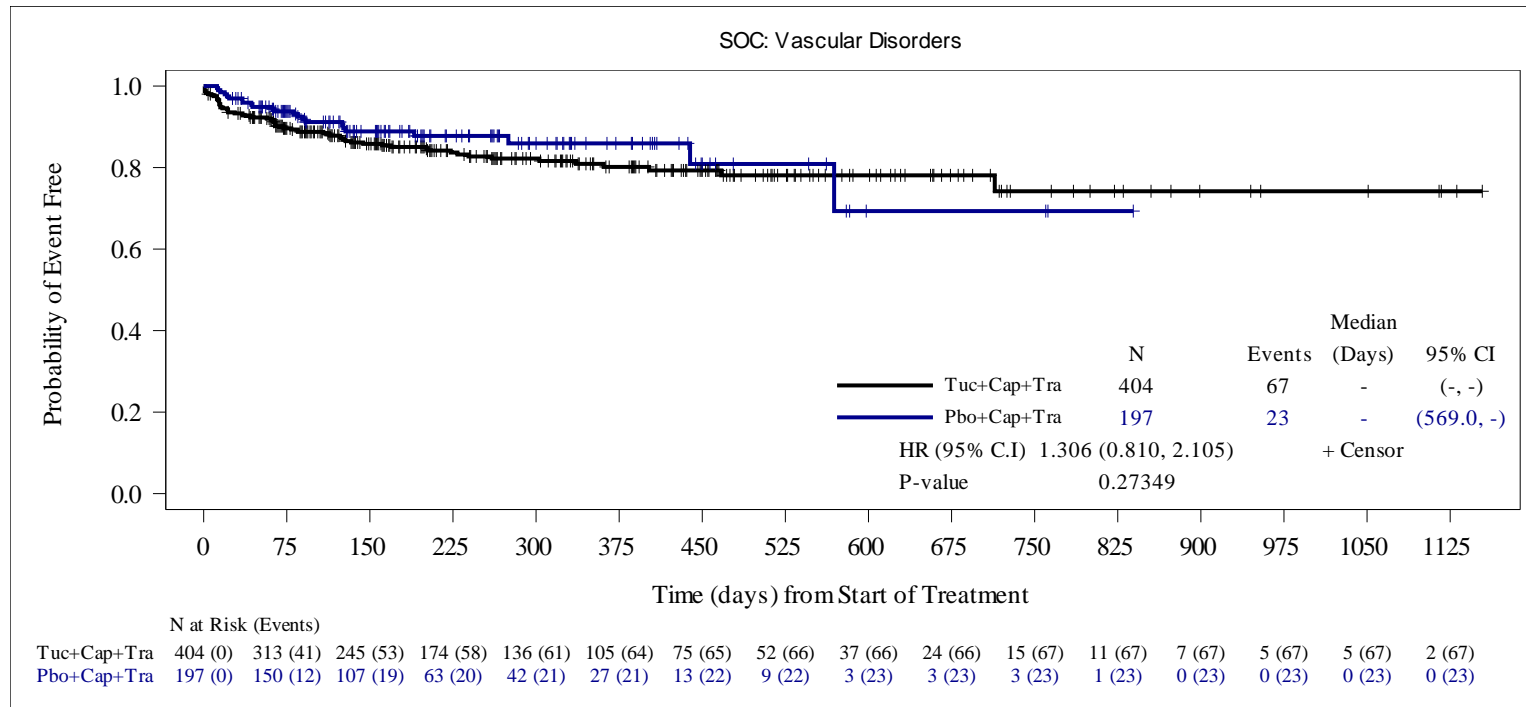
Two-sided p-value calculated from Cox proportional hazards model .

Snapshot date: 10SEP2020, data cutoff date: 29MAY2020.

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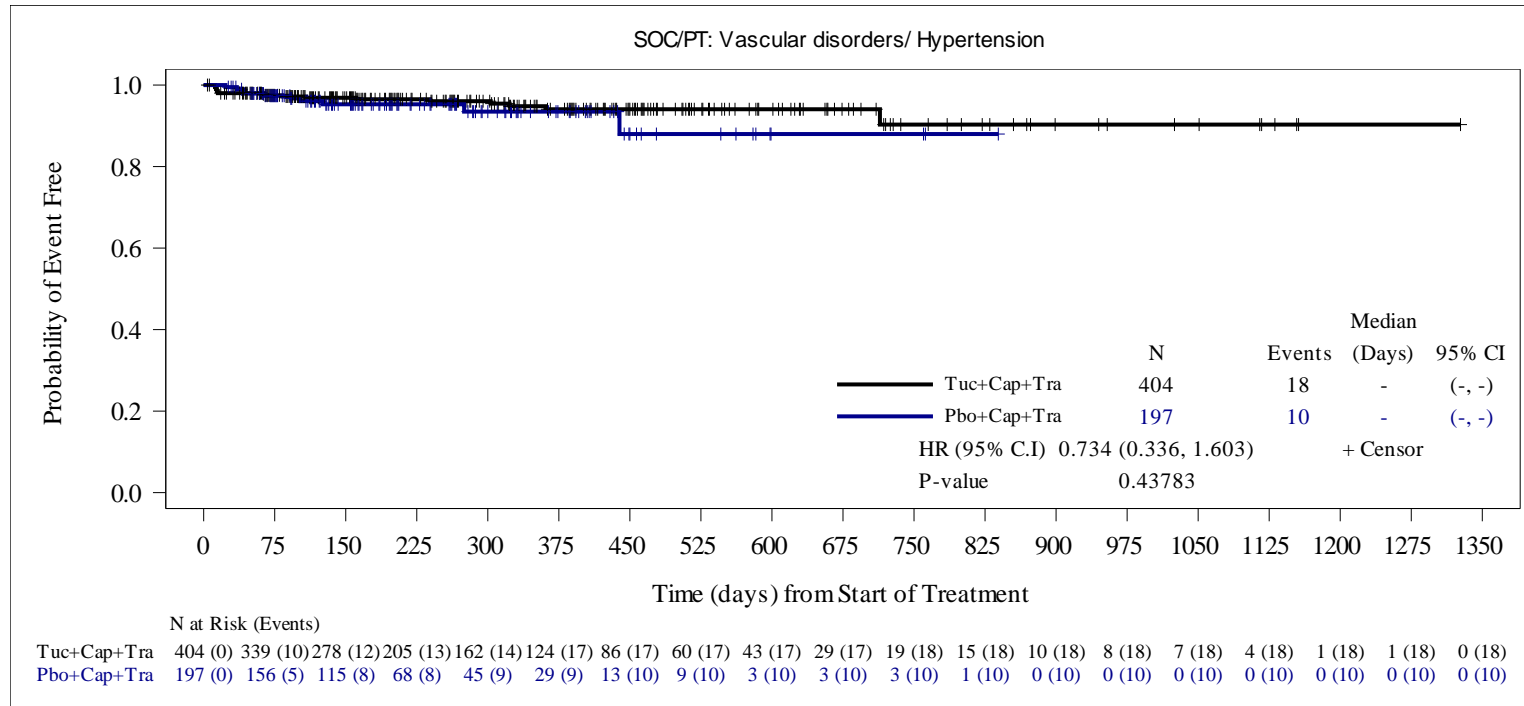
Two-sided p-value calculated from Cox proportional hazards model .

Snapshot date: 10SEP2020, data cutoff date: 29MAY2020.

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Safety Analysis Set**



HR is computed from the Cox proportional hazards model using stratification factors (Presence or history of brain metastases: Yes/No, ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization. When the number of subjects with at least one event was ≤ 30 , an unstratified Cox model was run.

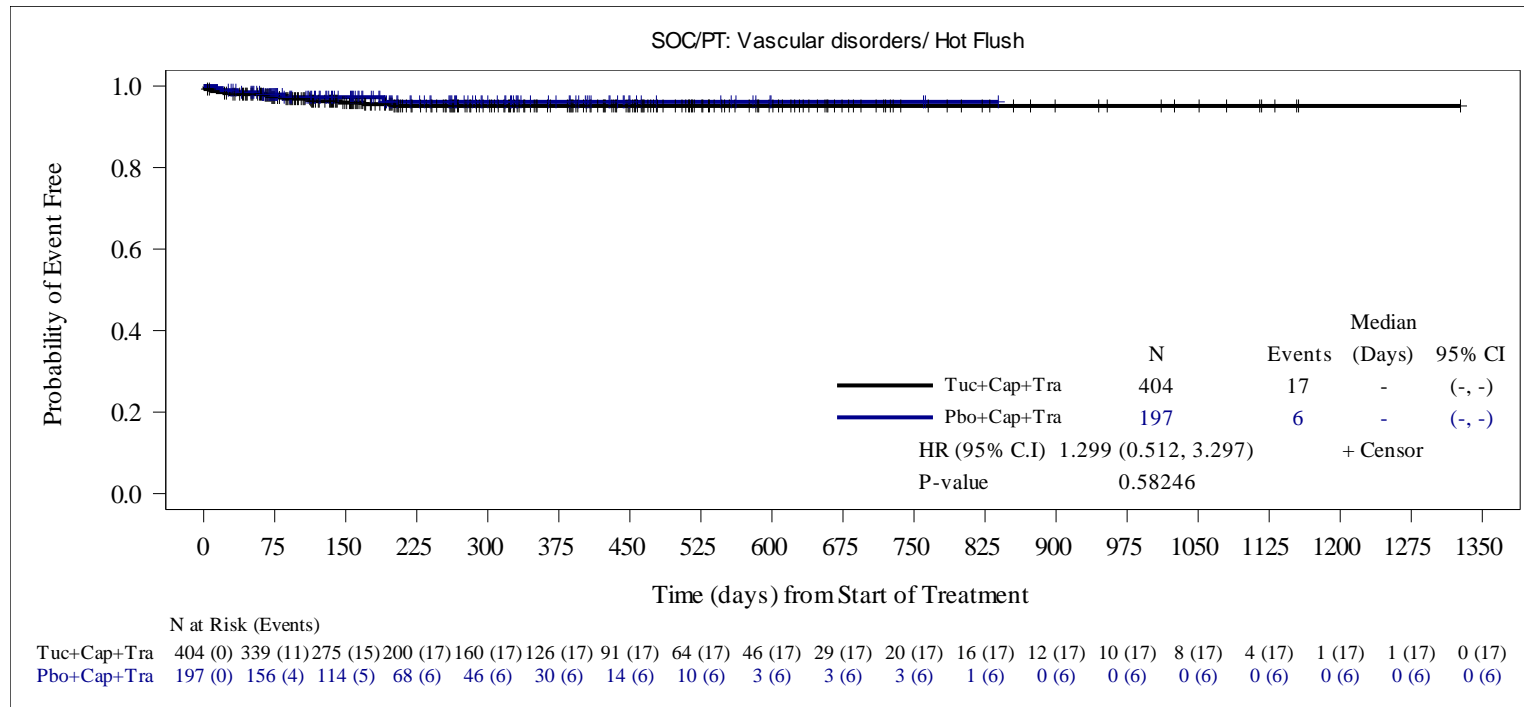
Two-sided p-value calculated from Cox proportional hazards model .

Snapshot date: 10SEP2020, data cutoff date: 29MAY2020.

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Safety Analysis Set**



HR is computed from the Cox proportional hazards model using stratification factors (Presence or history of brain metastases: Yes/No, ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization. When the number of subjects with at least one event was ≤ 30 , an unstratified Cox model was run.

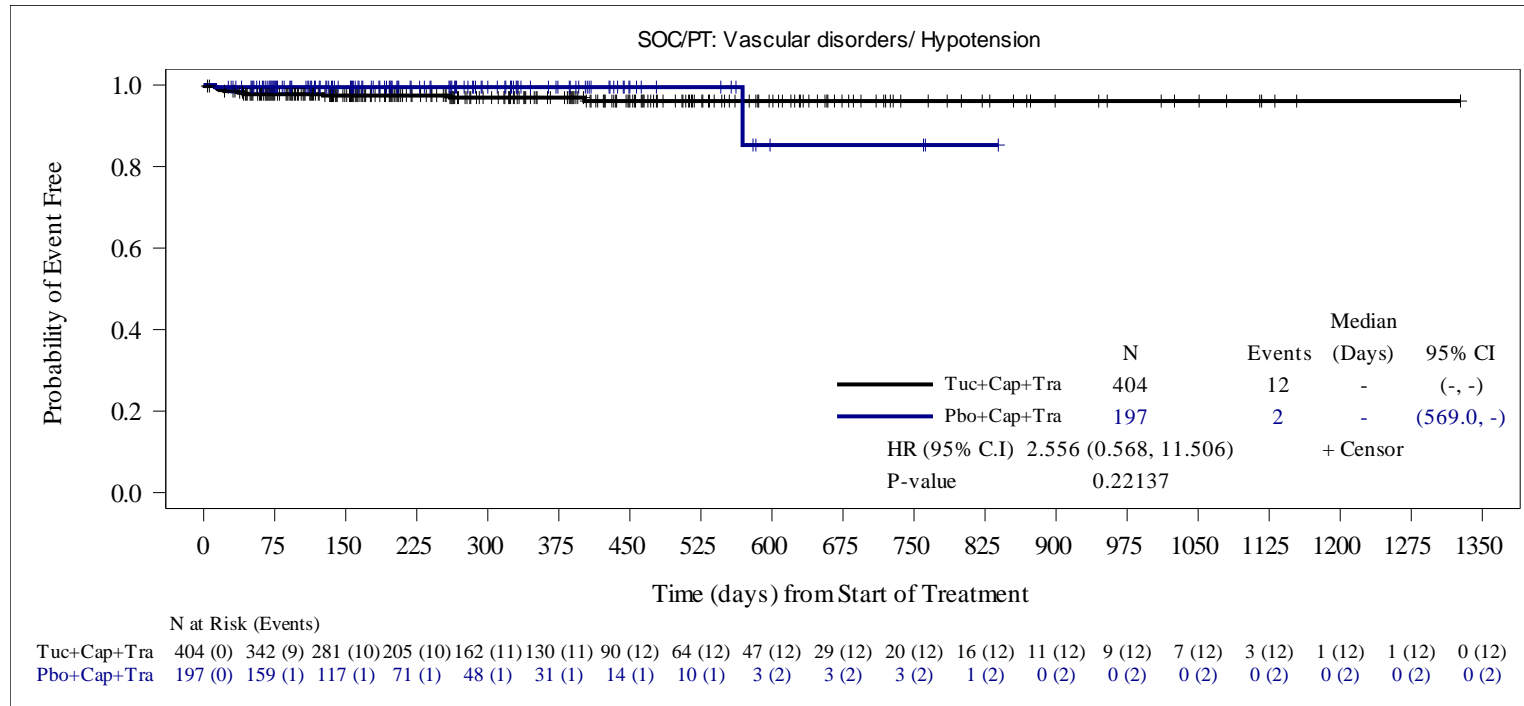
Two-sided p-value calculated from Cox proportional hazards model .

Snapshot date: 10SEP2020, data cutoff date: 29MAY2020.

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_may2020_dco_1943\v01\outputs\tlfs\pgms\ae-km-socpt-safs.sas Output:
f02-07-01-ae-km-socpt-safs.rtf(14DEC20:17:09) Data: adsl, adae, adttesaf

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Safety Analysis Set**



HR is computed from the Cox proportional hazards model using stratification factors (Presence or history of brain metastases: Yes/No, ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization. When the number of subjects with at least one event was ≤ 30 , an unstratified Cox model was run.

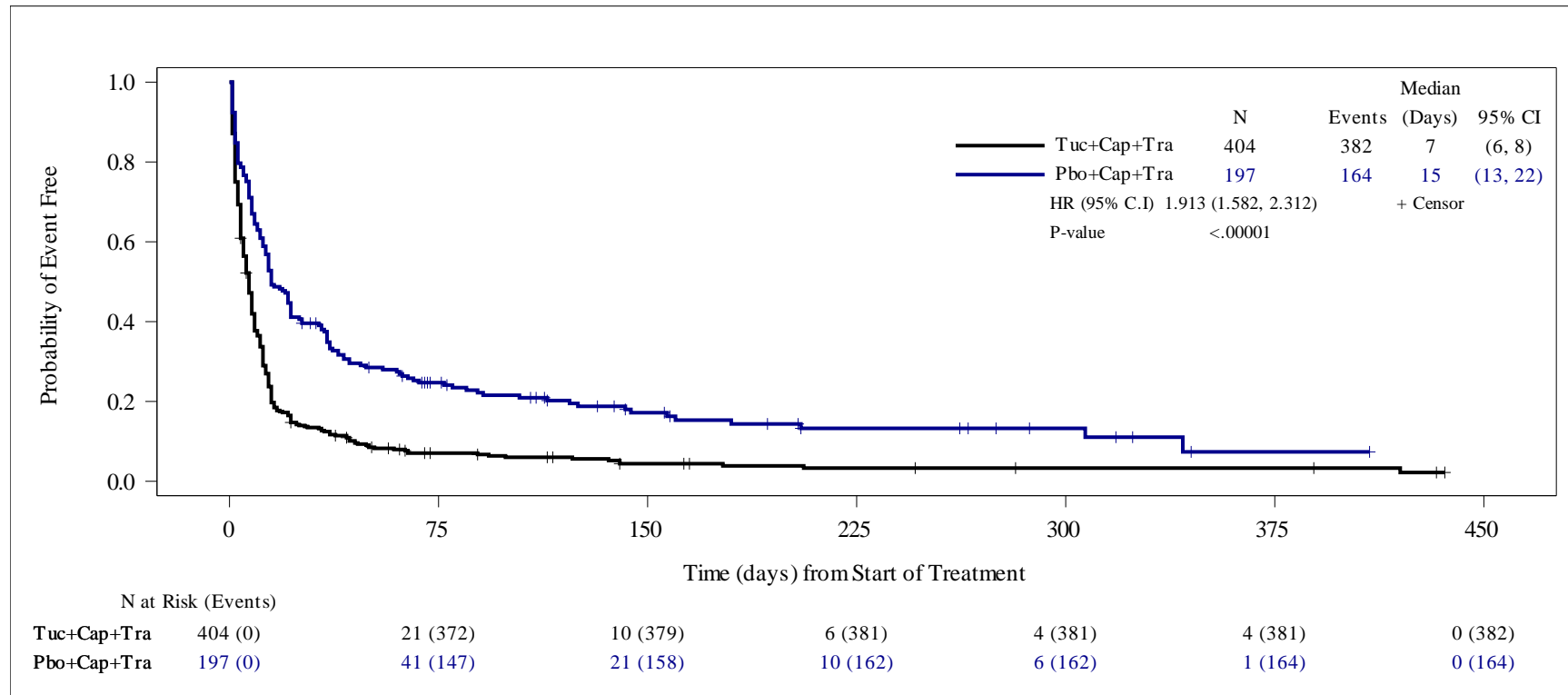
Two-sided p-value calculated from Cox proportional hazards model .

Snapshot date: 10SEP2020, data cutoff date: 29MAY2020.

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f02-07-01-ae-km-socpt-safs.rtf(14DEC20:17:09) Data: adsl, adae, adttesaf

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**Figure 2.3.1 Kaplan-Meier Estimate of Time to First Onset of Adverse Events - Gastrointestinal Disorder
Safety Analysis Set**



HR is computed from the Cox proportional hazards model using stratification factors (Presence or history of brain metastases: Yes/No, ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization.

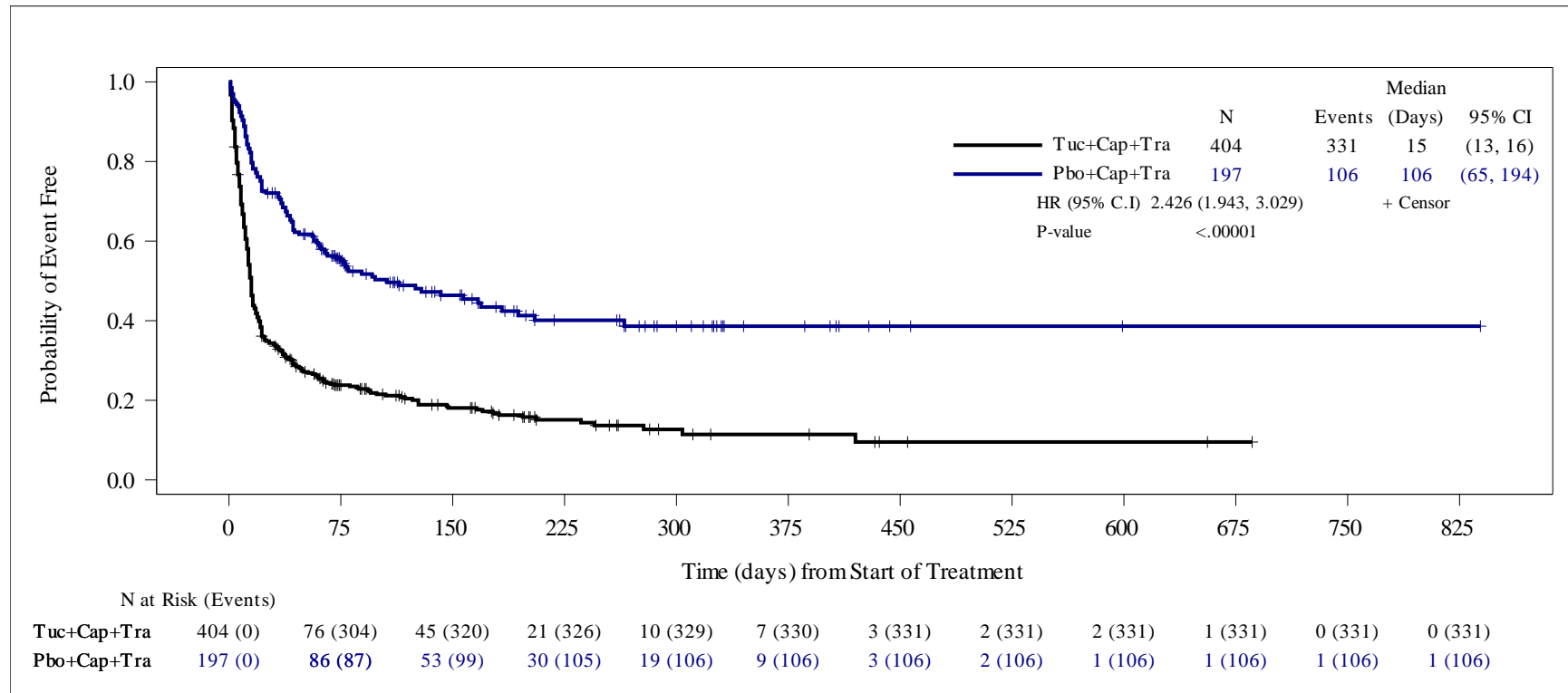
Two-sided p-value calculated from Cox proportional hazards model .

Snapshot date: 10SEP2020, data cutoff date: 29MAY2020.

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_may2020_dco_1943\v01\outputs\tlfs\pgms\f-ae-onset-gastro.sas Output: f02-03-01-ae-km-gisoc-safs.rtf(14DEC20:17:11) Data: adsl, adae, adttesaf

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**Figure 2.3.2 Kaplan-Meier Estimate of Time to First Onset of Adverse Events - Diarrhoea
Safety Analysis Set**



HR is computed from the Cox proportional hazards model using stratification factors (Presence or history of brain metastases: Yes/No, ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization.

Two-sided p-value calculated from Cox proportional hazards model .

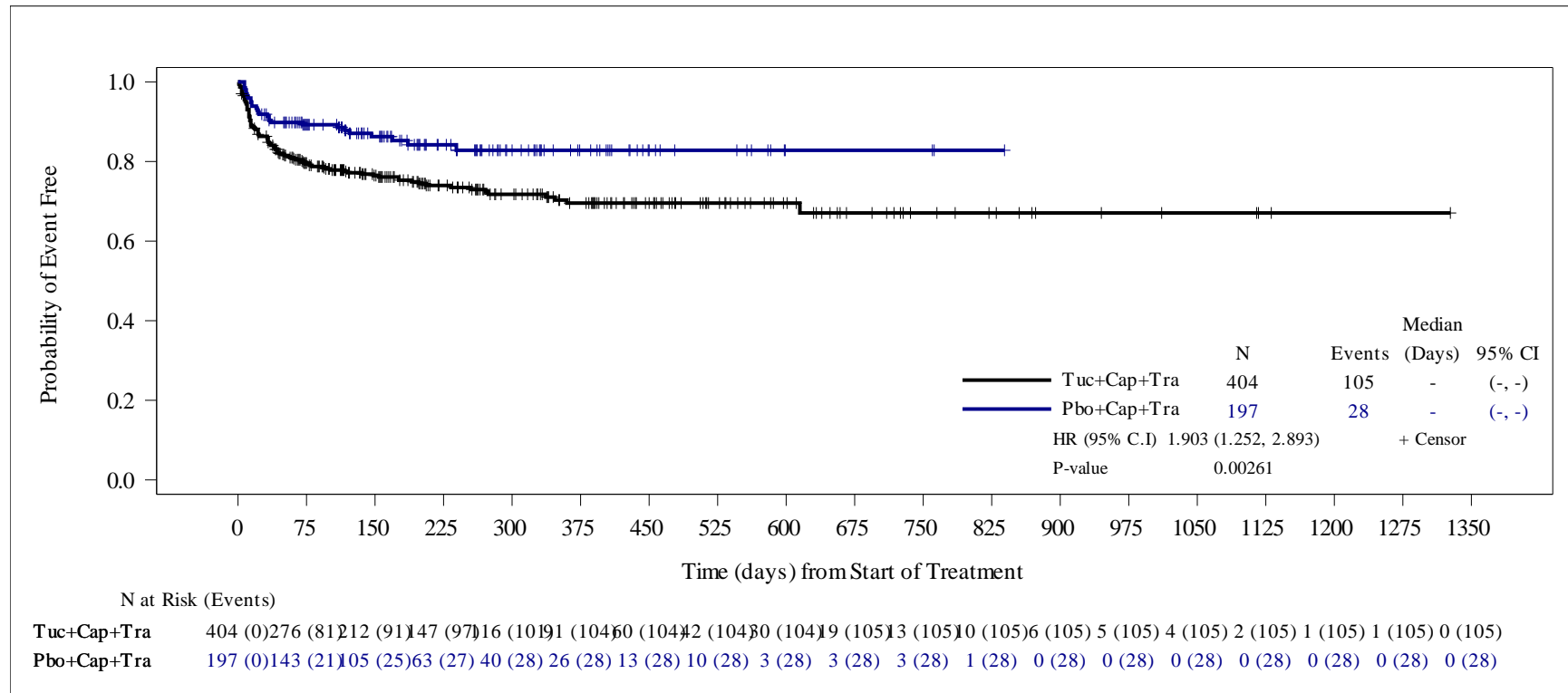
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**Figure 2.3.5 Kaplan-Meier Estimate of Time to First Onset of Adverse Events - Stomatitis
Safety Analysis Set**



HR is computed from the Cox proportional hazards model using stratification factors (Presence or history of brain metastases: Yes/No, ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization.

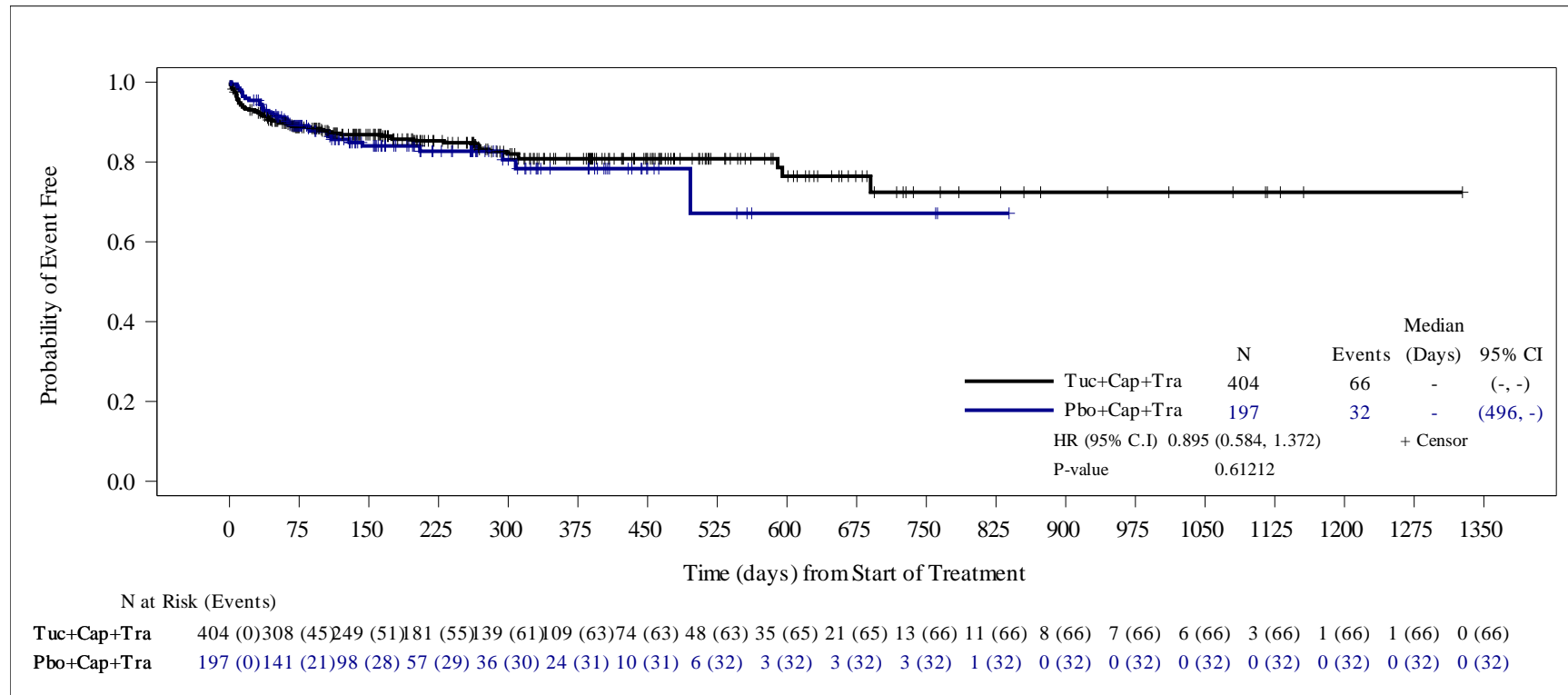
Two-sided p-value calculated from Cox proportional hazards model .

Snapshot date: 10SEP2020, data cutoff date: 29MAY2020.

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**Figure 2.3.6 Kaplan-Meier Estimate of Time to First Onset of Adverse Events - Abdominal Pain
Safety Analysis Set**



HR is computed from the Cox proportional hazards model using stratification factors (Presence or history of brain metastases: Yes/No, ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization.

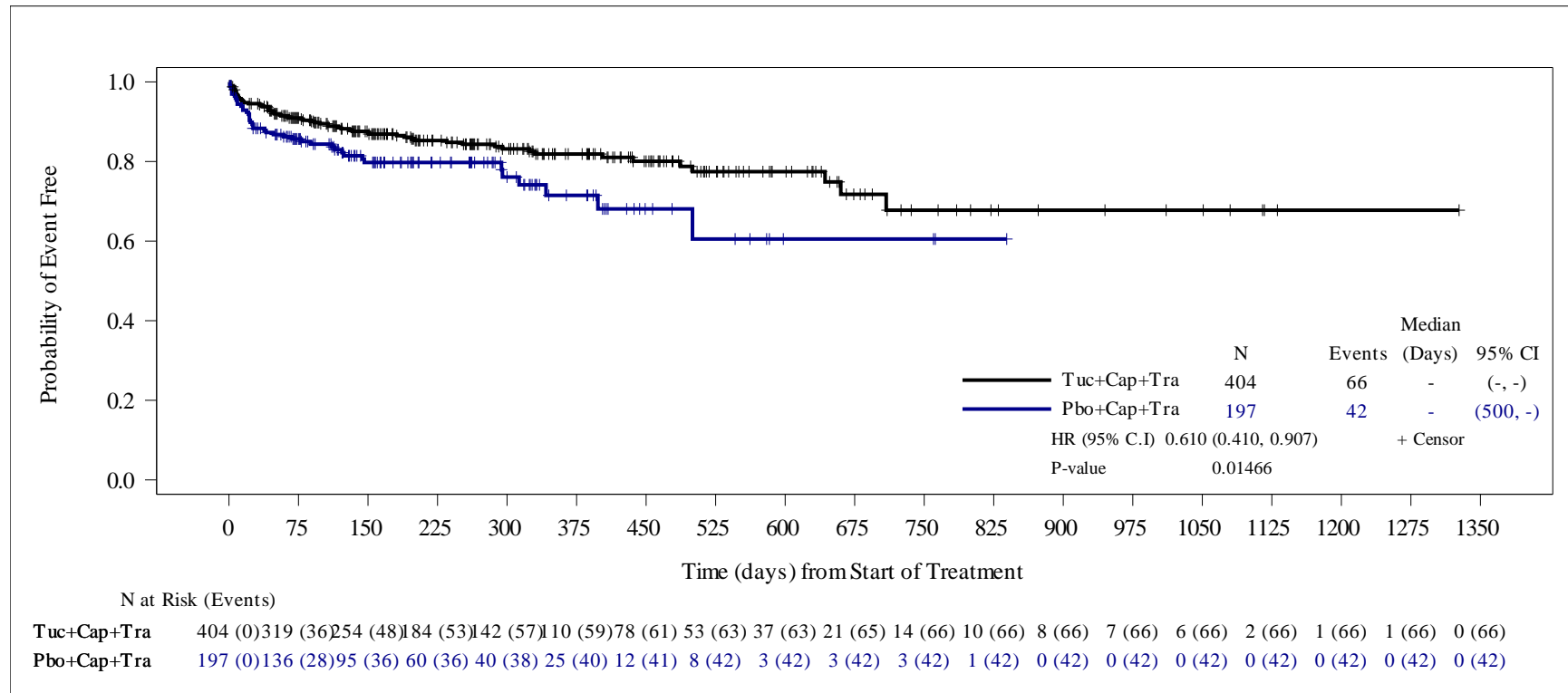
Two-sided p-value calculated from Cox proportional hazards model .

Snapshot date: 10SEP2020, data cutoff date: 29MAY2020.

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**Figure 2.3.7 Kaplan-Meier Estimate of Time to First Onset of Adverse Events - Constipation
Safety Analysis Set**



HR is computed from the Cox proportional hazards model using stratification factors (Presence or history of brain metastases: Yes/No, ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization.

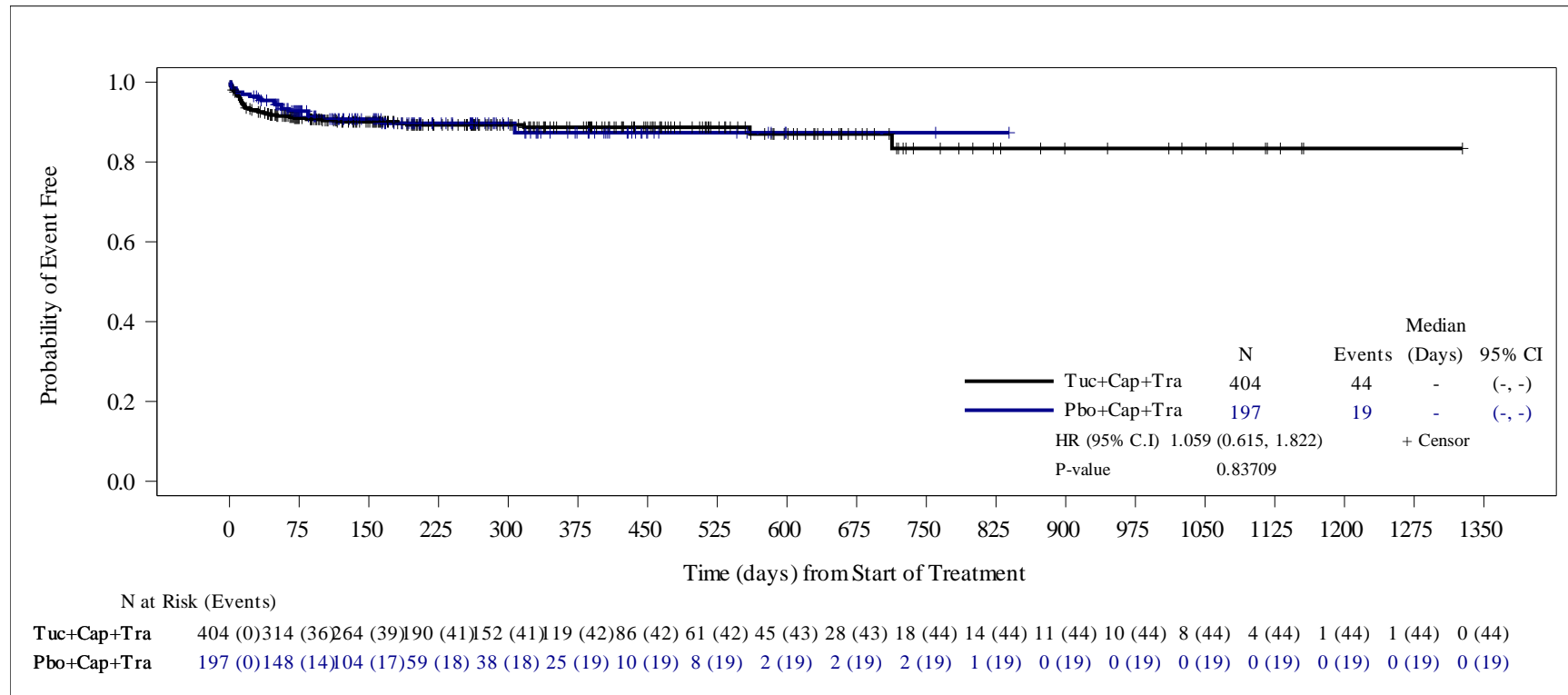
Two-sided p-value calculated from Cox proportional hazards model .

Snapshot date: 10SEP2020, data cutoff date: 29MAY2020.

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**Figure 2.3.8 Kaplan-Meier Estimate of Time to First Onset of Adverse Events - Dyspepsia
Safety Analysis Set**



HR is computed from the Cox proportional hazards model using stratification factors (Presence or history of brain metastases: Yes/No, ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization.

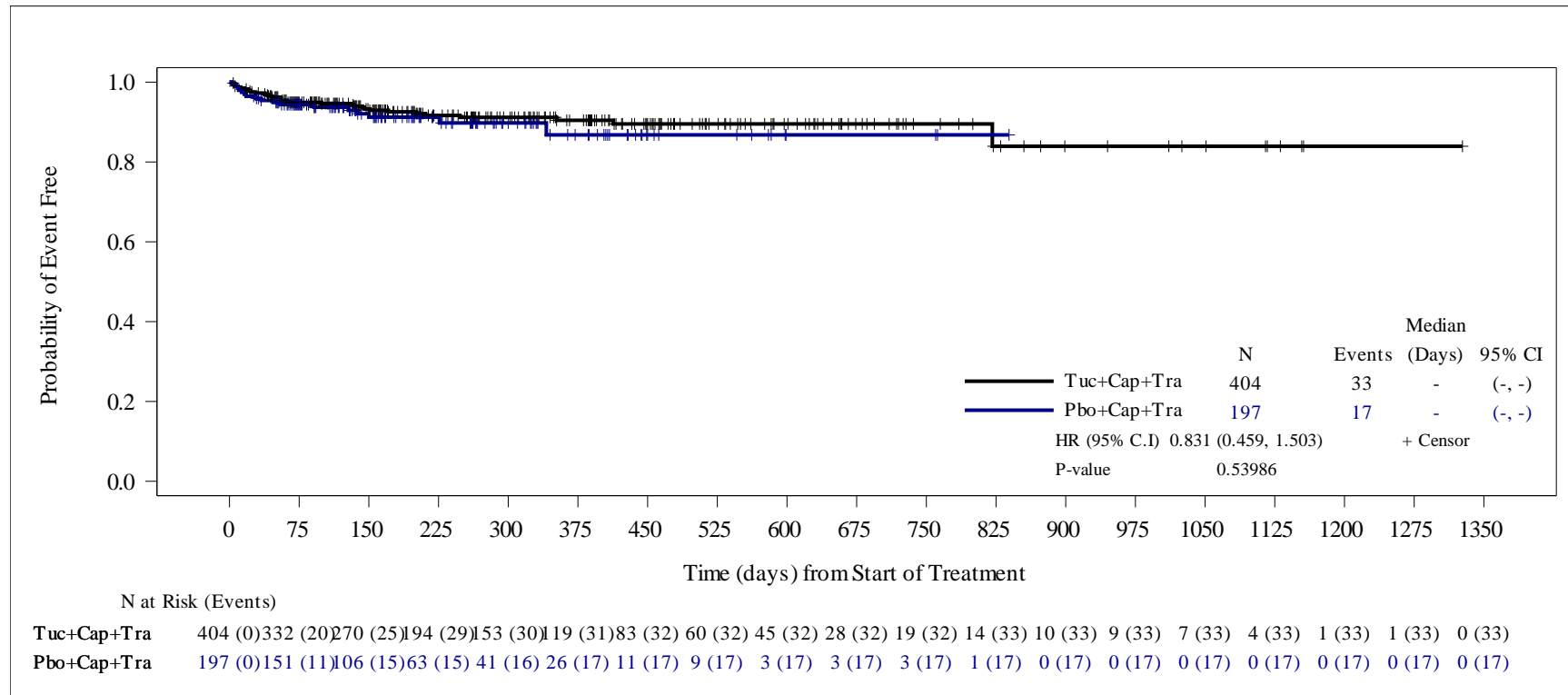
Two-sided p-value calculated from Cox proportional hazards model .

Snapshot date: 10SEP2020, data cutoff date: 29MAY2020.

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_may2020_dco_1943\v01\outputs\tlfs\pgms\f-ae-onset-gastro.sas Output: f02-03-08-ae-km-gi-dys-safs.rtf(14DEC20:17:11) Data: adsl, adae, adttesaf

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Figure 2.3.9 Kaplan-Meier Estimate of Time to First Onset of Adverse Events - Abdominal Pain Upper Safety Analysis Set



HR is computed from the Cox proportional hazards model using stratification factors (Presence or history of brain metastases: Yes/No, ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization.

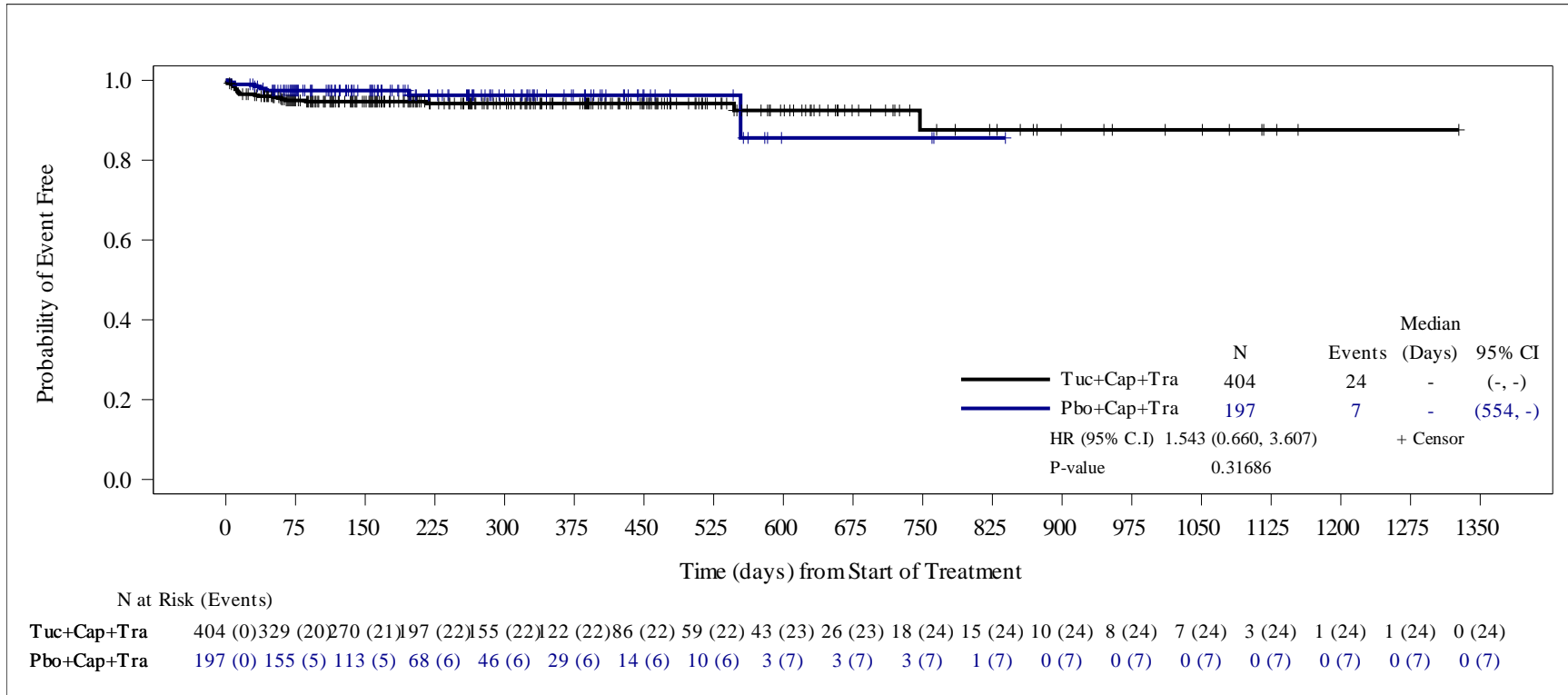
Two-sided p-value calculated from Cox proportional hazards model .

Snapshot date: 10SEP2020, data cutoff date: 29MAY2020.

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_may2020_dco_1943\v01\outputs\tlfs\pgms\f-ae-onset-gastro.sas Output: f02-03-09-ae-km-gi-abu-safs.rtf(14DEC20:17:11) Data: adsl, adae, adttesaf

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**Figure 2.3.10 Kaplan-Meier Estimate of Time to First Onset of Adverse Events - Gastroesophageal Reflux Disease
Safety Analysis Set**



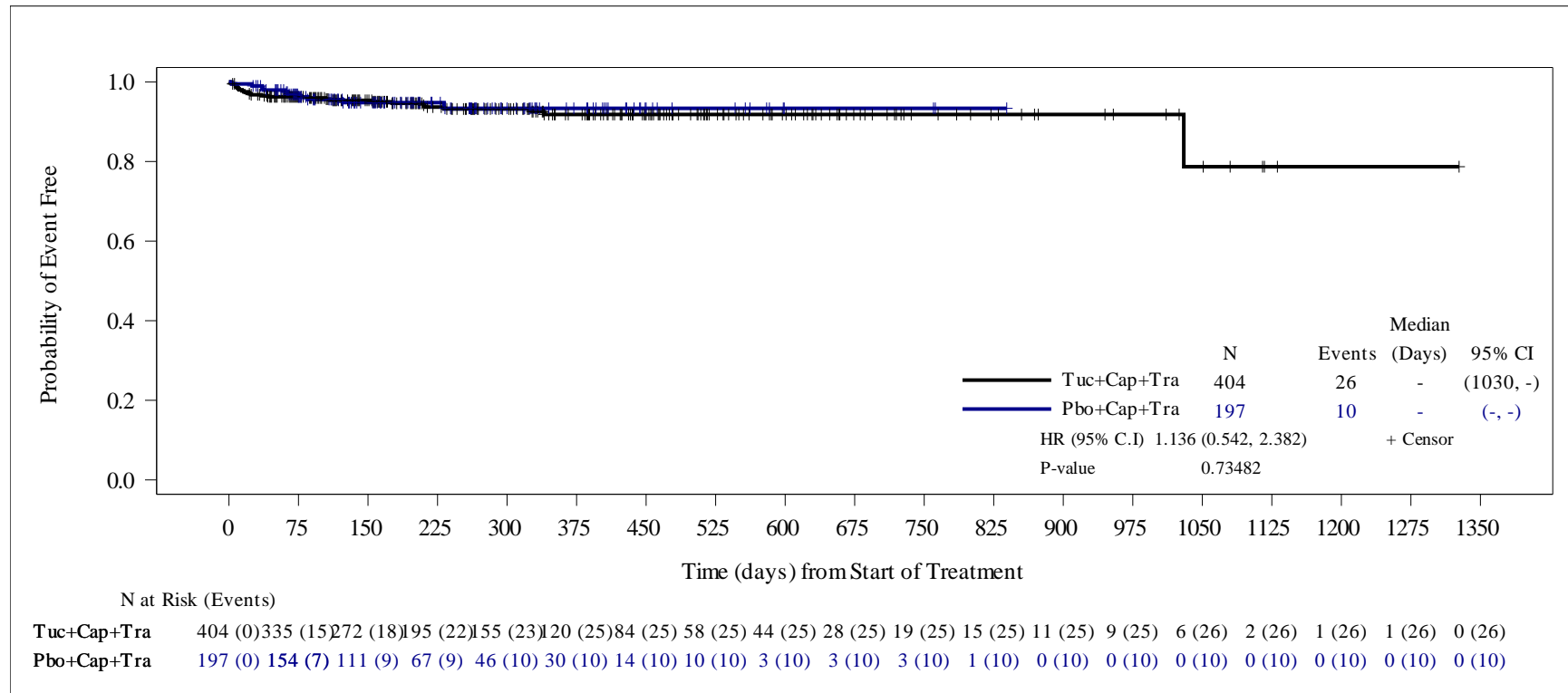
HR and two-sided p-value were computed from the unstratified Cox proportional hazards model.

Snapshot date: 10SEP2020, data cutoff date: 29MAY2020.

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_may2020_dco_1943\01\outputs\tlfs\pgms\f-ae-onset-gastro.sas Output: f02-03-10-ae-km-gi-grd-safs.rtf(14DEC20:17:11) Data: adsl, adae, adttesaf

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**Figure 2.3.11 Kaplan-Meier Estimate of Time to First Onset of Adverse Events - Abdominal Distension
Safety Analysis Set**



HR is computed from the Cox proportional hazards model using stratification factors (Presence or history of brain metastases: Yes/No, ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization.

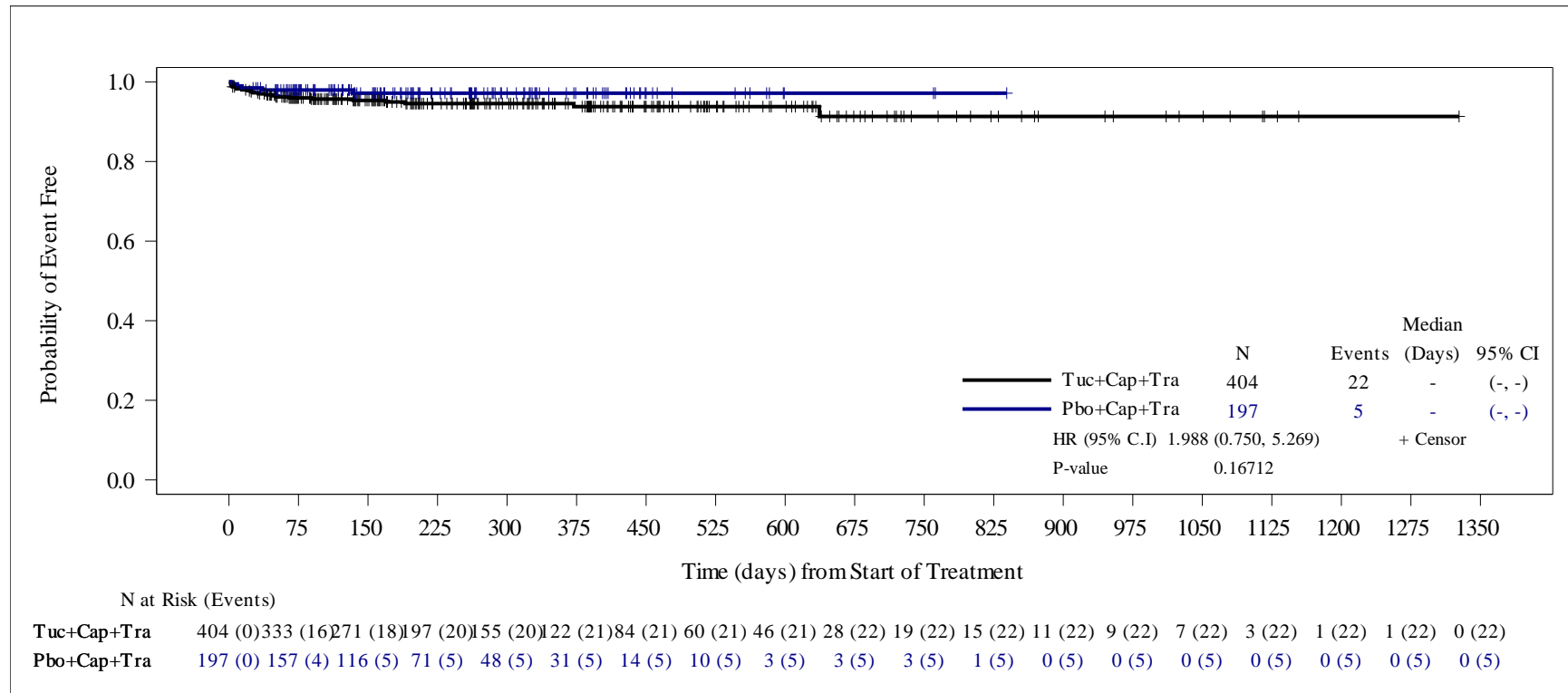
Two-sided p-value calculated from Cox proportional hazards model .

Snapshot date: 10SEP2020, data cutoff date: 29MAY2020.

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_may2020_dco_1943\v01\outputs\tlfs\pgms\f-ae-onset-gastro.sas Output: f02-03-11-ae-km-gi-abd-safs.rtf(14DEC20:17:11) Data: adsl, adae, adttesaf

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**Figure 2.3.12 Kaplan-Meier Estimate of Time to First Onset of Adverse Events - Dry Mouth
Safety Analysis Set**



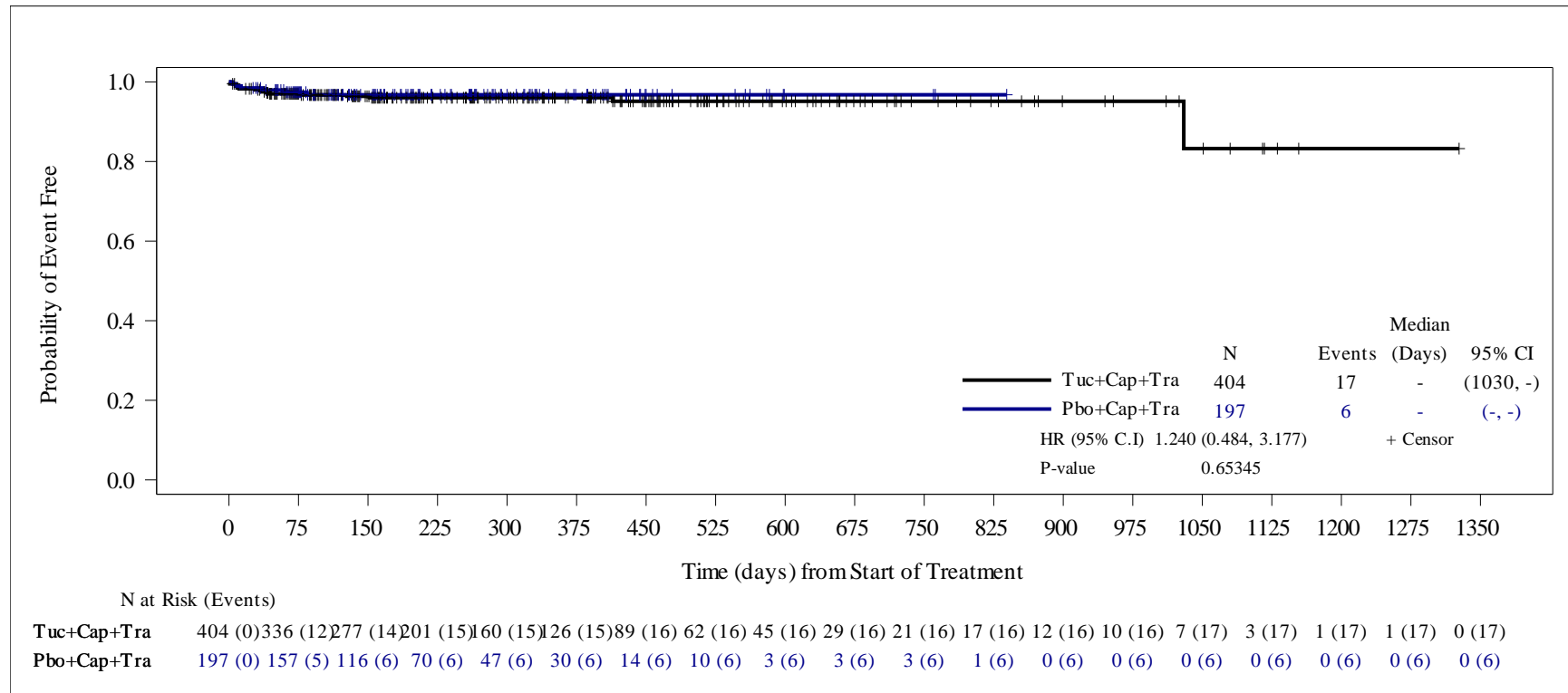
HR and two-sided p-value were computed from the unstratified Cox proportional hazards model.

Snapshot date: 10SEP2020, data cutoff date: 29MAY2020.

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_may2020_dco_1943\01\outputs\tlfs\pgms\f-ae-onset-gastro.sas Output: f02-03-12-ae-km-gi-drm-safs.rtf(14DEC20:17:11) Data: adsl, adae, adttesaf

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**Figure 2.3.13 Kaplan-Meier Estimate of Time to First Onset of Adverse Events - Flatulence
Safety Analysis Set**



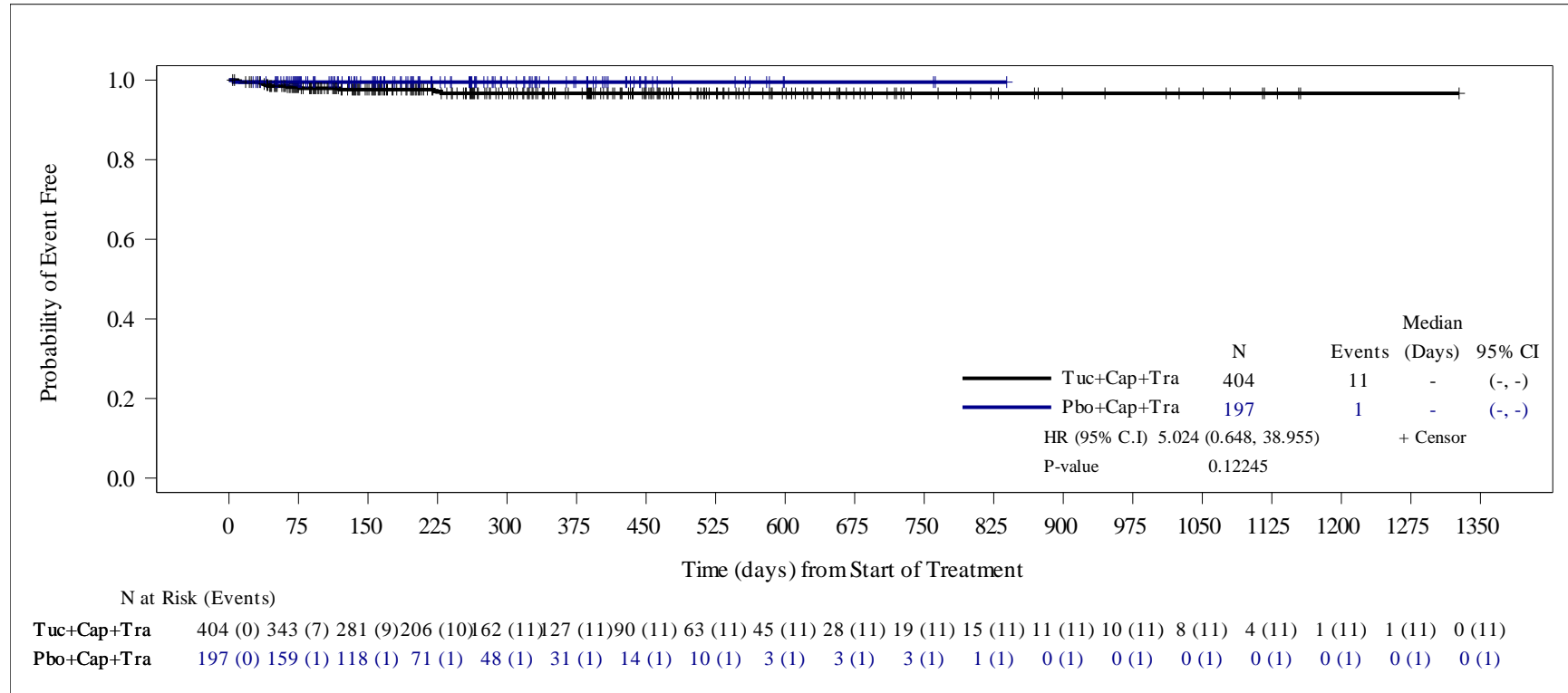
HR and two-sided p-value were computed from the unstratified Cox proportional hazards model.

Snapshot date: 10SEP2020, data cutoff date: 29MAY2020.

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_may2020_dco_1943\01\outputs\tlfs\pgms\f-ae-onset-gastro.sas Output: f02-03-13-ae-km-gi-ftu-safs.rtf(14DEC20:17:11) Data: adsl, adae, adttesaf

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**Figure 2.3.14 Kaplan-Meier Estimate of Time to First Onset of Adverse Events - Haemorrhoids
Safety Analysis Set**



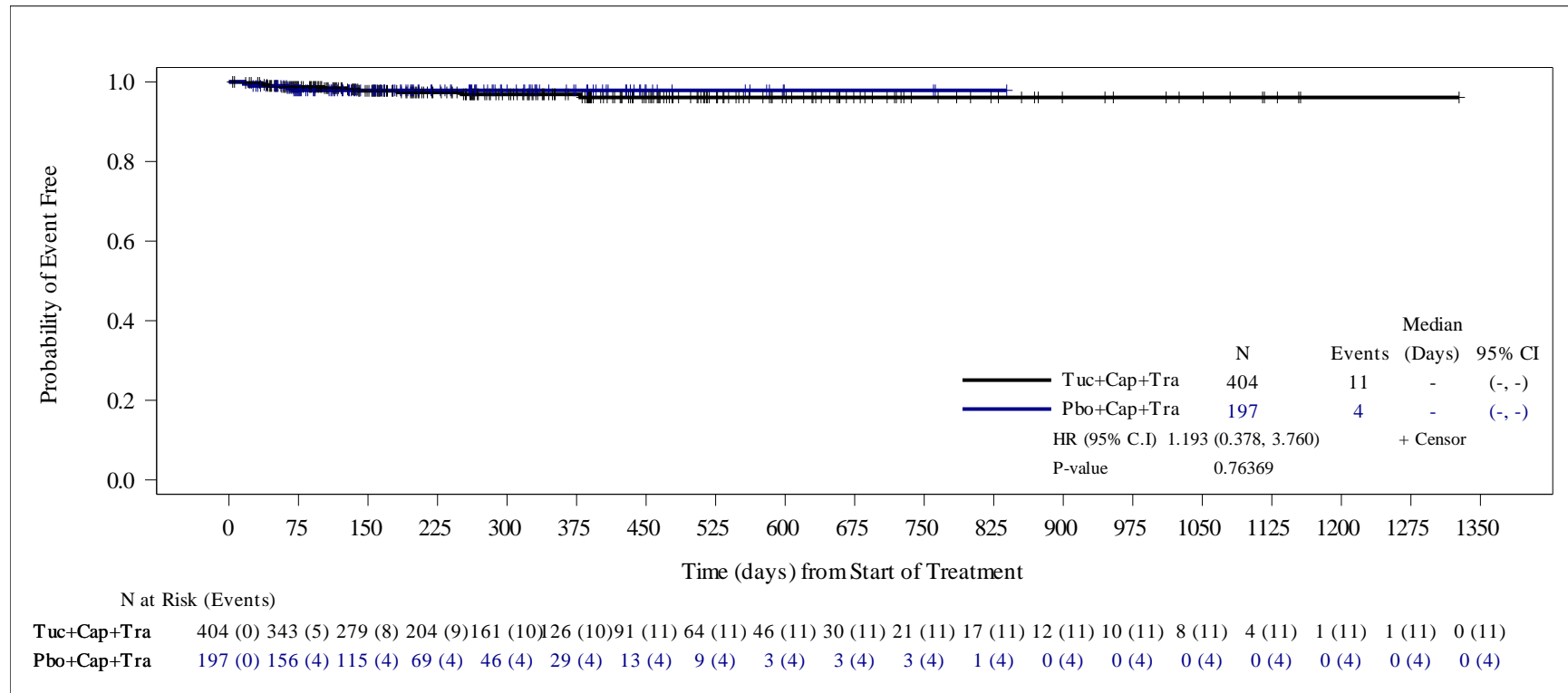
HR and two-sided p-value were computed from the unstratified Cox proportional hazards model.

Snapshot date: 10SEP2020, data cutoff date: 29MAY2020.

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**Figure 2.3.15 Kaplan-Meier Estimate of Time to First Onset of Adverse Events - Mouth Ulceration
Safety Analysis Set**



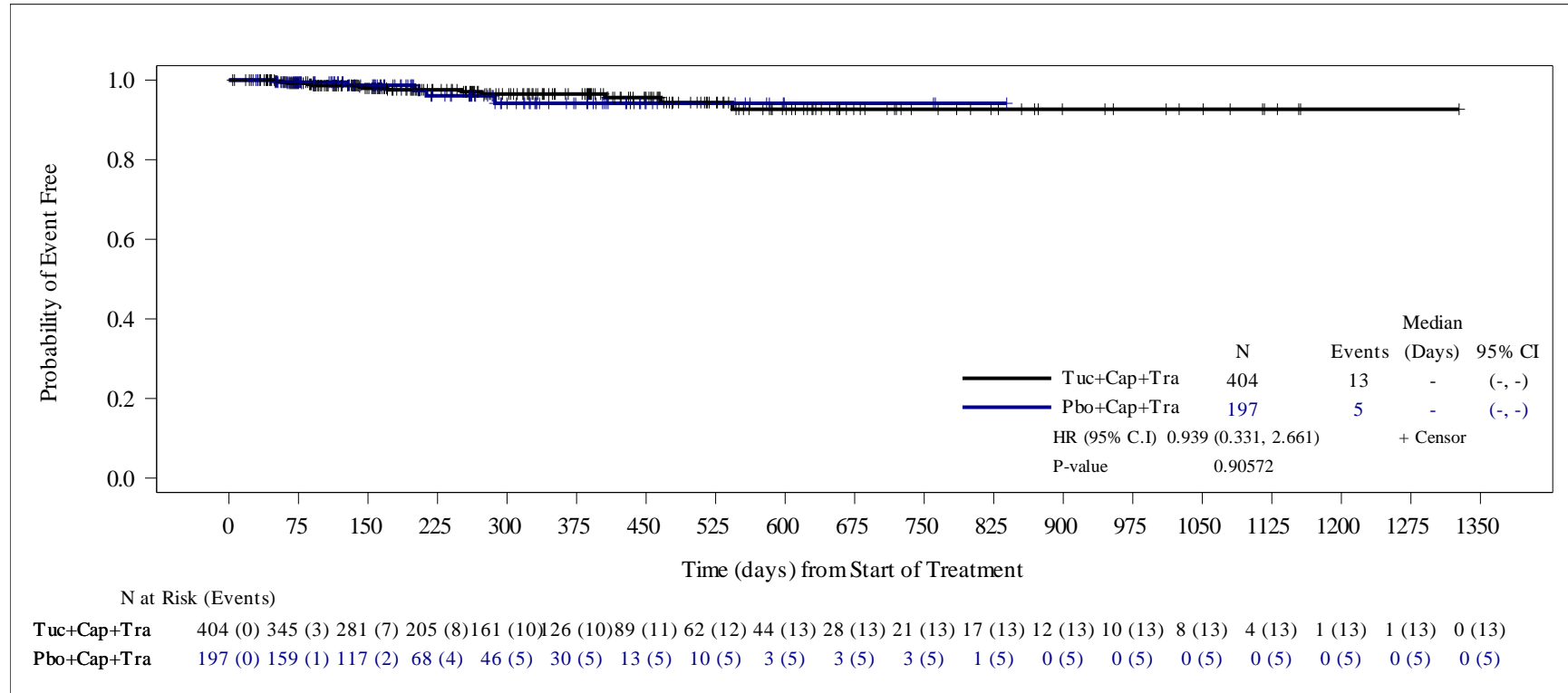
HR and two-sided p-value were computed from the unstratified Cox proportional hazards model.

Snapshot date: 10SEP2020, data cutoff date: 29MAY2020.

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_may2020_dco_1943\01\outputs\tlfs\pgms\f-ae-onset-gastro.sas Output: f02-03-15-ae-km-gi-ulc-safs.rtf(14DEC20:17:11) Data: adsl, adae, adttesaf

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**Figure 2.3.16 Kaplan-Meier Estimate of Time to First Onset of Adverse Events - Toothache
Safety Analysis Set**



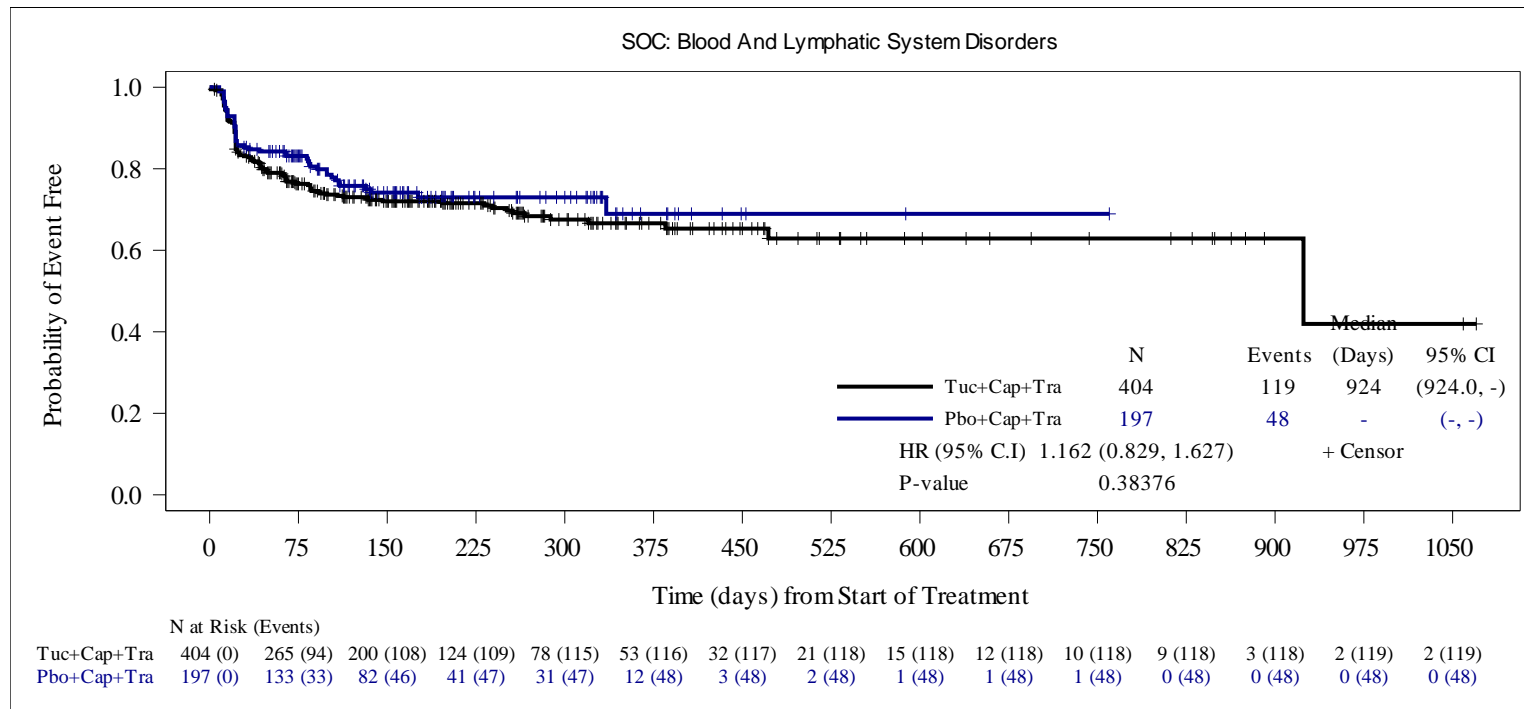
HR and two-sided p-value were computed from the unstratified Cox proportional hazards model.

Snapshot date: 10SEP2020, data cutoff date: 29MAY2020.

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_may2020_dco_1943\01\outputs\tlfs\pgms\f-ae-onset-gastro.sas Output: f02-03-16-ae-km-gi-toa-safs.rtf(14DEC20:17:11) Data: adsl, adae, adttasaf

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**Figure 2.7.1 Kaplan-Meier Estimate of Time to First Onset of Treatment-Emergent Adverse Events by System Organ Class and Preferred Term
Safety Analysis Set**



HR is computed from the Cox proportional hazards model using stratification factors (Presence or history of brain metastases: Yes/No, ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization. When the number of subjects with at least one event was ≤ 30 , an unstratified Cox model was run.

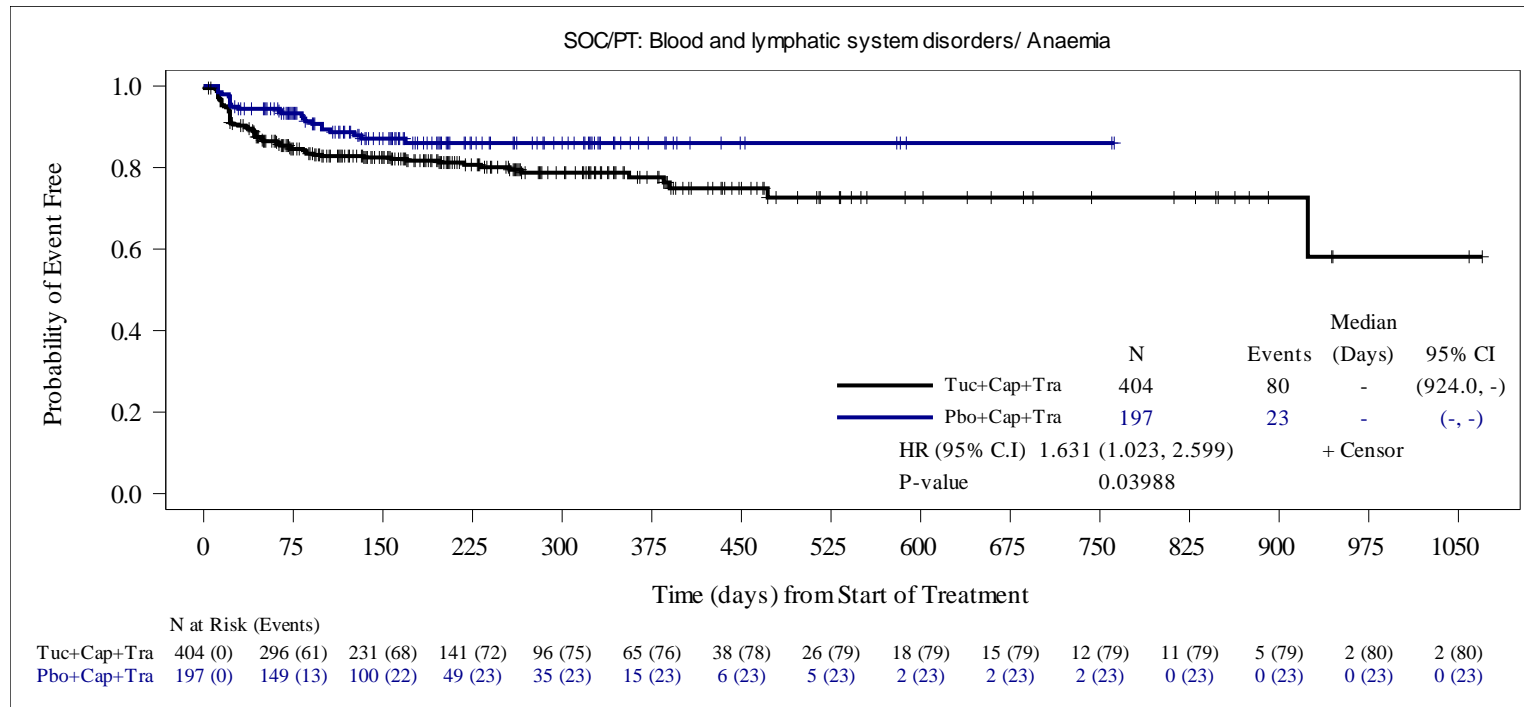
Two-sided p-value calculated from Cox proportional hazards model .

Data Snapshot: 14OCT2019, Data Cutoff Date: 04SEP2019

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_1753\v01\outputs\tlfs\pgms\f-ae-km-socpt-safs.sas Output: f-ae-km-socpt-safs.rtf(17JUL20:16:07) Data: adsl, adae, adttesaf

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**Figure 2.7.1 Kaplan-Meier Estimate of Time to First Onset of Treatment-Emergent Adverse Events by System Organ Class and Preferred Term
Safety Analysis Set**



HR is computed from the Cox proportional hazards model using stratification factors (Presence or history of brain metastases: Yes/No, ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization. When the number of subjects with at least one event was ≤ 30 , an unstratified Cox model was run.

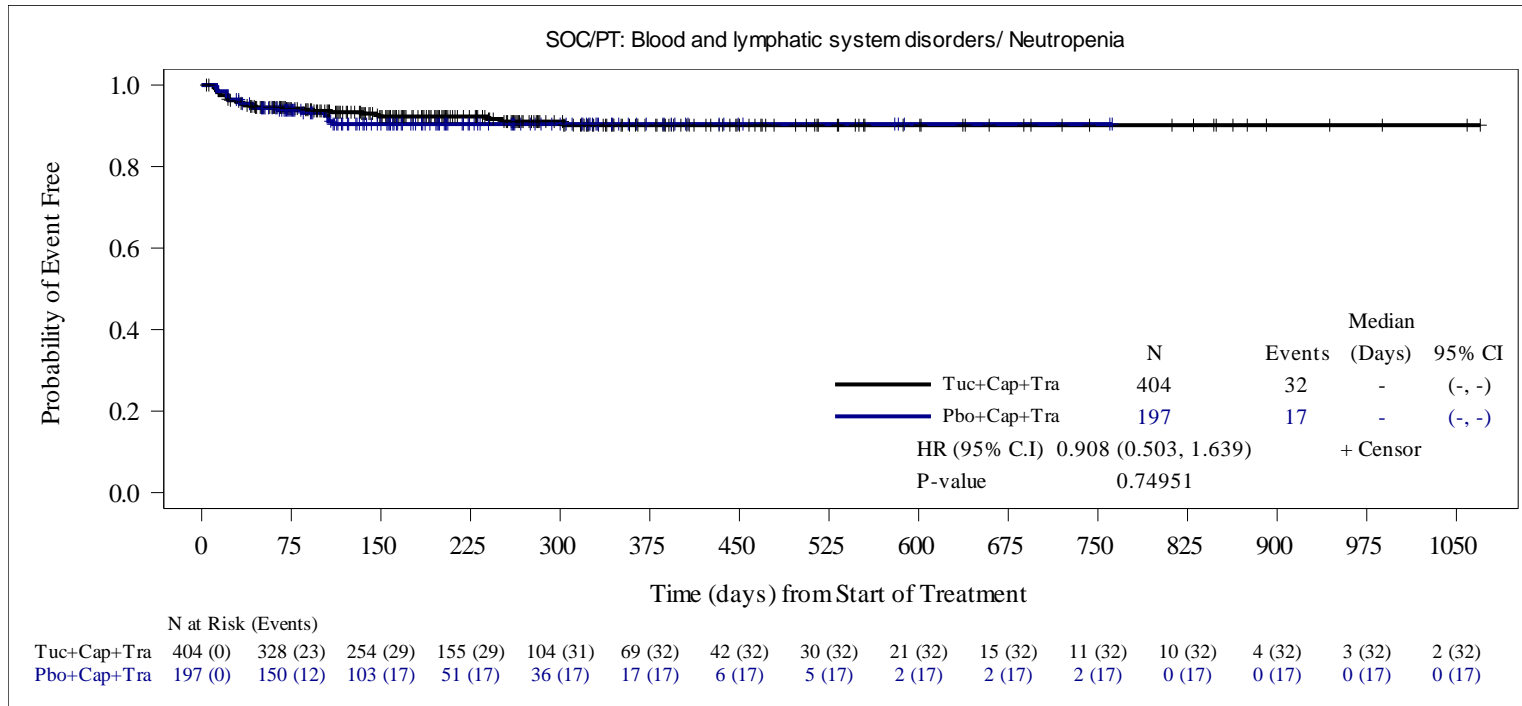
Two-sided p-value calculated from Cox proportional hazards model .

Data Snapshot: 14OCT2019, Data Cutoff Date: 04SEP2019

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**Figure 2.7.1 Kaplan-Meier Estimate of Time to First Onset of Treatment-Emergent Adverse Events by System Organ Class and Preferred Term
Safety Analysis Set**



HR is computed from the Cox proportional hazards model using stratification factors (Presence or history of brain metastases: Yes/No, ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization. When the number of subjects with at least one event was ≤ 30 , an unstratified Cox model was run.

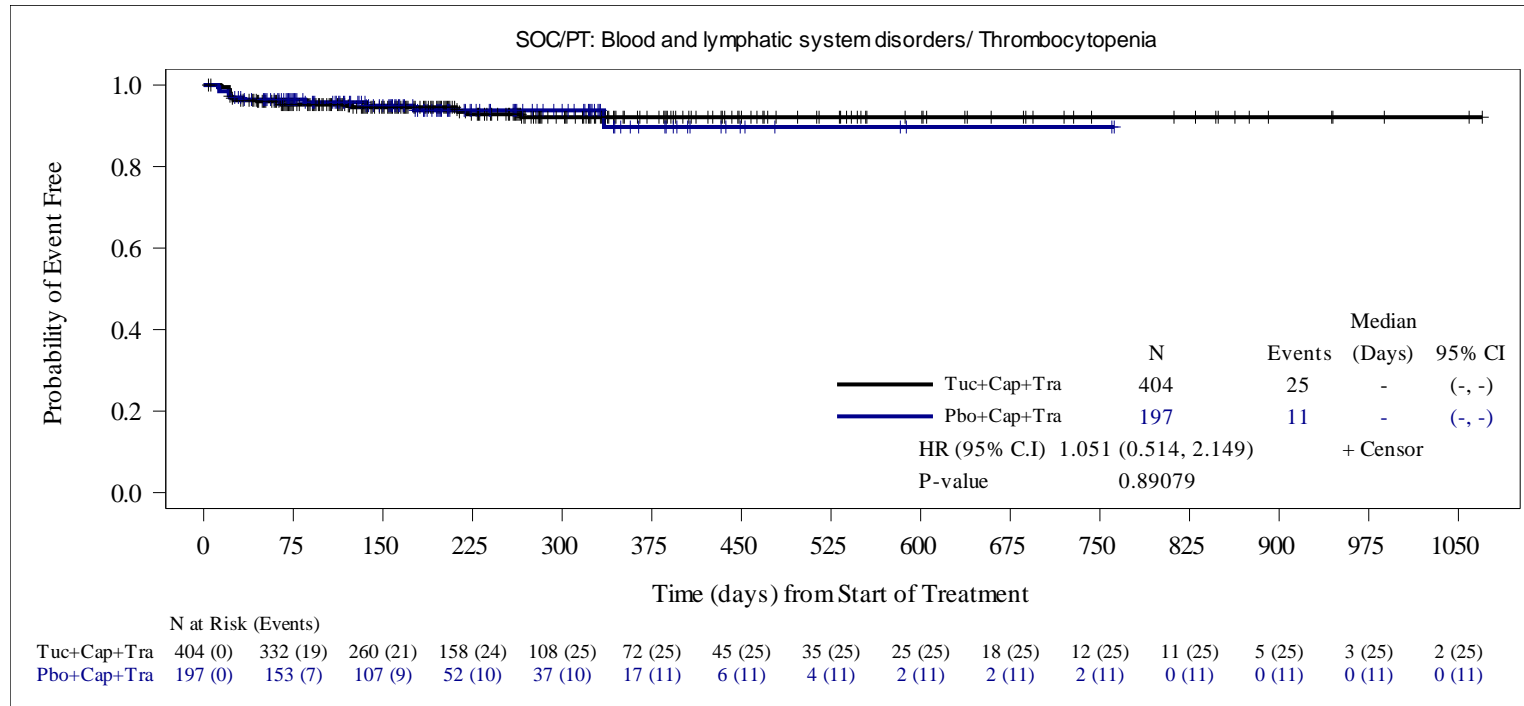
Two-sided p-value calculated from Cox proportional hazards model .

Data Snapshot: 14OCT2019, Data Cutoff Date: 04SEP2019

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**Figure 2.7.1 Kaplan-Meier Estimate of Time to First Onset of Treatment-Emergent Adverse Events by System Organ Class and Preferred Term
Safety Analysis Set**



HR is computed from the Cox proportional hazards model using stratification factors (Presence or history of brain metastases: Yes/No, ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization. When the number of subjects with at least one event was ≤ 30 , an unstratified Cox model was run.

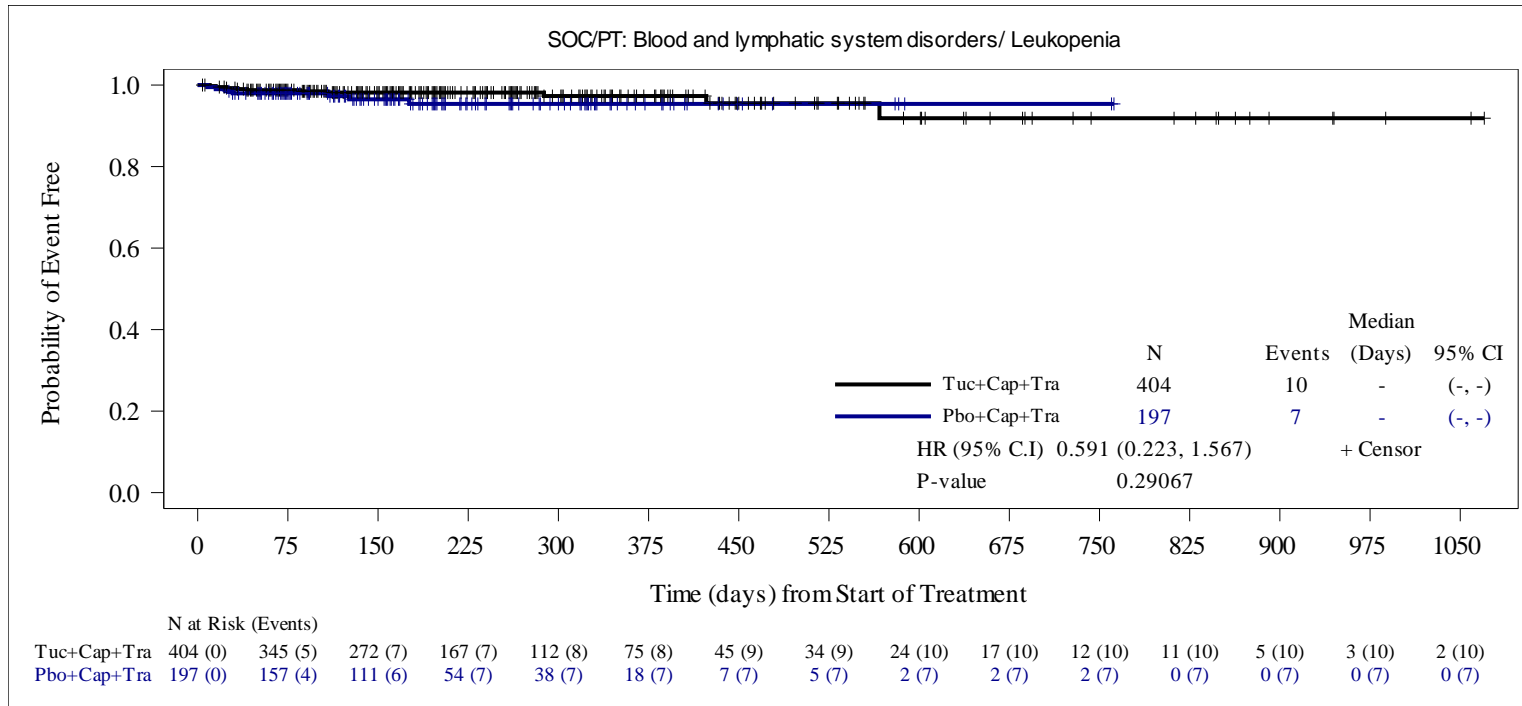
Two-sided p-value calculated from Cox proportional hazards model .

Data Snapshot: 14OCT2019, Data Cutoff Date: 04SEP2019

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**Figure 2.7.1 Kaplan-Meier Estimate of Time to First Onset of Treatment-Emergent Adverse Events by System Organ Class and Preferred Term
Safety Analysis Set**



HR is computed from the Cox proportional hazards model using stratification factors (Presence or history of brain metastases: Yes/No, ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization. When the number of subjects with at least one event was ≤ 30 , an unstratified Cox model was run.

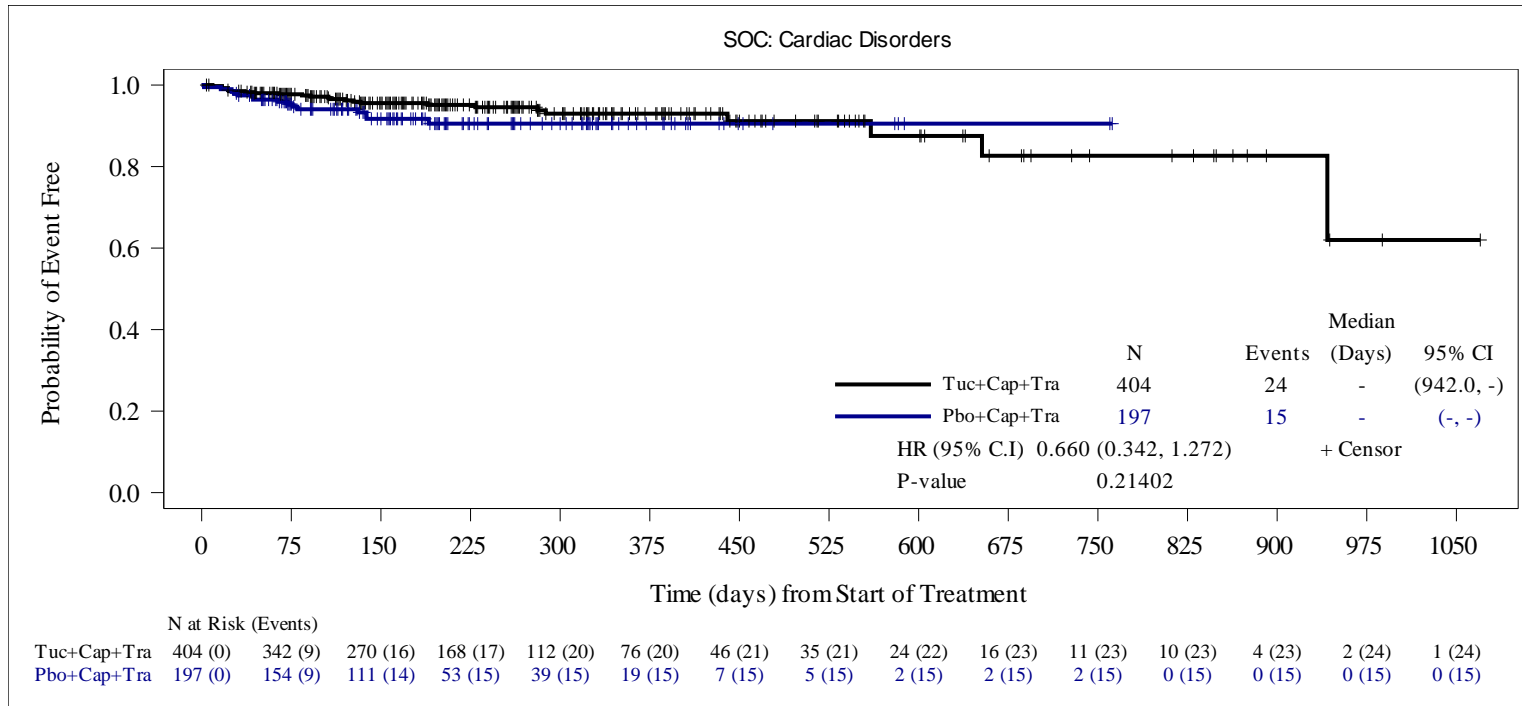
Two-sided p-value calculated from Cox proportional hazards model .

Data Snapshot: 14OCT2019, Data Cutoff Date: 04SEP2019

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**Figure 2.7.1 Kaplan-Meier Estimate of Time to First Onset of Treatment-Emergent Adverse Events by System Organ Class and Preferred Term
Term
Safety Analysis Set**



HR is computed from the Cox proportional hazards model using stratification factors (Presence or history of brain metastases: Yes/No, ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization. When the number of subjects with at least one event was ≤ 30, an unstratified Cox model was run.

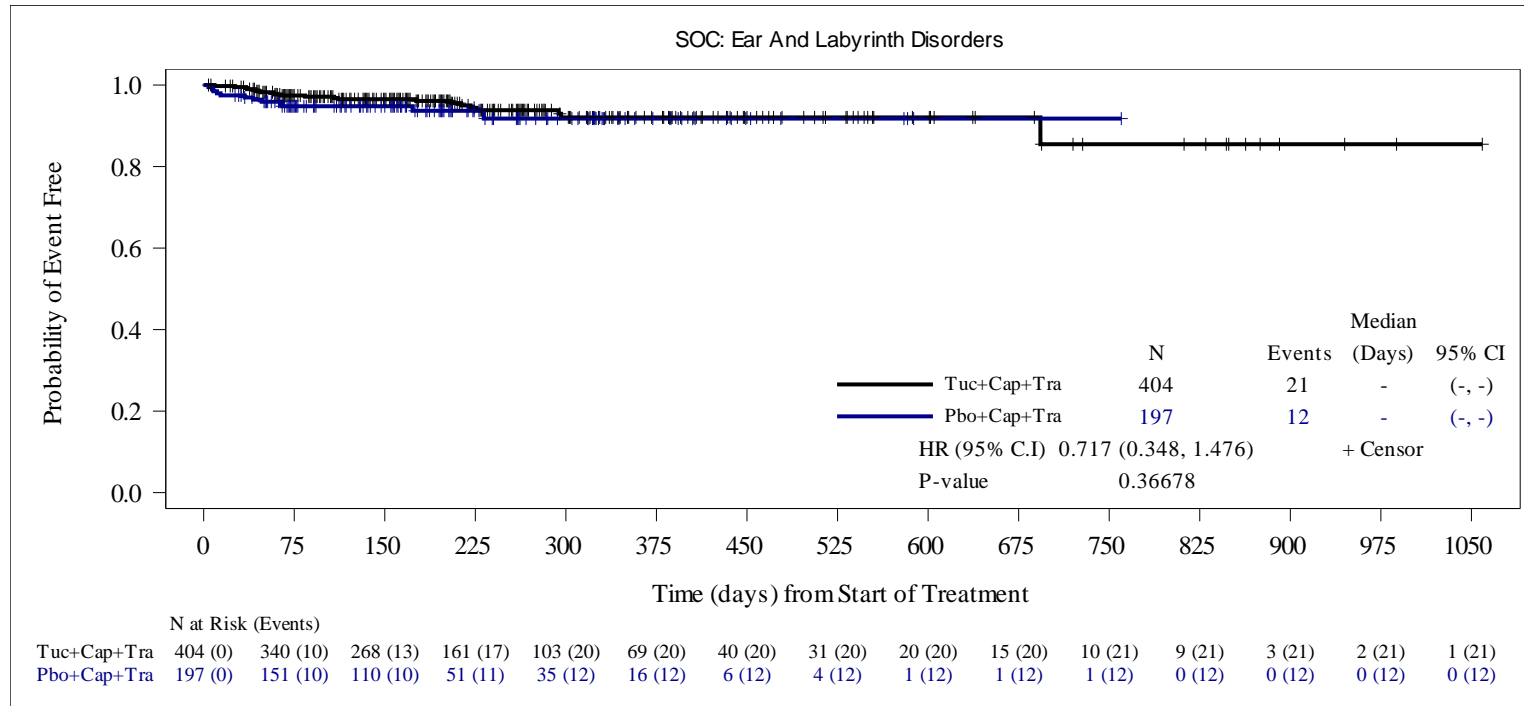
Two-sided p-value calculated from Cox proportional hazards model .

Data Snapshot: 14OCT2019, Data Cutoff Date: 04SEP2019

Source: O:\Projects\Tucatinib\ONT380-206_germanreimburse_1753\v01\outputs\tlfs\pgms\f-ae-km-socpt-safs.sas Output: f-ae-km-socpt-safs.rtf(17JUL20:16:07) Data: adsl, adae, adttesaf

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**Figure 2.7.1 Kaplan-Meier Estimate of Time to First Onset of Treatment-Emergent Adverse Events by System Organ Class and Preferred Term
Safety Analysis Set**



HR is computed from the Cox proportional hazards model using stratification factors (Presence or history of brain metastases: Yes/No, ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization. When the number of subjects with at least one event was ≤ 30 , an unstratified Cox model was run.

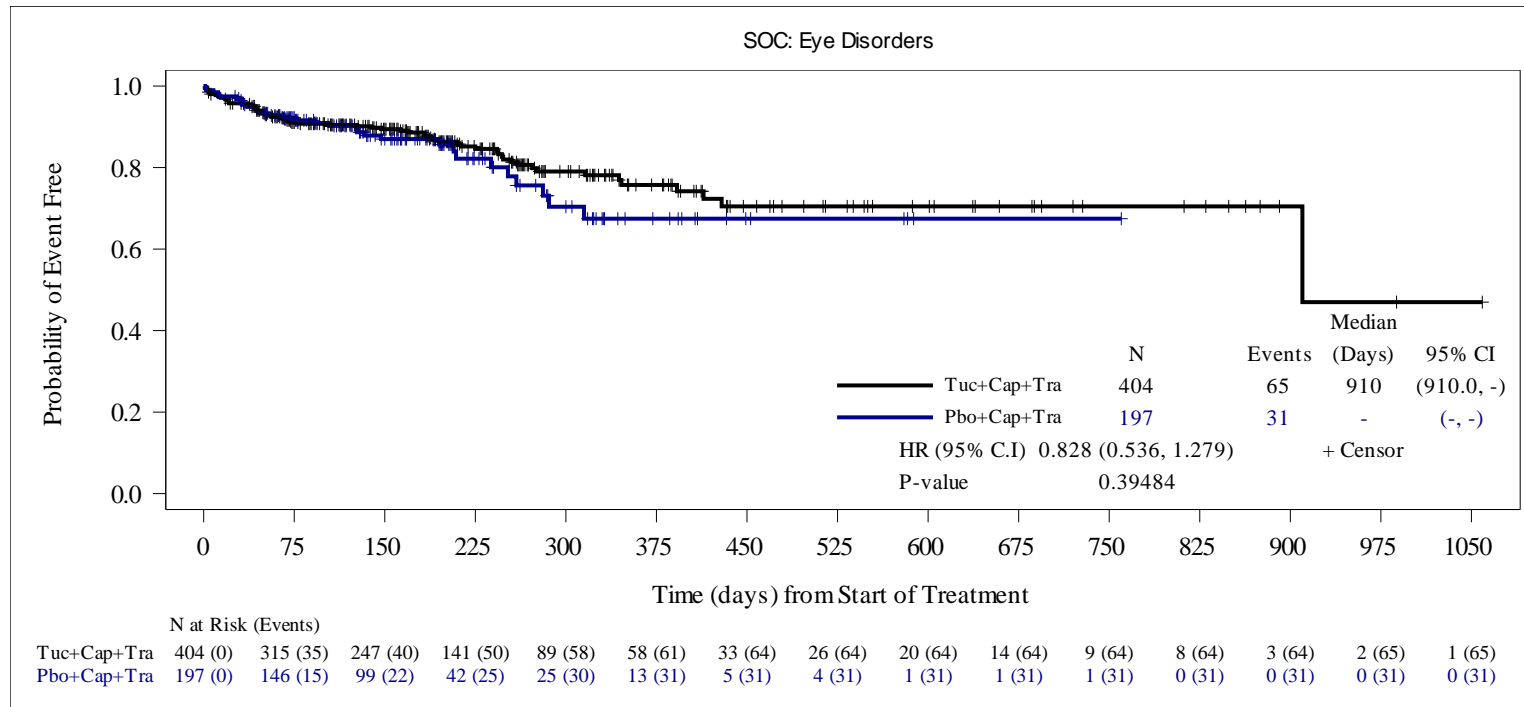
Two-sided p-value calculated from Cox proportional hazards model .

Data Snapshot: 14OCT2019, Data Cutoff Date: 04SEP2019

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**Figure 2.7.1 Kaplan-Meier Estimate of Time to First Onset of Treatment-Emergent Adverse Events by System Organ Class and Preferred Term
Safety Analysis Set**



HR is computed from the Cox proportional hazards model using stratification factors (Presence or history of brain metastases: Yes/No, ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization. When the number of subjects with at least one event was ≤ 30 , an unstratified Cox model was run.

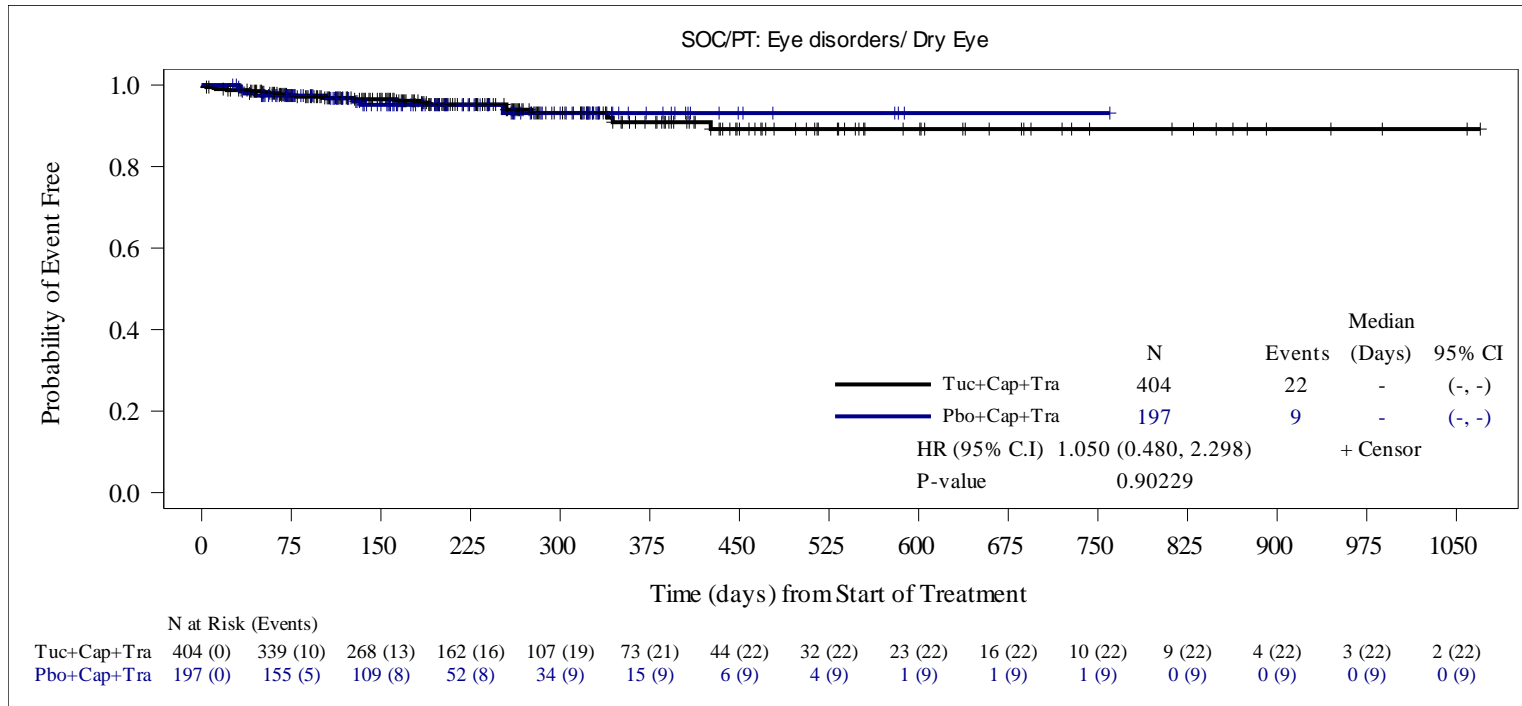
Two-sided p-value calculated from Cox proportional hazards model .

Data Snapshot: 14OCT2019, Data Cutoff Date: 04SEP2019

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**Figure 2.7.1 Kaplan-Meier Estimate of Time to First Onset of Treatment-Emergent Adverse Events by System Organ Class and Preferred Term
Safety Analysis Set**



HR is computed from the Cox proportional hazards model using stratification factors (Presence or history of brain metastases: Yes/No, ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization. When the number of subjects with at least one event was ≤ 30 , an unstratified Cox model was run.

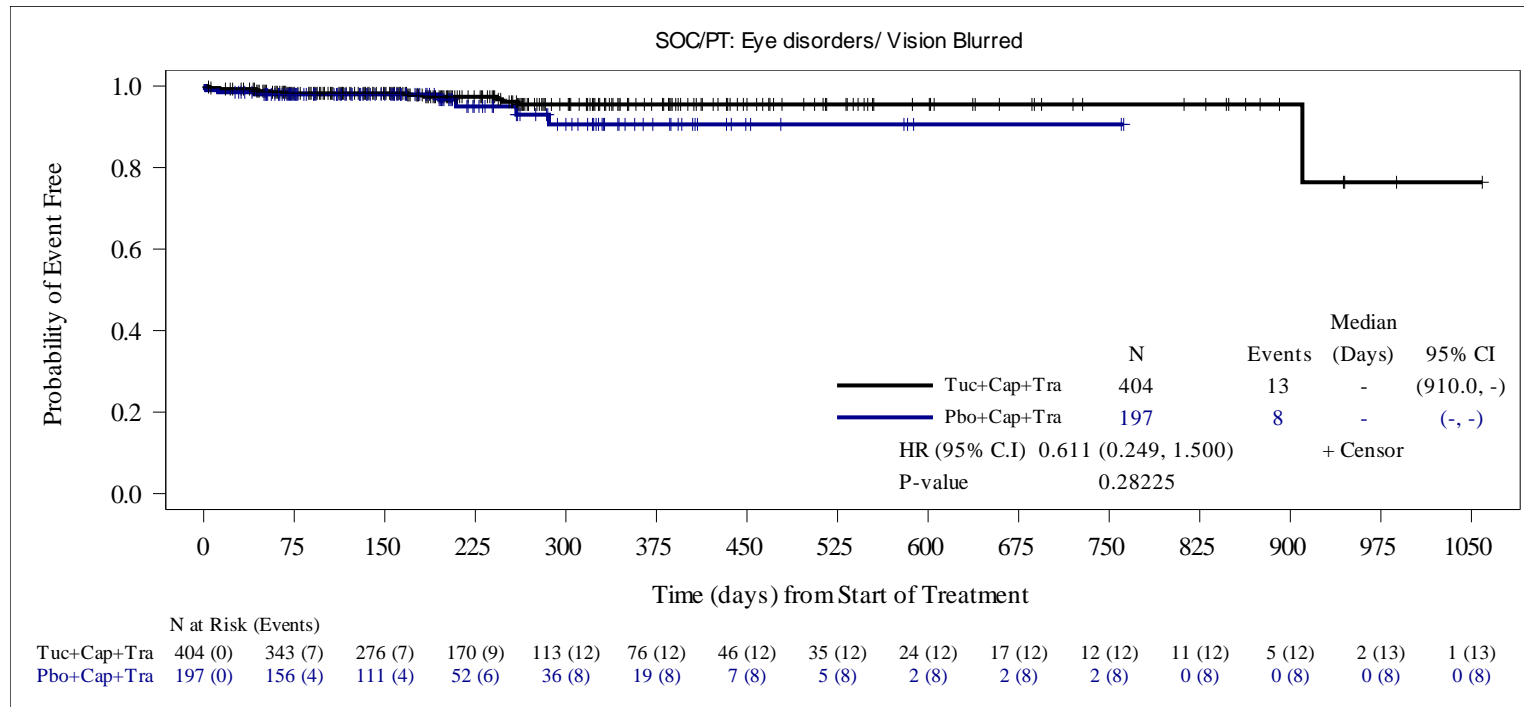
Two-sided p-value calculated from Cox proportional hazards model .

Data Snapshot: 14OCT2019, Data Cutoff Date: 04SEP2019

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**Figure 2.7.1 Kaplan-Meier Estimate of Time to First Onset of Treatment-Emergent Adverse Events by System Organ Class and Preferred Term
Safety Analysis Set**



HR is computed from the Cox proportional hazards model using stratification factors (Presence or history of brain metastases: Yes/No, ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization. When the number of subjects with at least one event was ≤ 30 , an unstratified Cox model was run.

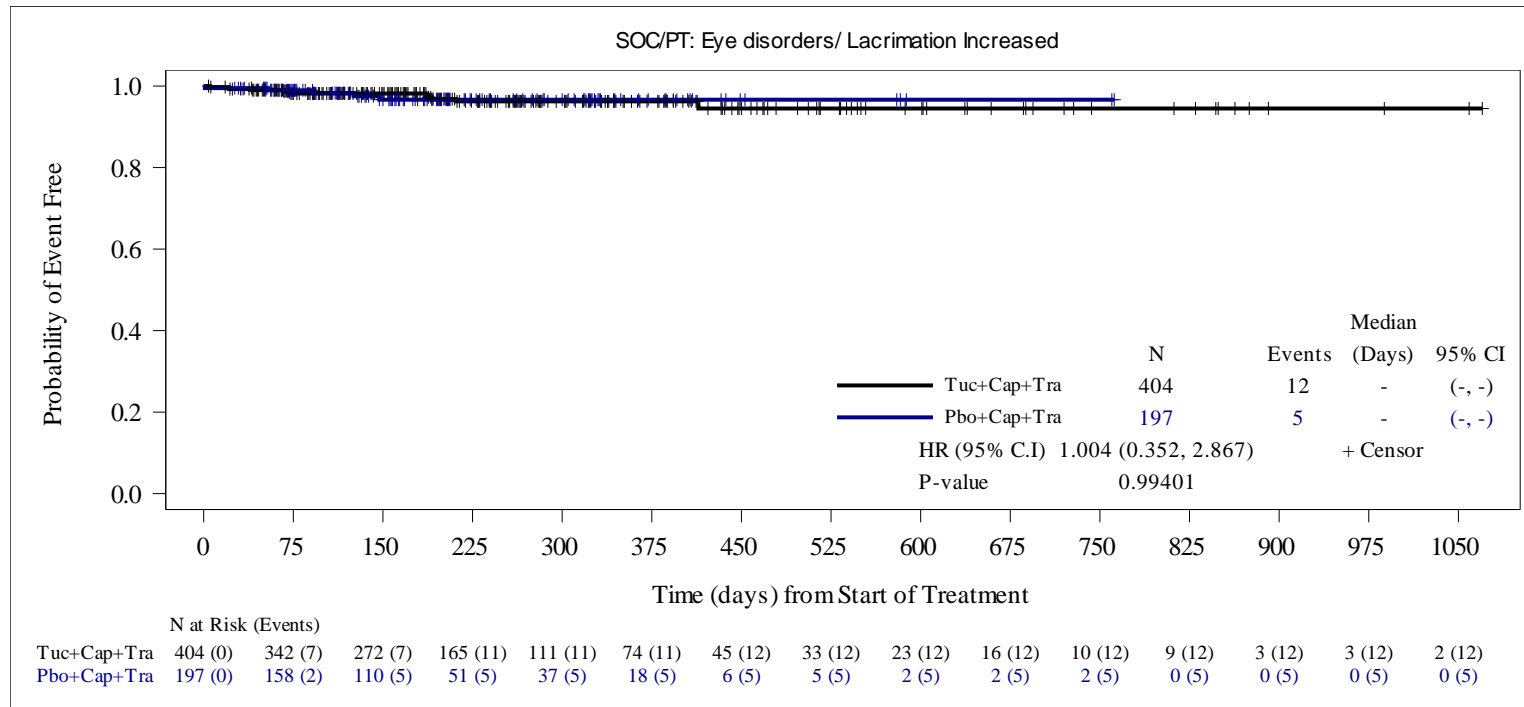
Two-sided p-value calculated from Cox proportional hazards model .

Data Snapshot: 14OCT2019, Data Cutoff Date: 04SEP2019

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**Figure 2.7.1 Kaplan-Meier Estimate of Time to First Onset of Treatment-Emergent Adverse Events by System Organ Class and Preferred Term
Safety Analysis Set**



HR is computed from the Cox proportional hazards model using stratification factors (Presence or history of brain metastases: Yes/No, ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization. When the number of subjects with at least one event was ≤ 30 , an unstratified Cox model was run.

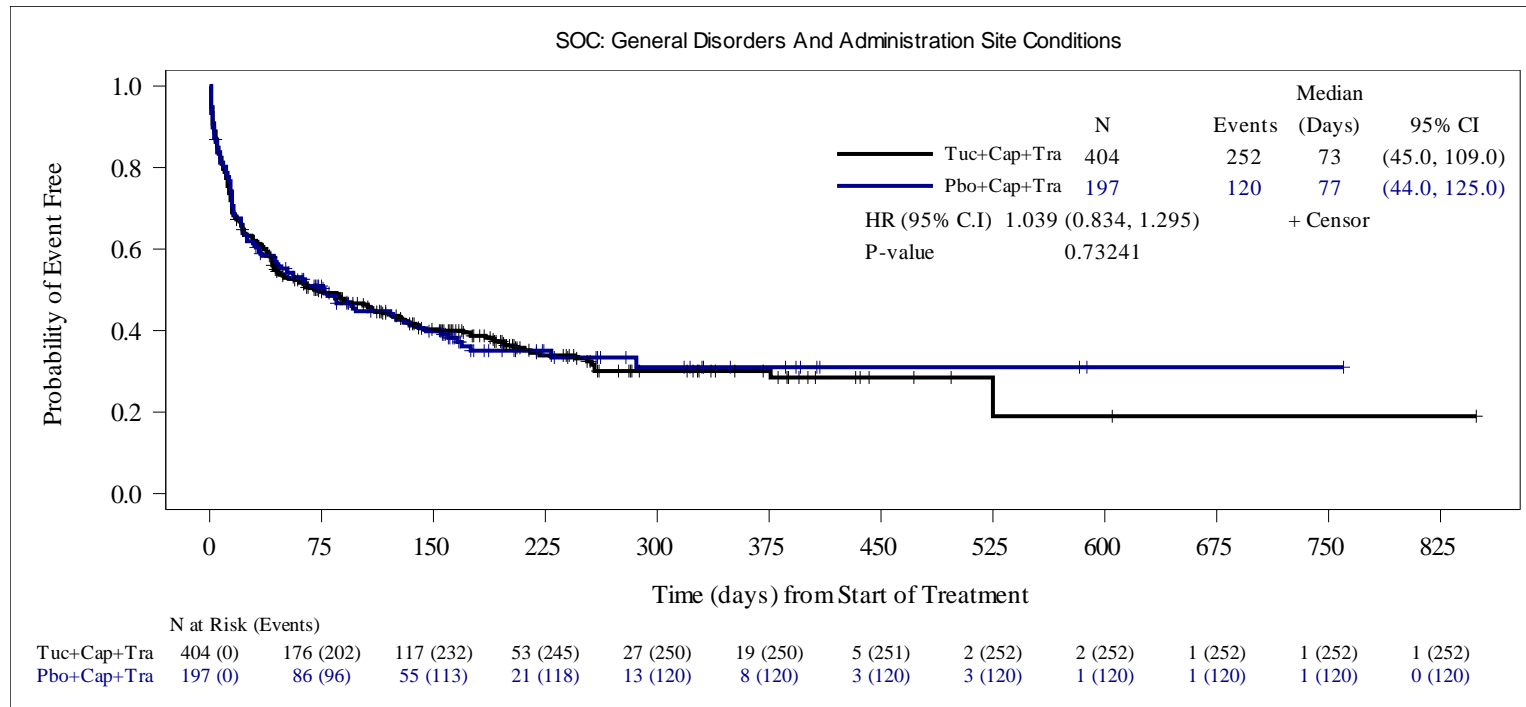
Two-sided p-value calculated from Cox proportional hazards model .

Data Snapshot: 14OCT2019, Data Cutoff Date: 04SEP2019

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**Figure 2.7.1 Kaplan-Meier Estimate of Time to First Onset of Treatment-Emergent Adverse Events by System Organ Class and Preferred Term
Term
Safety Analysis Set**



HR is computed from the Cox proportional hazards model using stratification factors (Presence or history of brain metastases: Yes/No, ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization. When the number of subjects with at least one event was ≤ 30 , an unstratified Cox model was run.

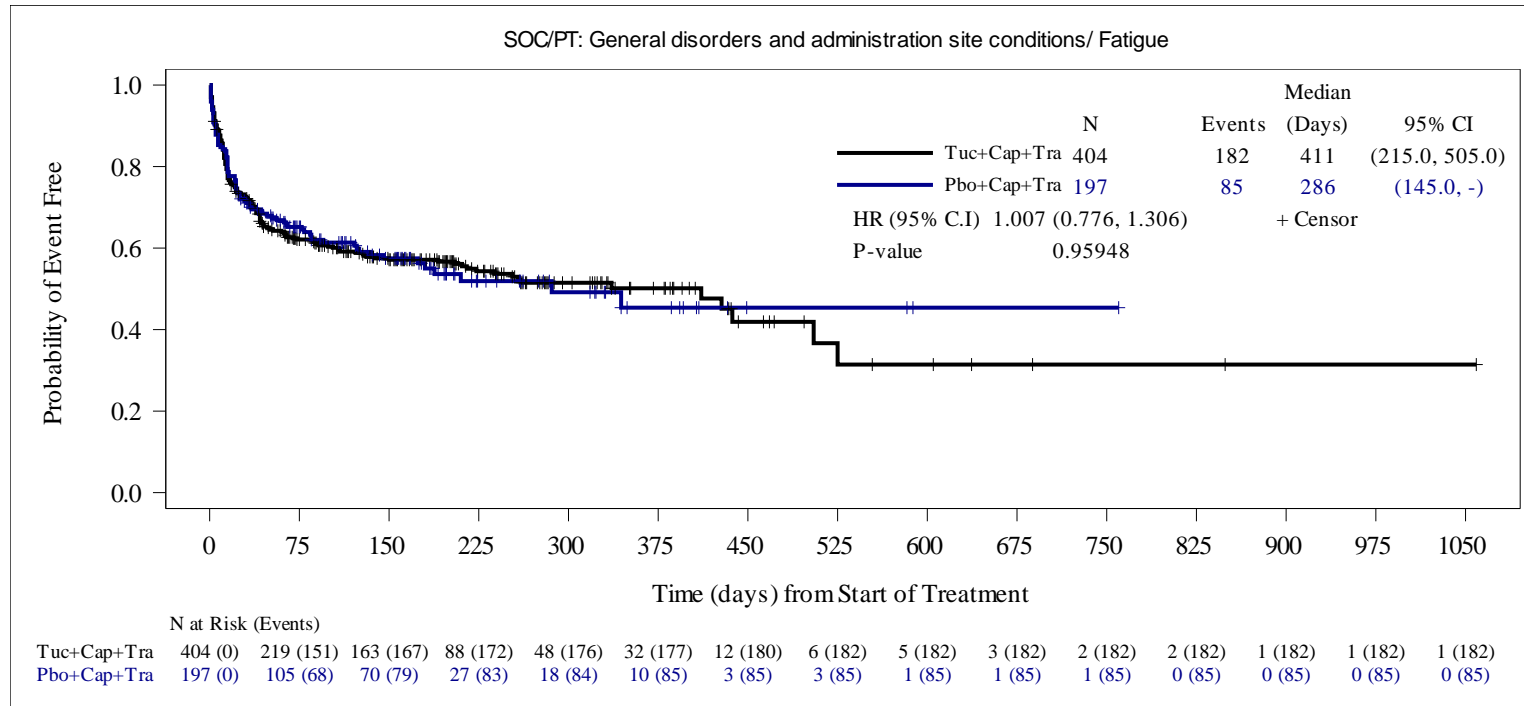
Two-sided p-value calculated from Cox proportional hazards model .

Data Snapshot: 14OCT2019, Data Cutoff Date: 04SEP2019

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_1753\v01\outputs\tlfs\pgms\f-ae-km-socpt-safs.sas Output: f-ae-km-socpt-safs.rtf(17JUL20:16:07) Data: adsl, adae, adttesaf

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**Figure 2.7.1 Kaplan-Meier Estimate of Time to First Onset of Treatment-Emergent Adverse Events by System Organ Class and Preferred Term
Term
Safety Analysis Set**



HR is computed from the Cox proportional hazards model using stratification factors (Presence or history of brain metastases: Yes/No, ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization. When the number of subjects with at least one event was ≤ 30 , an unstratified Cox model was run.

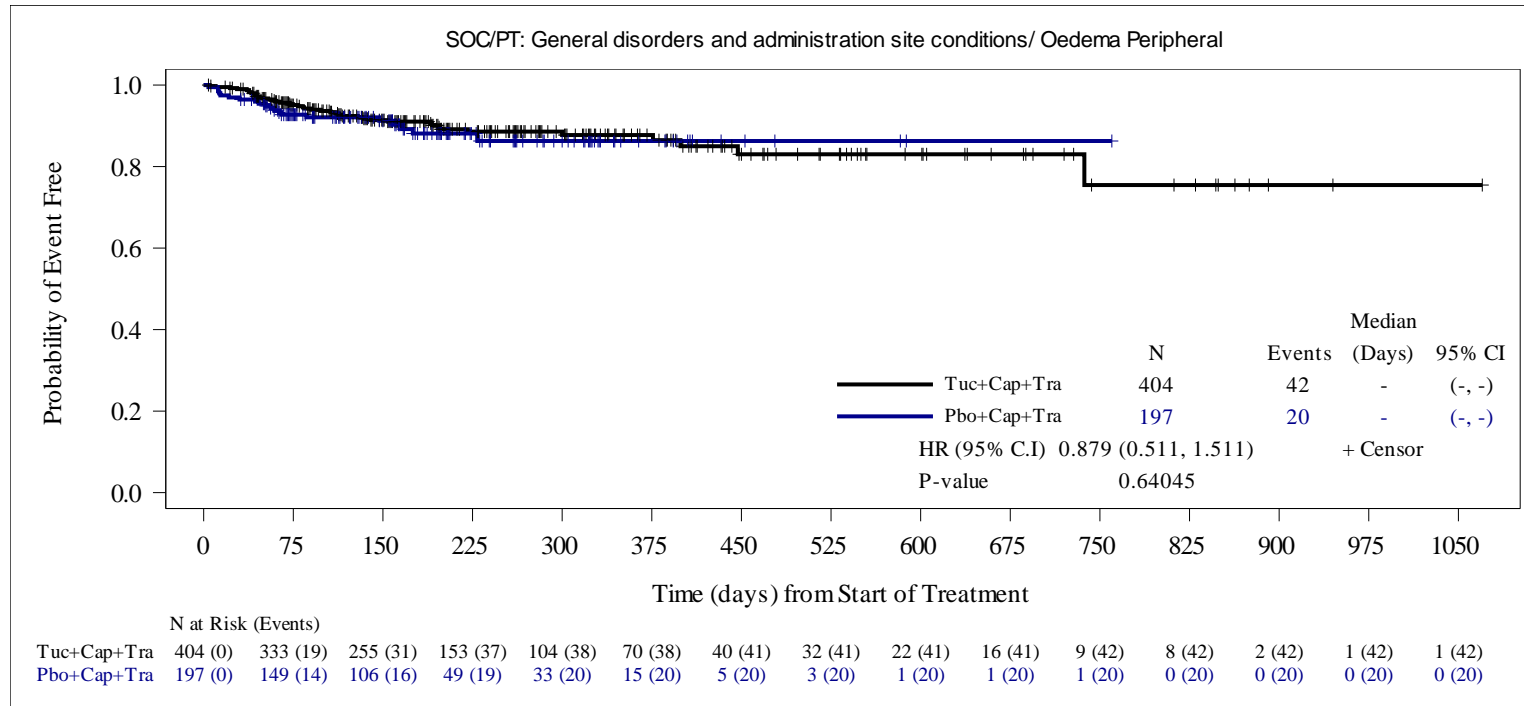
Two-sided p-value calculated from Cox proportional hazards model .

Data Snapshot: 14OCT2019, Data Cutoff Date: 04SEP2019

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**Figure 2.7.1 Kaplan-Meier Estimate of Time to First Onset of Treatment-Emergent Adverse Events by System Organ Class and Preferred Term
Safety Analysis Set**



HR is computed from the Cox proportional hazards model using stratification factors (Presence or history of brain metastases: Yes/No, ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization. When the number of subjects with at least one event was ≤ 30 , an unstratified Cox model was run.

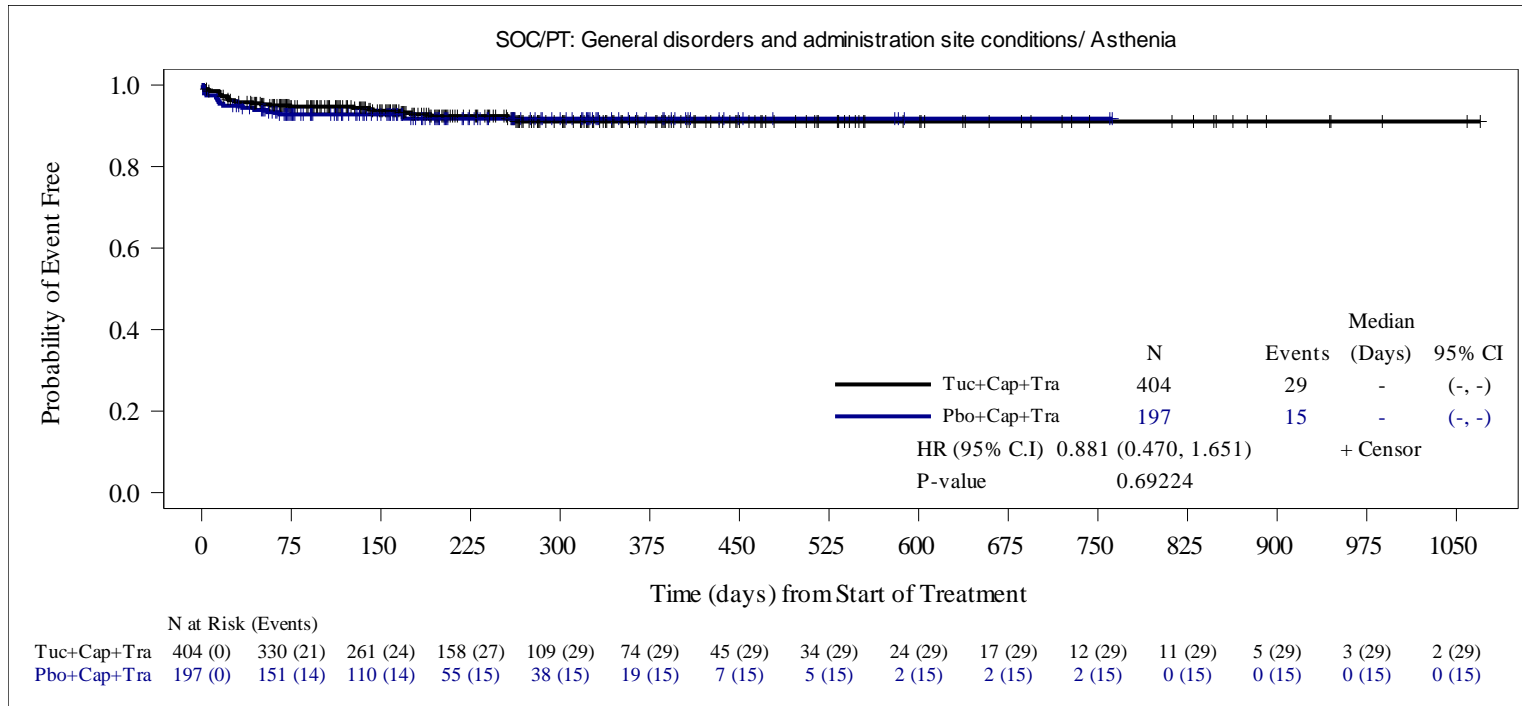
Two-sided p-value calculated from Cox proportional hazards model .

Data Snapshot: 14OCT2019, Data Cutoff Date: 04SEP2019

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**Figure 2.7.1 Kaplan-Meier Estimate of Time to First Onset of Treatment-Emergent Adverse Events by System Organ Class and Preferred Term
Safety Analysis Set**



HR is computed from the Cox proportional hazards model using stratification factors (Presence or history of brain metastases: Yes/No, ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization. When the number of subjects with at least one event was ≤ 30 , an unstratified Cox model was run.

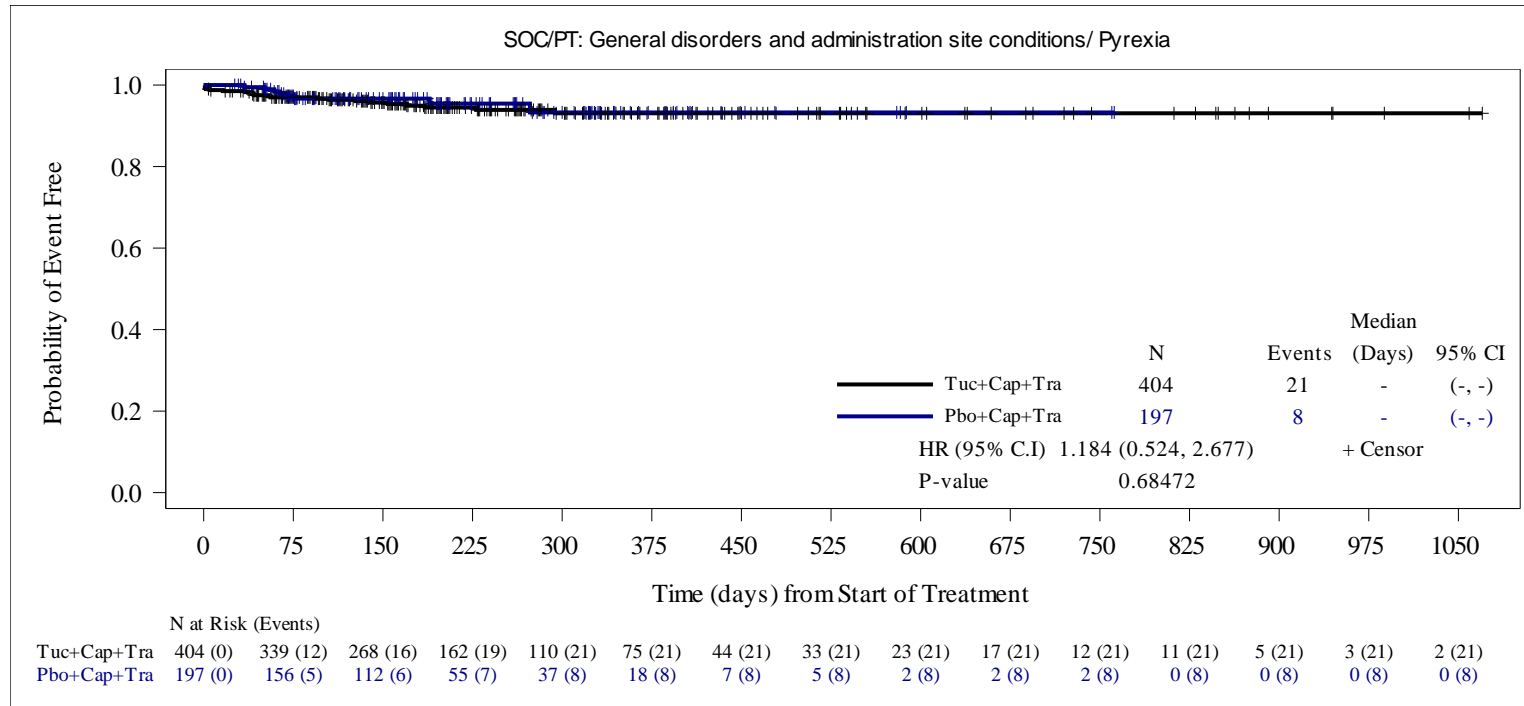
Two-sided p-value calculated from Cox proportional hazards model .

Data Snapshot: 14OCT2019, Data Cutoff Date: 04SEP2019

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Seattle Genetics Protocol ONT-380-206

**Figure 2.7.1 Kaplan-Meier Estimate of Time to First Onset of Treatment-Emergent Adverse Events by System Organ Class and Preferred Term
Safety Analysis Set**



HR is computed from the Cox proportional hazards model using stratification factors (Presence or history of brain metastases: Yes/No, ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization. When the number of subjects with at least one event was ≤ 30 , an unstratified Cox model was run.

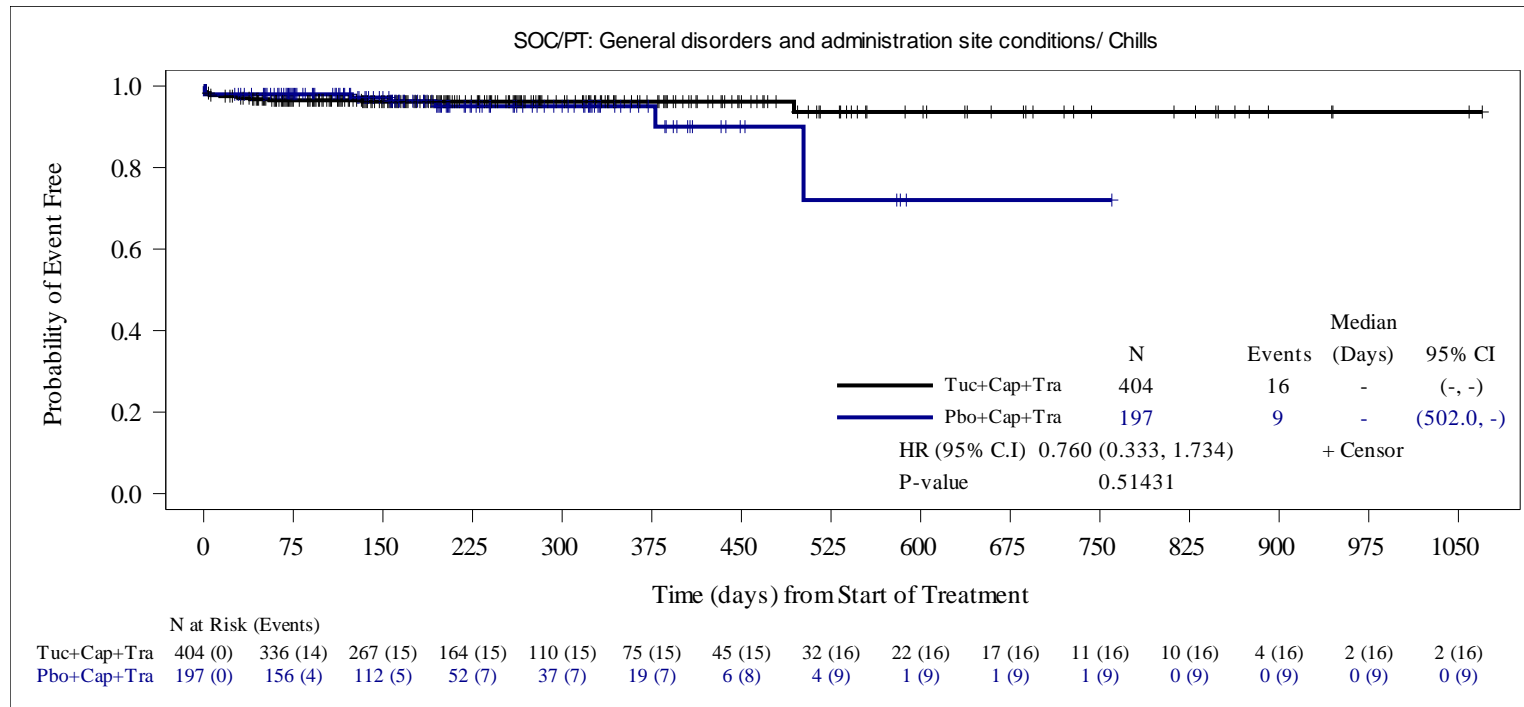
Two-sided p-value calculated from Cox proportional hazards model .

Data Snapshot: 14OCT2019, Data Cutoff Date: 04SEP2019

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Seattle Genetics Protocol ONT-380-206

**Figure 2.7.1 Kaplan-Meier Estimate of Time to First Onset of Treatment-Emergent Adverse Events by System Organ Class and Preferred Term
Safety Analysis Set**



HR is computed from the Cox proportional hazards model using stratification factors (Presence or history of brain metastases: Yes/No, ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization. When the number of subjects with at least one event was ≤ 30 , an unstratified Cox model was run.

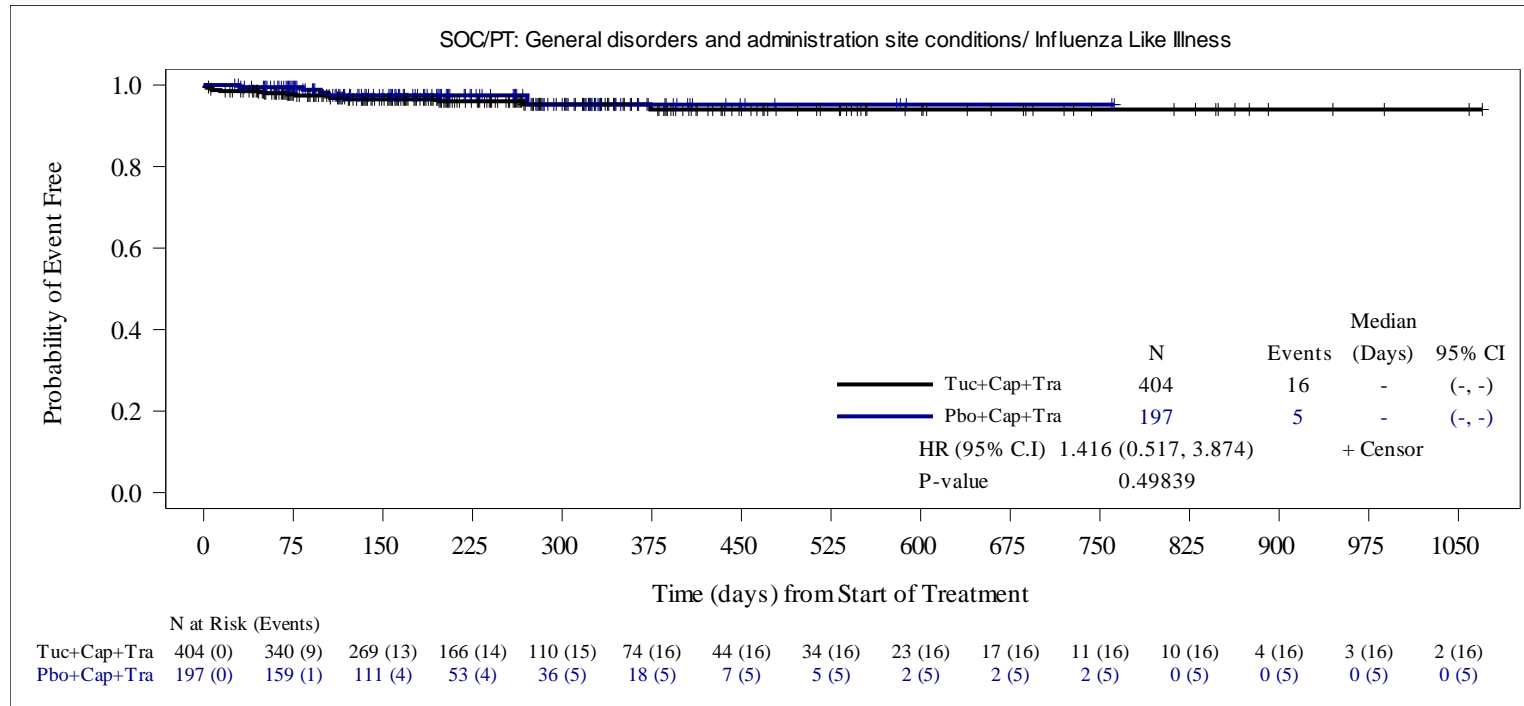
Two-sided p-value calculated from Cox proportional hazards model .

Data Snapshot: 14OCT2019, Data Cutoff Date: 04SEP2019

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**Figure 2.7.1 Kaplan-Meier Estimate of Time to First Onset of Treatment-Emergent Adverse Events by System Organ Class and Preferred Term
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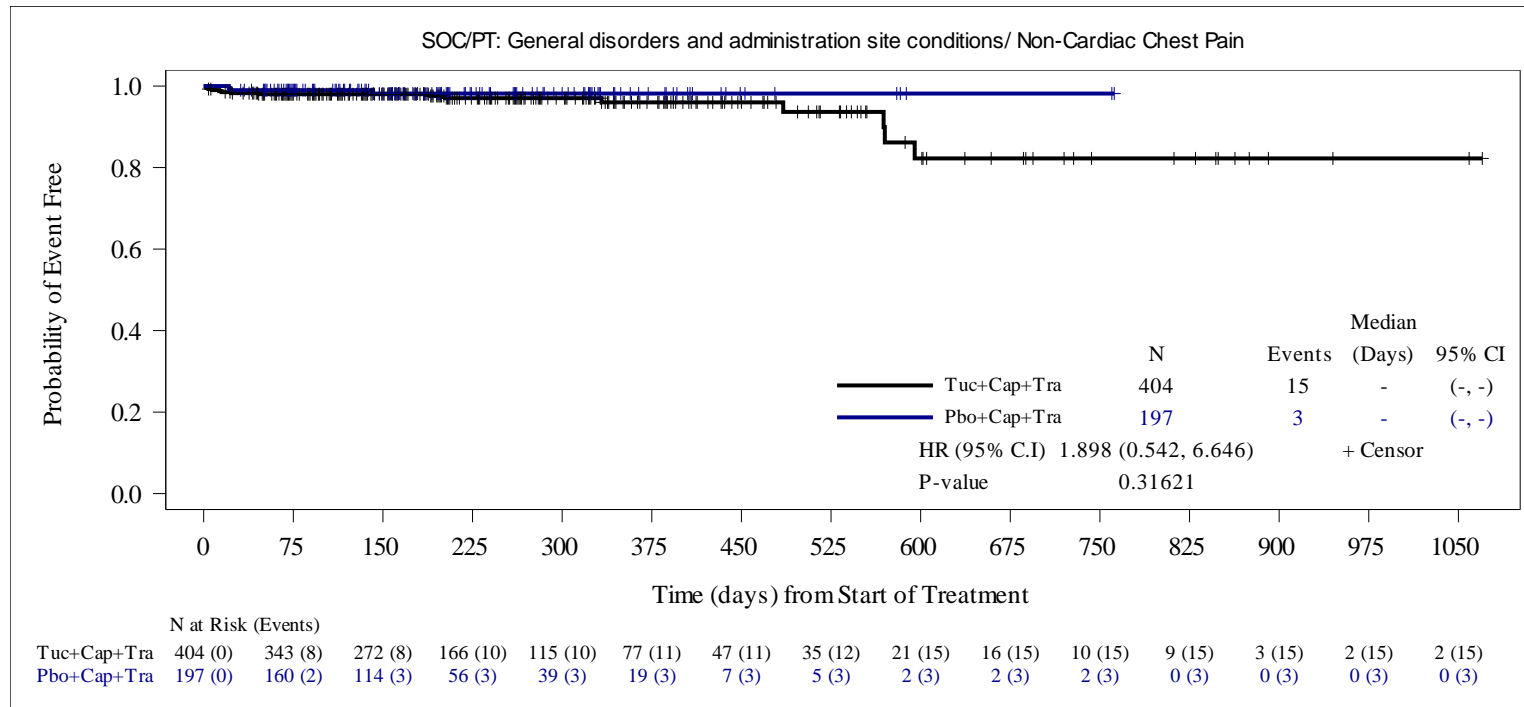
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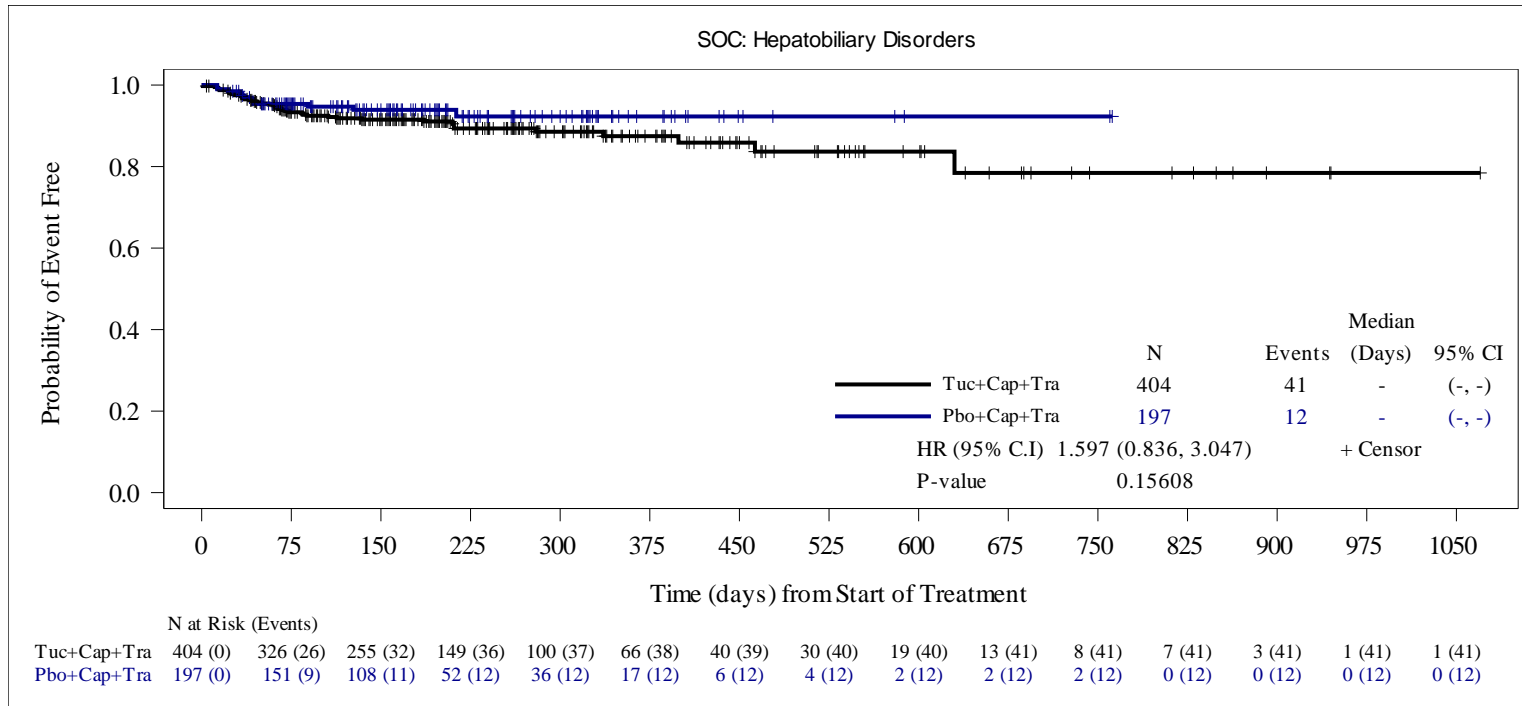
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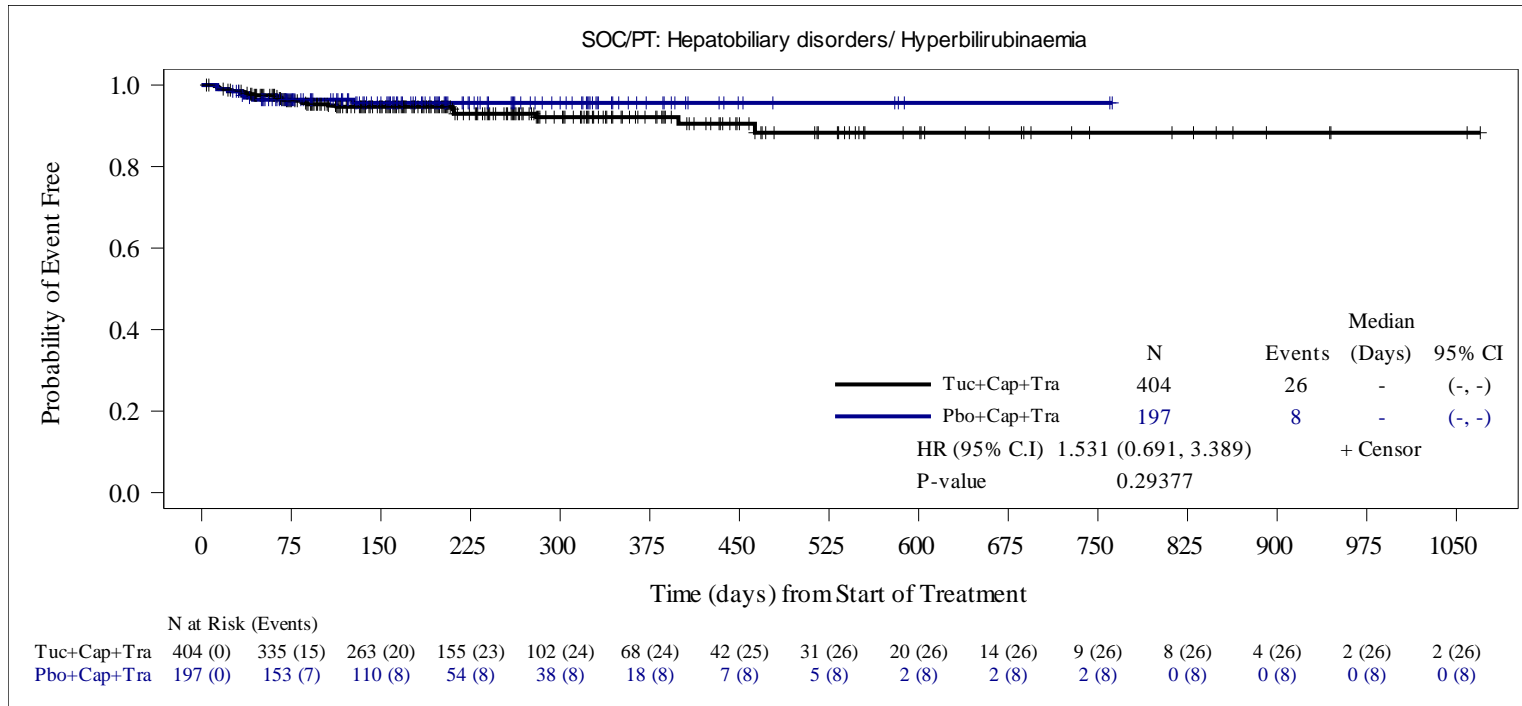
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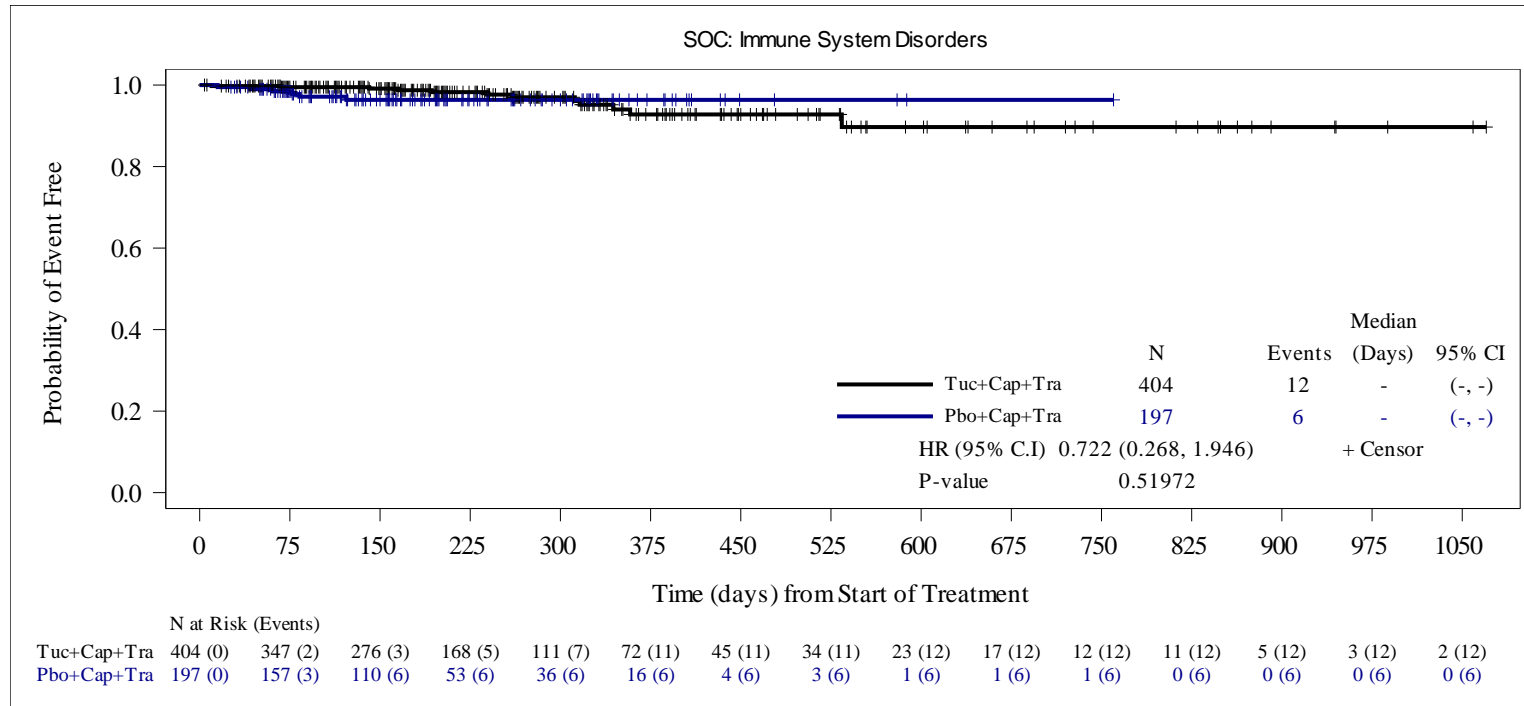
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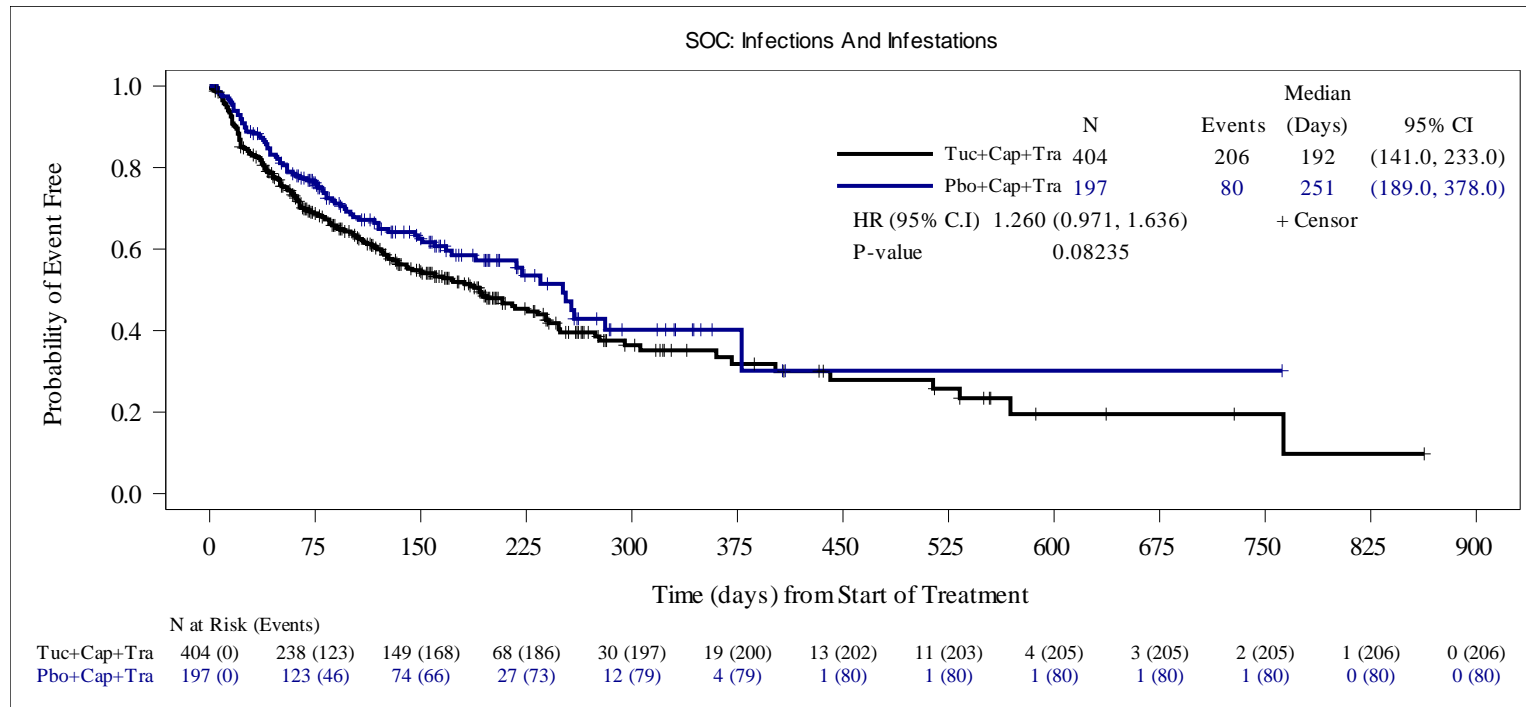
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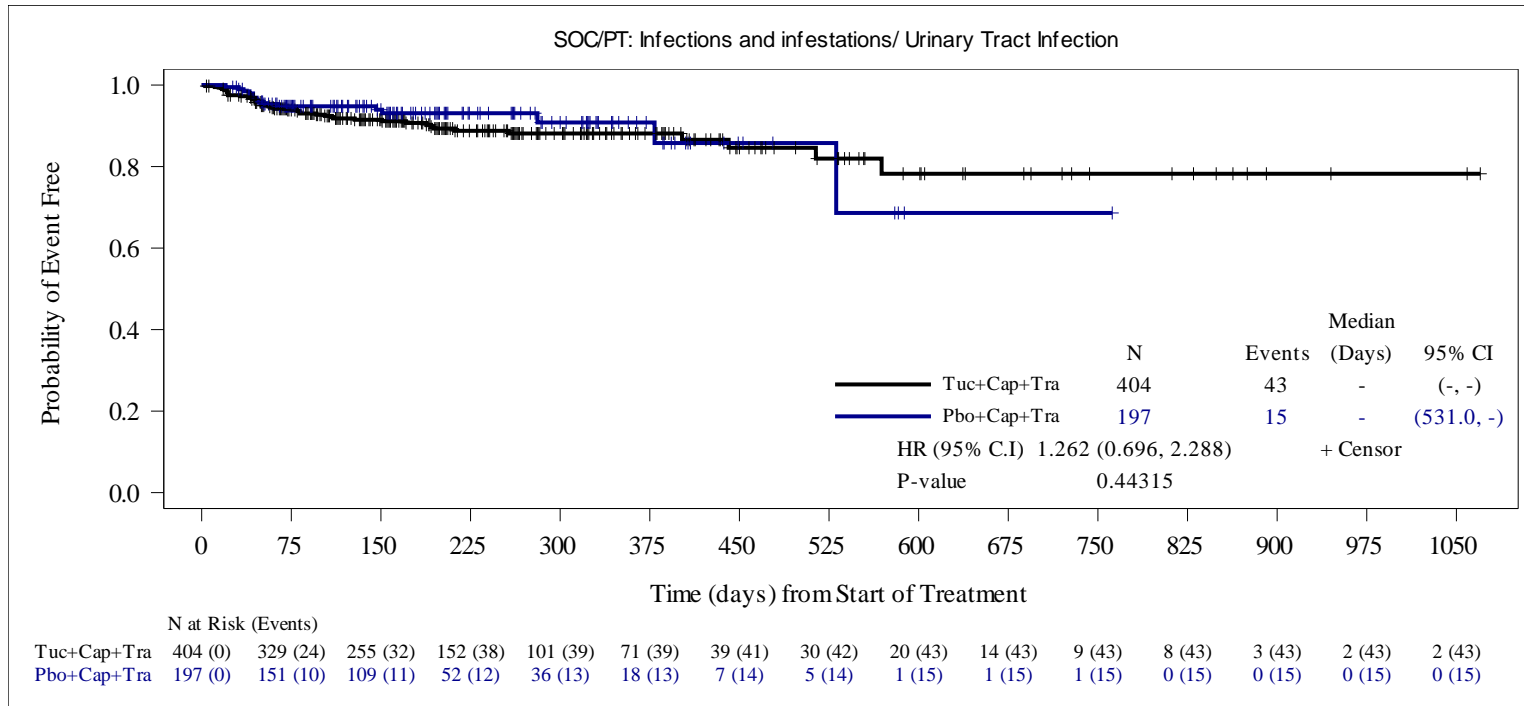
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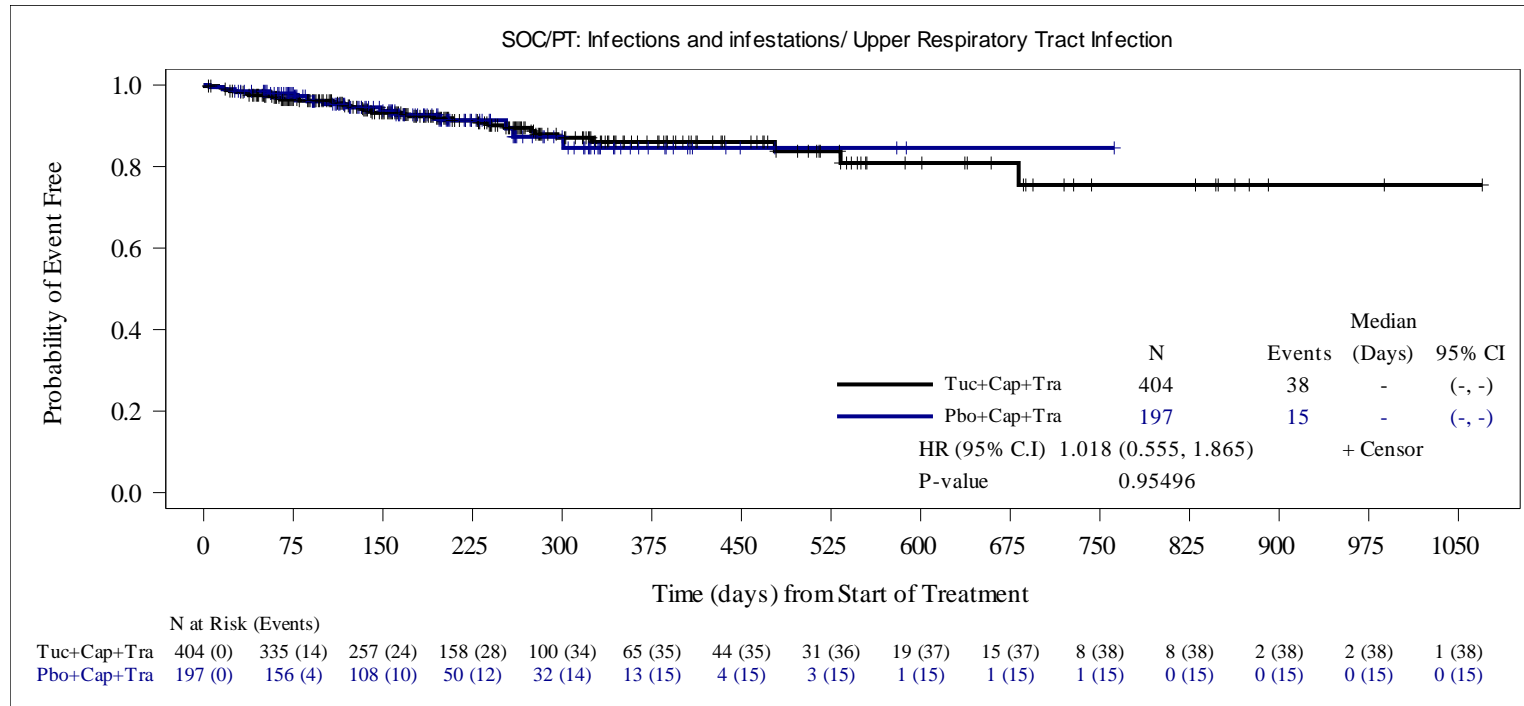
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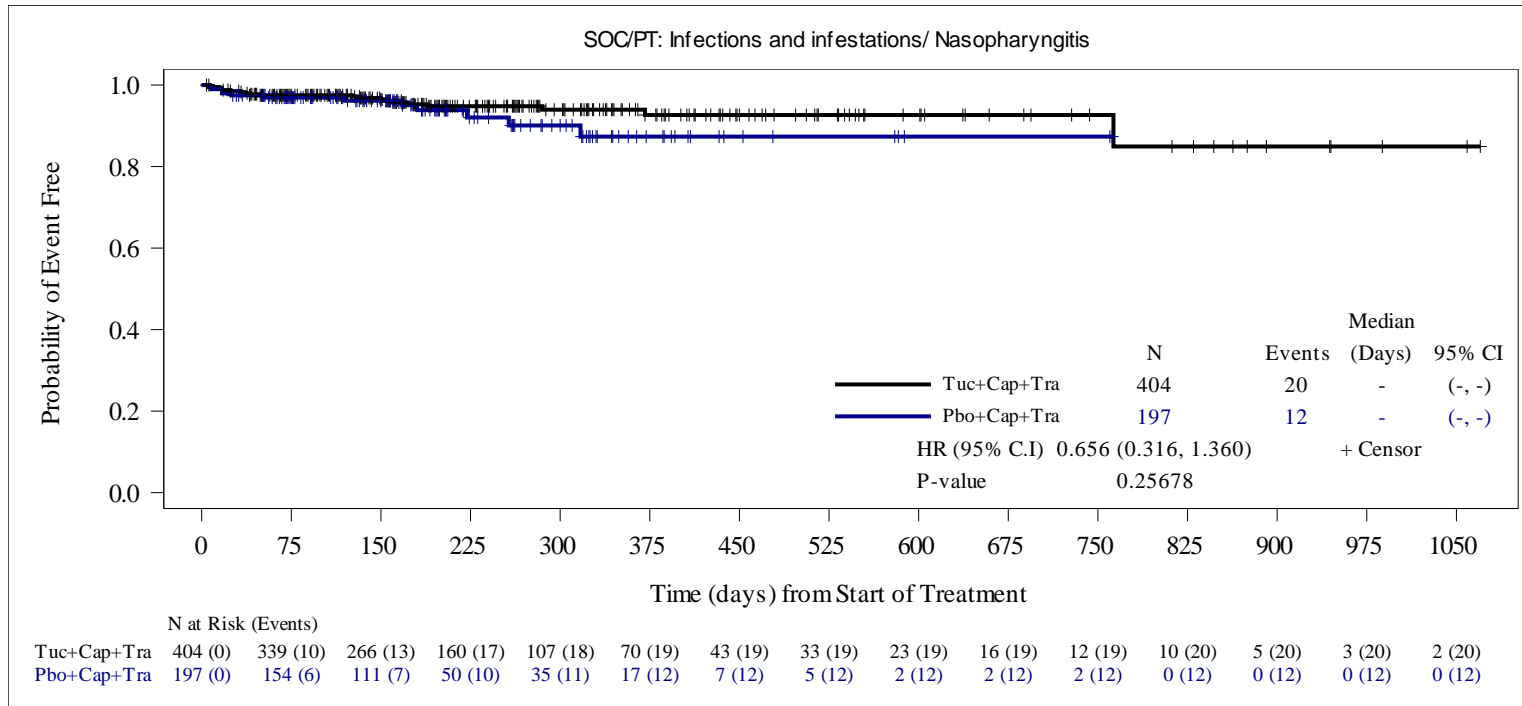
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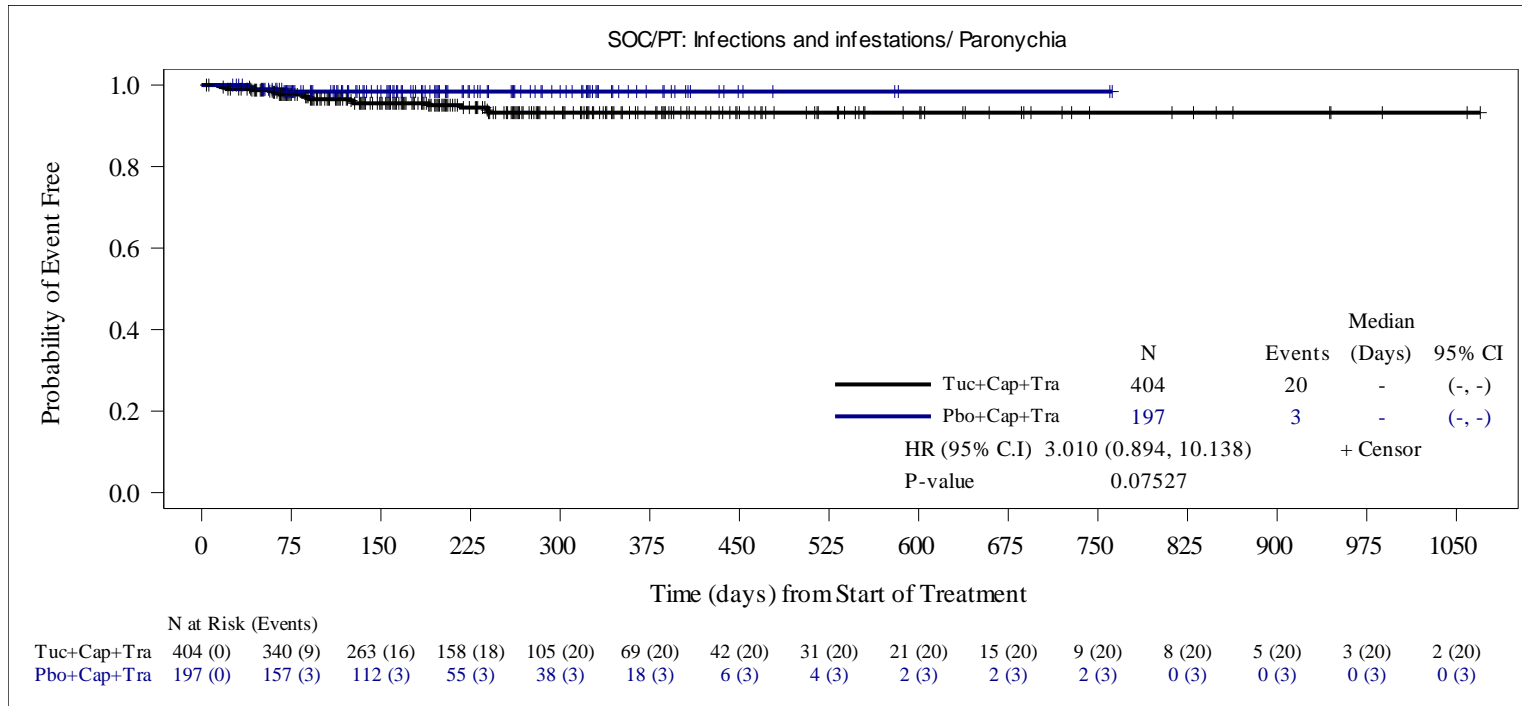
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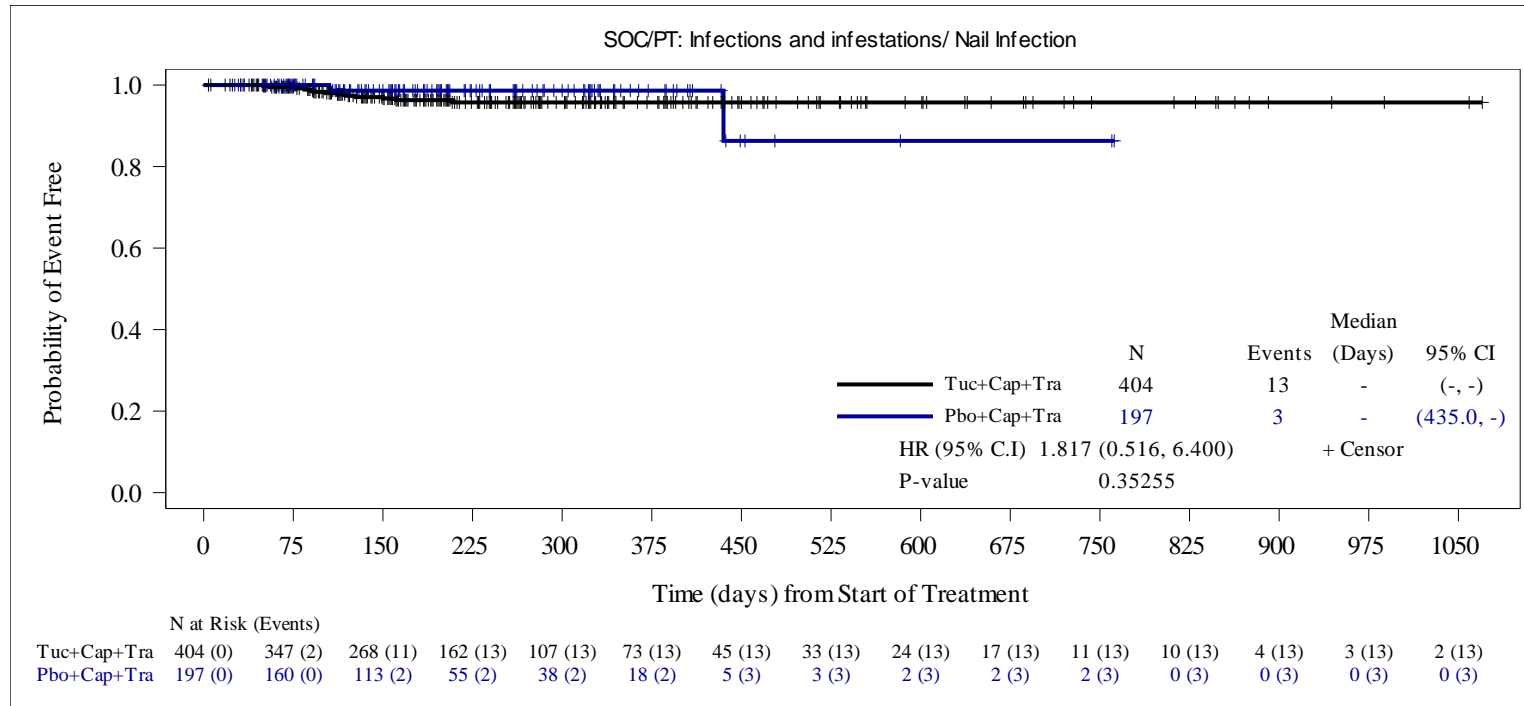
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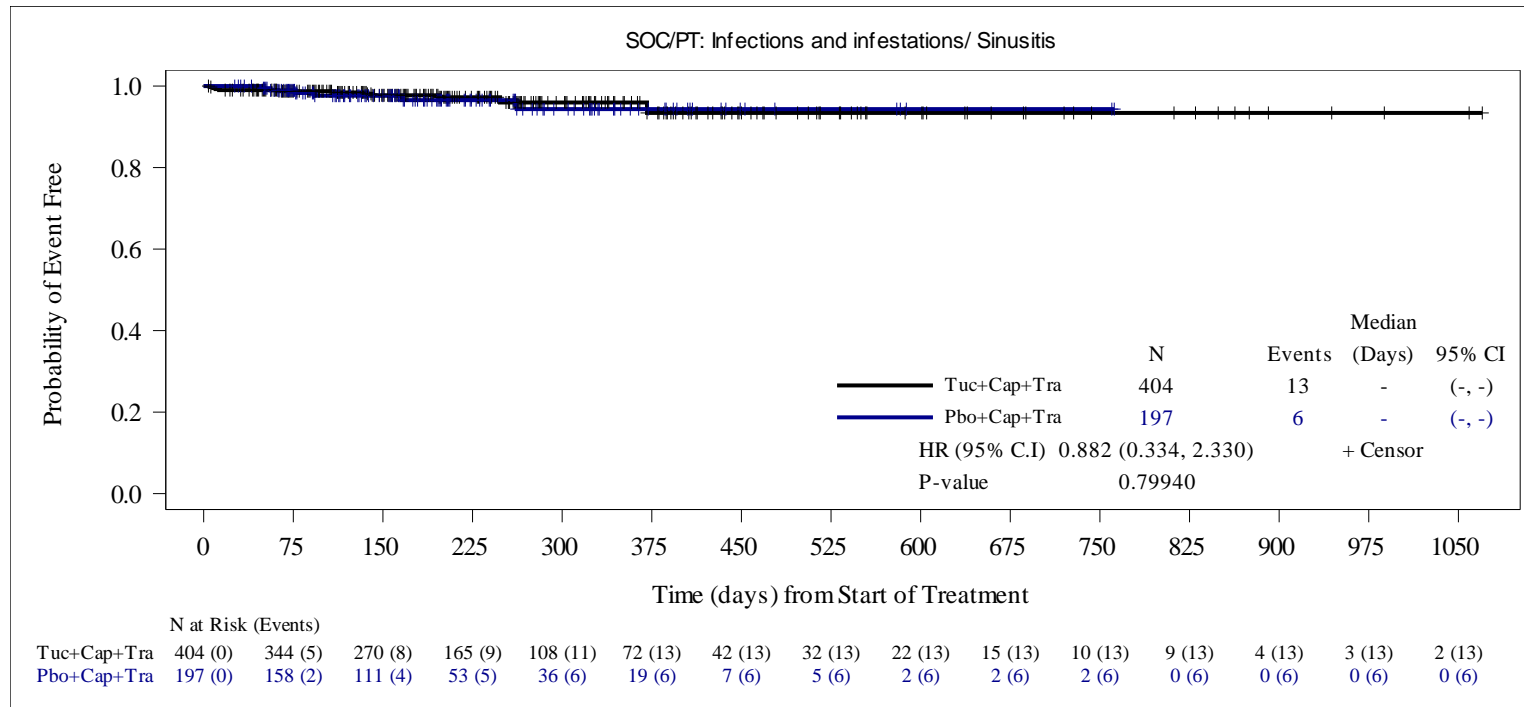
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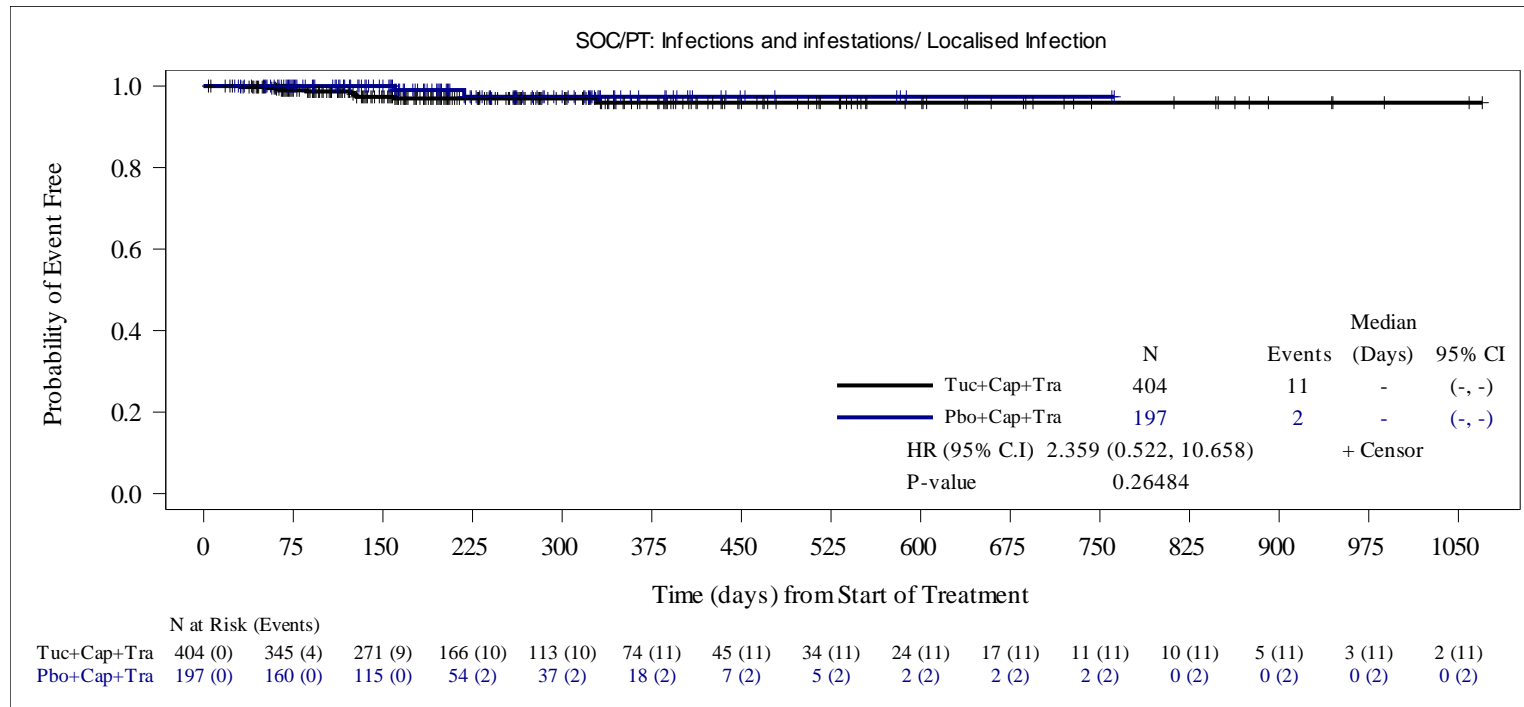
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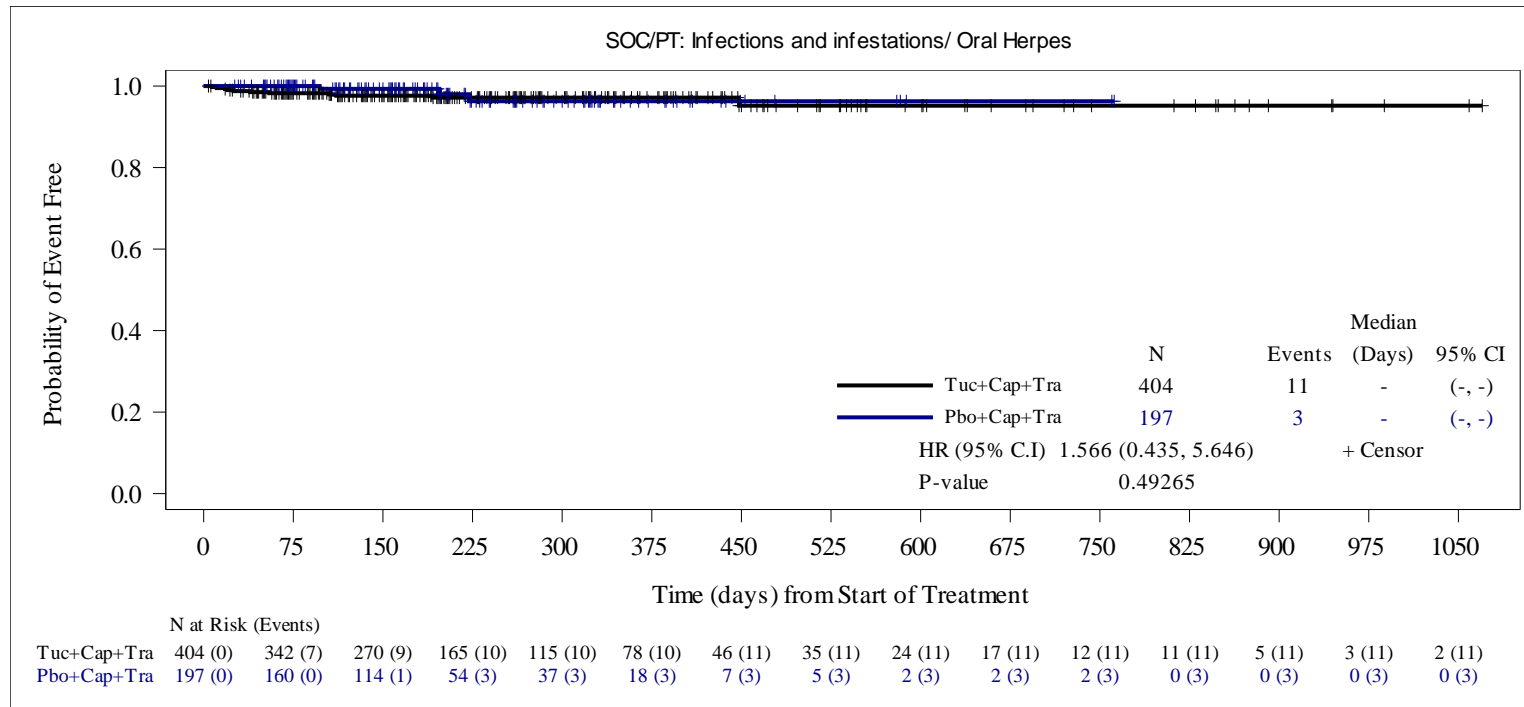
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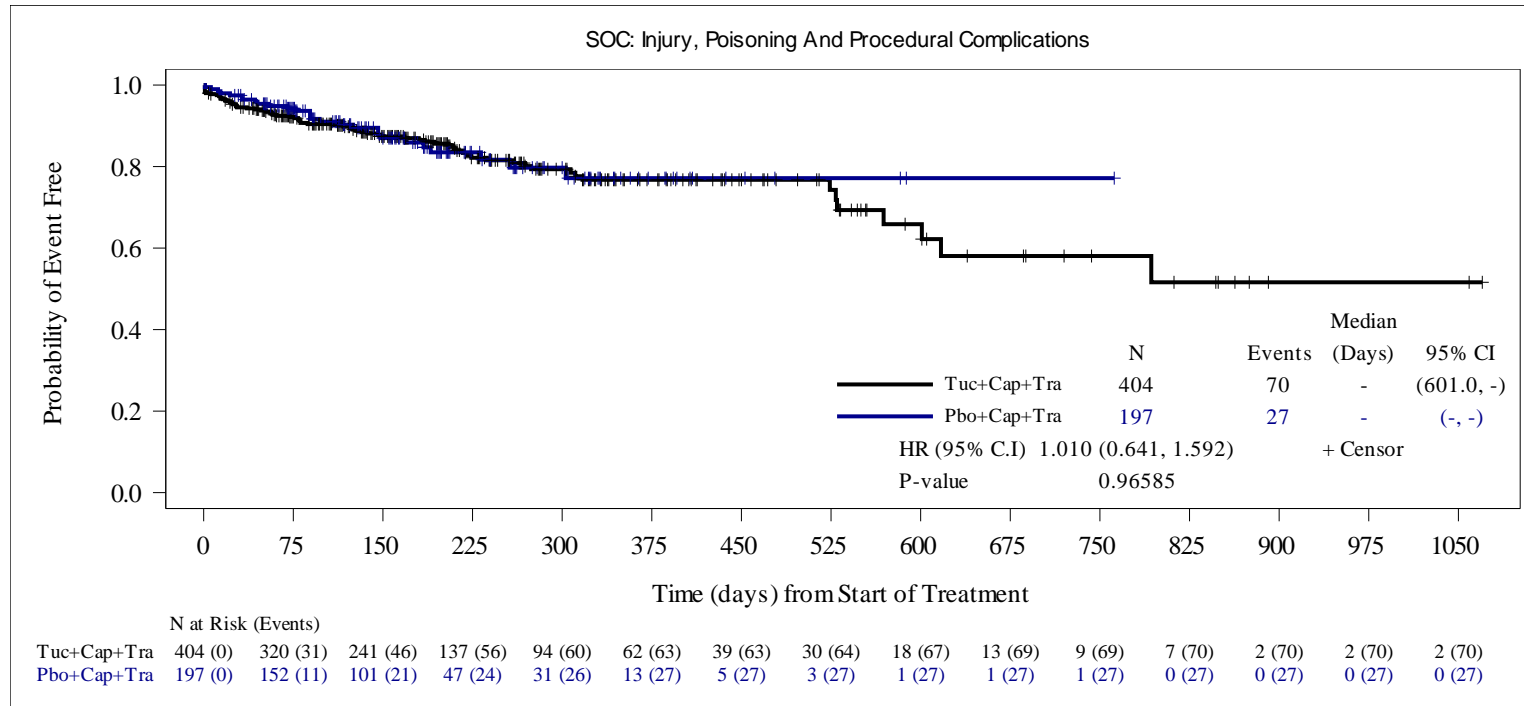
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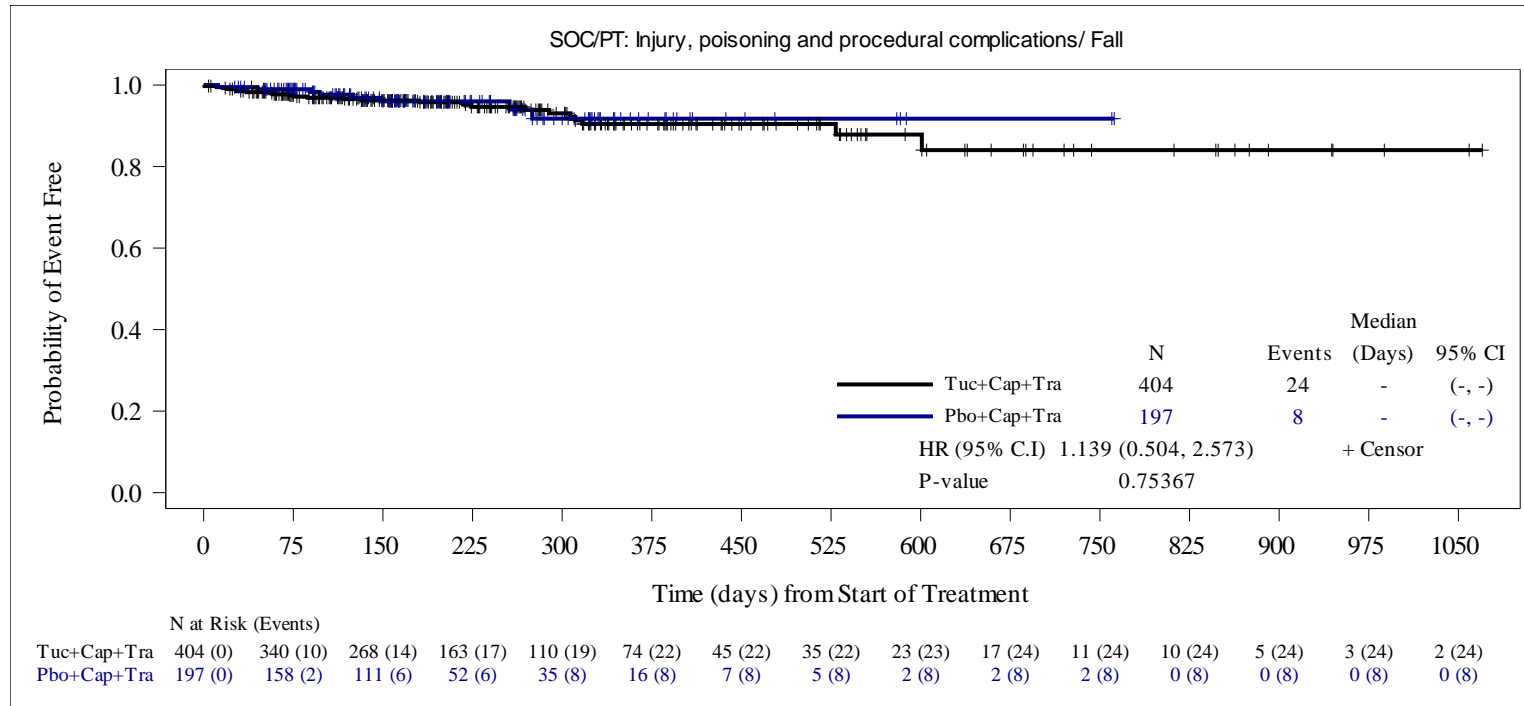
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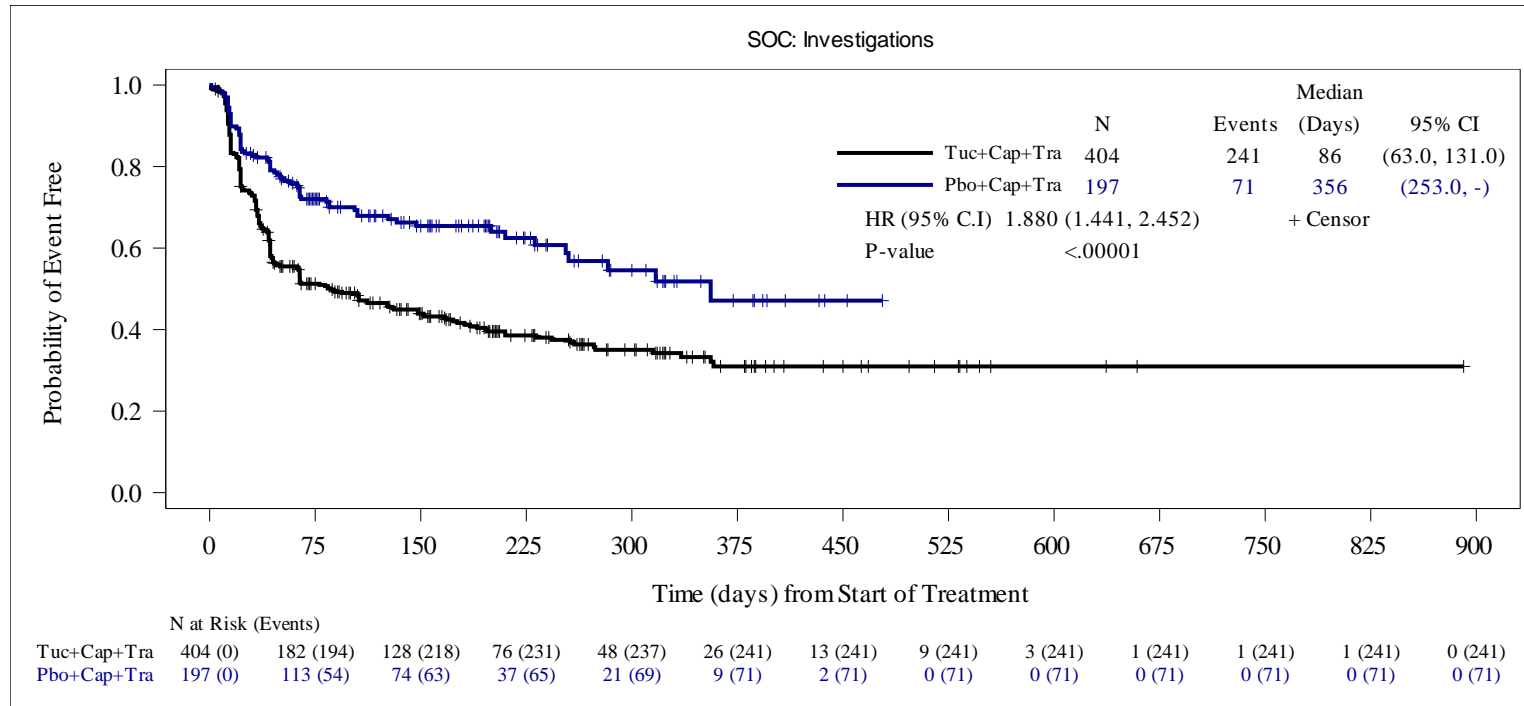
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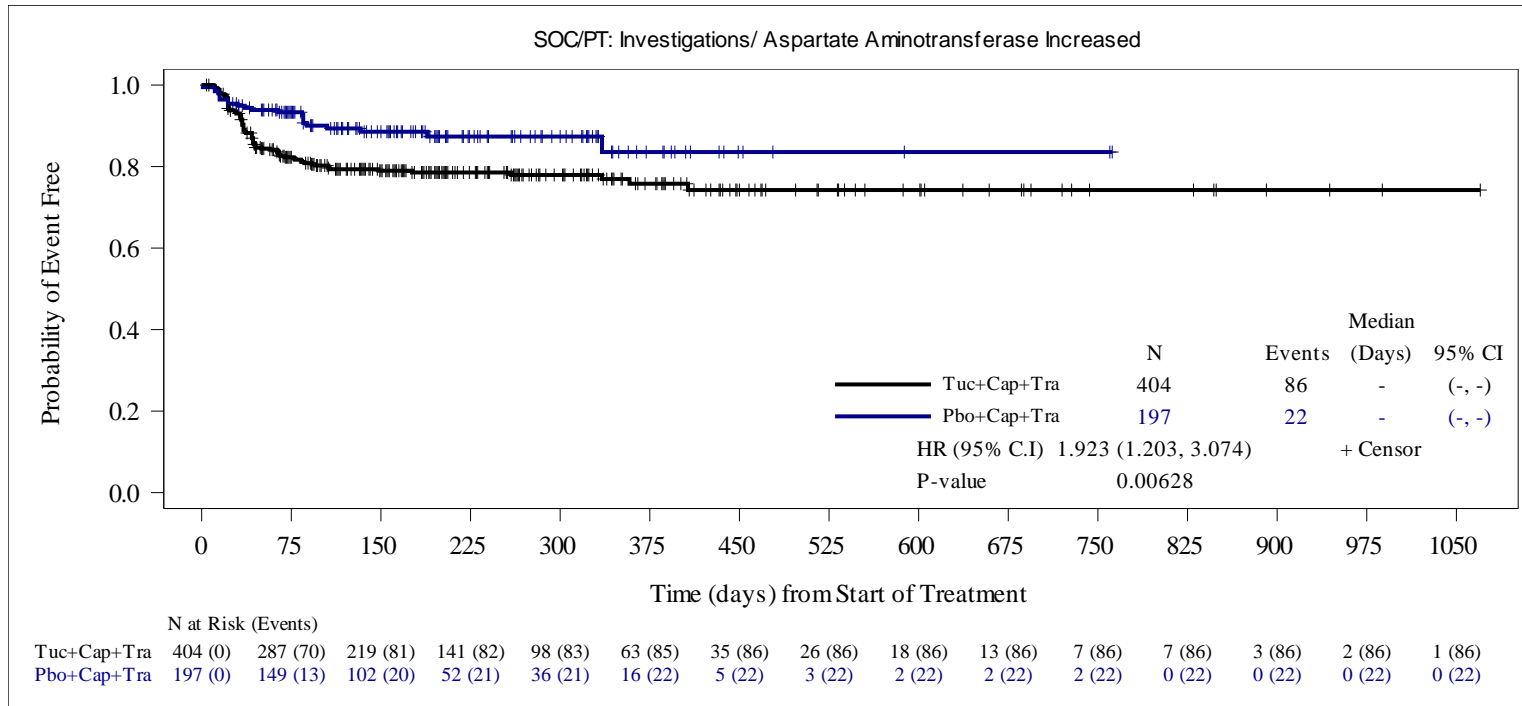
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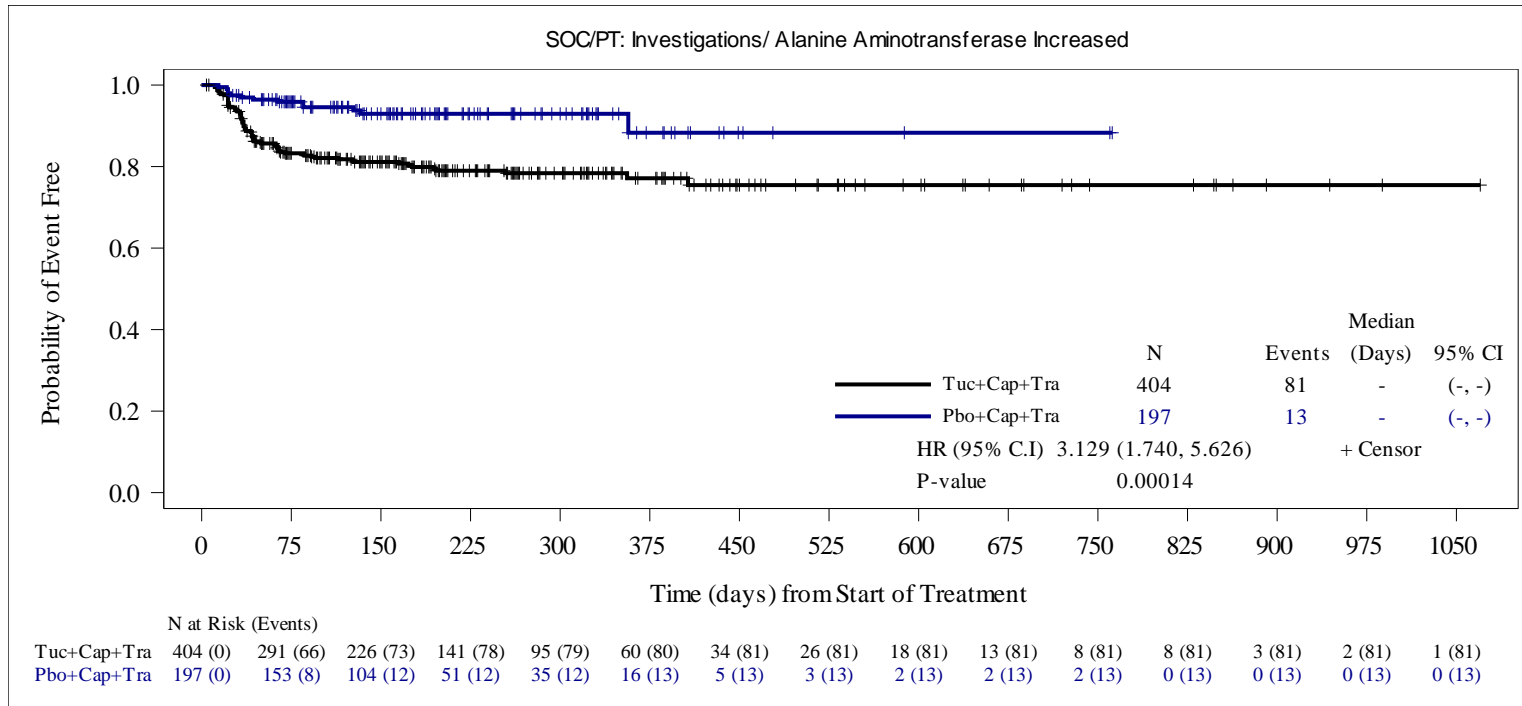
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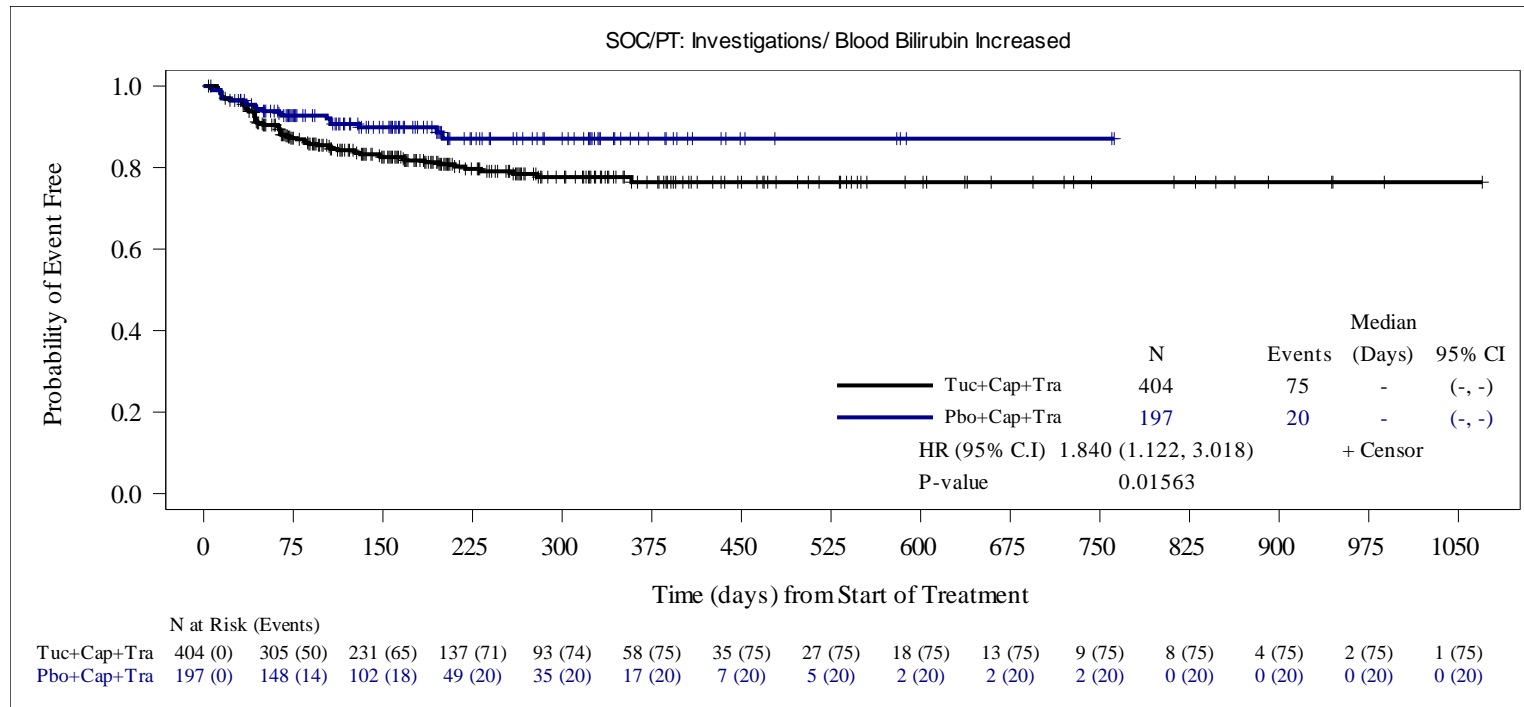
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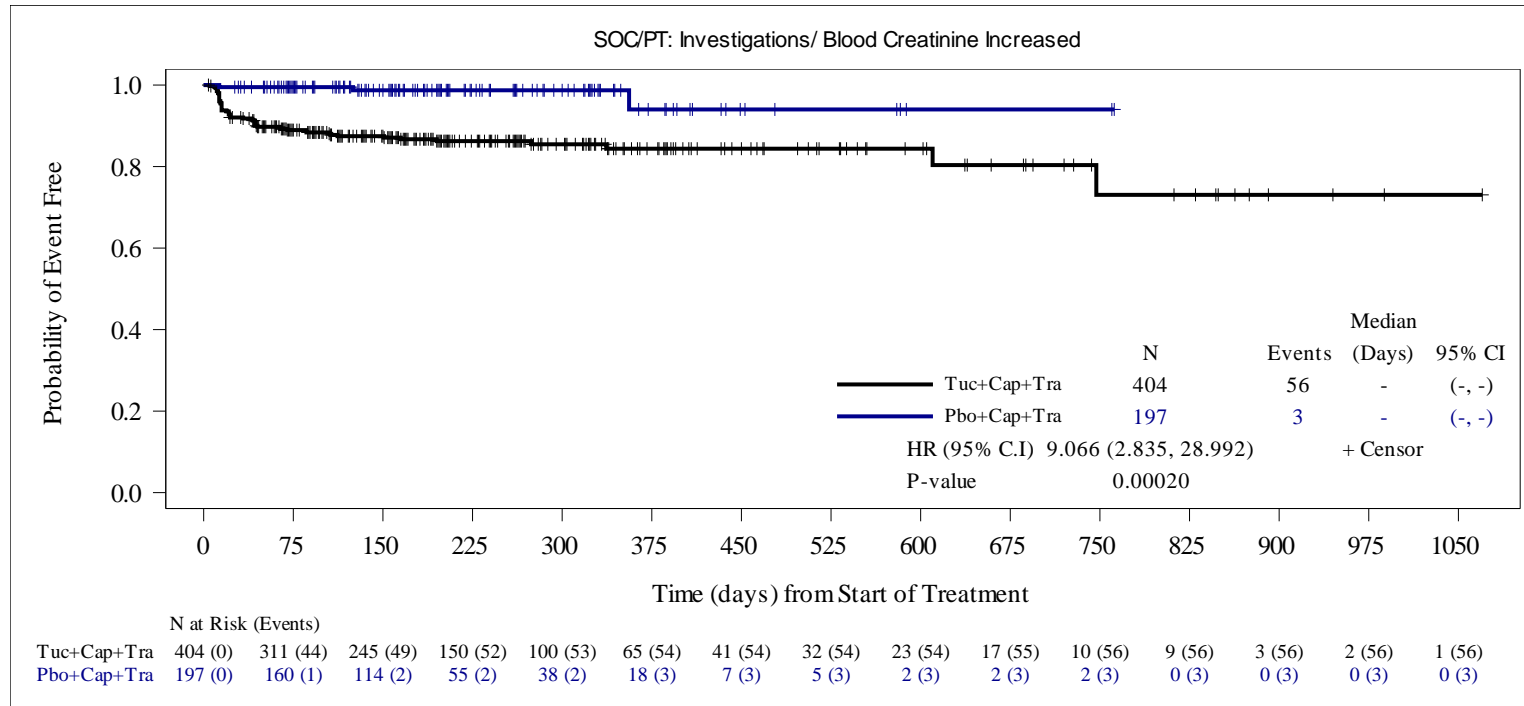
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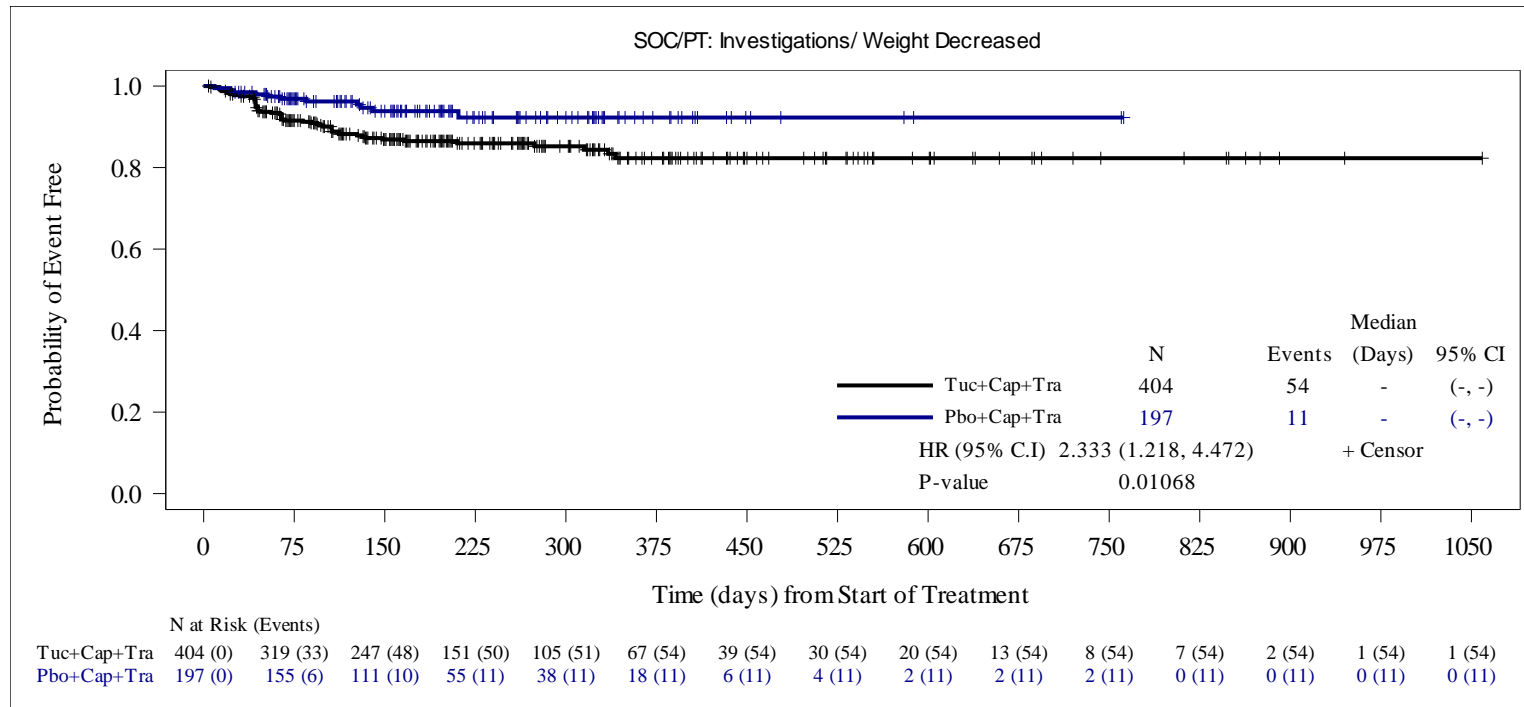
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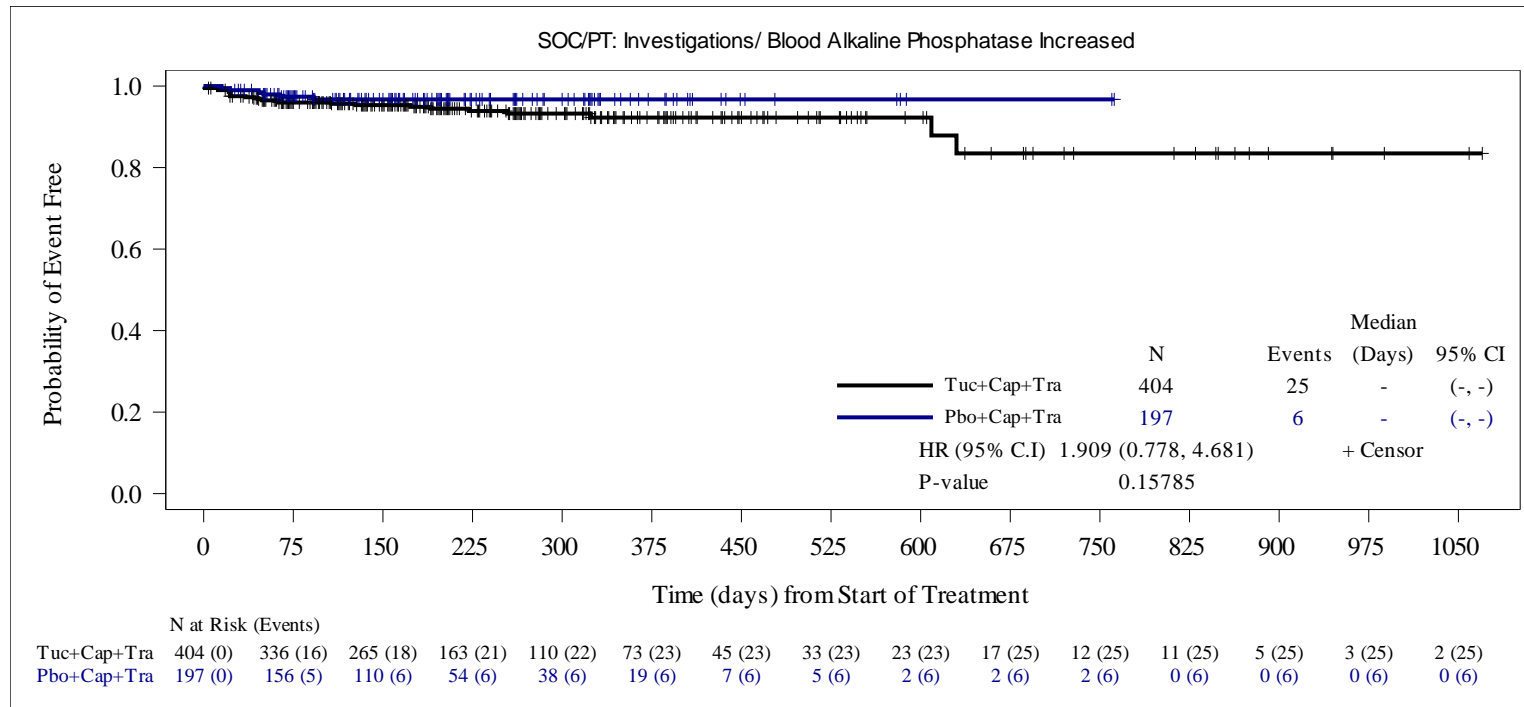
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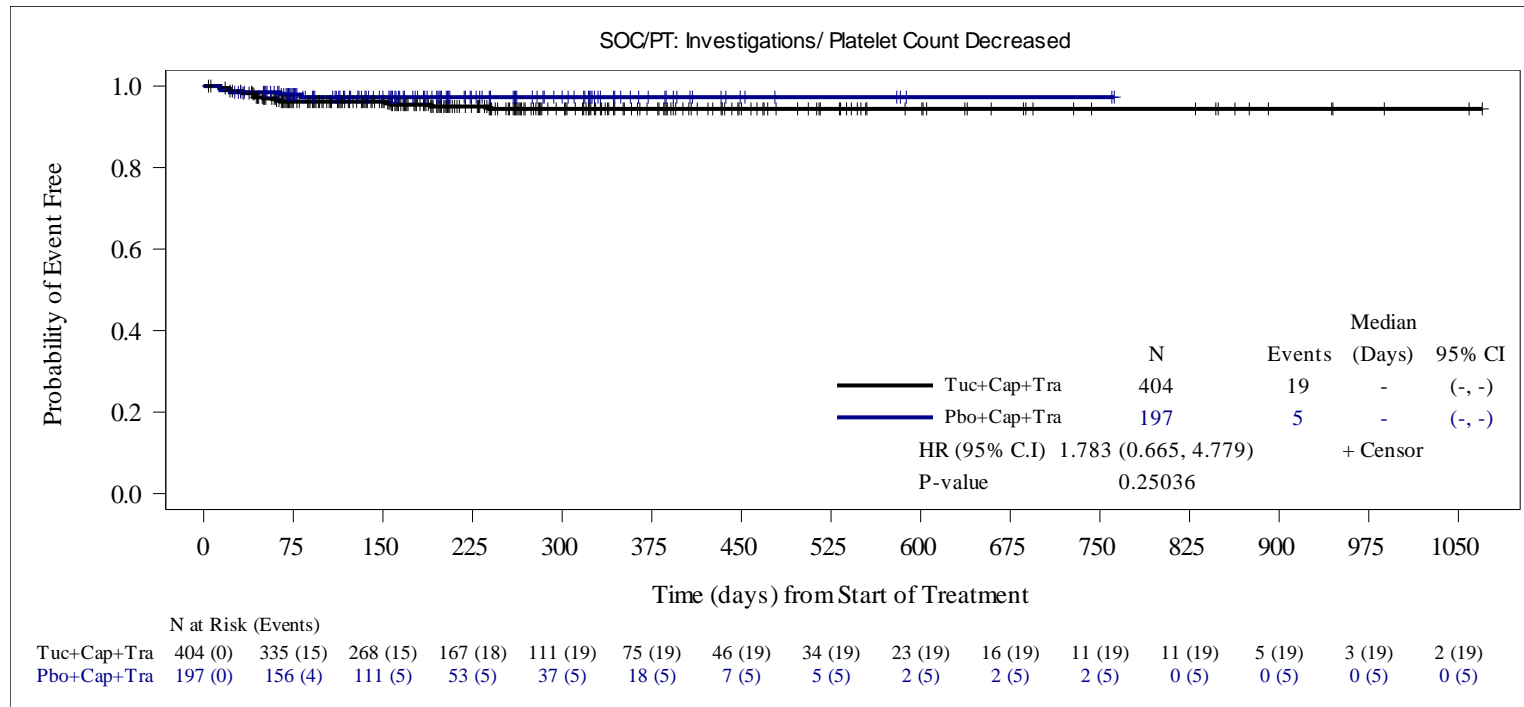
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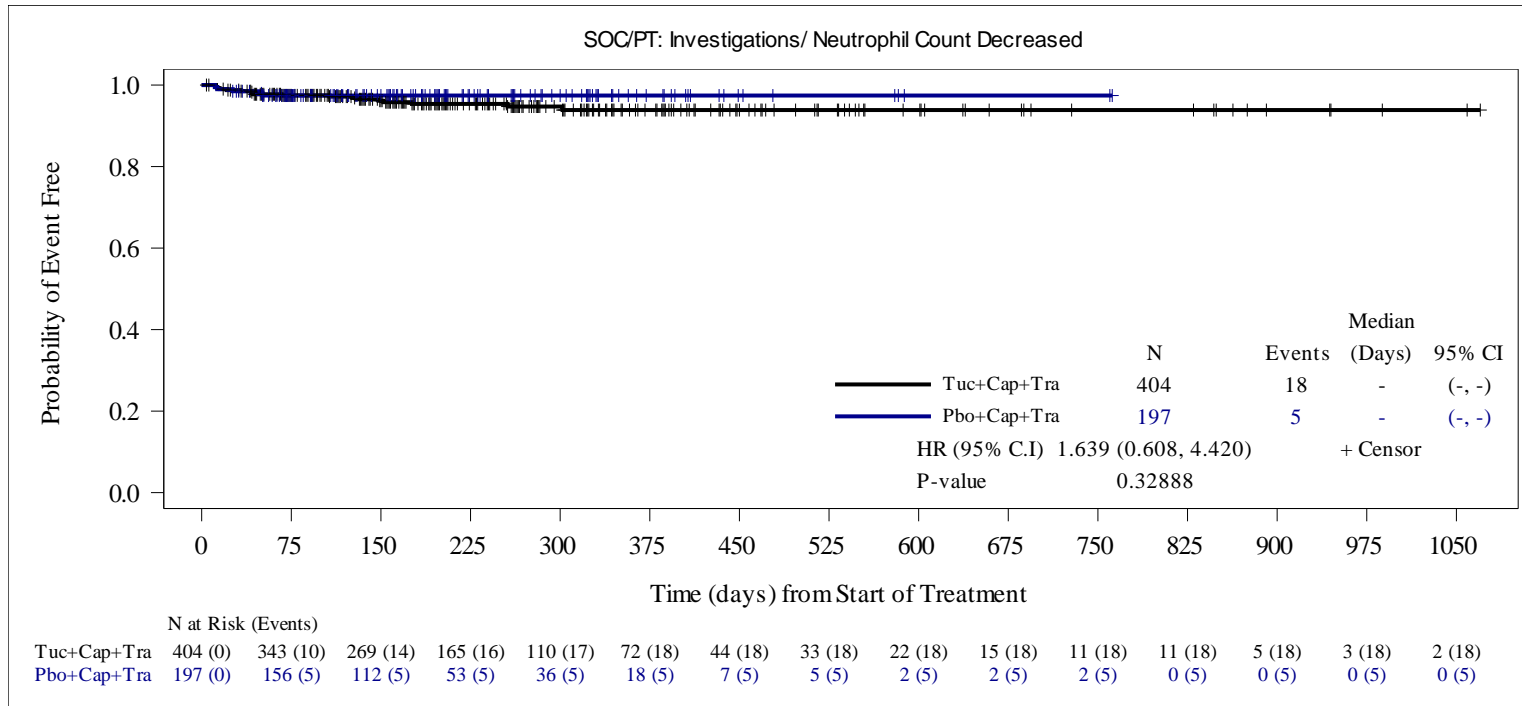
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**Figure 2.7.1 Kaplan-Meier Estimate of Time to First Onset of Treatment-Emergent Adverse Events by System Organ Class and Preferred Term
Safety Analysis Set**



HR is computed from the Cox proportional hazards model using stratification factors (Presence or history of brain metastases: Yes/No, ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization. When the number of subjects with at least one event was ≤ 30 , an unstratified Cox model was run.

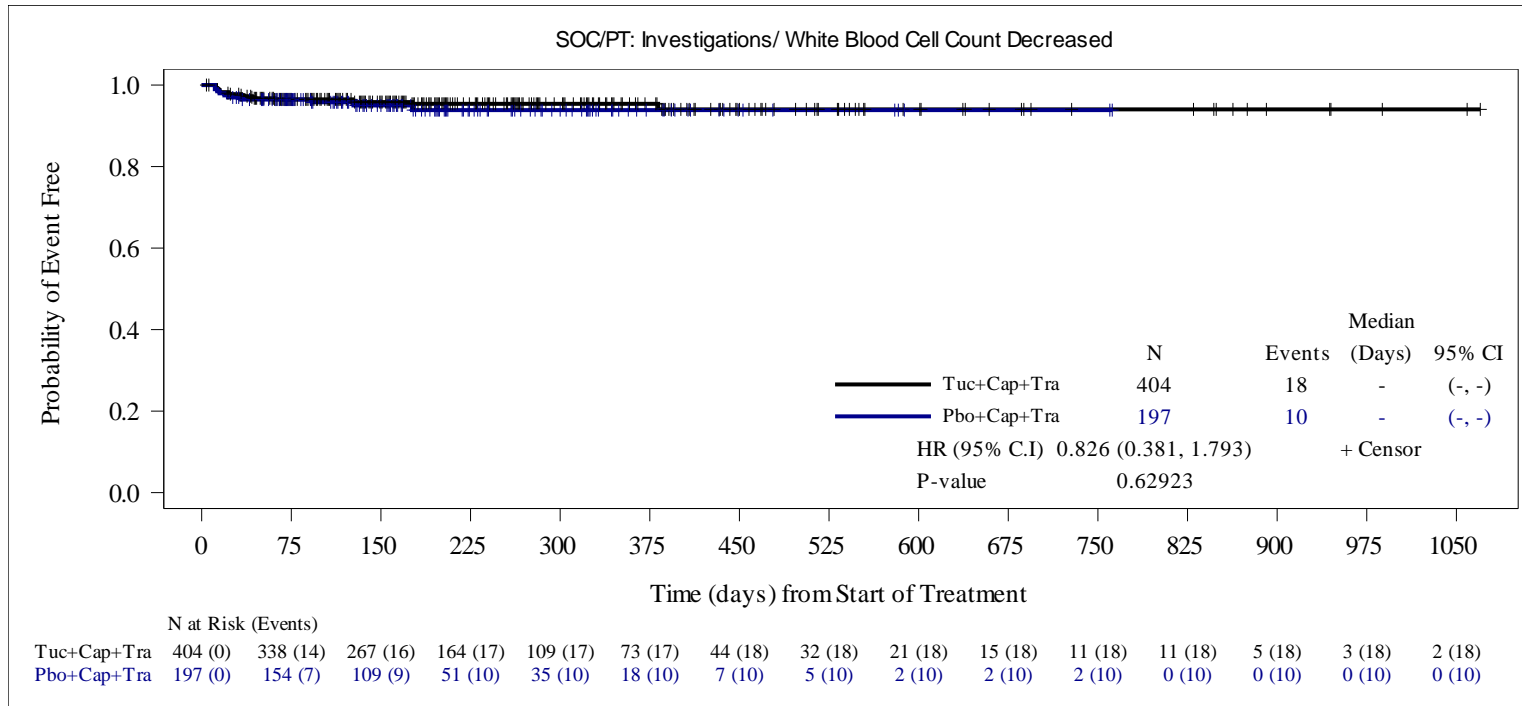
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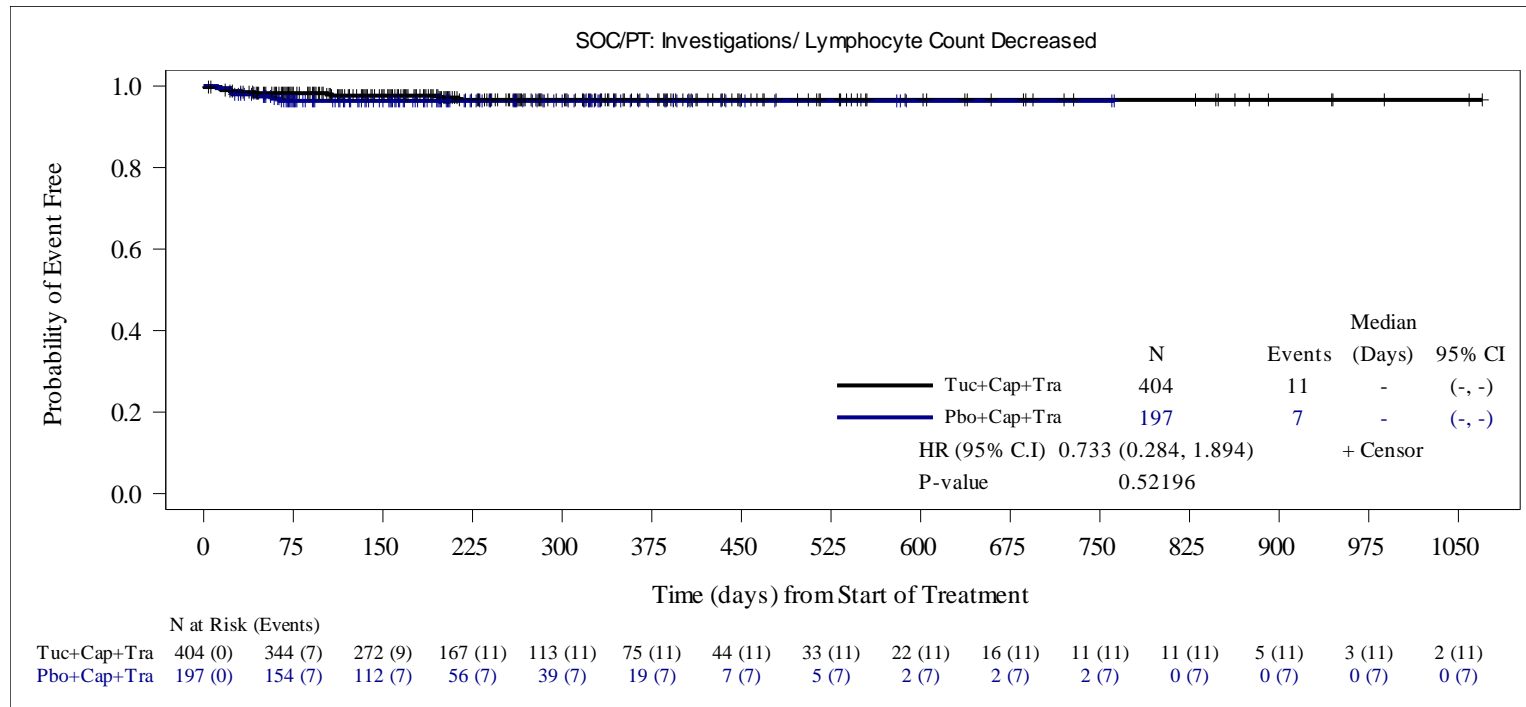
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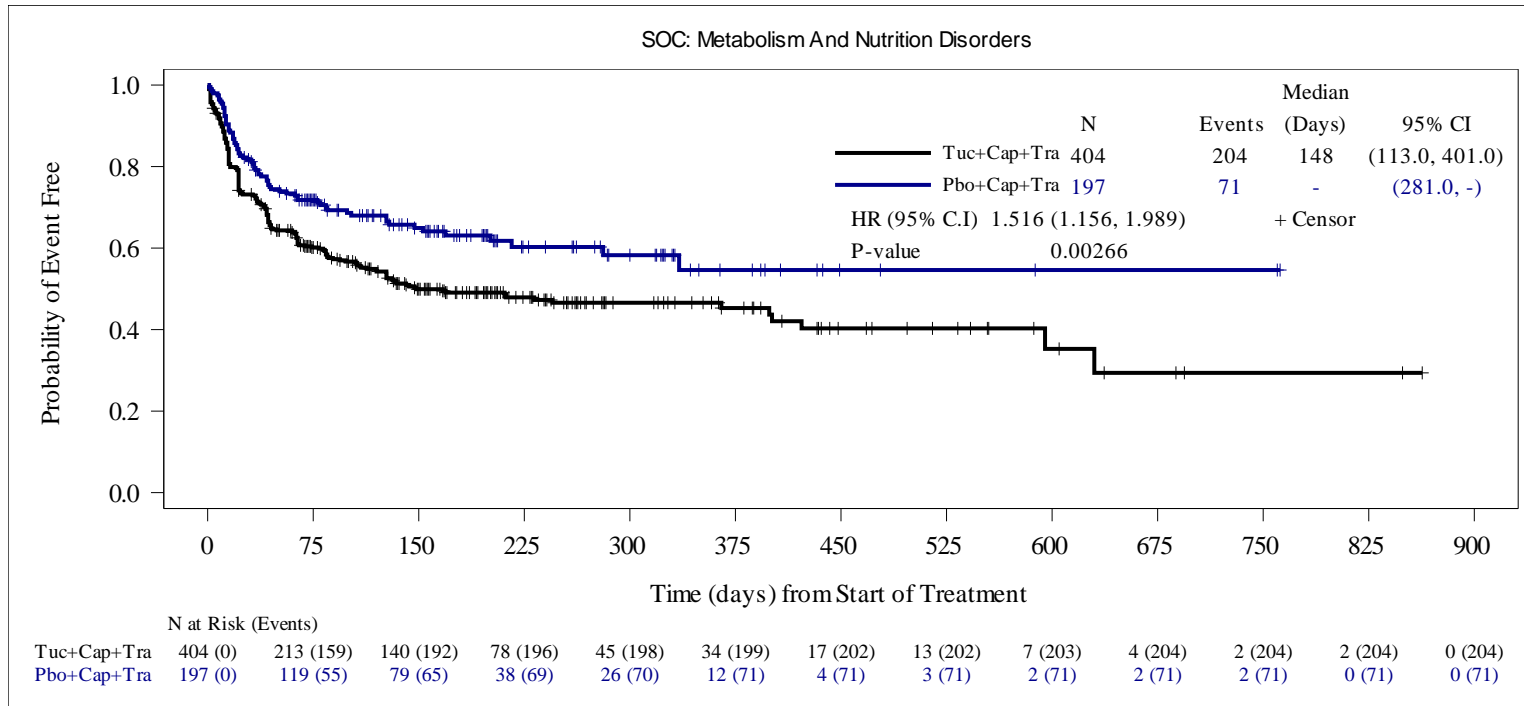
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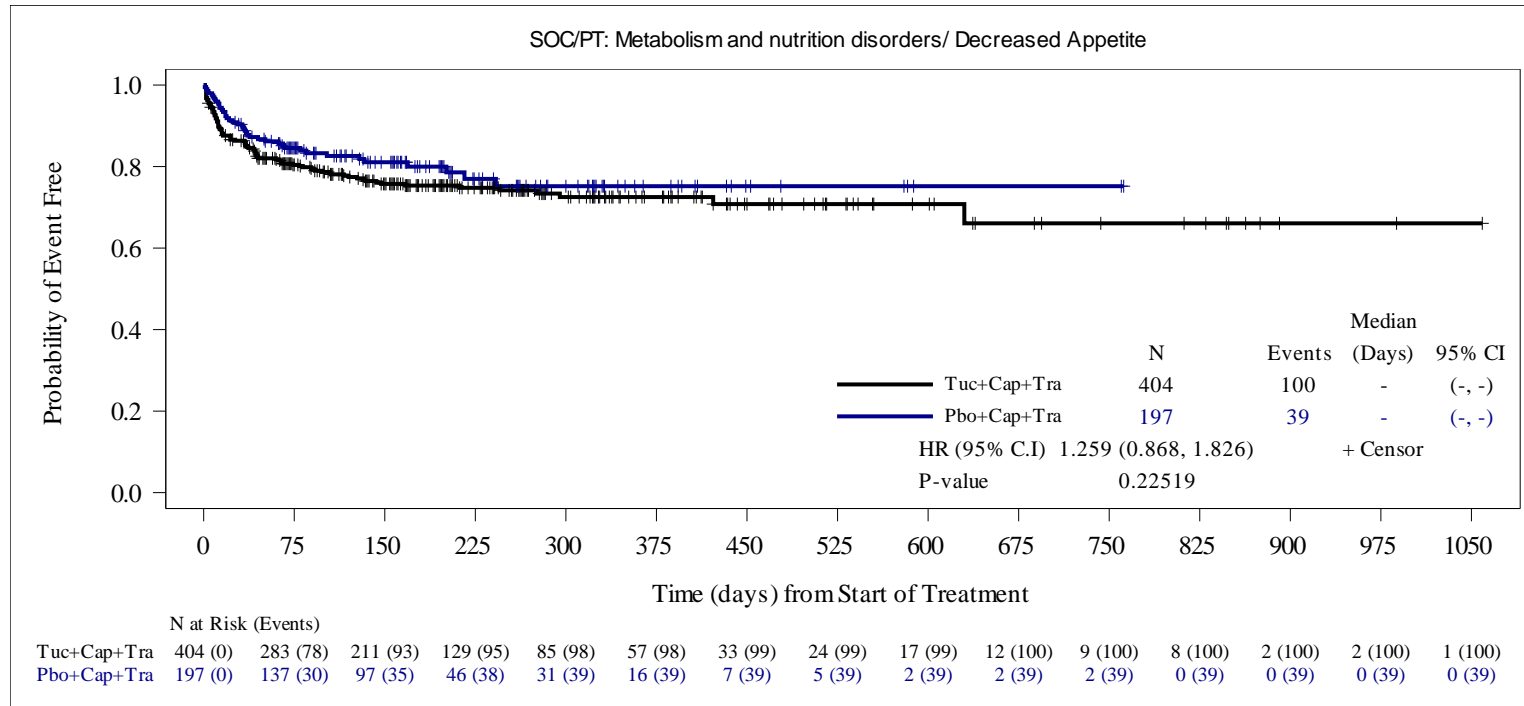
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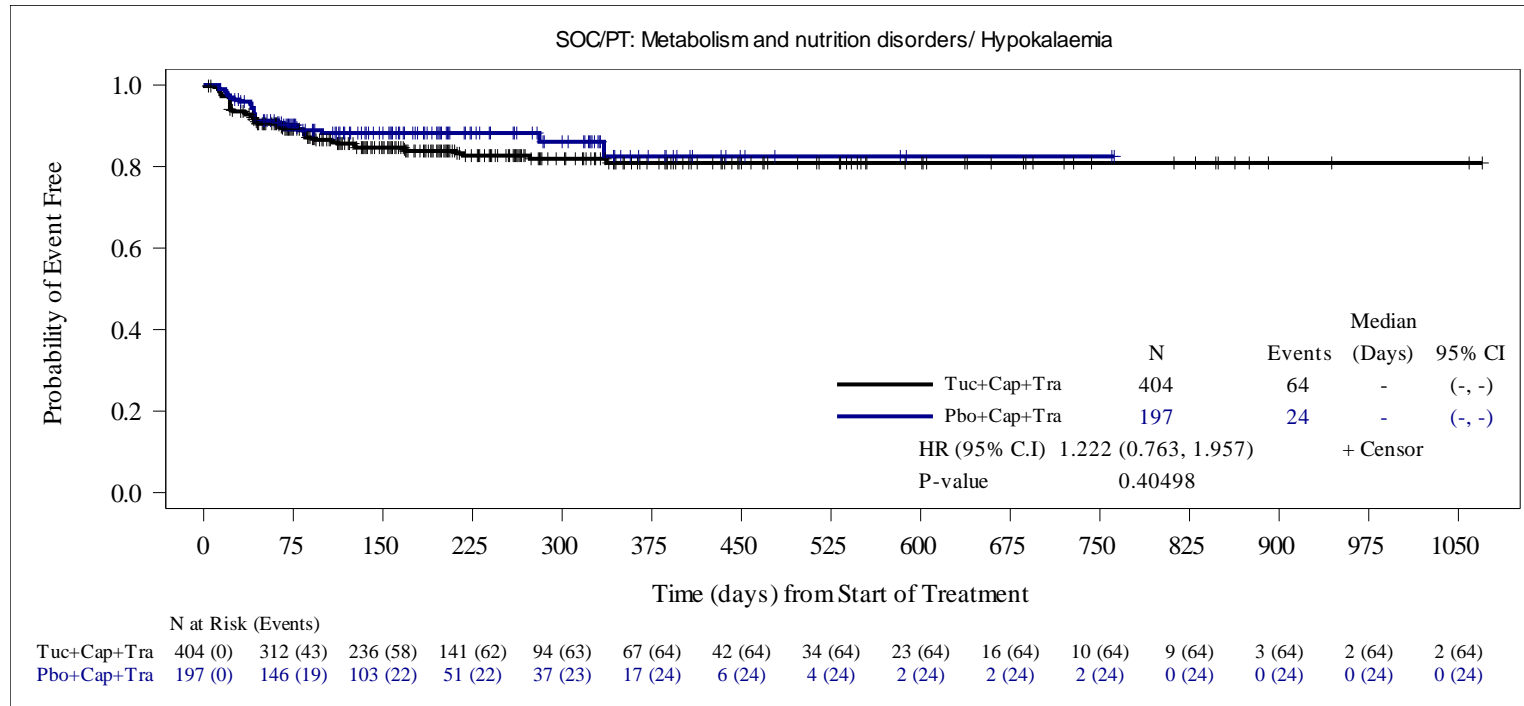
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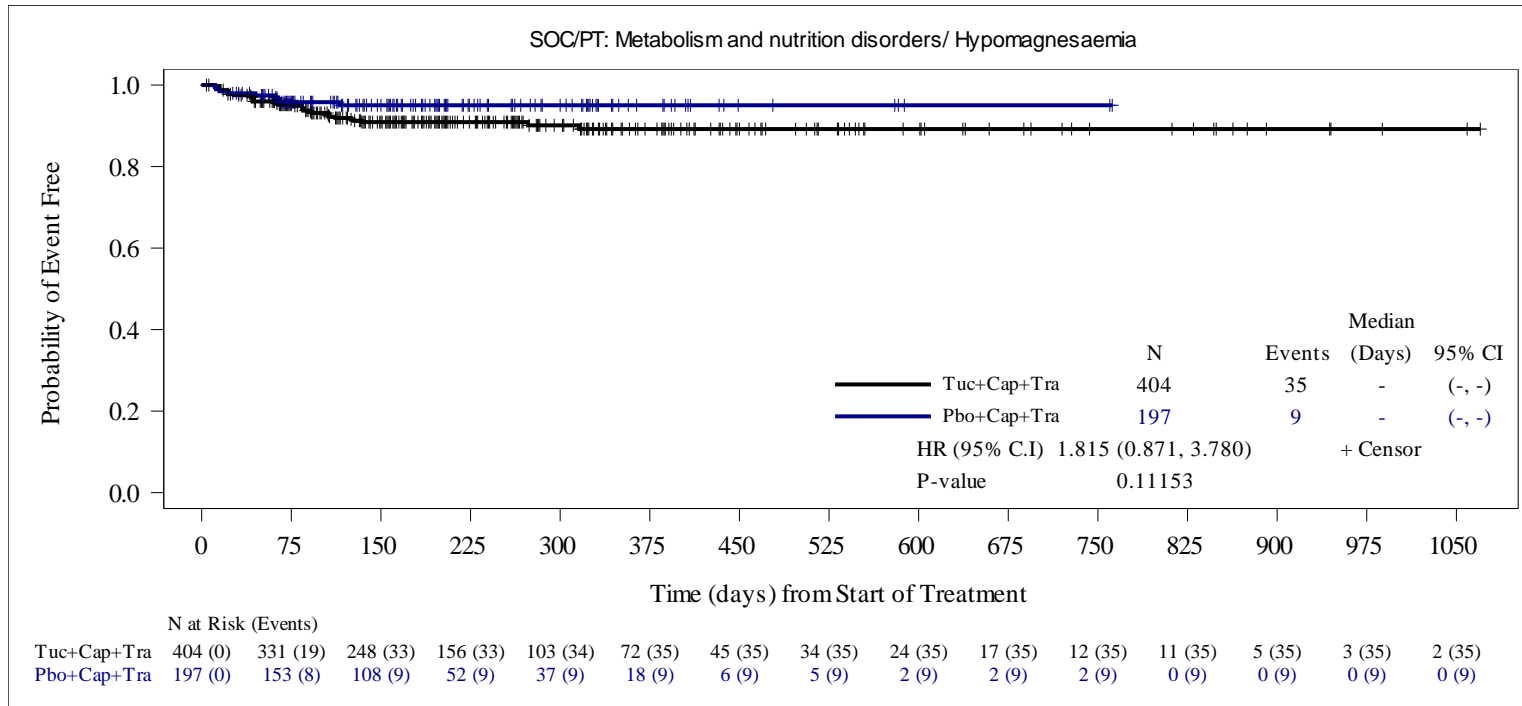
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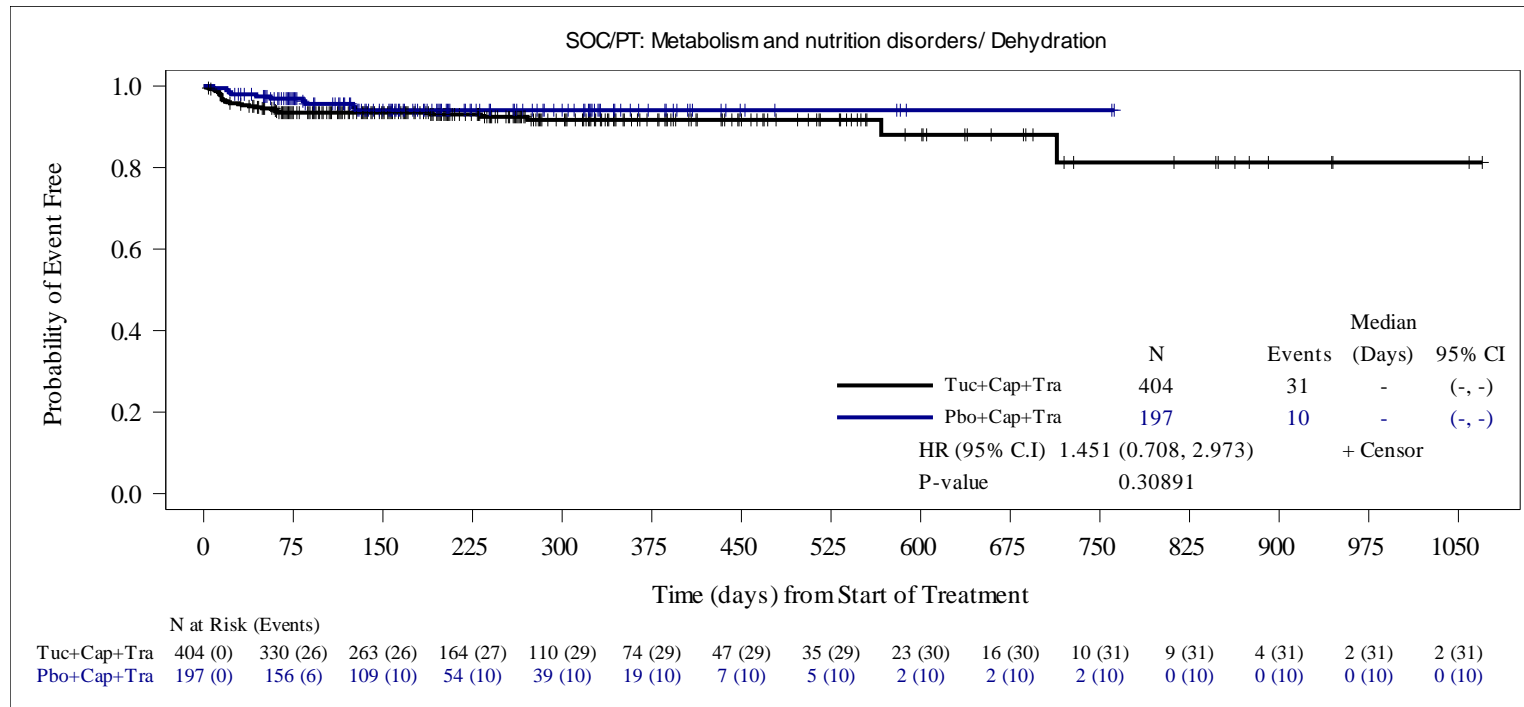
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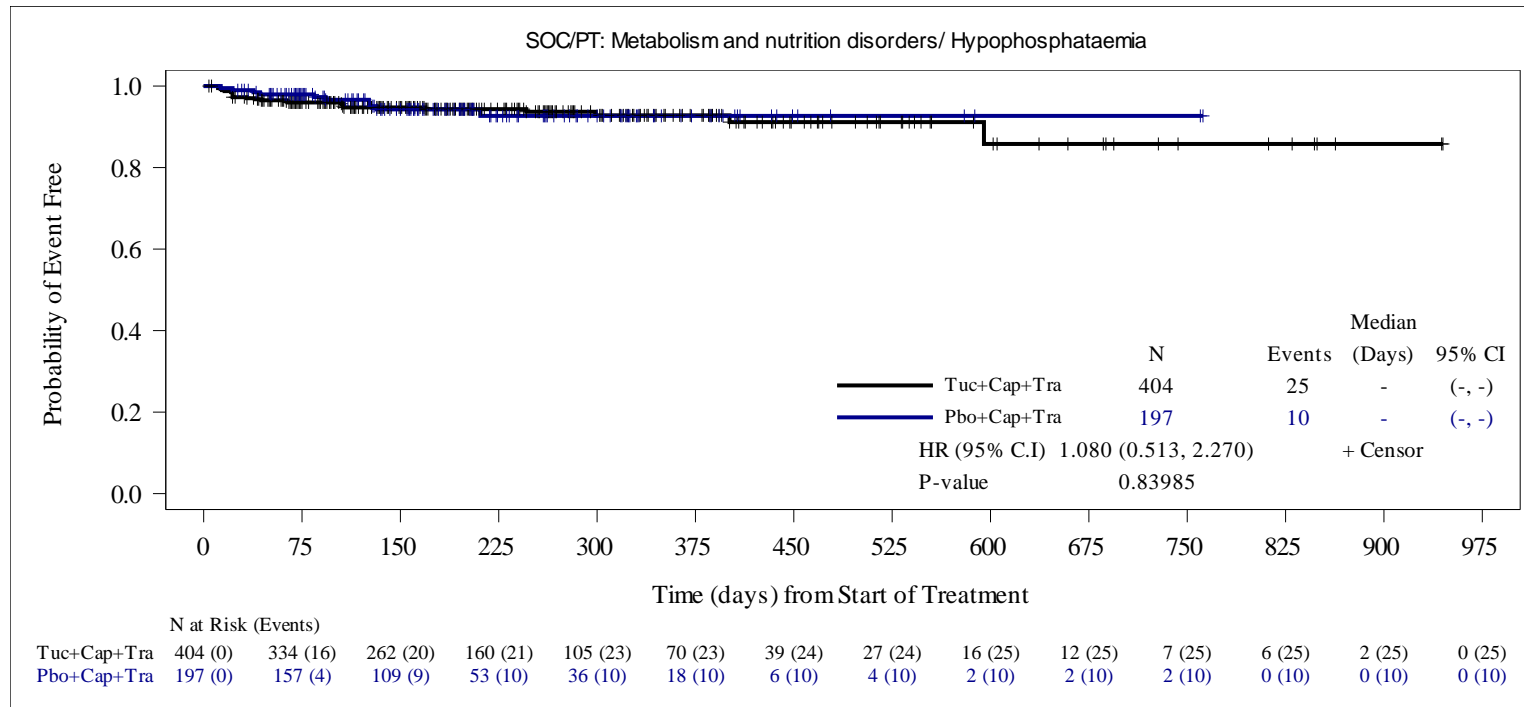
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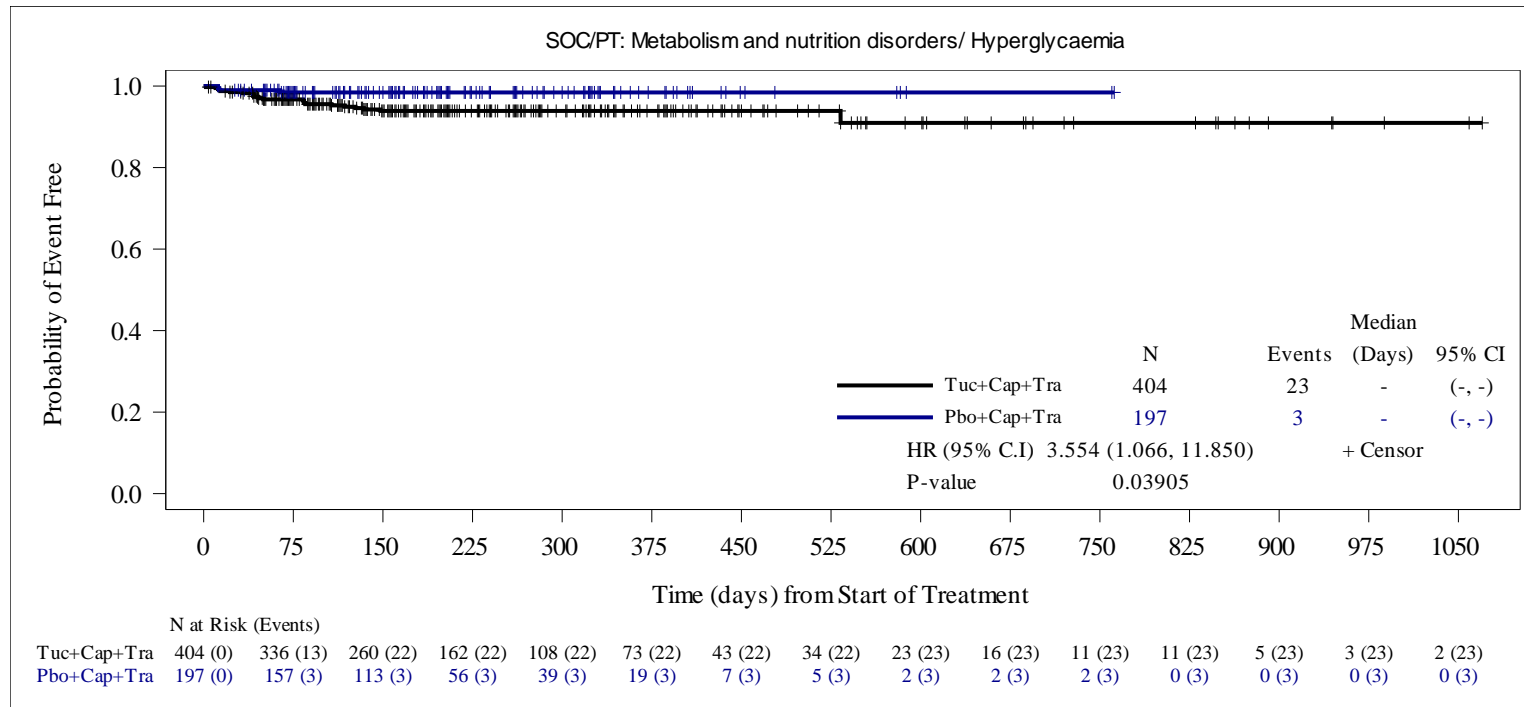
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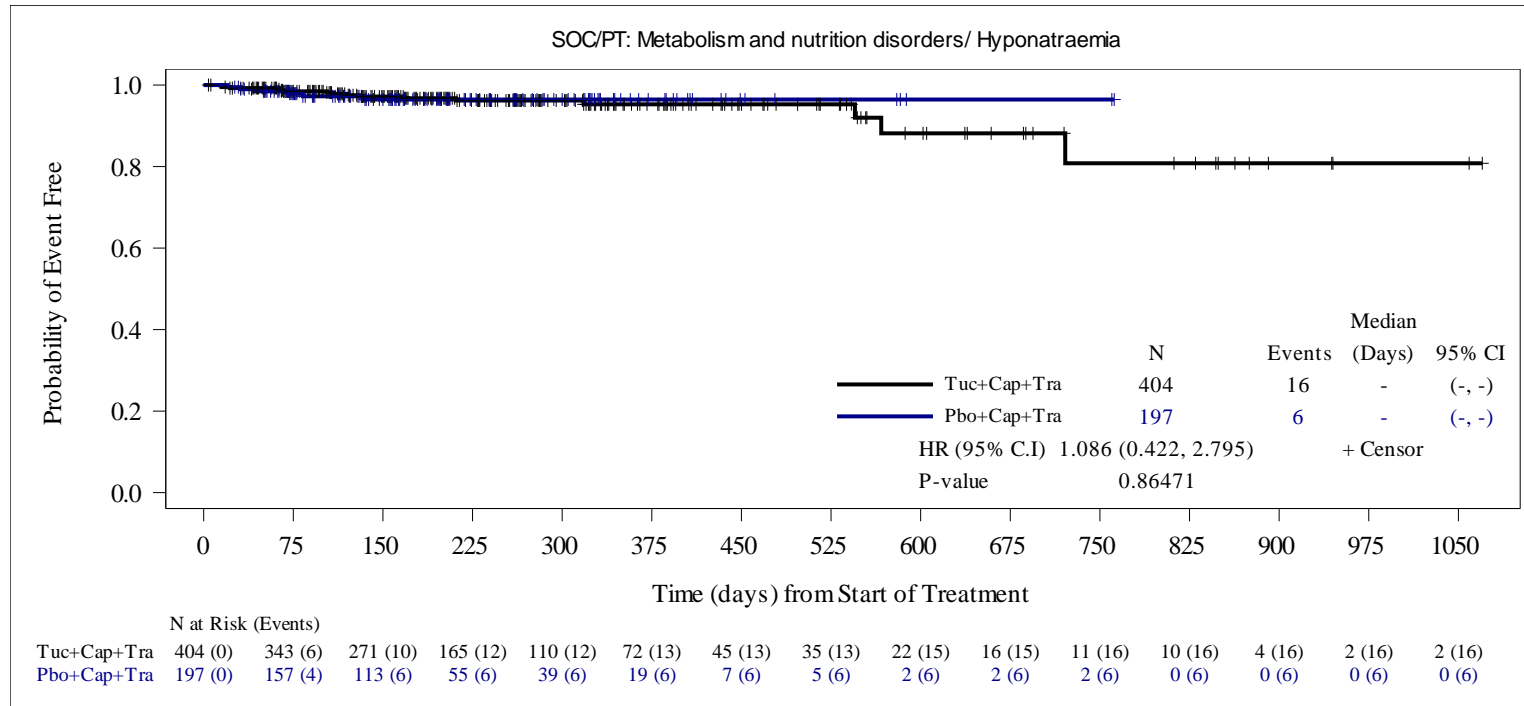
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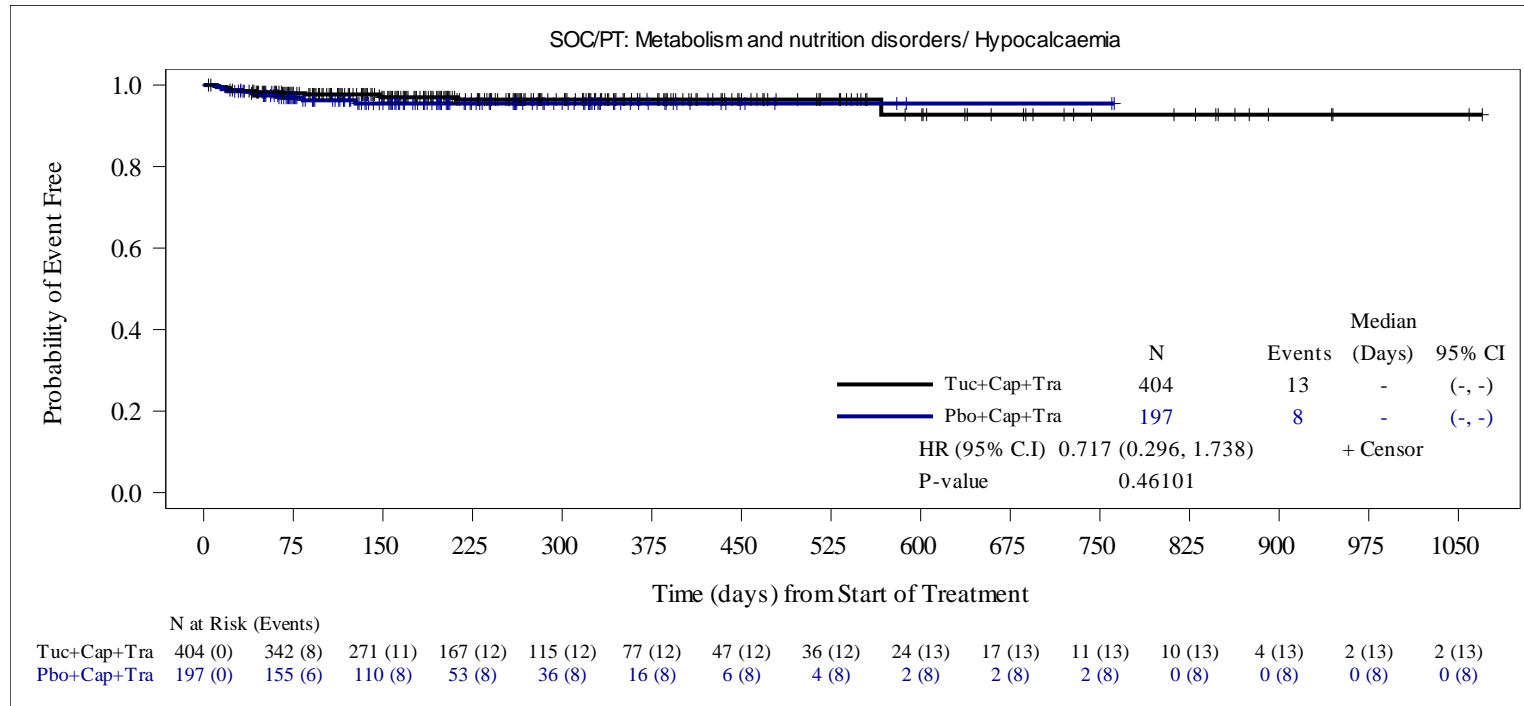
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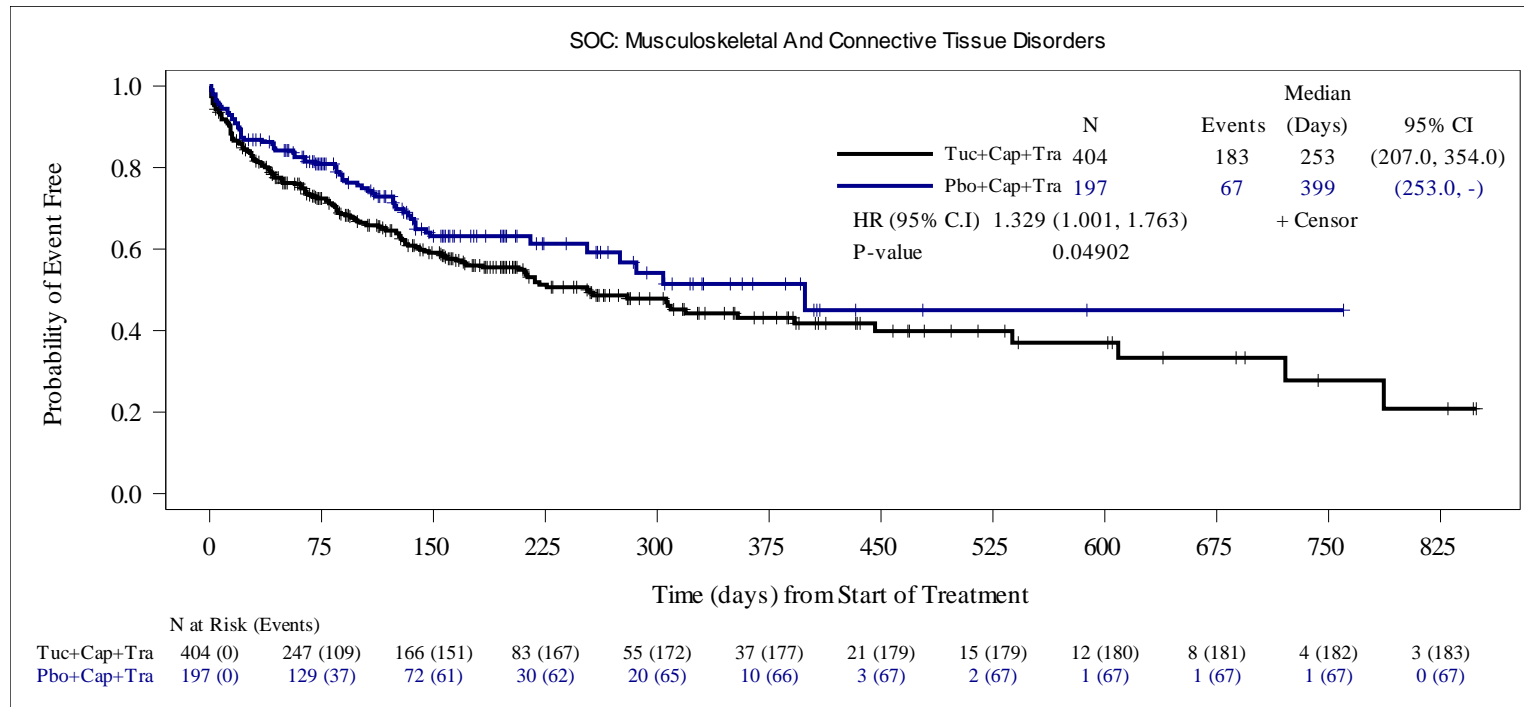
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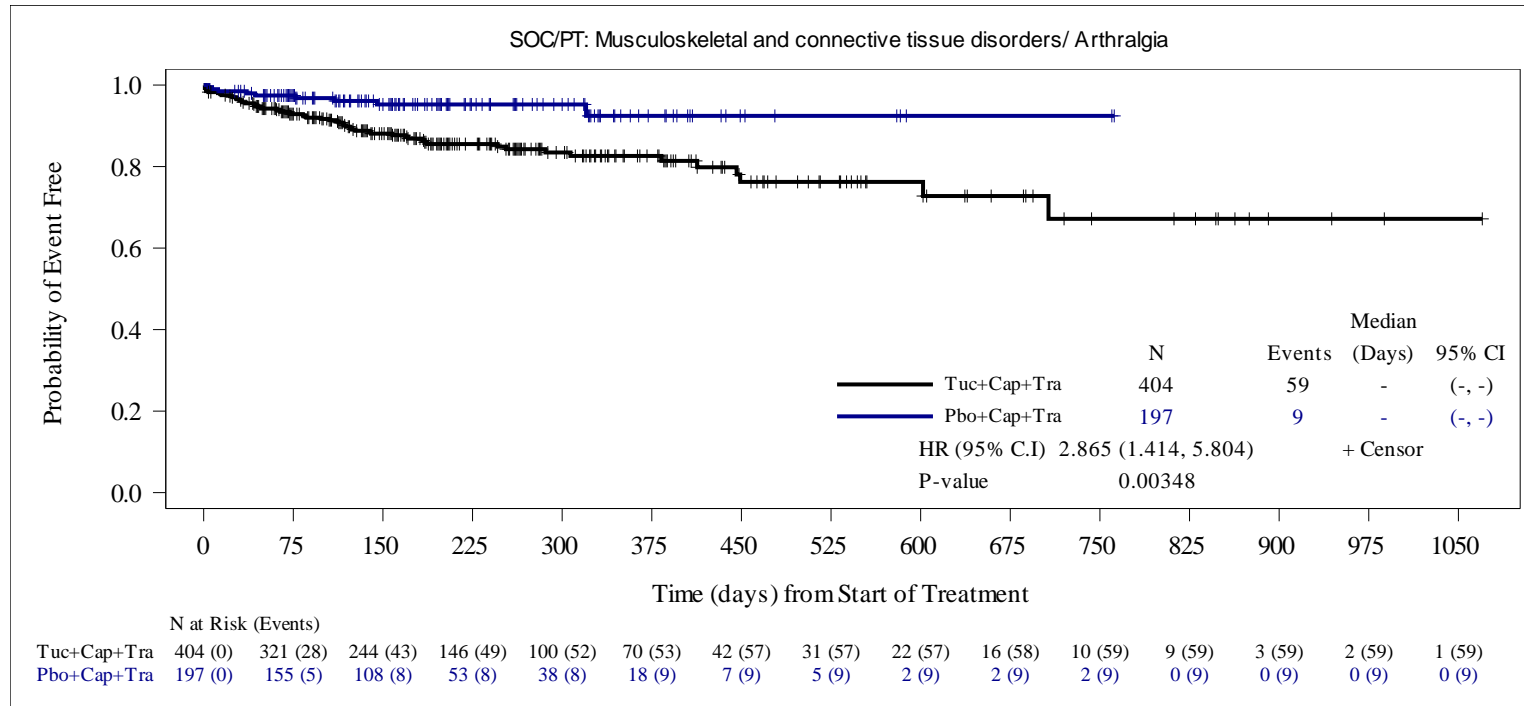
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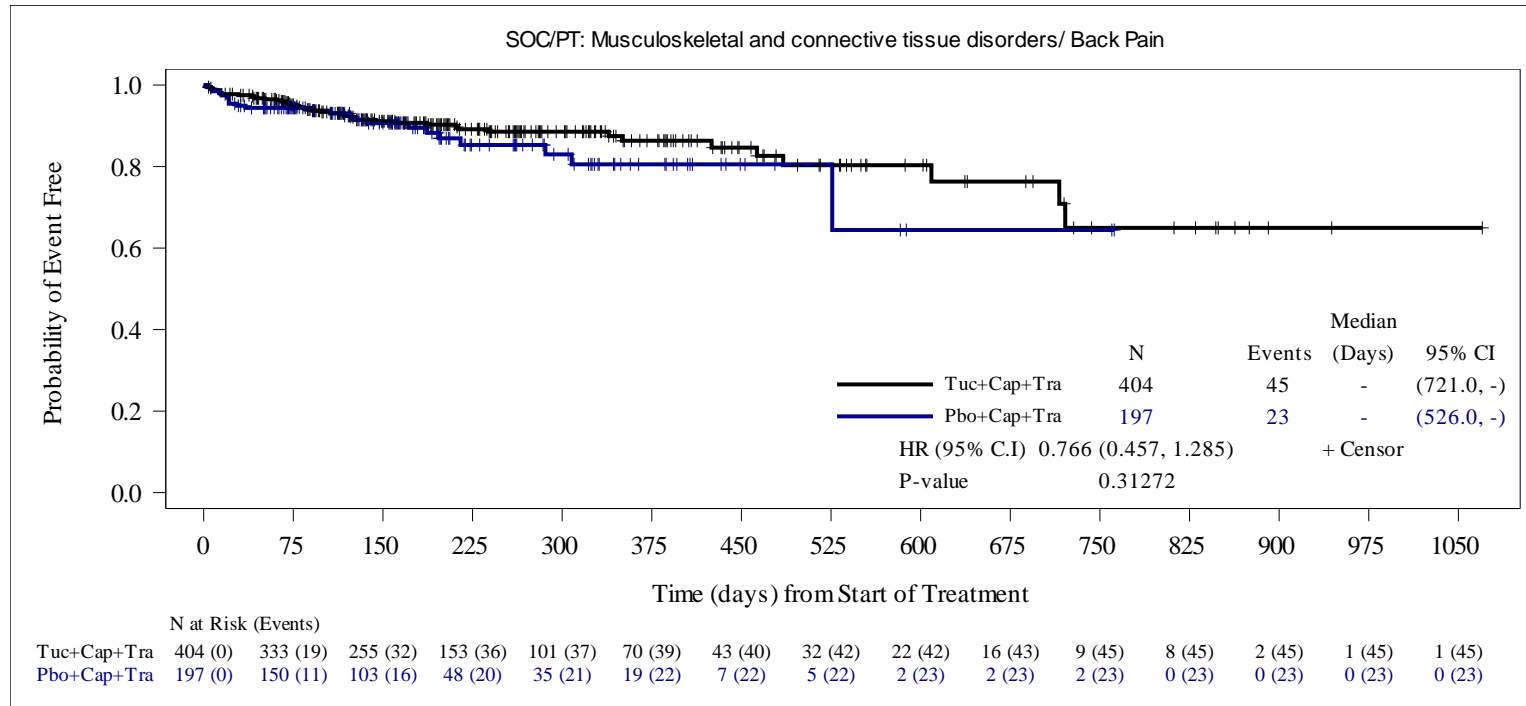
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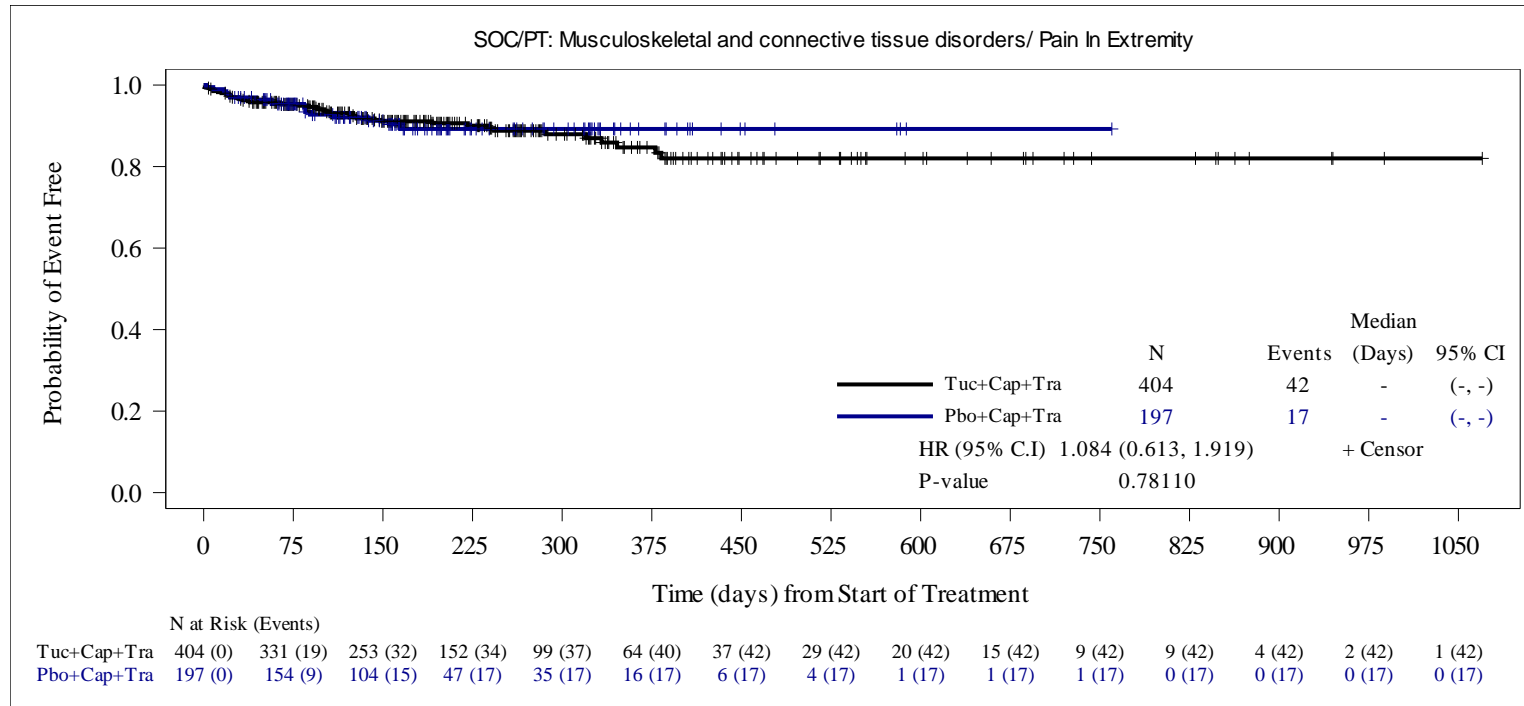
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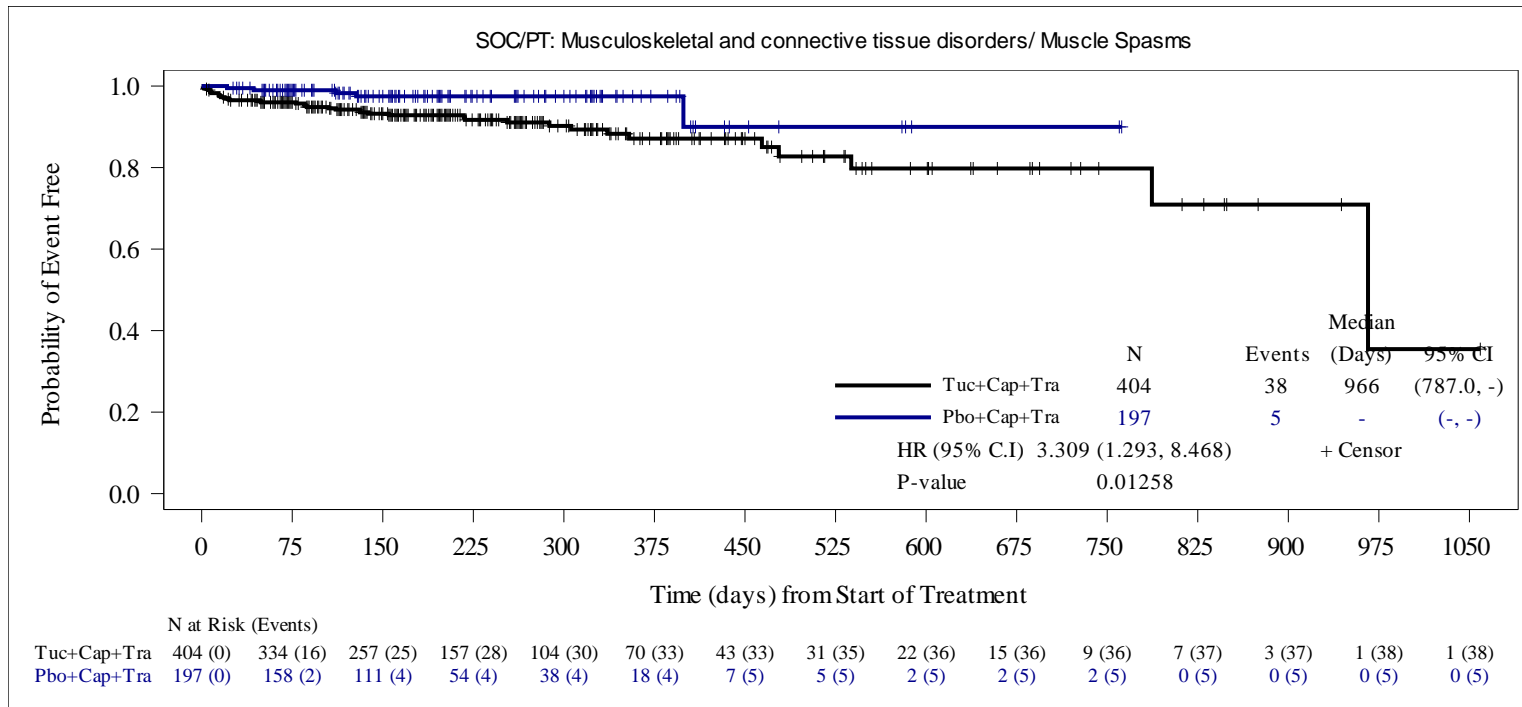
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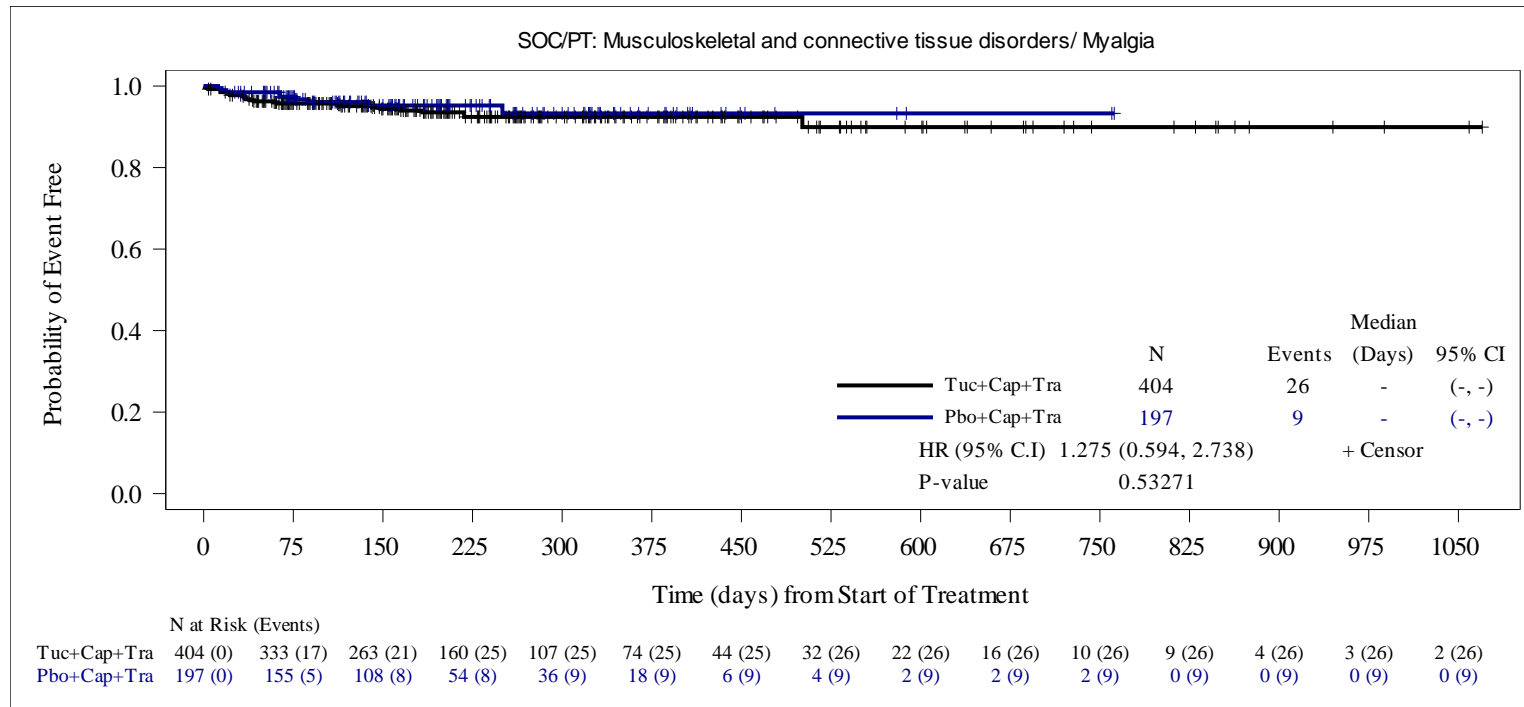
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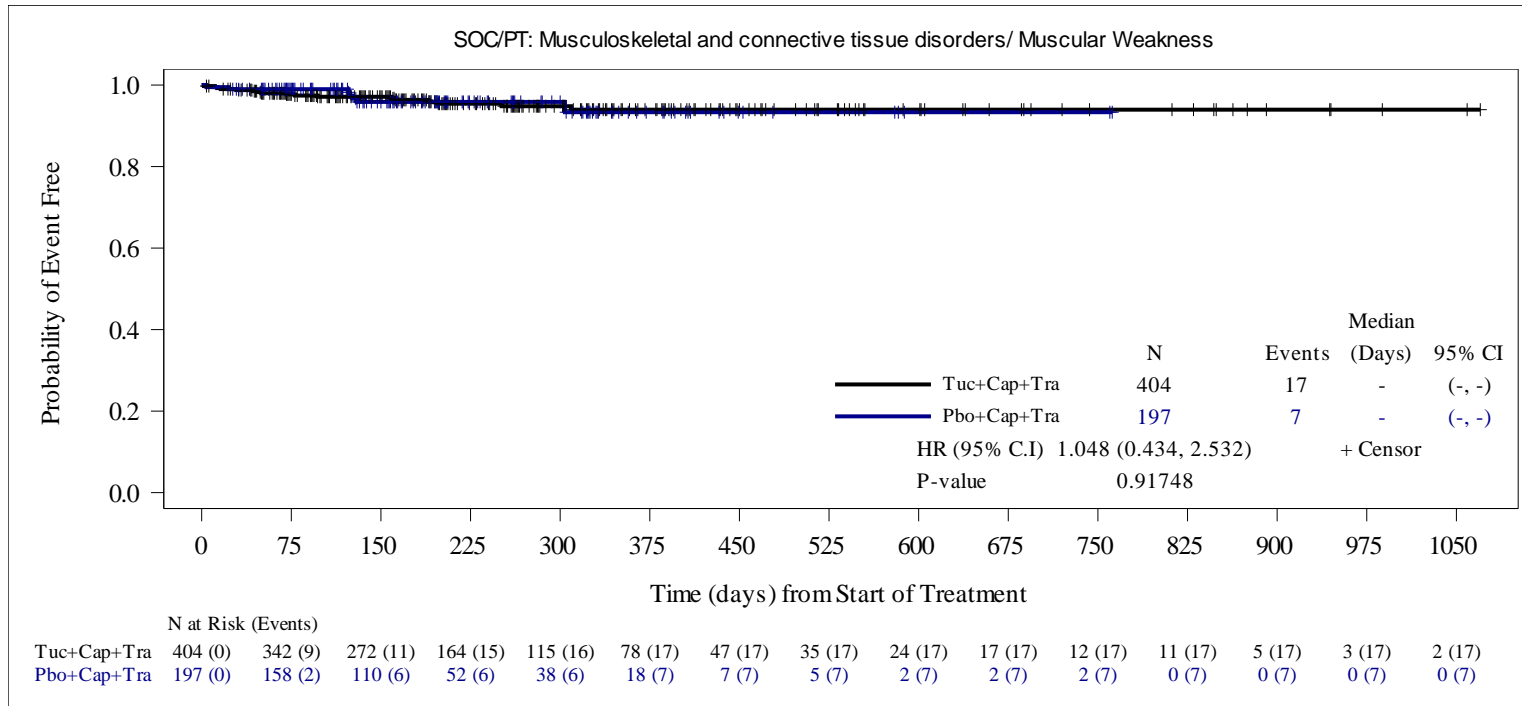
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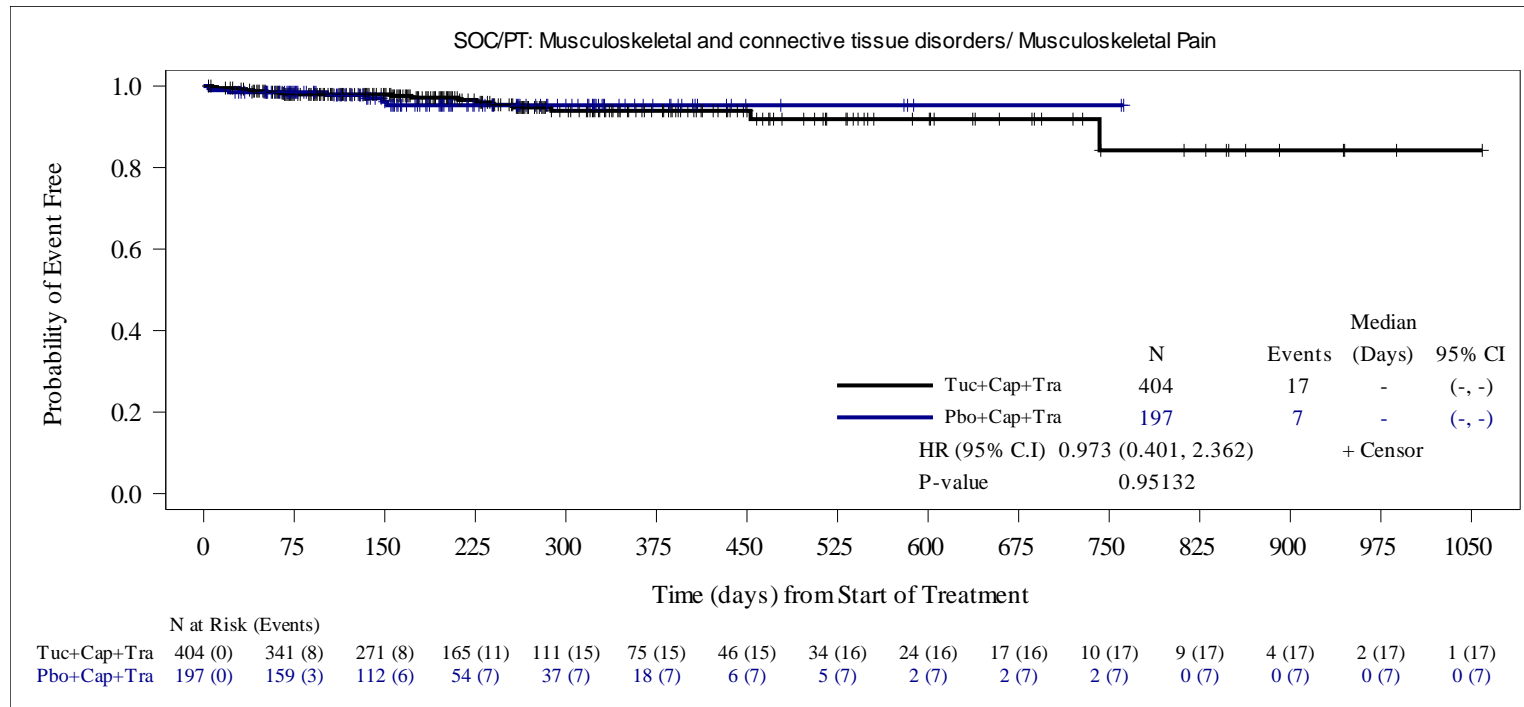
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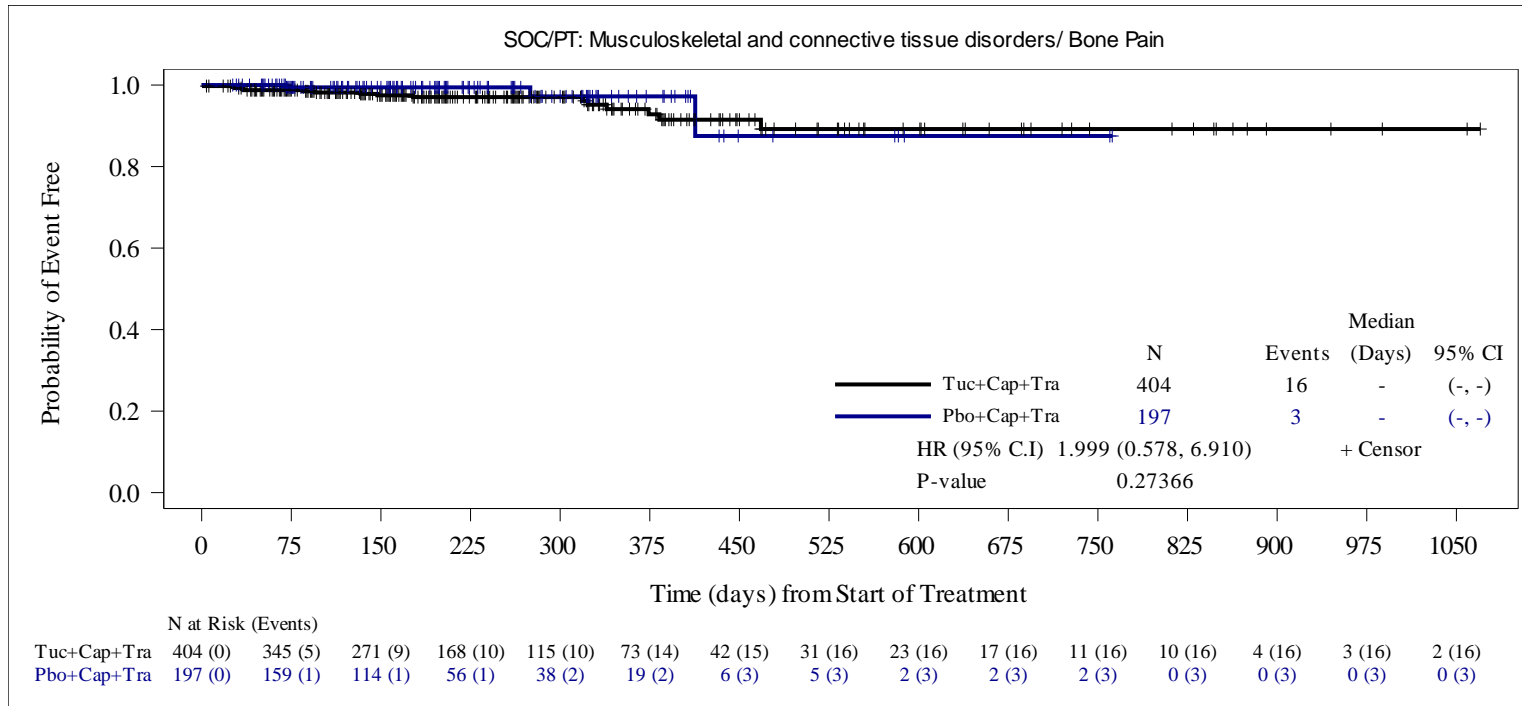
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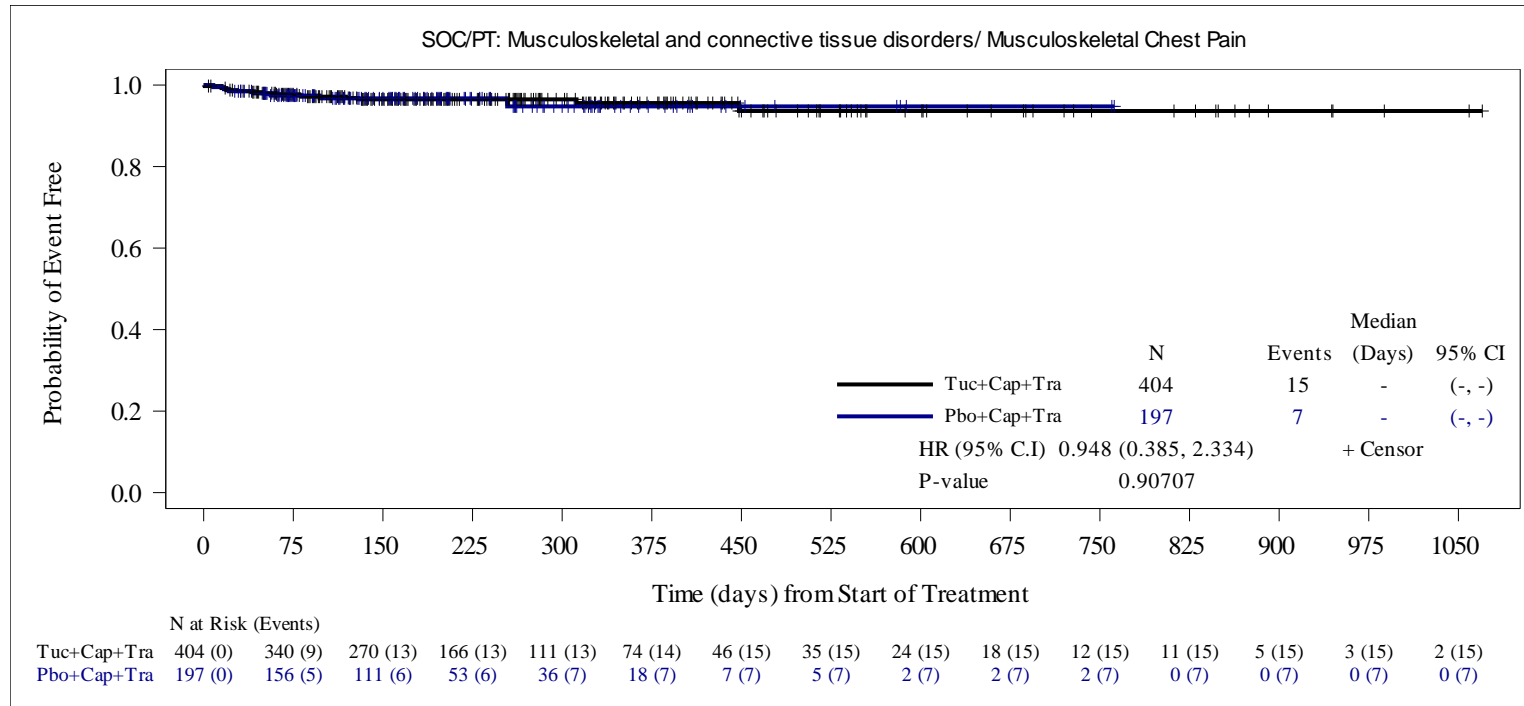
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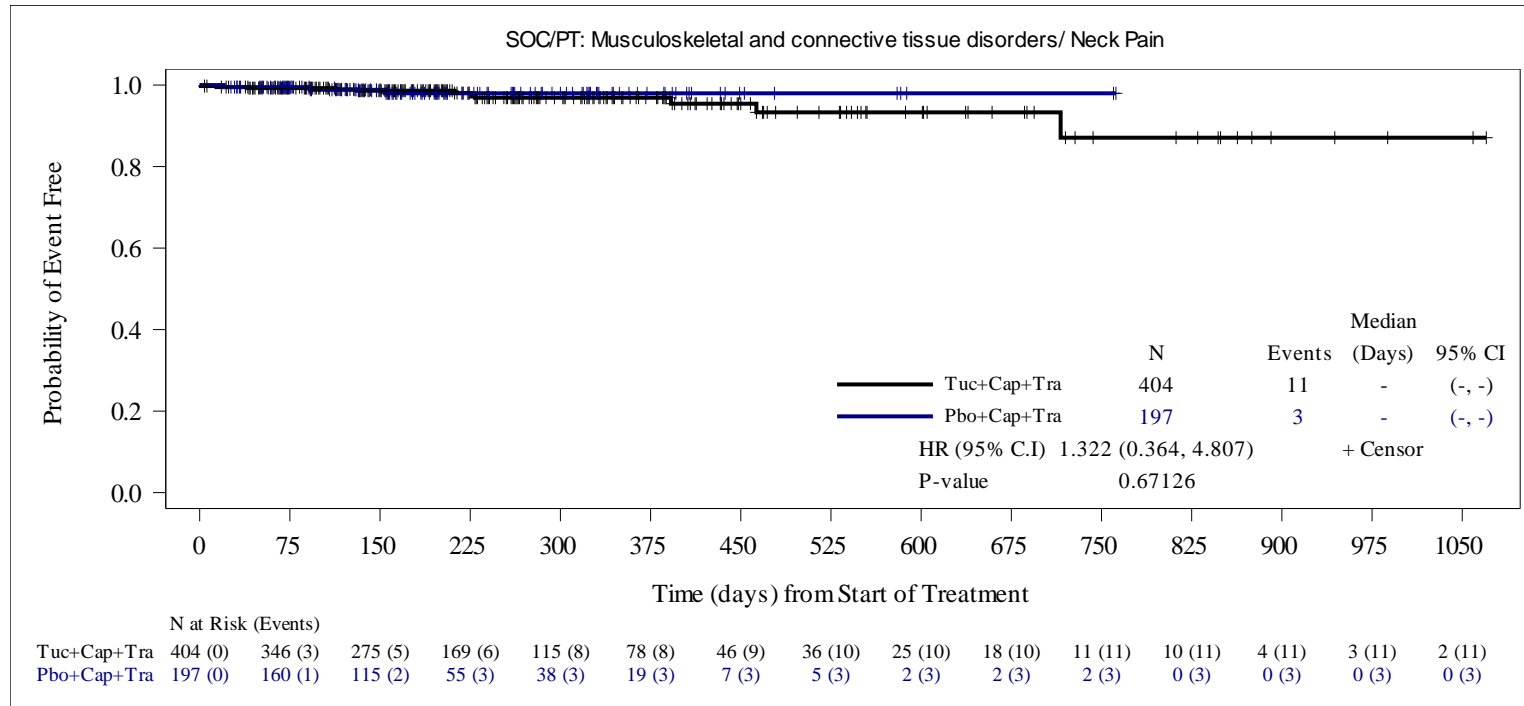
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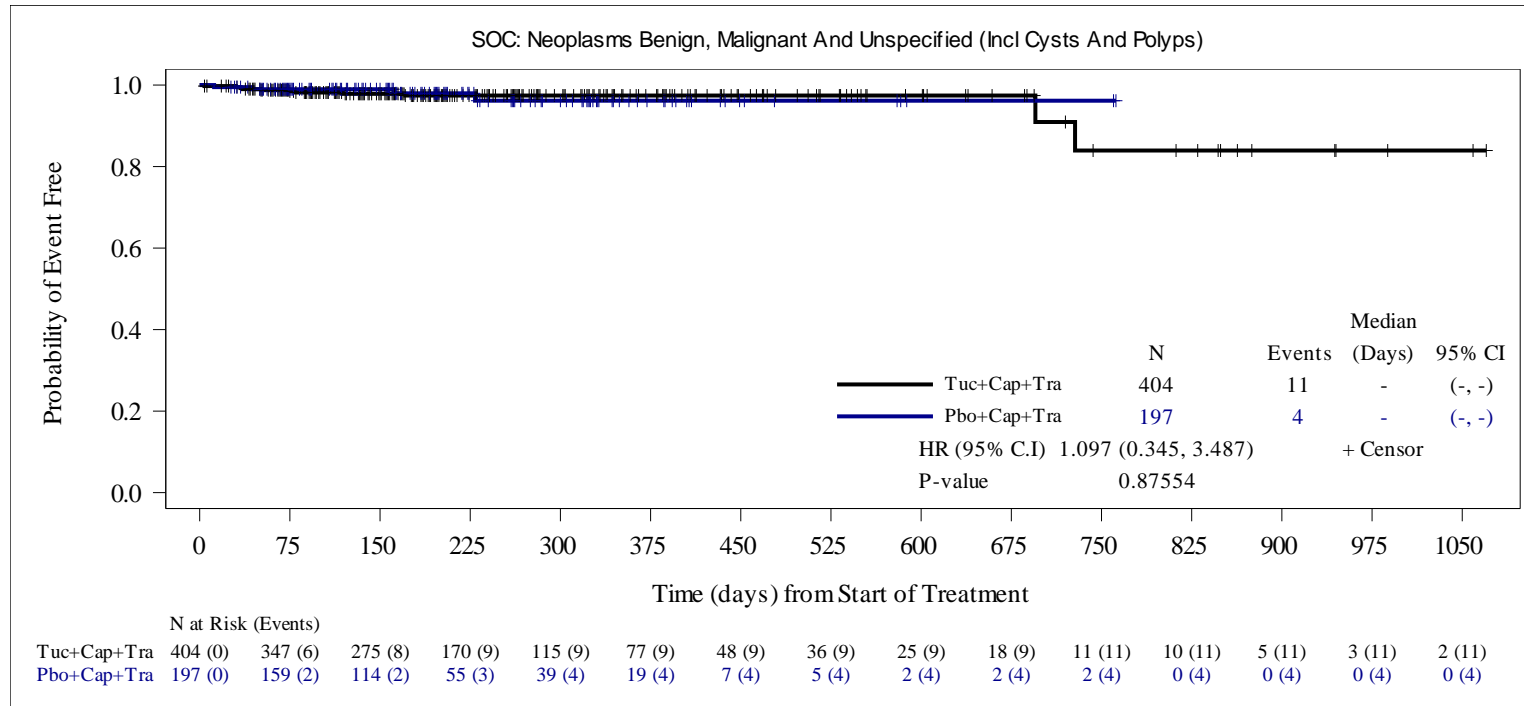
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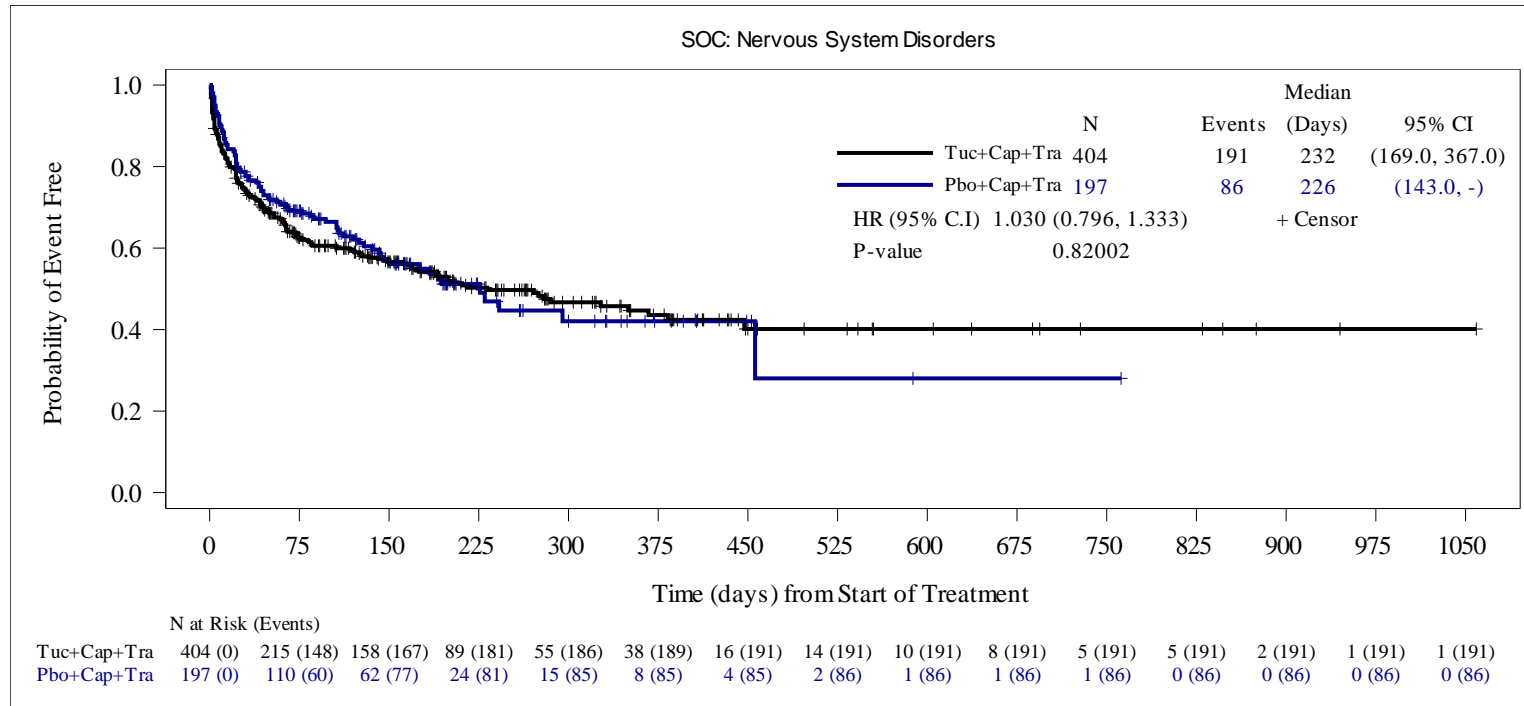
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**Figure 2.7.1 Kaplan-Meier Estimate of Time to First Onset of Treatment-Emergent Adverse Events by System Organ Class and Preferred Term
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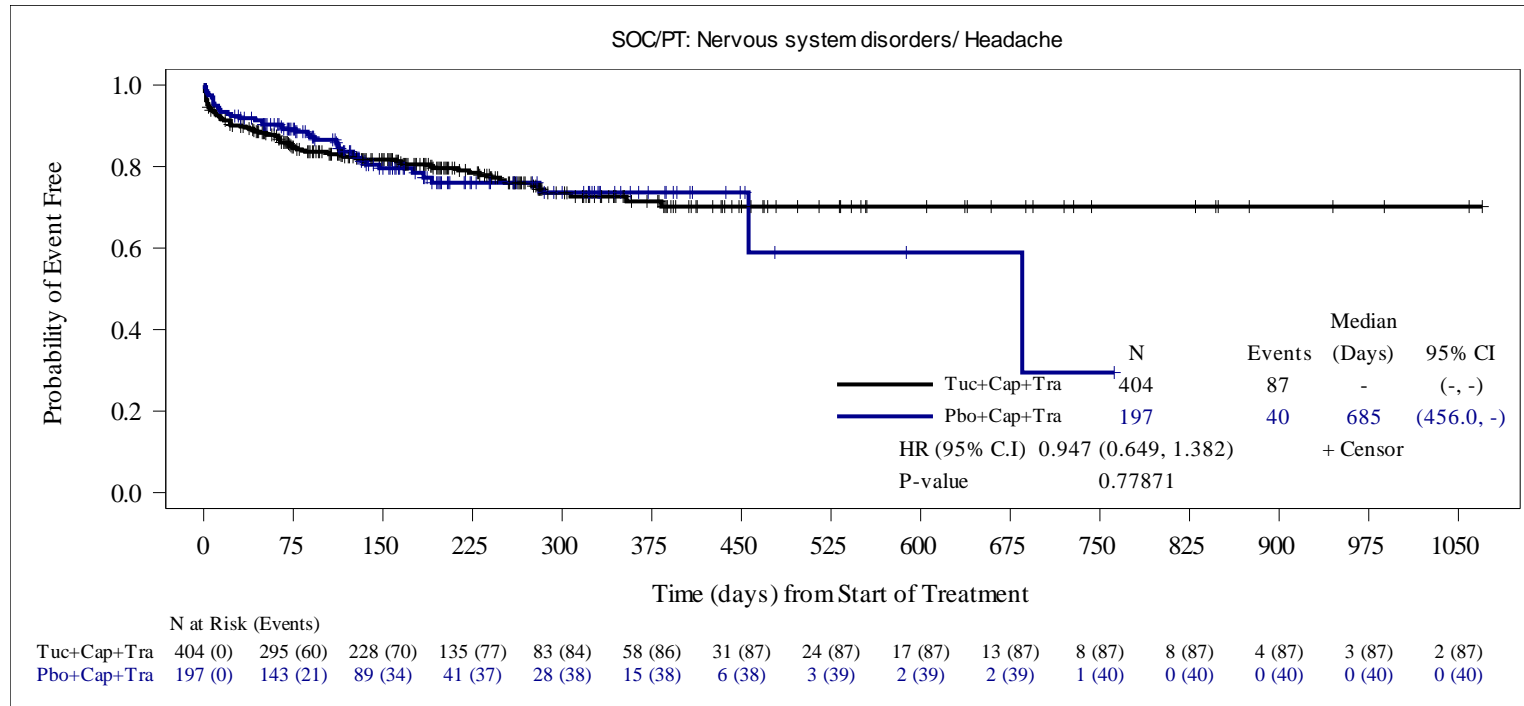
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Data Snapshot: 14OCT2019, Data Cutoff Date: 04SEP2019

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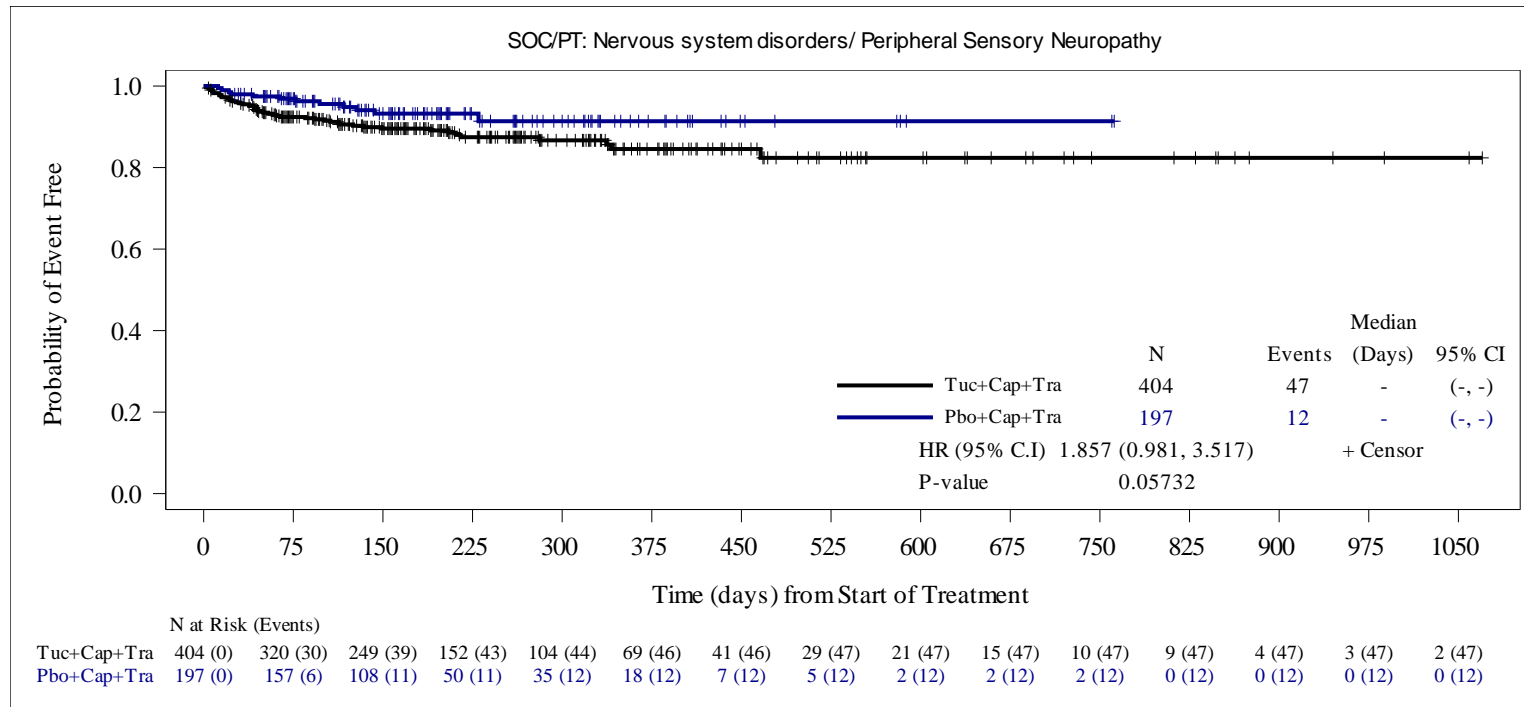
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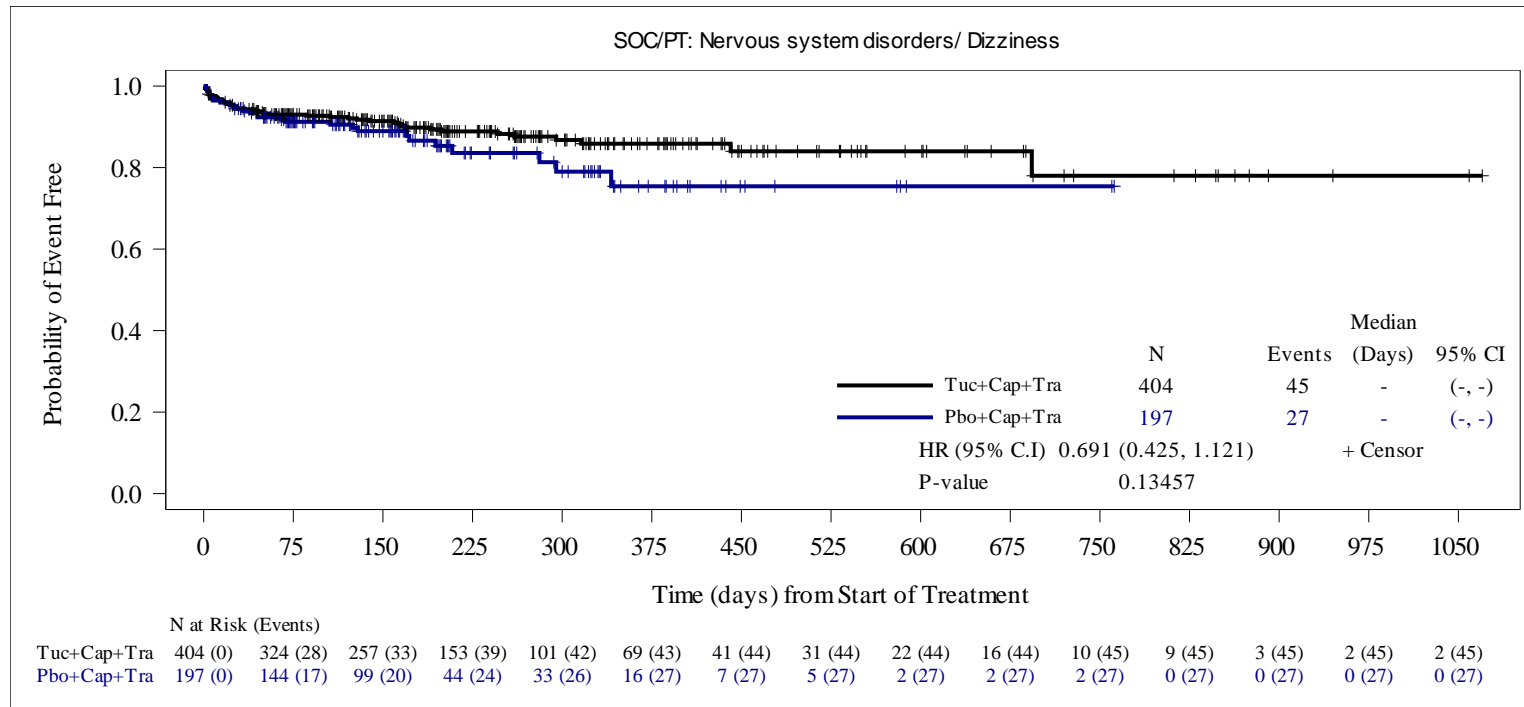
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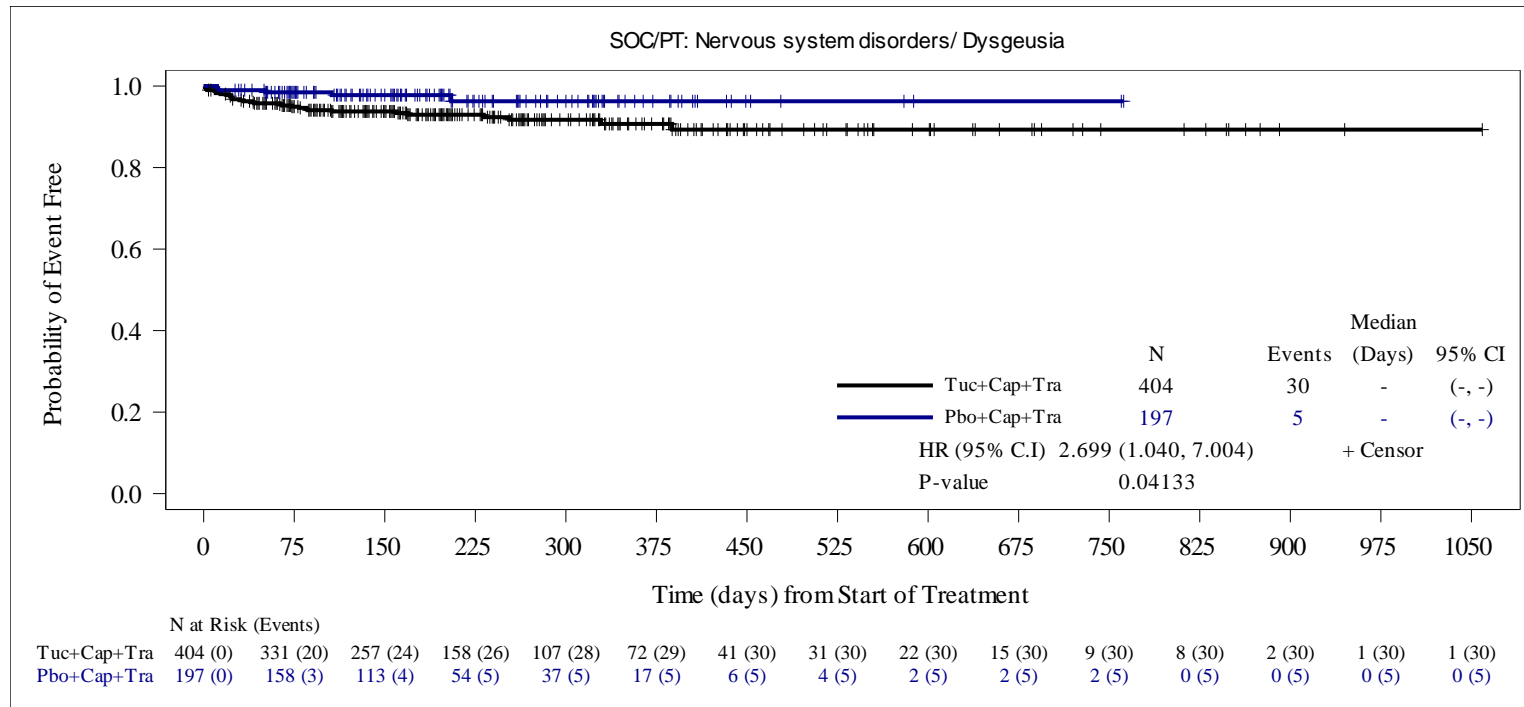
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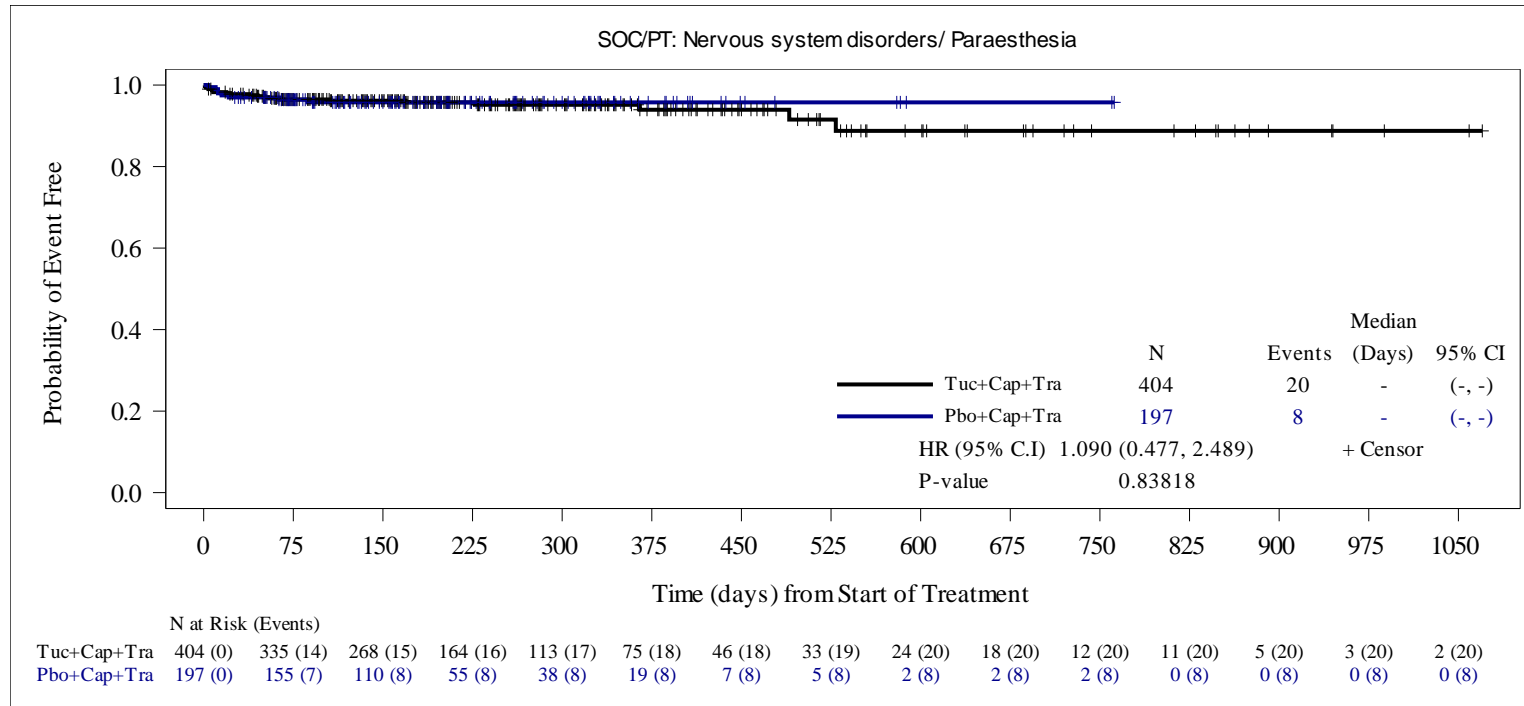
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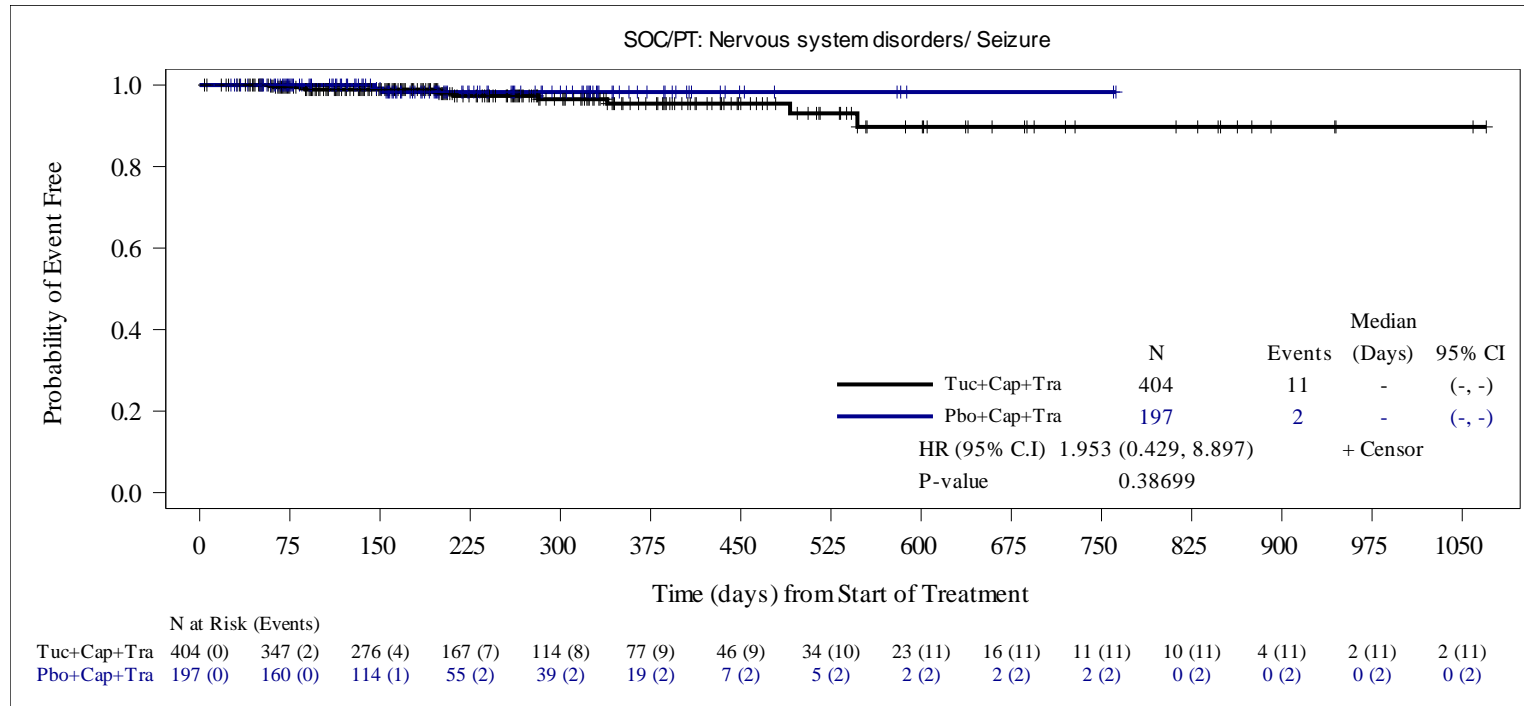
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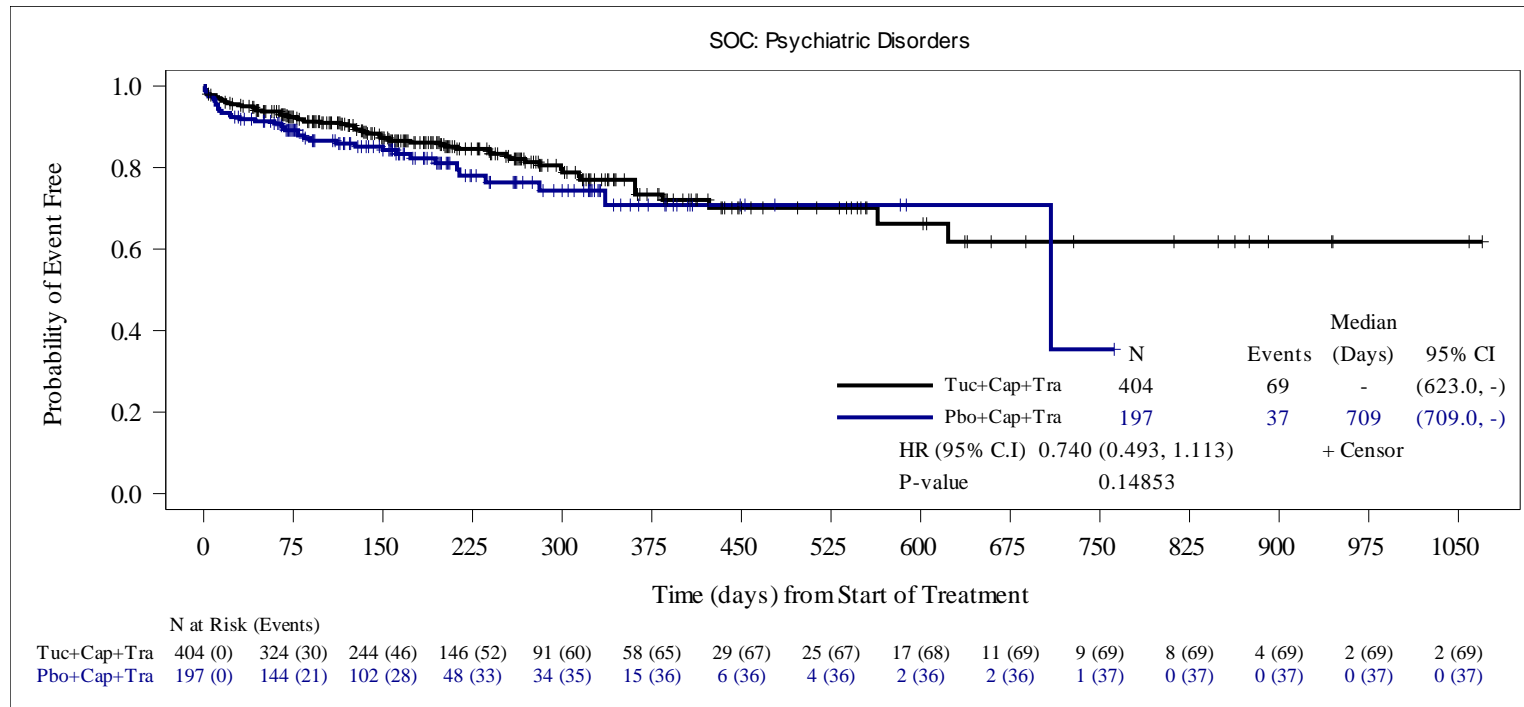
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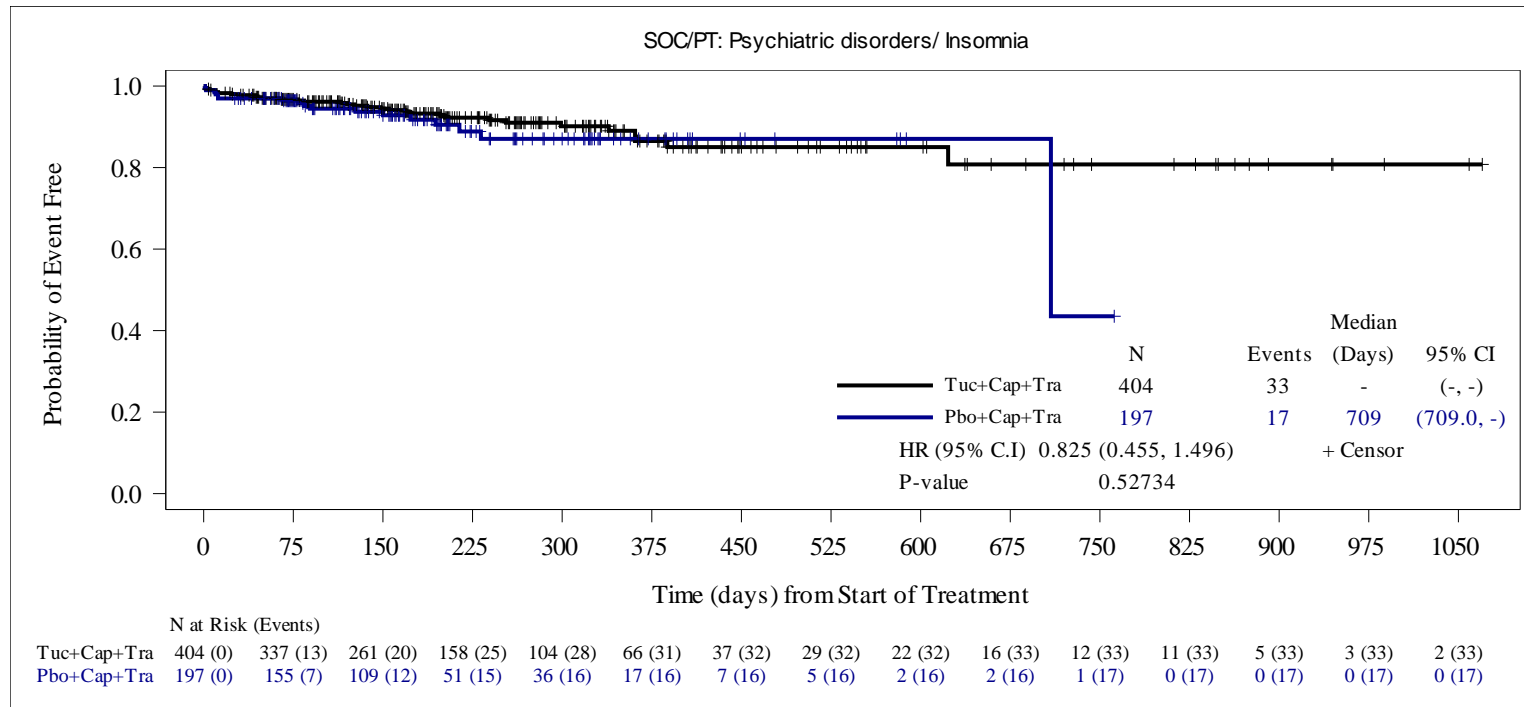
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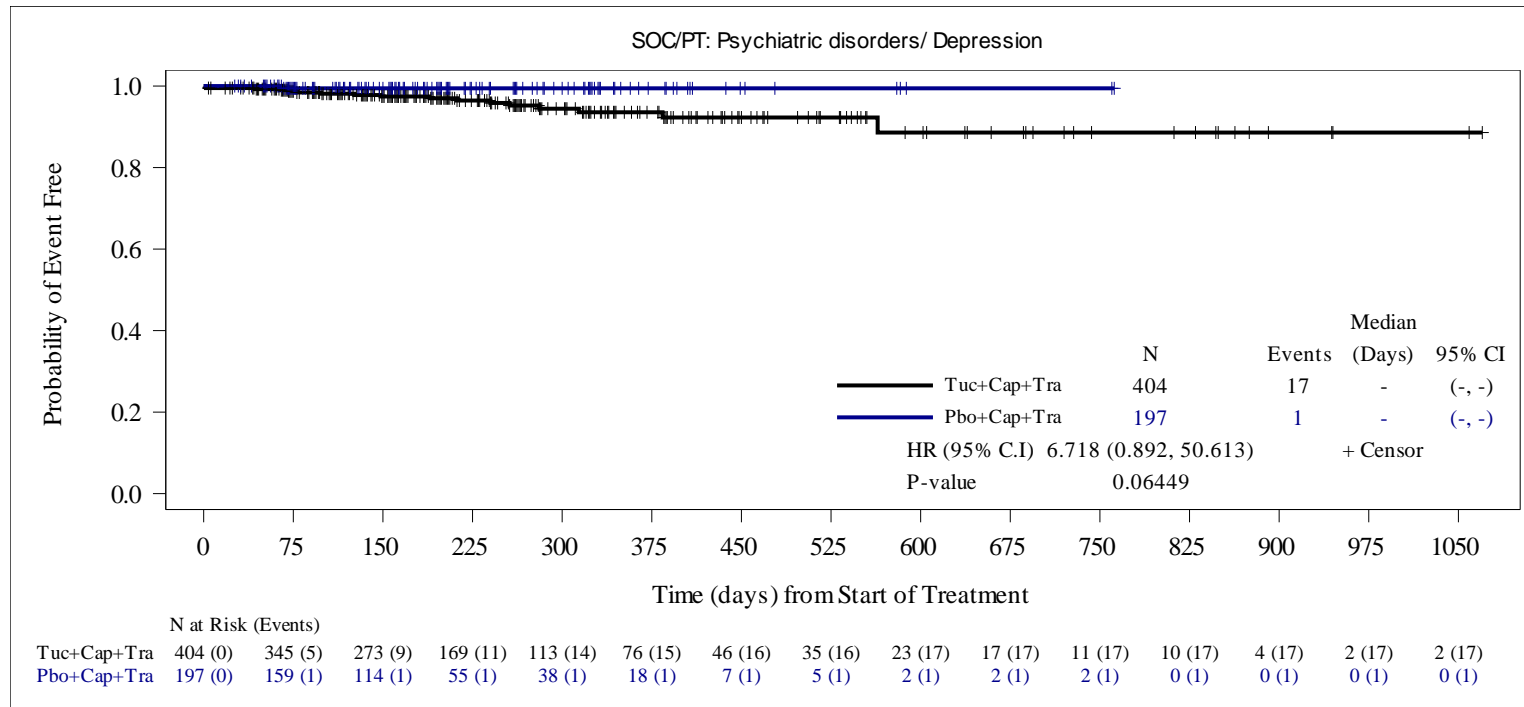
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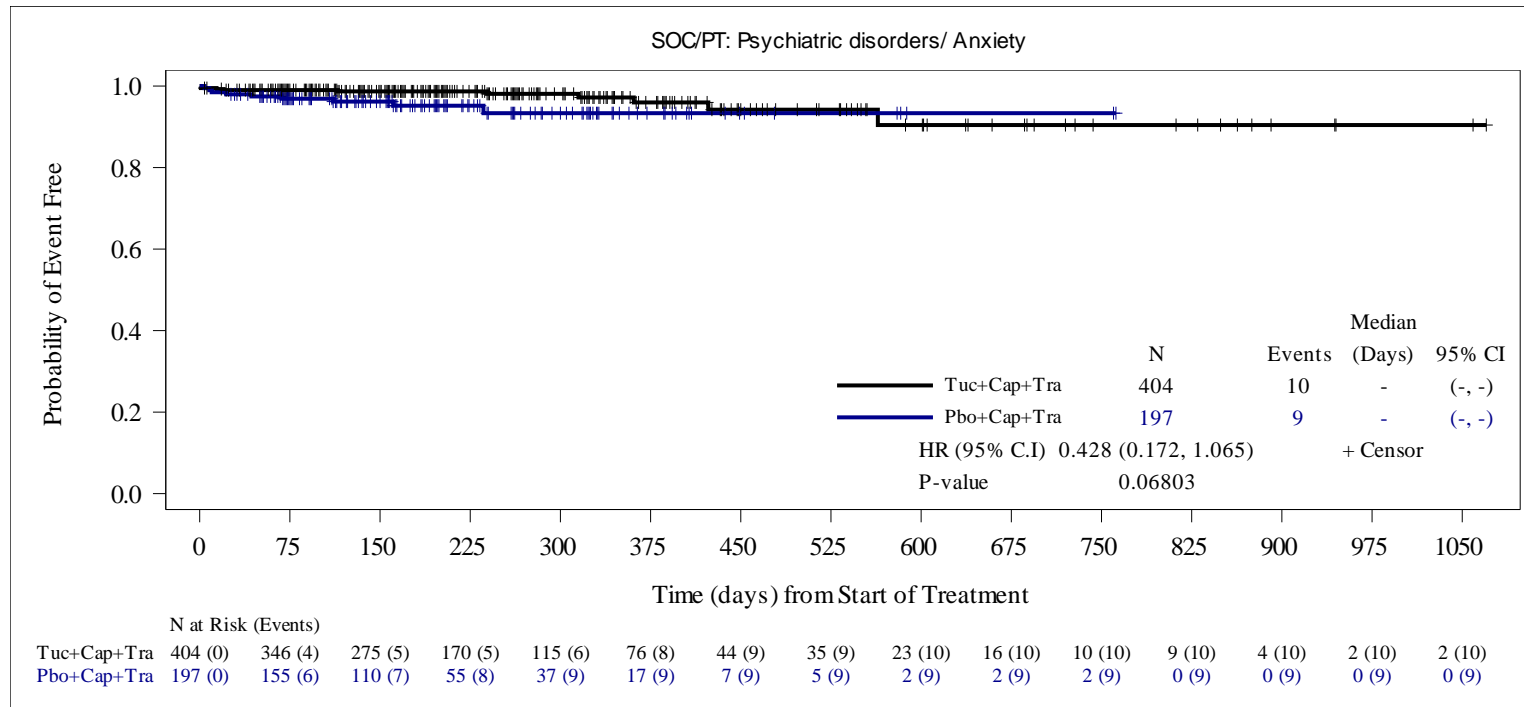
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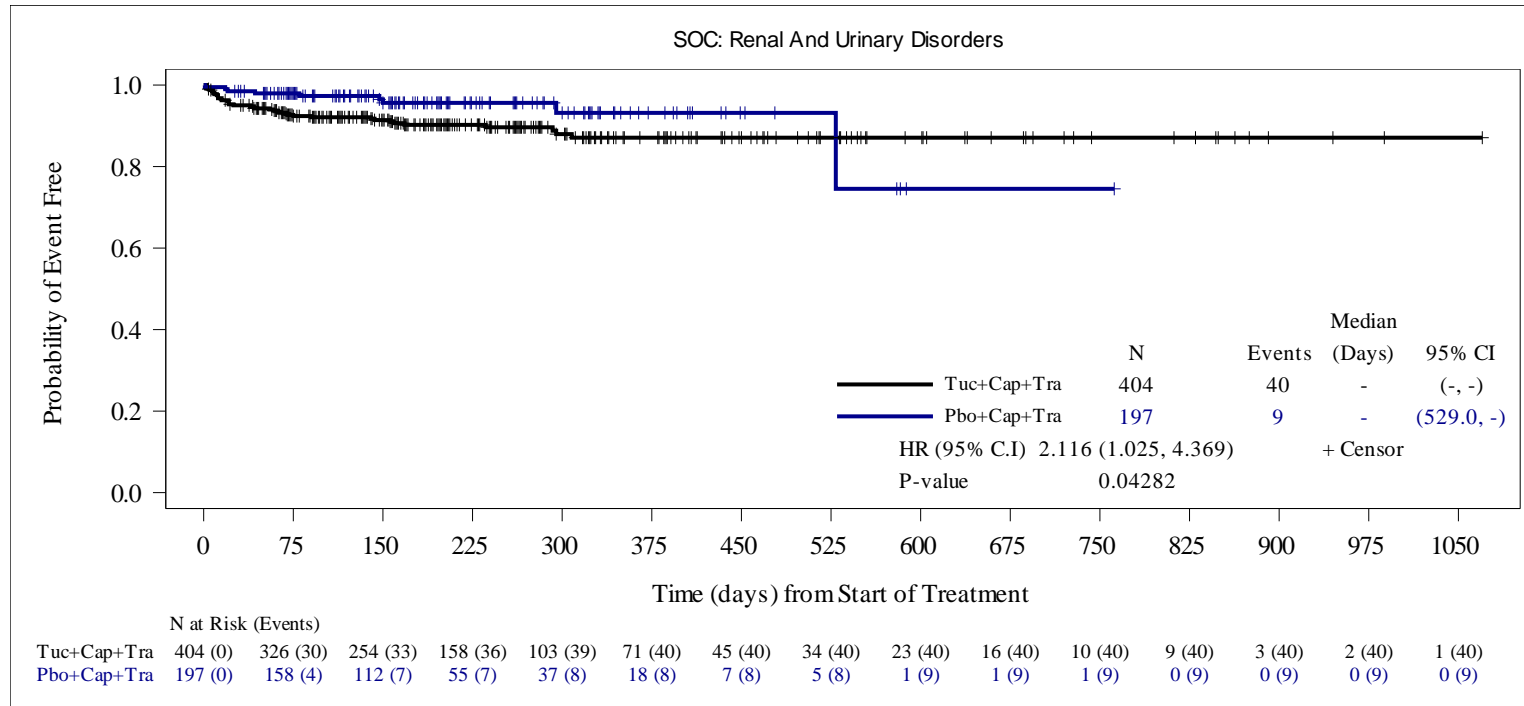
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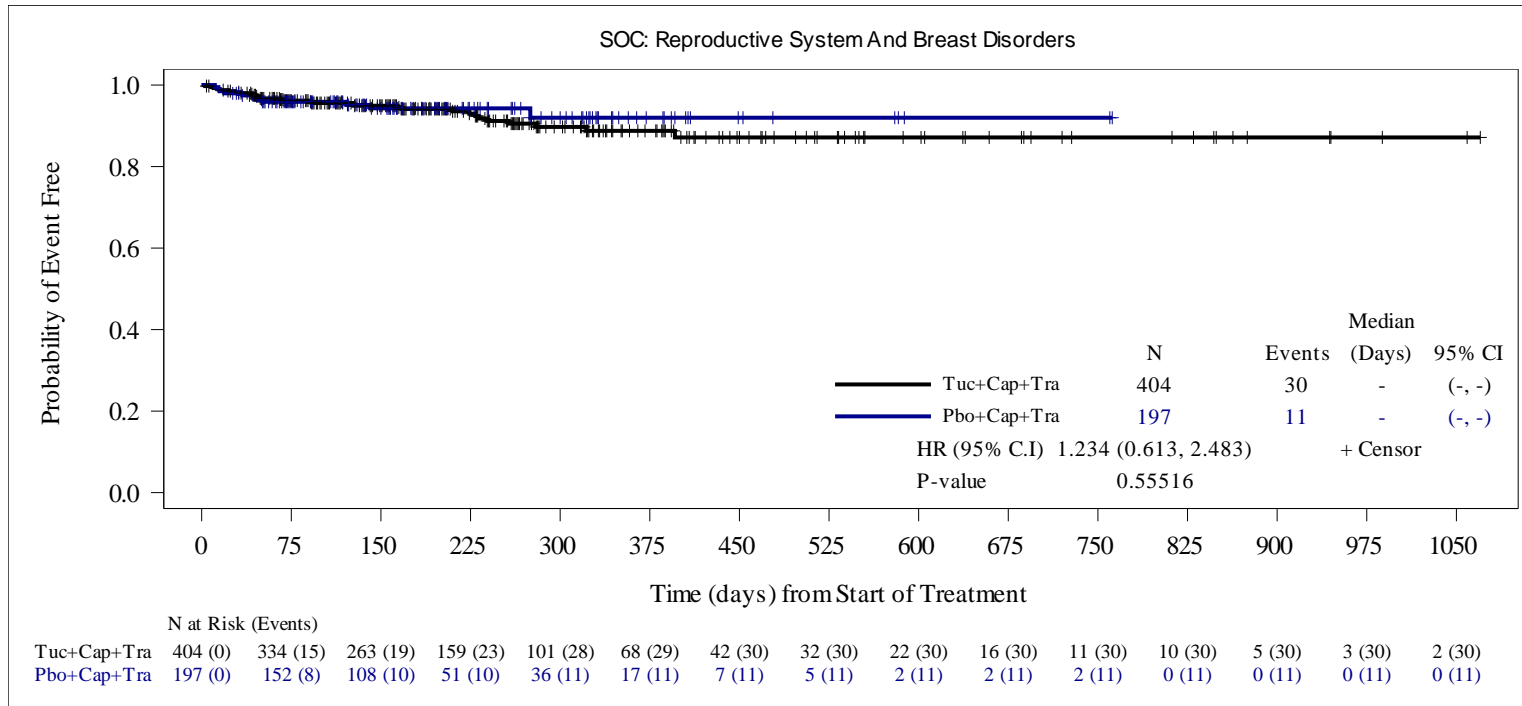
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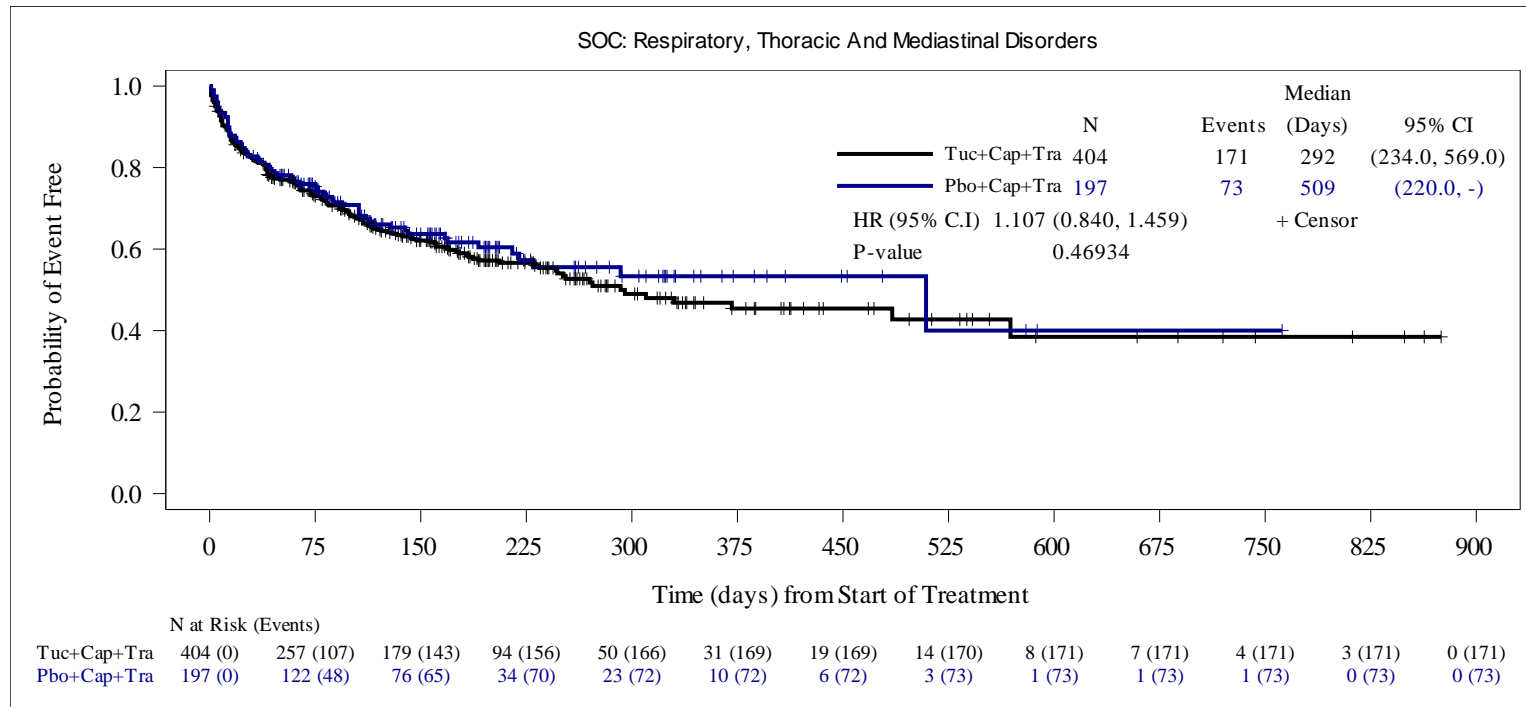
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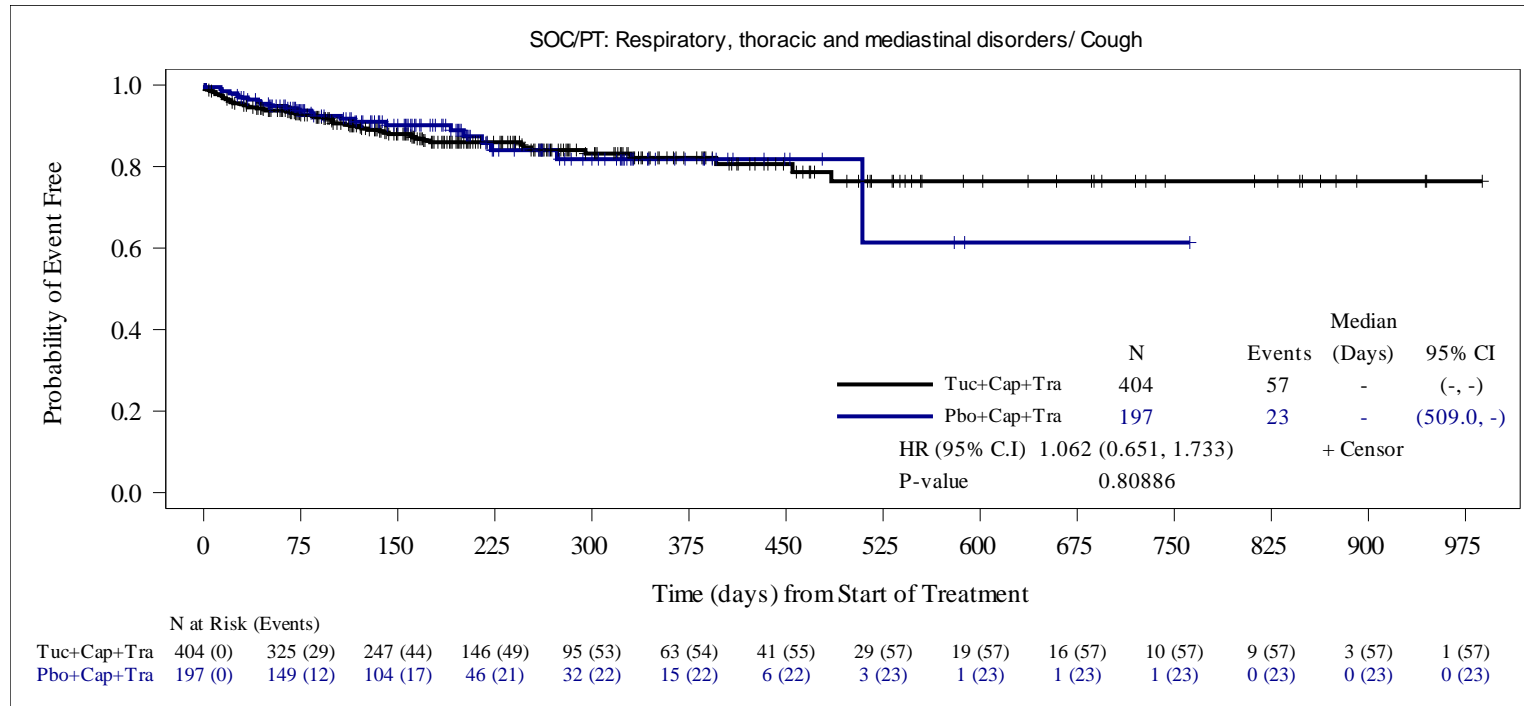
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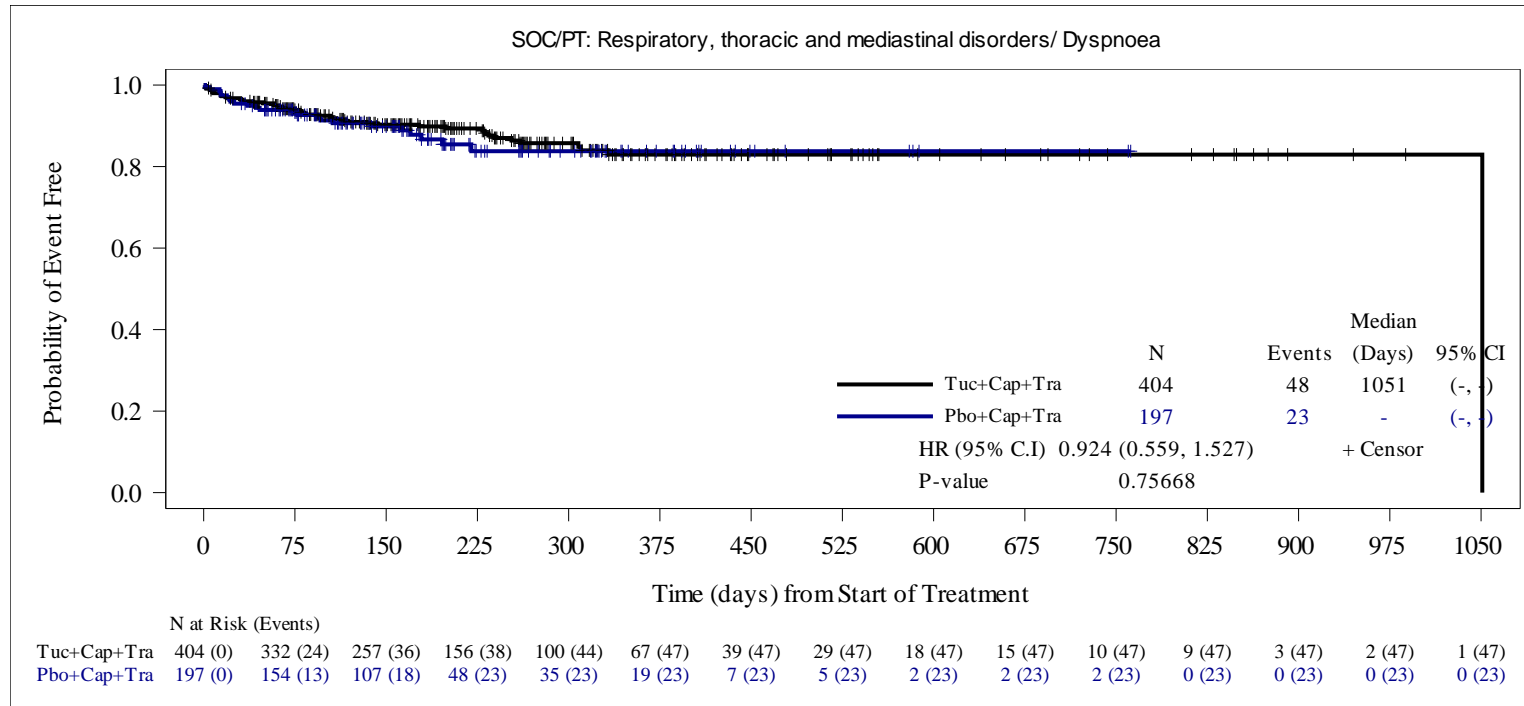
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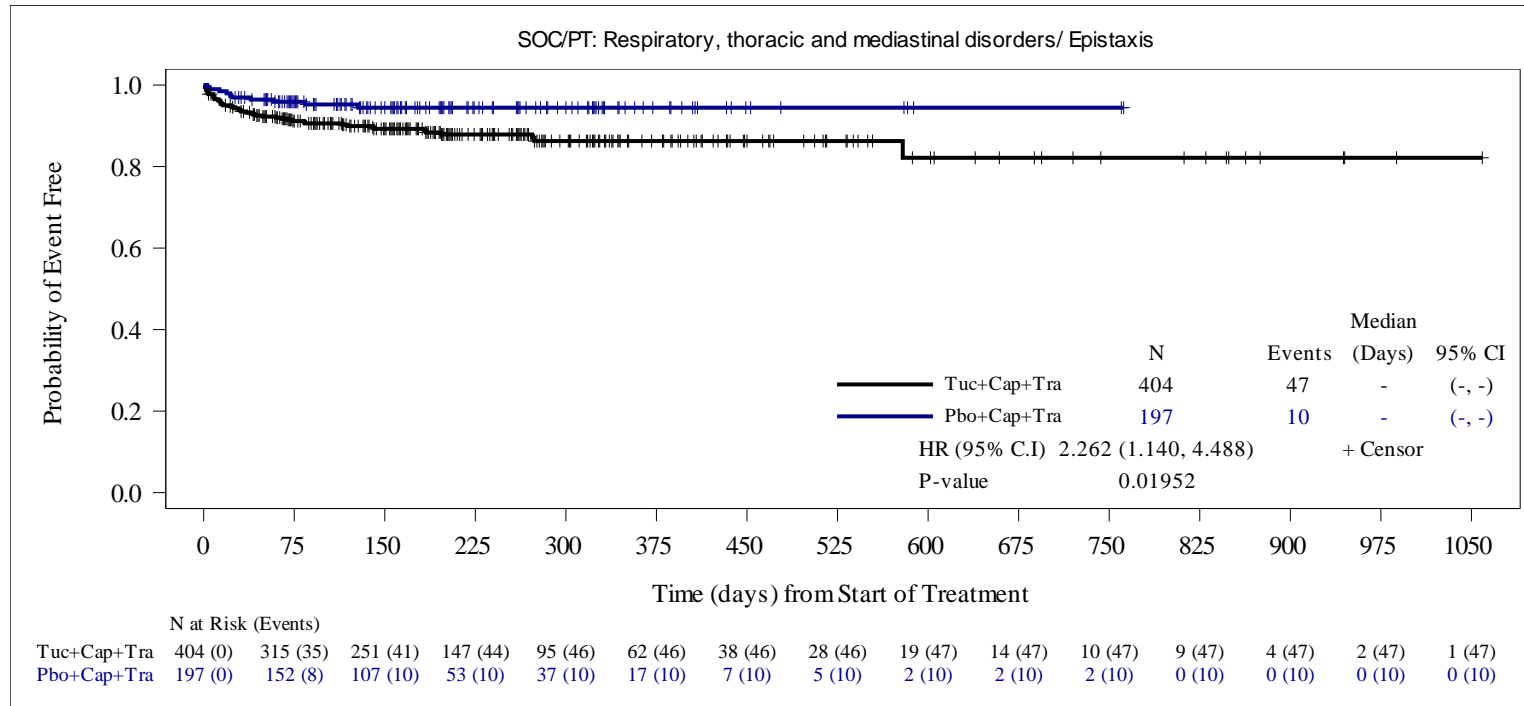
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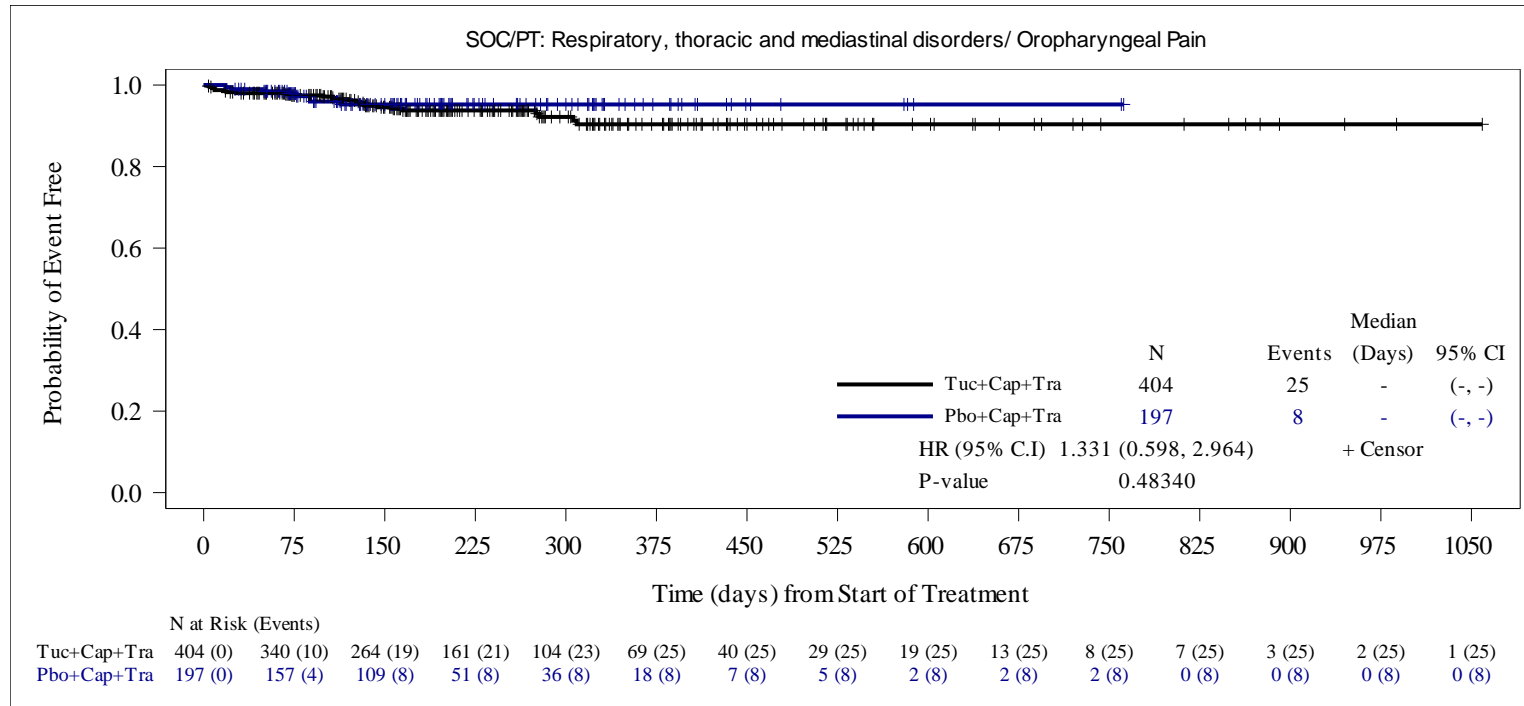
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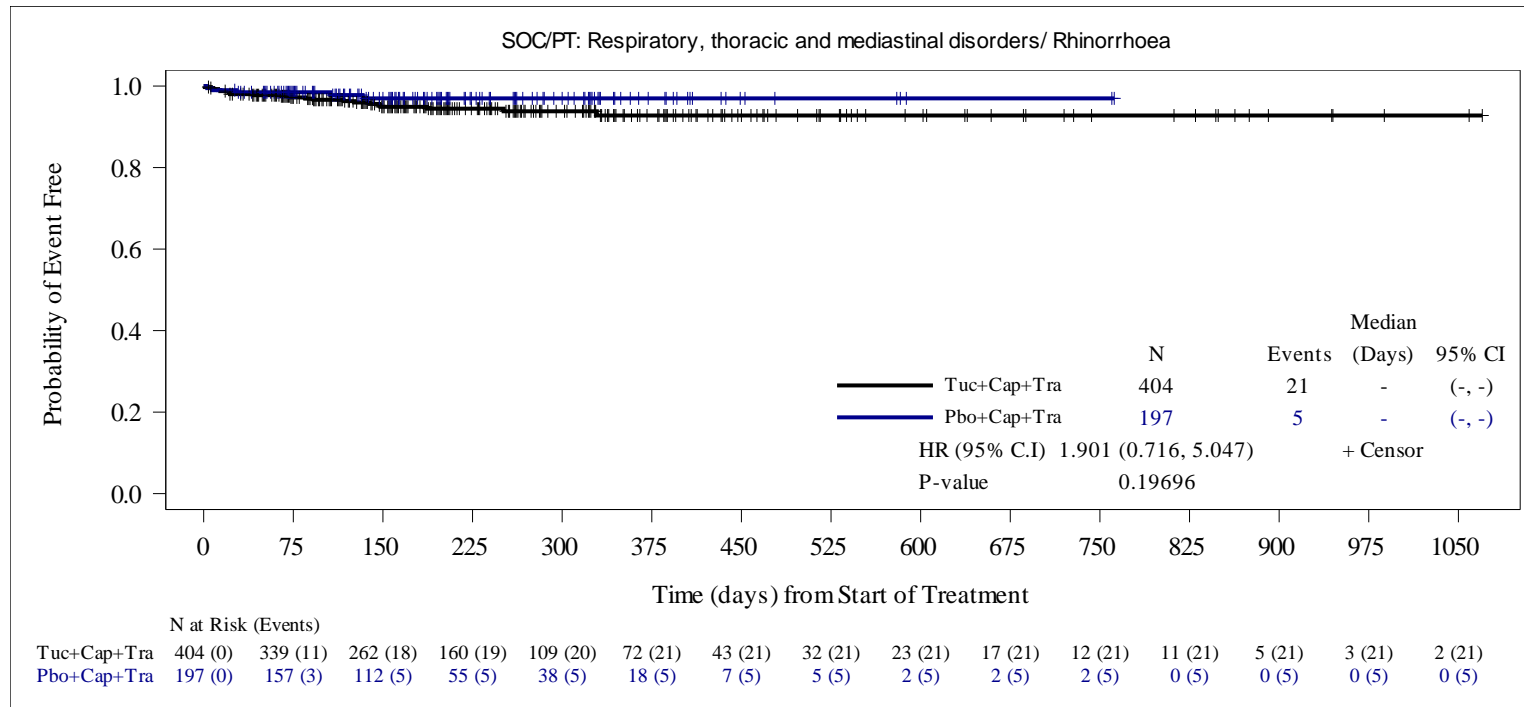
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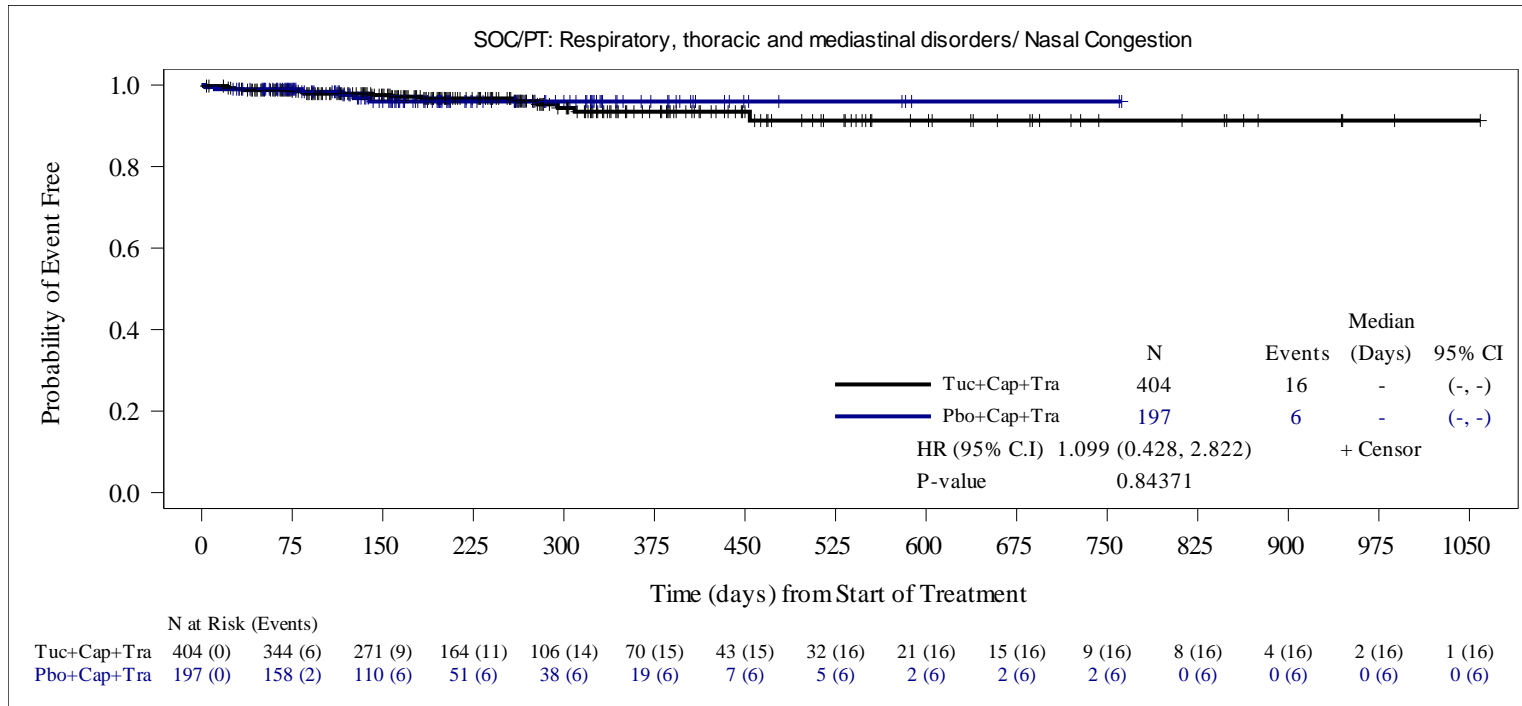
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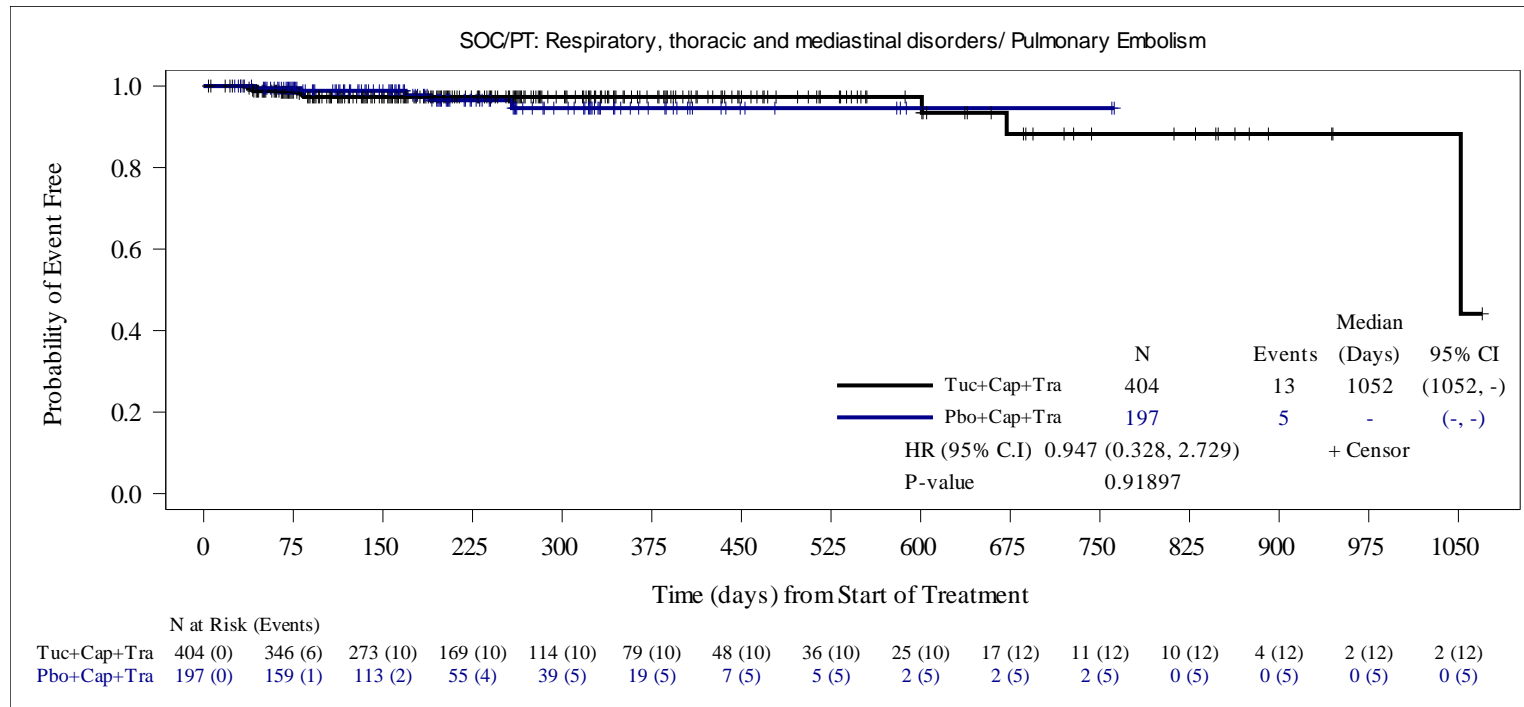
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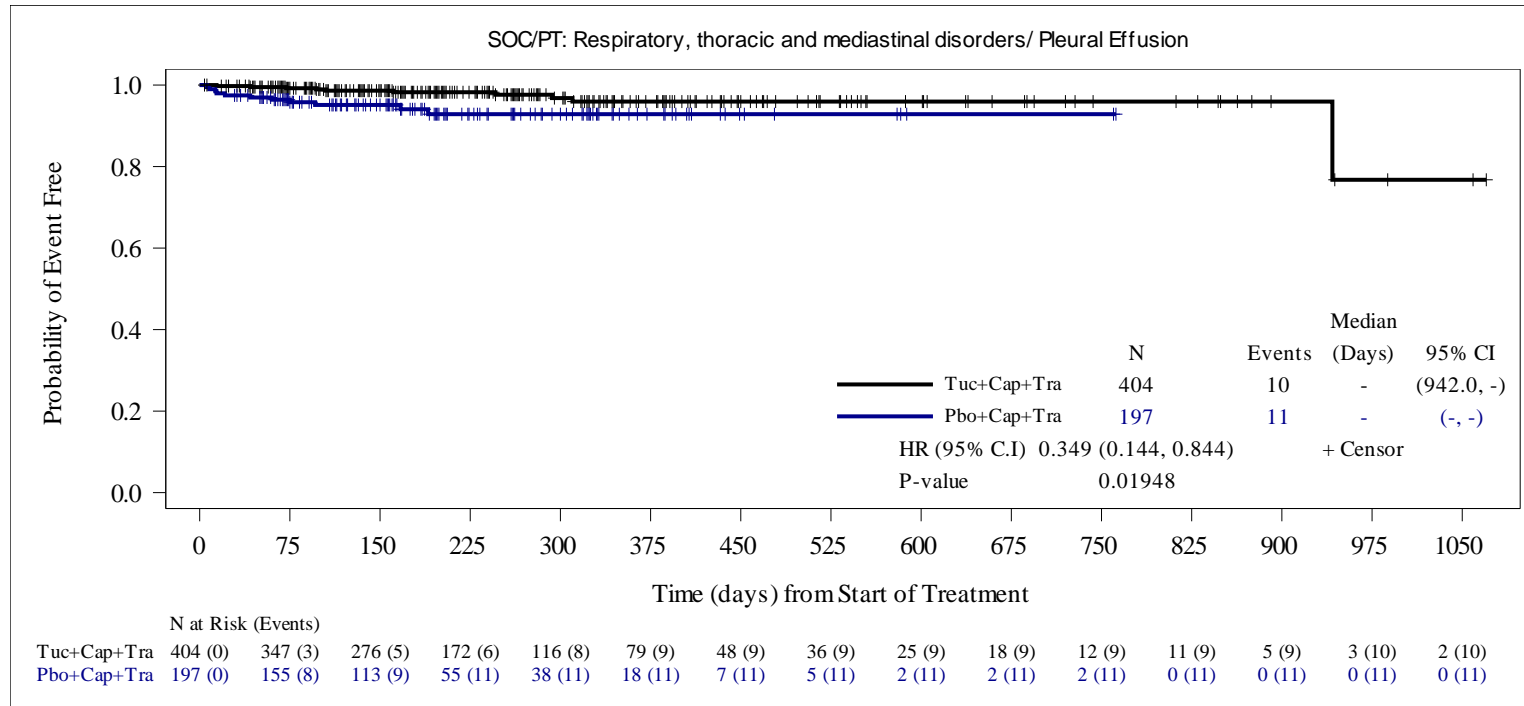
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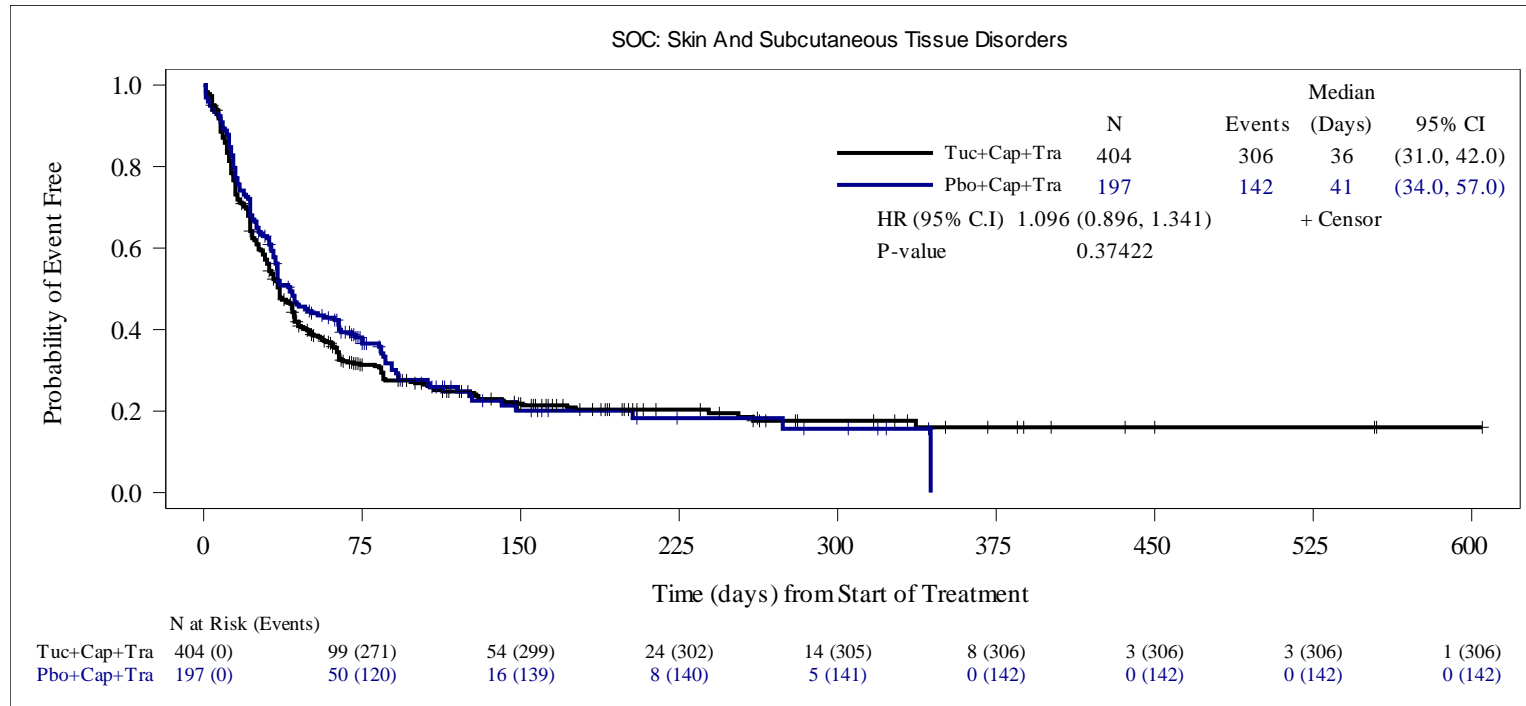
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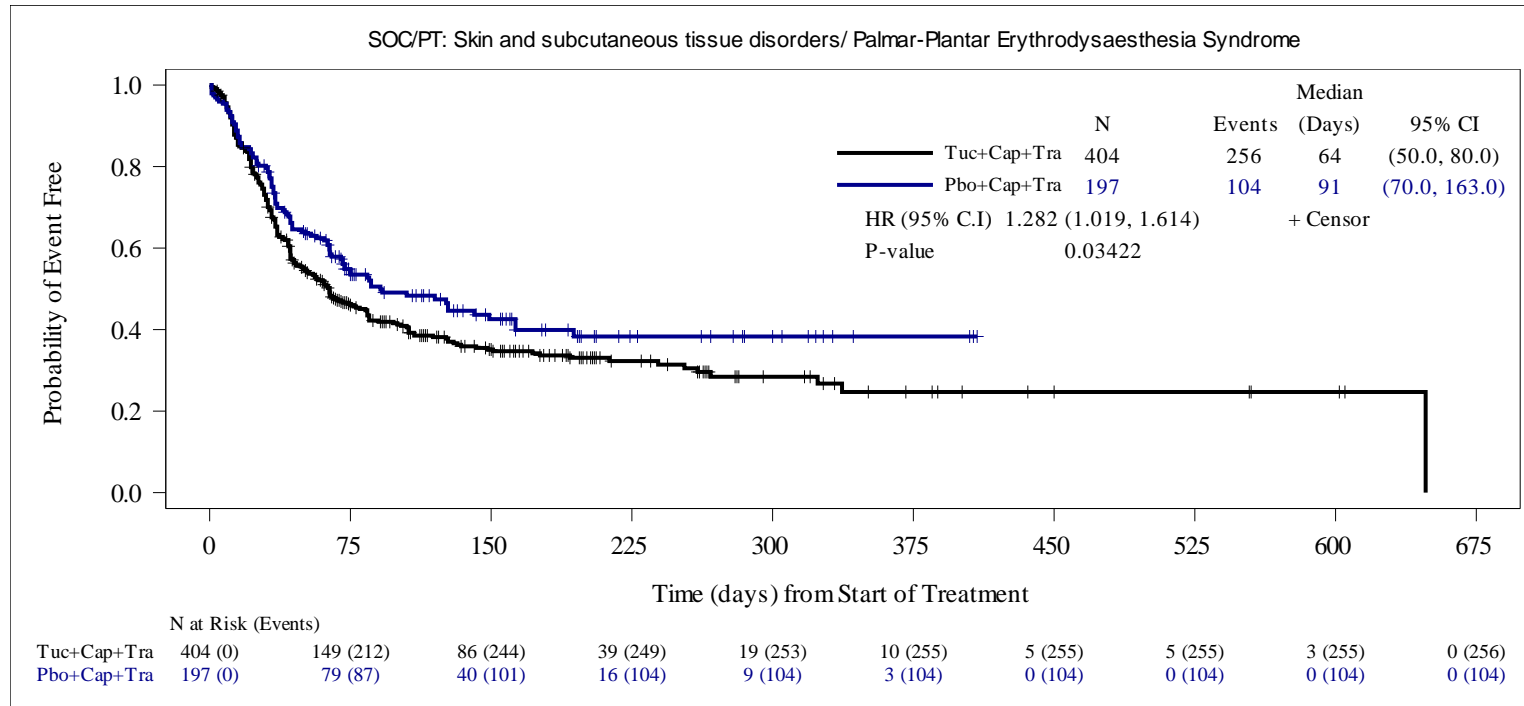
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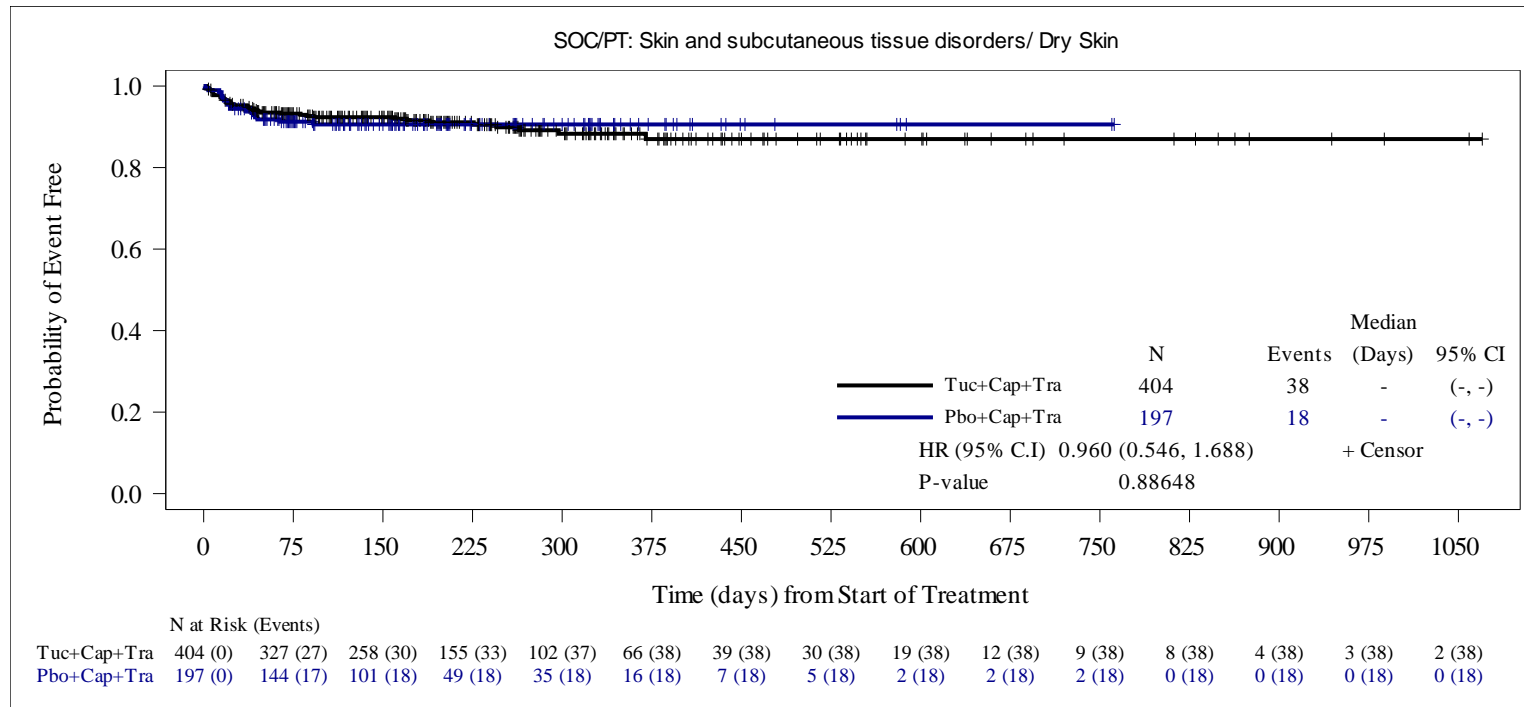
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Seattle Genetics Protocol ONT-380-206

**Figure 2.7.1 Kaplan-Meier Estimate of Time to First Onset of Treatment-Emergent Adverse Events by System Organ Class and Preferred Term
Safety Analysis Set**



HR is computed from the Cox proportional hazards model using stratification factors (Presence or history of brain metastases: Yes/No, ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization. When the number of subjects with at least one event was ≤ 30 , an unstratified Cox model was run.

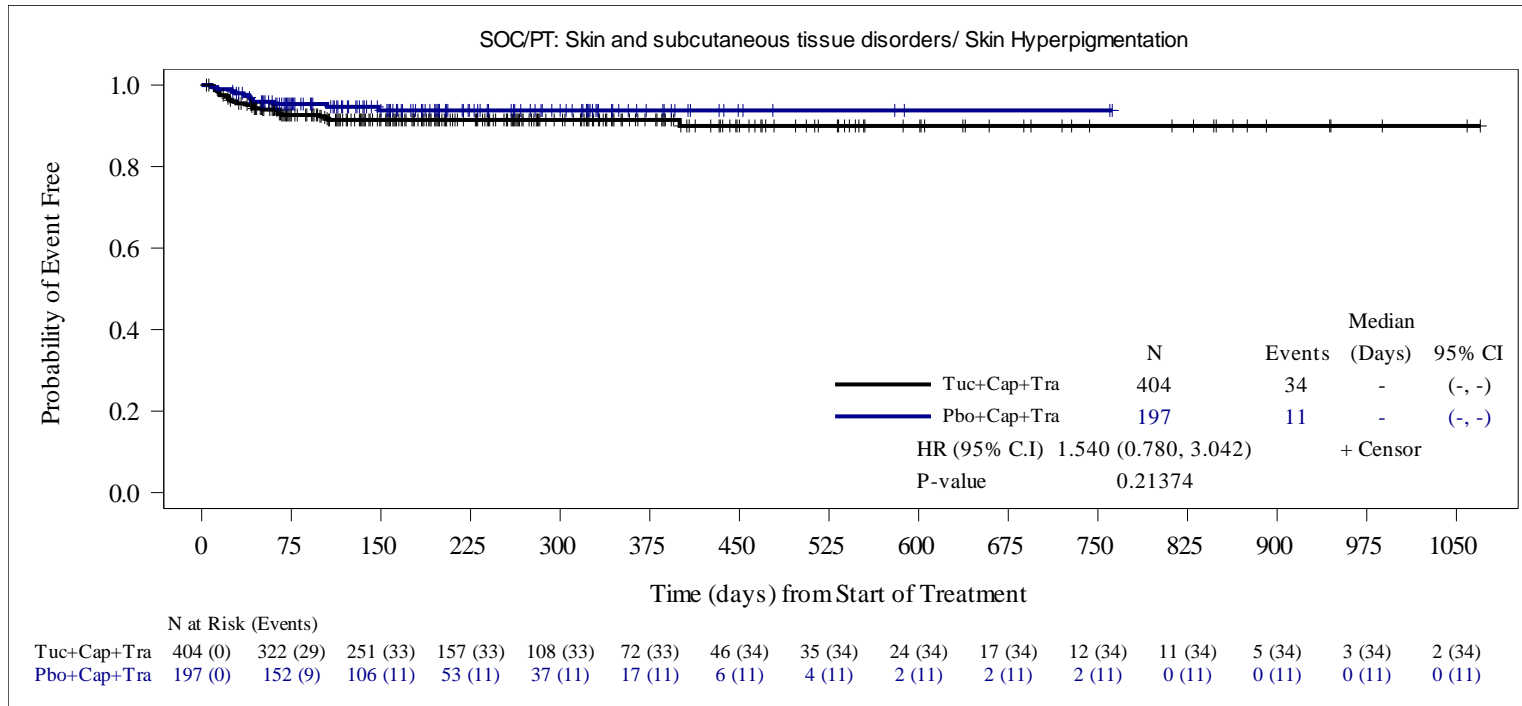
Two-sided p-value calculated from Cox proportional hazards model .

Data Snapshot: 14OCT2019, Data Cutoff Date: 04SEP2019

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Seattle Genetics Protocol ONT-380-206

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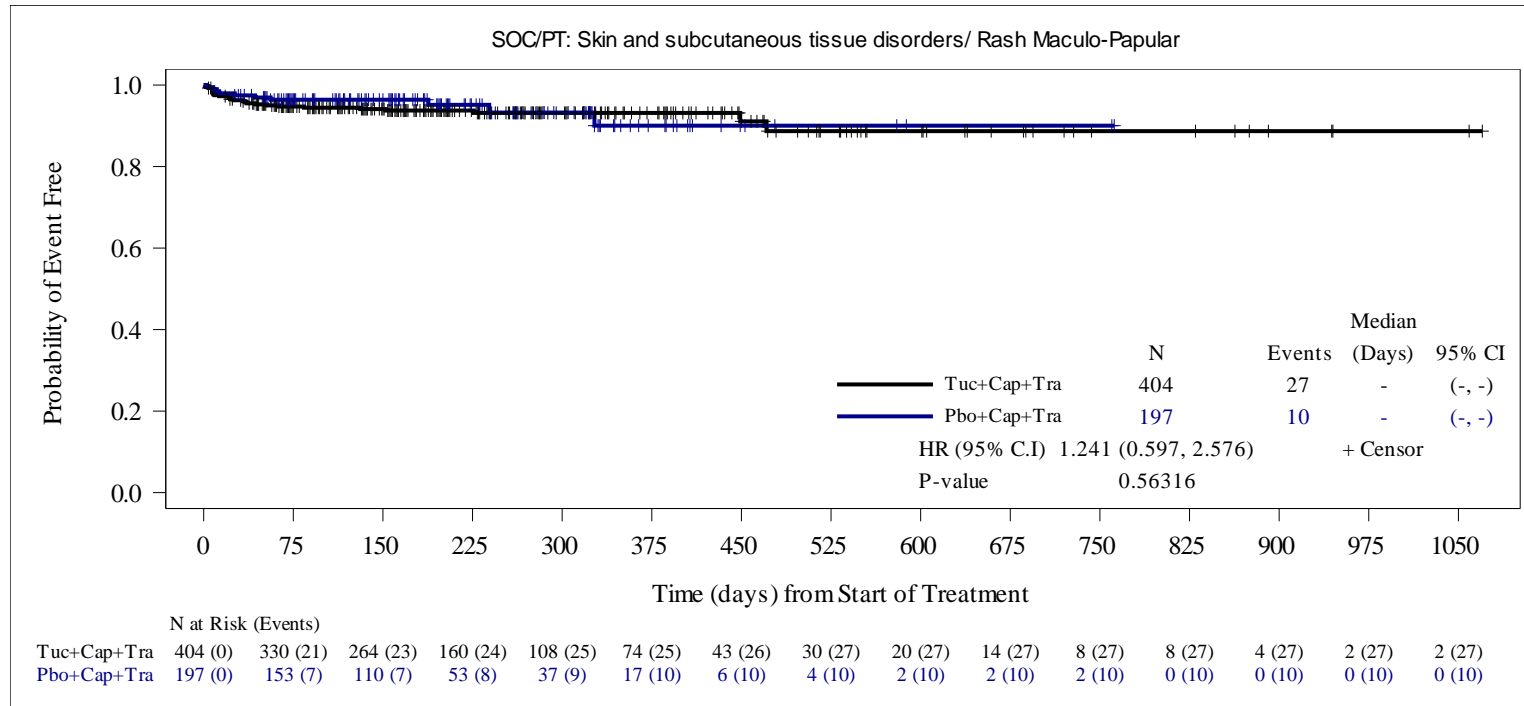
Two-sided p-value calculated from Cox proportional hazards model .

Data Snapshot: 14OCT2019, Data Cutoff Date: 04SEP2019

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Seattle Genetics Protocol ONT-380-206

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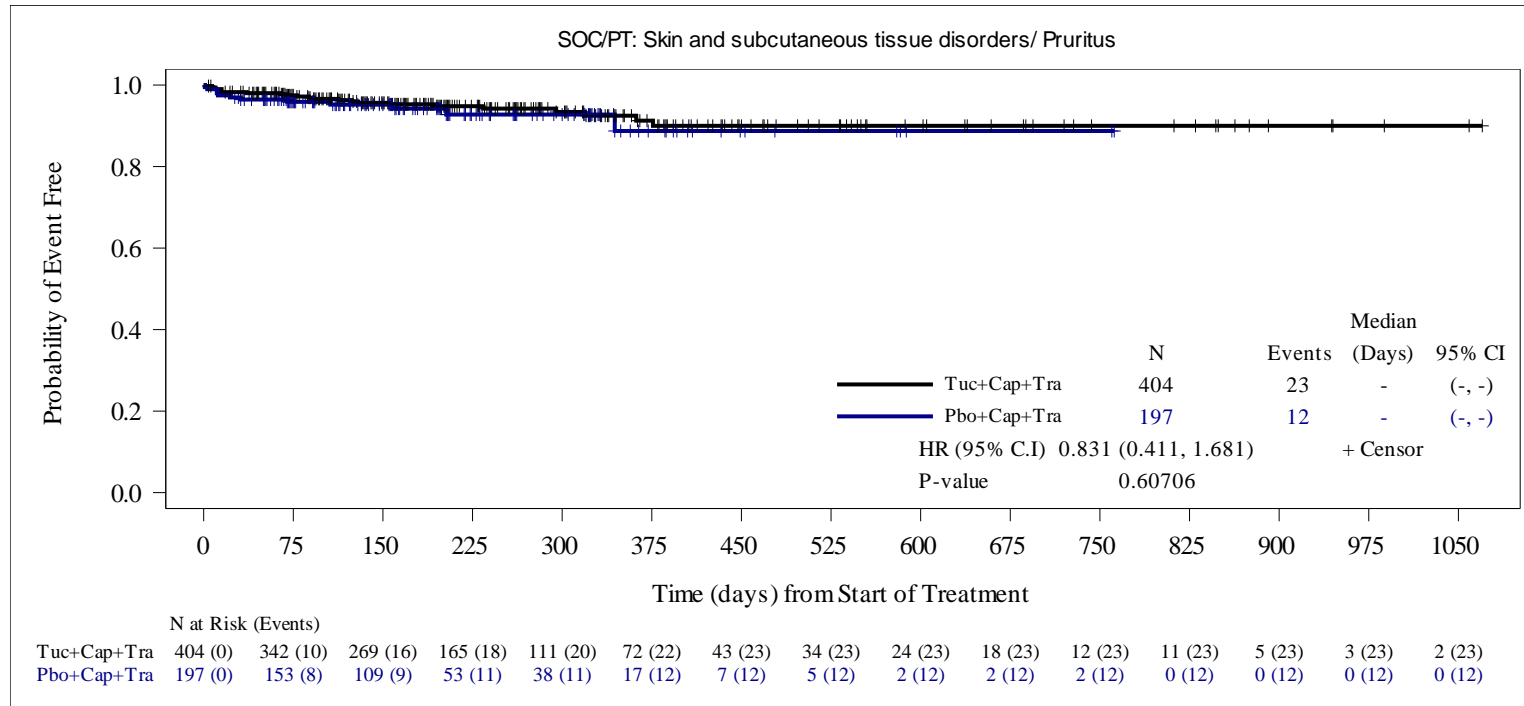
Two-sided p-value calculated from Cox proportional hazards model .

Data Snapshot: 14OCT2019, Data Cutoff Date: 04SEP2019

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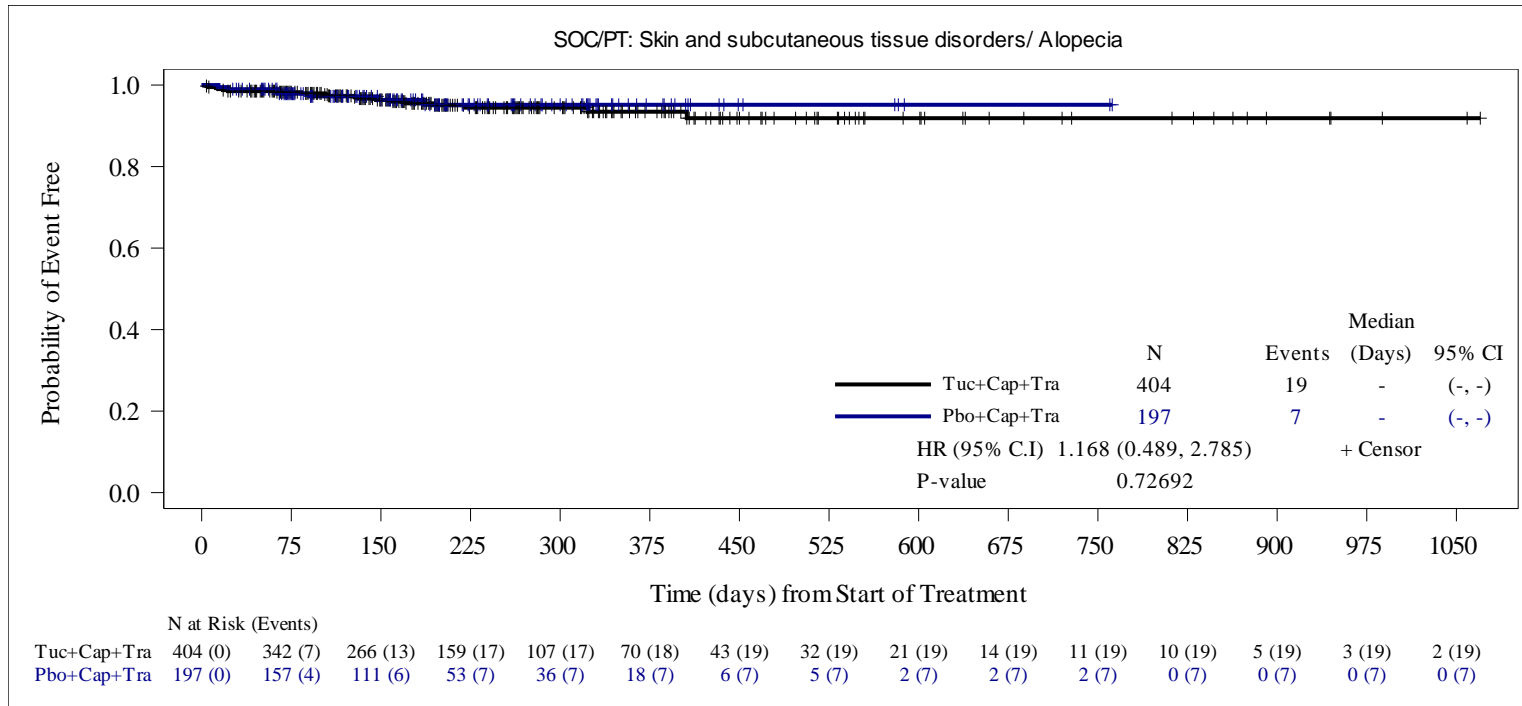
Two-sided p-value calculated from Cox proportional hazards model .

Data Snapshot: 14OCT2019, Data Cutoff Date: 04SEP2019

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Seattle Genetics Protocol ONT-380-206

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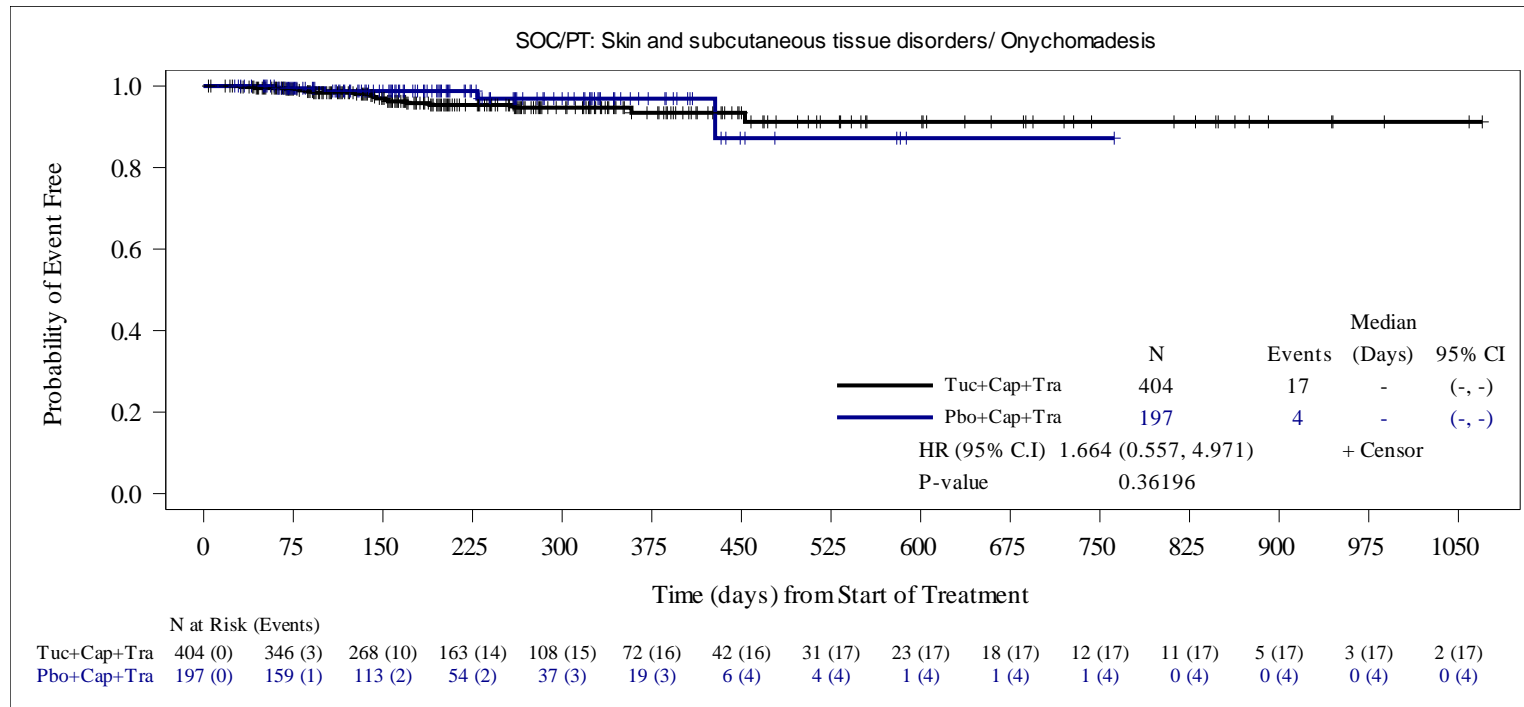
Two-sided p-value calculated from Cox proportional hazards model .

Data Snapshot: 14OCT2019, Data Cutoff Date: 04SEP2019

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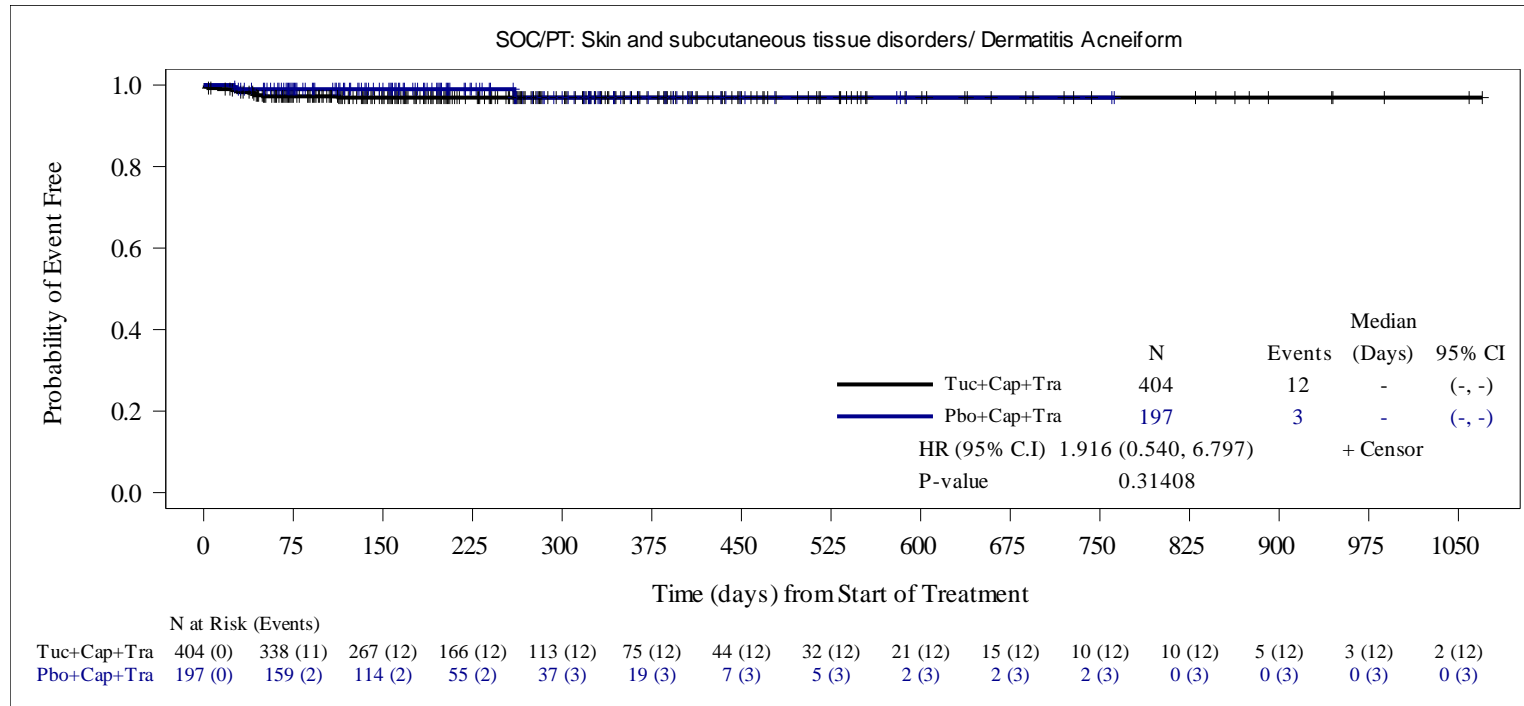
Two-sided p-value calculated from Cox proportional hazards model .

Data Snapshot: 14OCT2019, Data Cutoff Date: 04SEP2019

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Seattle Genetics Protocol ONT-380-206

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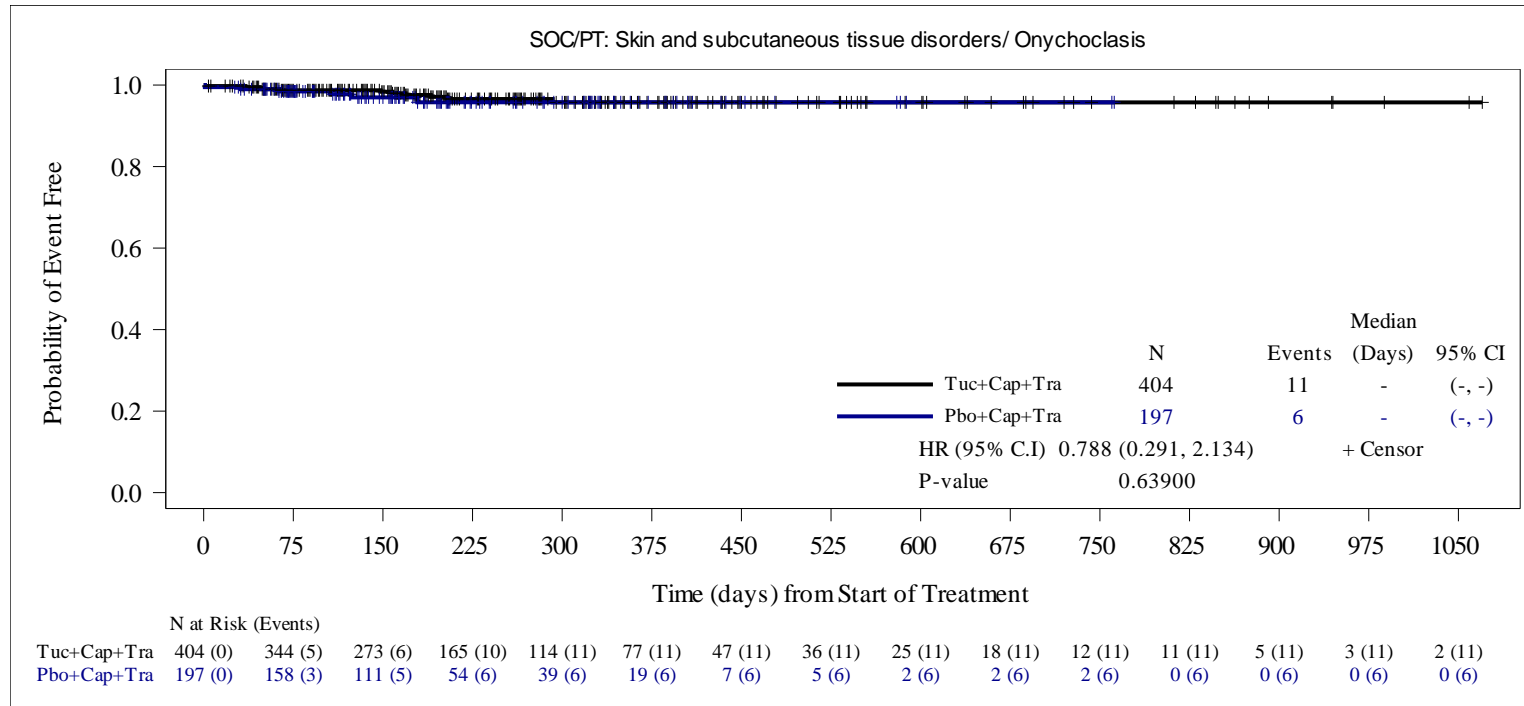
Two-sided p-value calculated from Cox proportional hazards model .

Data Snapshot: 14OCT2019, Data Cutoff Date: 04SEP2019

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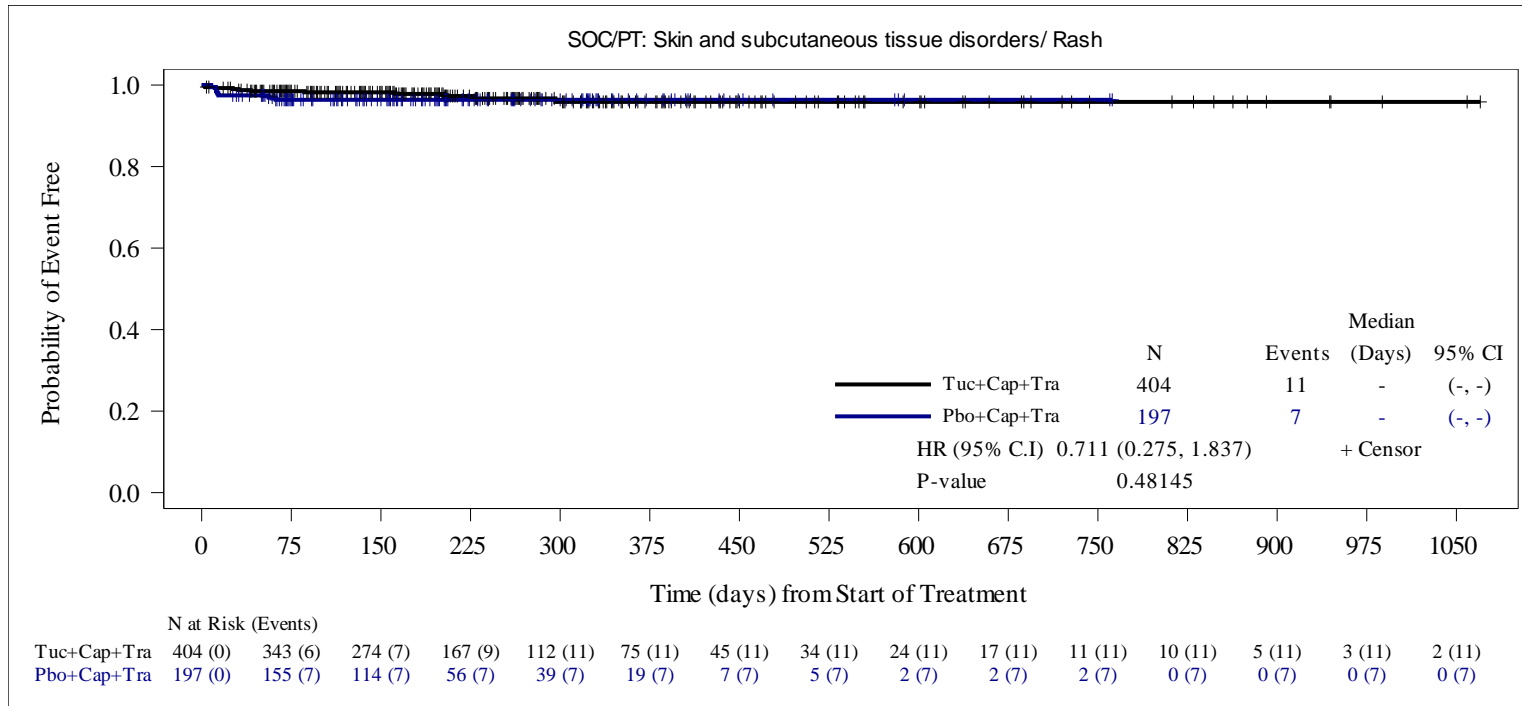
Two-sided p-value calculated from Cox proportional hazards model .

Data Snapshot: 14OCT2019, Data Cutoff Date: 04SEP2019

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Seattle Genetics Protocol ONT-380-206

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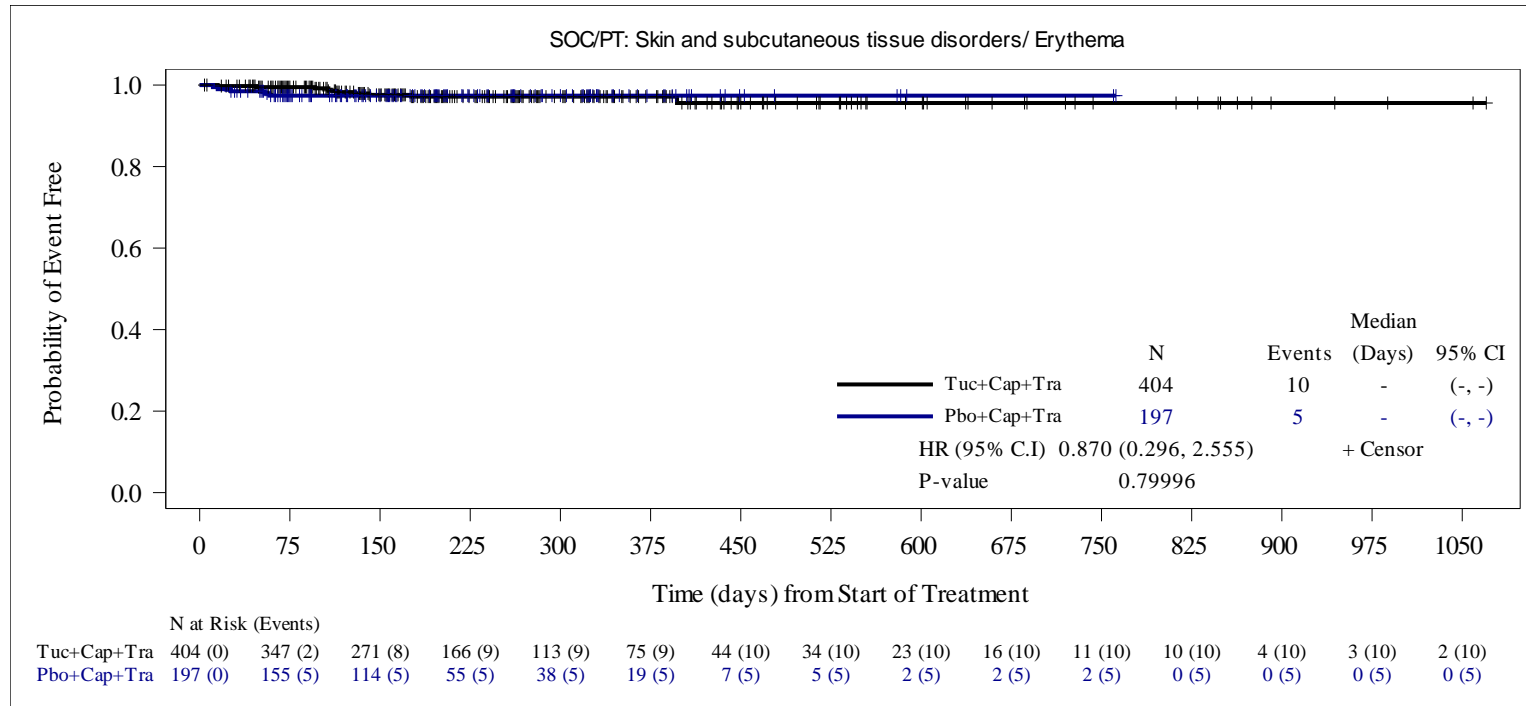
Two-sided p-value calculated from Cox proportional hazards model .

Data Snapshot: 14OCT2019, Data Cutoff Date: 04SEP2019

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Seattle Genetics Protocol ONT-380-206

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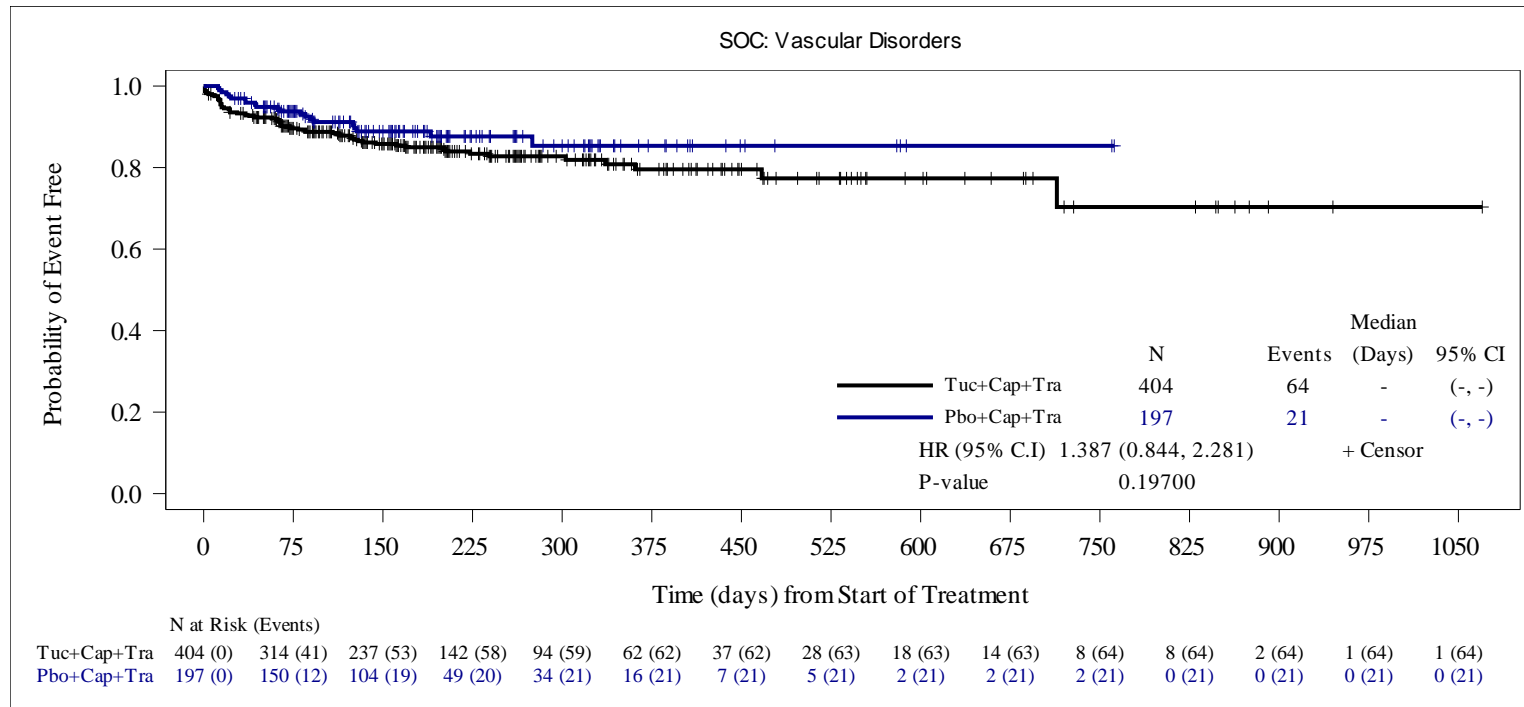
Two-sided p-value calculated from Cox proportional hazards model .

Data Snapshot: 14OCT2019, Data Cutoff Date: 04SEP2019

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Safety Analysis Set**



HR is computed from the Cox proportional hazards model using stratification factors (Presence or history of brain metastases: Yes/No, ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization. When the number of subjects with at least one event was ≤ 30 , an unstratified Cox model was run.

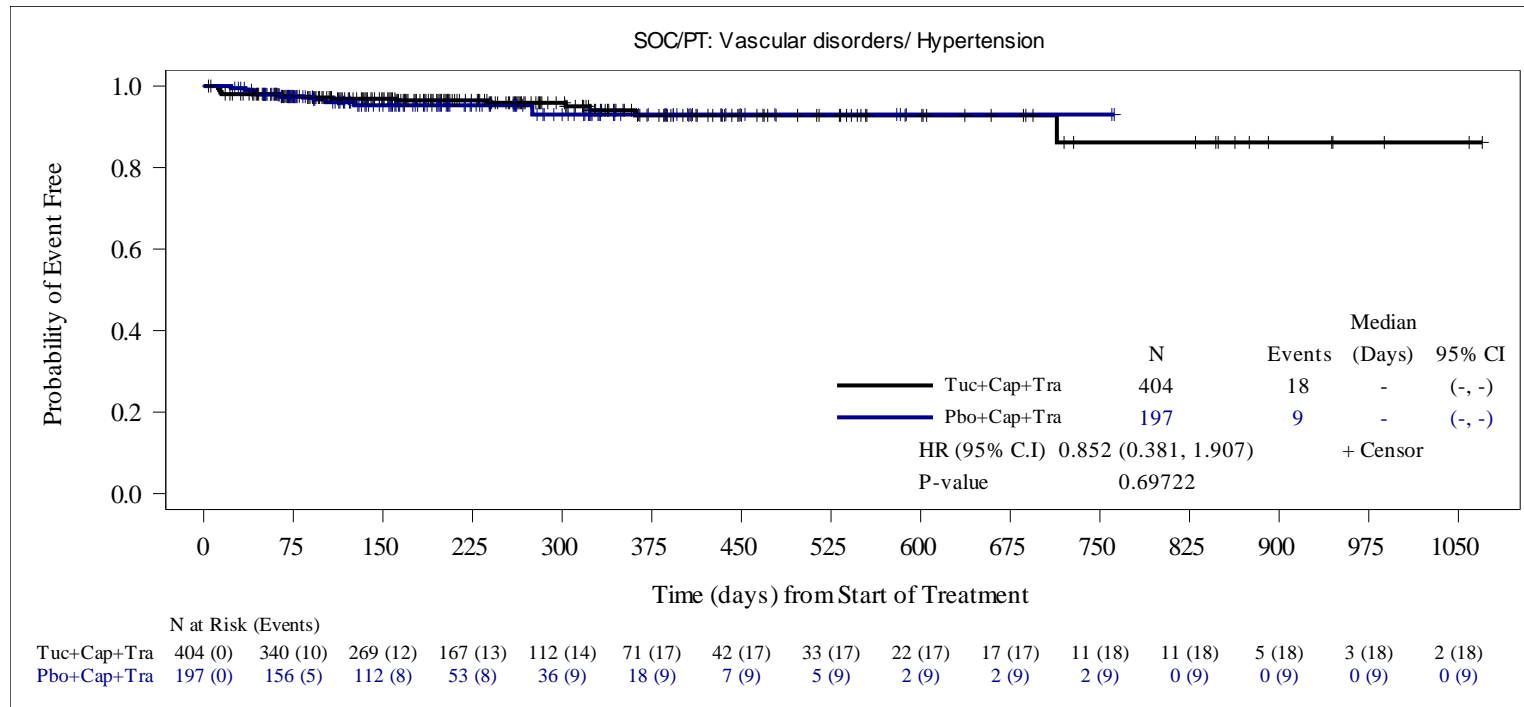
Two-sided p-value calculated from Cox proportional hazards model .

Data Snapshot: 14OCT2019, Data Cutoff Date: 04SEP2019

Source: O:\Projects\Tucatinib\ONT380-206_germanreimburse_1753\v01\outputs\tlfs\pgms\f-ae-km-socpt-safs.sas Output: f-ae-km-socpt-safs.rtf(17JUL20:16:07) Data: adsl, adae, adttesaf

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HR is computed from the Cox proportional hazards model using stratification factors (Presence or history of brain metastases: Yes/No, ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization. When the number of subjects with at least one event was ≤ 30 , an unstratified Cox model was run.

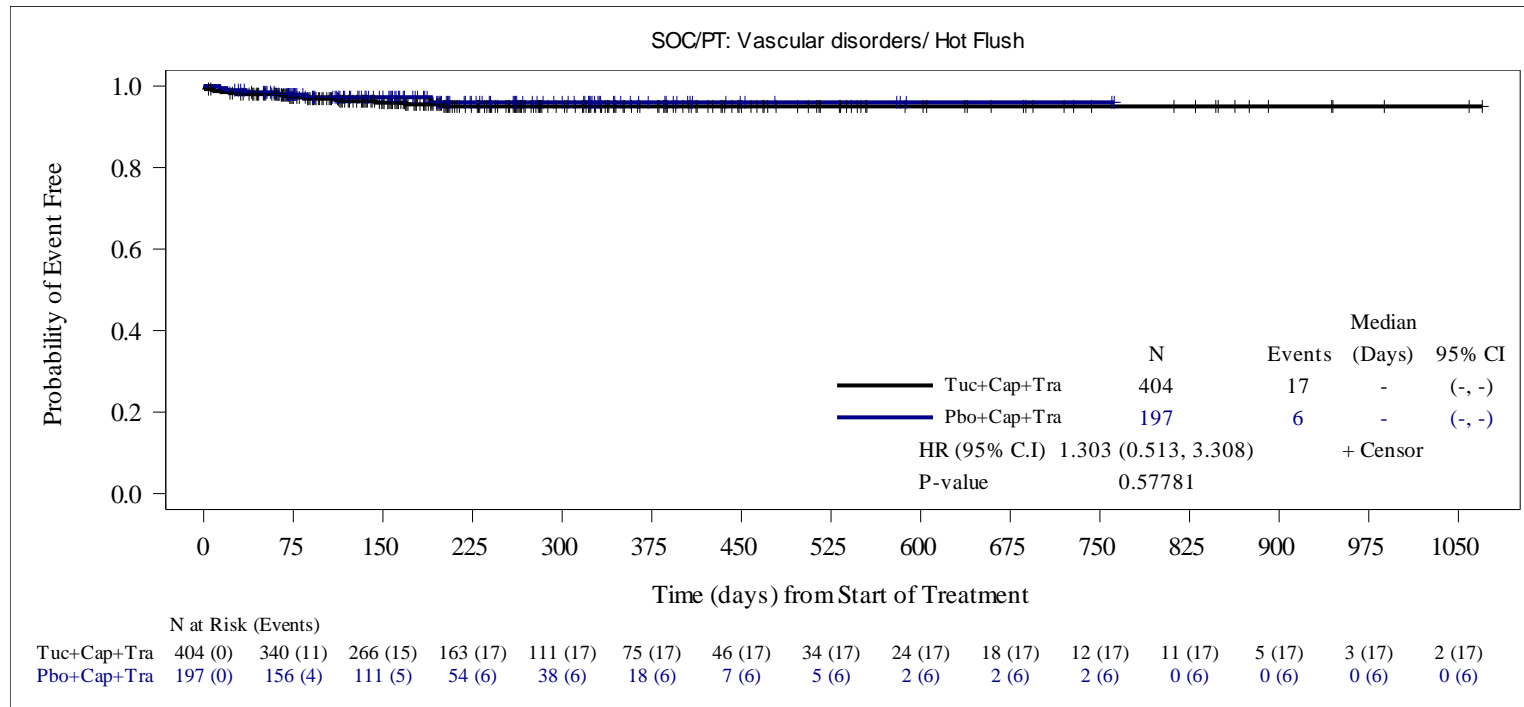
Two-sided p-value calculated from Cox proportional hazards model .

Data Snapshot: 14OCT2019, Data Cutoff Date: 04SEP2019

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Safety Analysis Set**



HR is computed from the Cox proportional hazards model using stratification factors (Presence or history of brain metastases: Yes/No, ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization. When the number of subjects with at least one event was ≤ 30 , an unstratified Cox model was run.

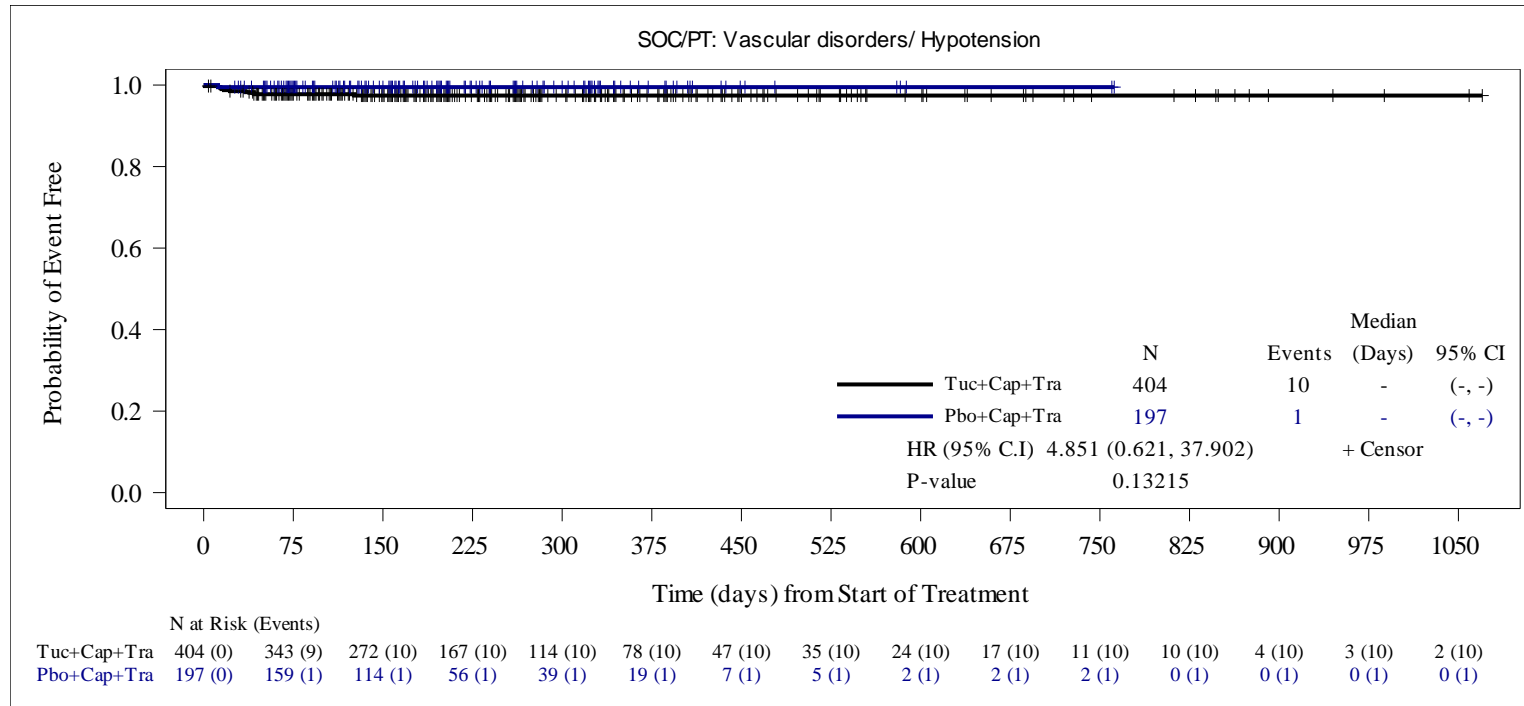
Two-sided p-value calculated from Cox proportional hazards model .

Data Snapshot: 14OCT2019, Data Cutoff Date: 04SEP2019

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Safety Analysis Set**



HR is computed from the Cox proportional hazards model using stratification factors (Presence or history of brain metastases: Yes/No, ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization. When the number of subjects with at least one event was ≤ 30 , an unstratified Cox model was run.

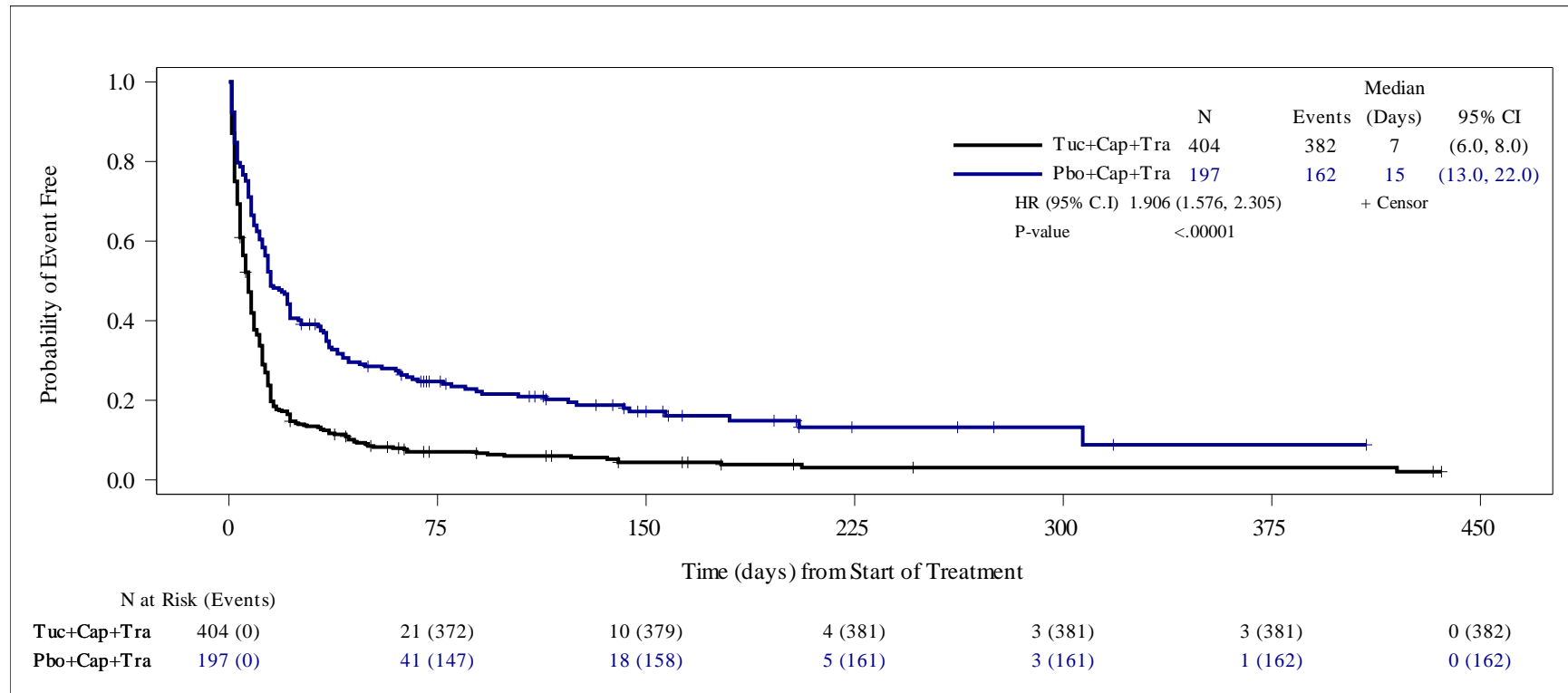
Two-sided p-value calculated from Cox proportional hazards model .

Data Snapshot: 14OCT2019, Data Cutoff Date: 04SEP2019

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**Figure 2.3.1 Kaplan-Meier Estimate of Time to First Onset of Adverse Events - Gastrointestinal Disorder
Safety Analysis Set**



HR is computed from the Cox proportional hazards model using stratification factors (Presence or history of brain metastases: Yes/No, ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization.

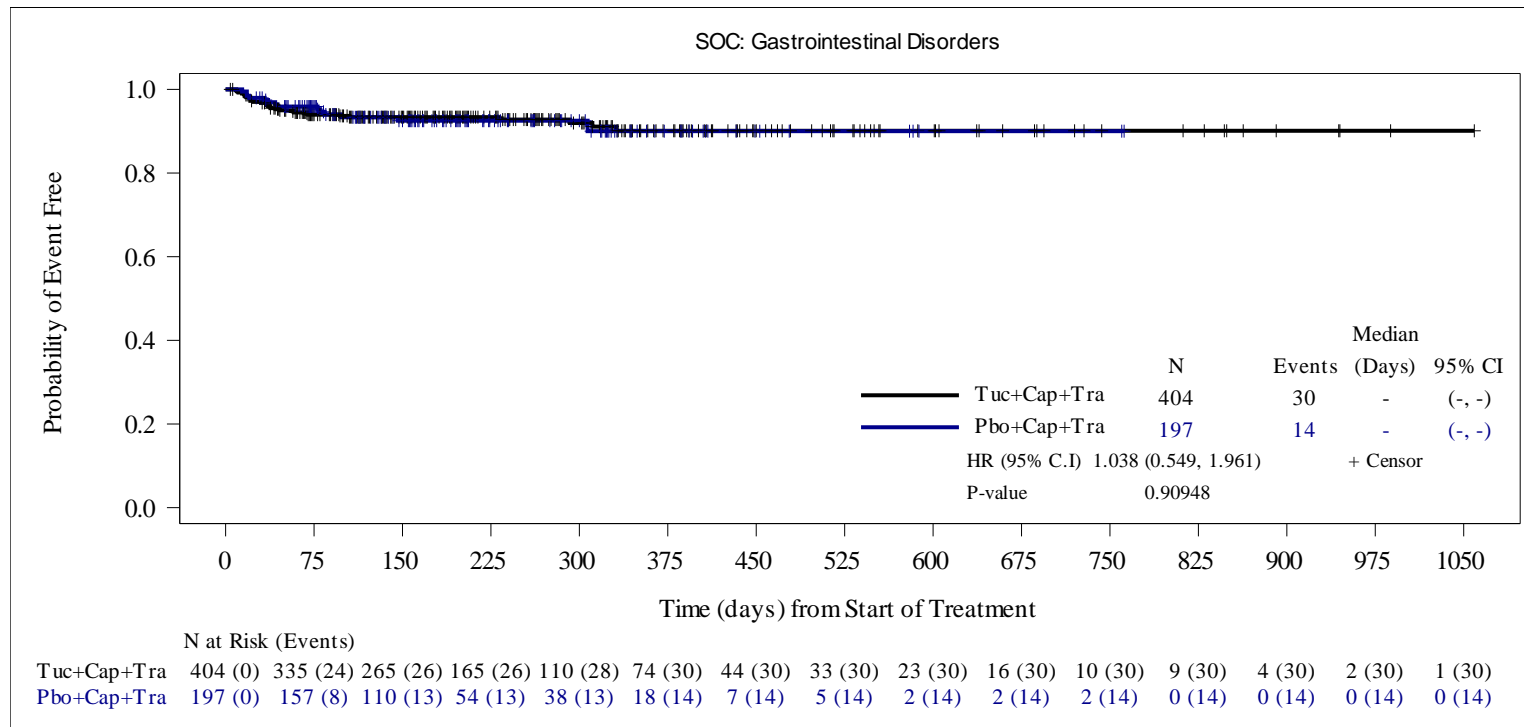
Two-sided p-value calculated from Cox proportional hazards model .

Data Snapshot: 14OCT2019, Data Cutoff Date: 04SEP2019

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**Figure 2.9.1 Kaplan-Meier Estimate of Time to First Onset of Serious Treatment-Emergent Adverse Events by System Organ Class and Preferred Term
Safety Analysis Set**



HR is computed from the Cox proportional hazards model using stratification factors (Presence or history of brain metastases: Yes/No, ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization. When the number of subjects with at least one event was ≤ 30 , an unstratified Cox model was run.

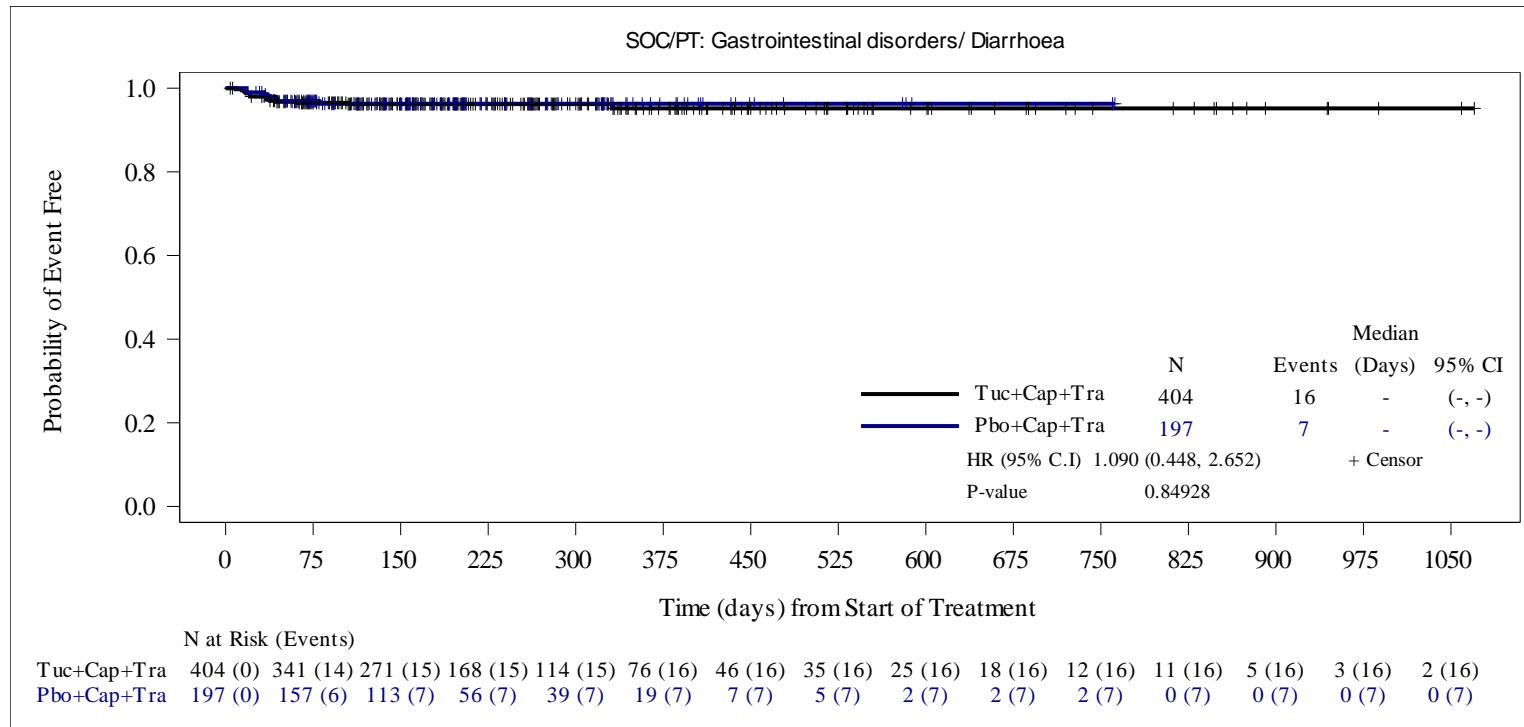
Two-sided p-value calculated from Cox proportional hazards model .

Data Snapshot: 14OCT2019, Data Cutoff Date: 04SEP2019

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Figure 2.9.1 Kaplan-Meier Estimate of Time to First Onset of Serious Treatment-Emergent Adverse Events by System Organ Class and Preferred Term Safety Analysis Set



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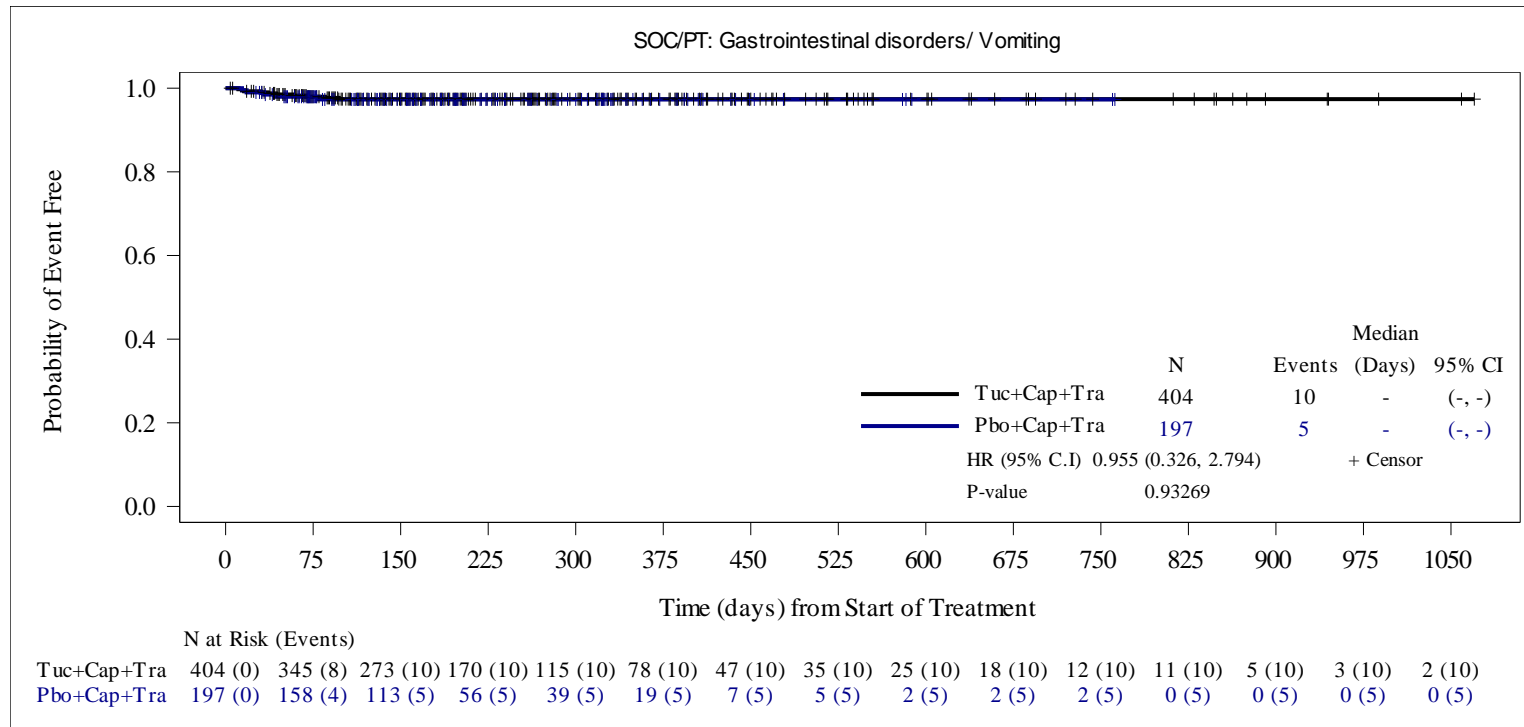
Two-sided p-value calculated from Cox proportional hazards model .

Data Snapshot: 14OCT2019, Data Cutoff Date: 04SEP2019

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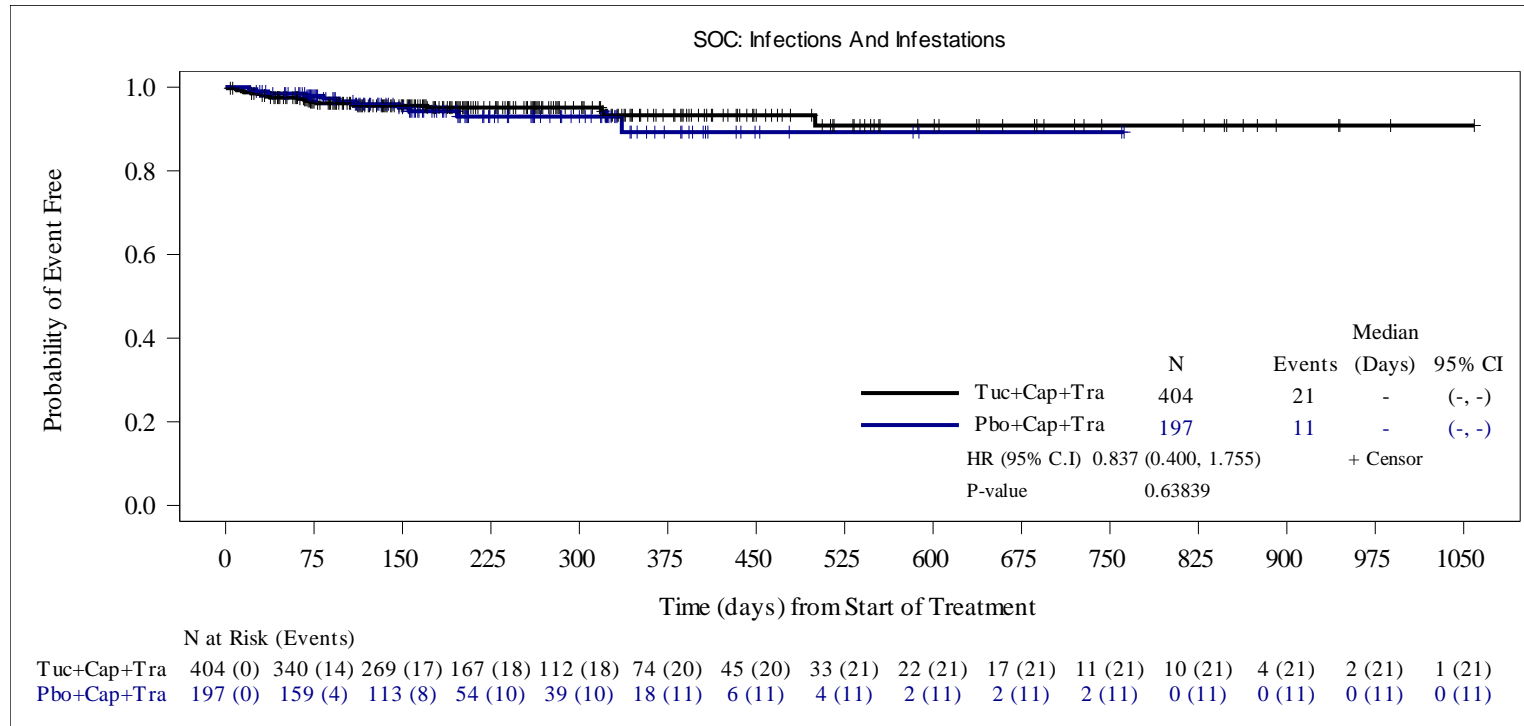
Two-sided p-value calculated from Cox proportional hazards model .

Data Snapshot: 14OCT2019, Data Cutoff Date: 04SEP2019

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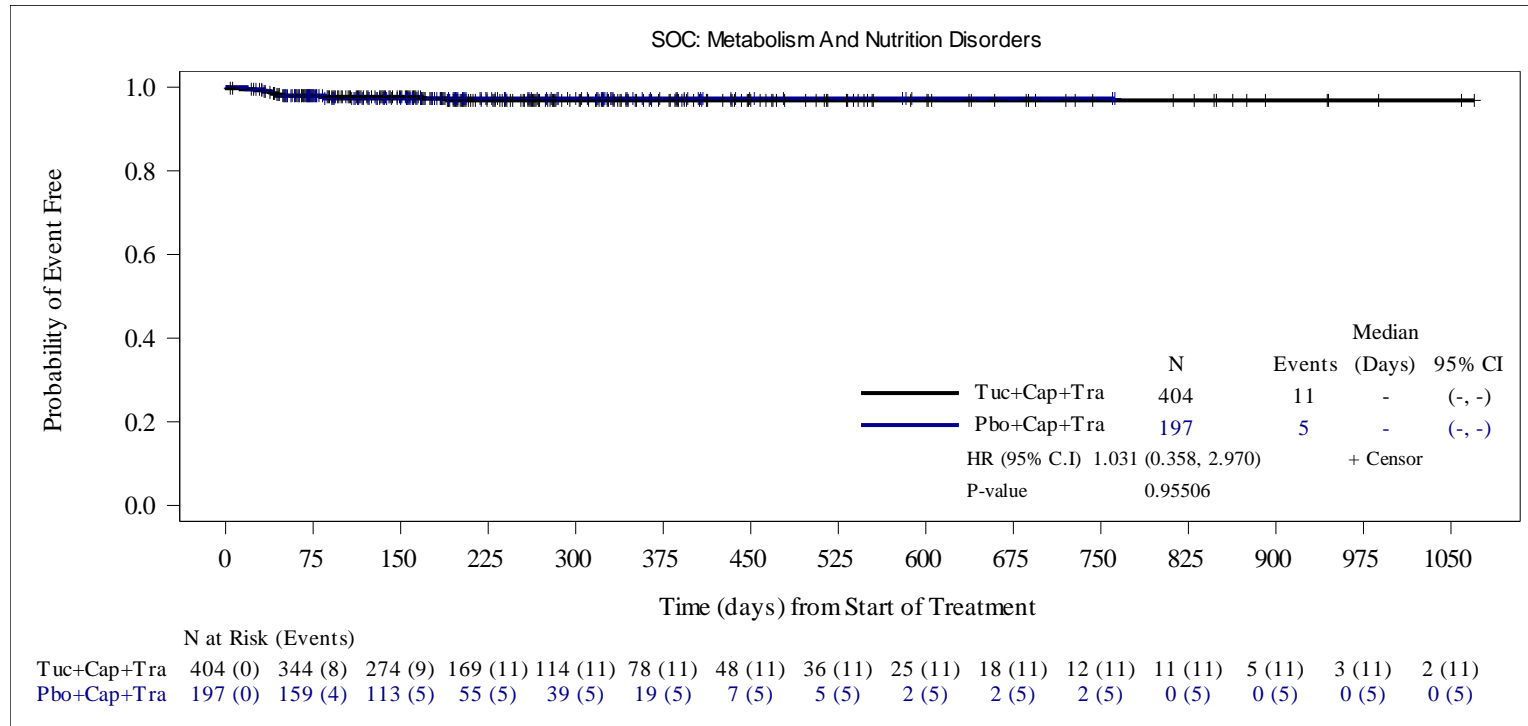
Two-sided p-value calculated from Cox proportional hazards model .

Data Snapshot: 14OCT2019, Data Cutoff Date: 04SEP2019

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Seattle Genetics Protocol ONT-380-206

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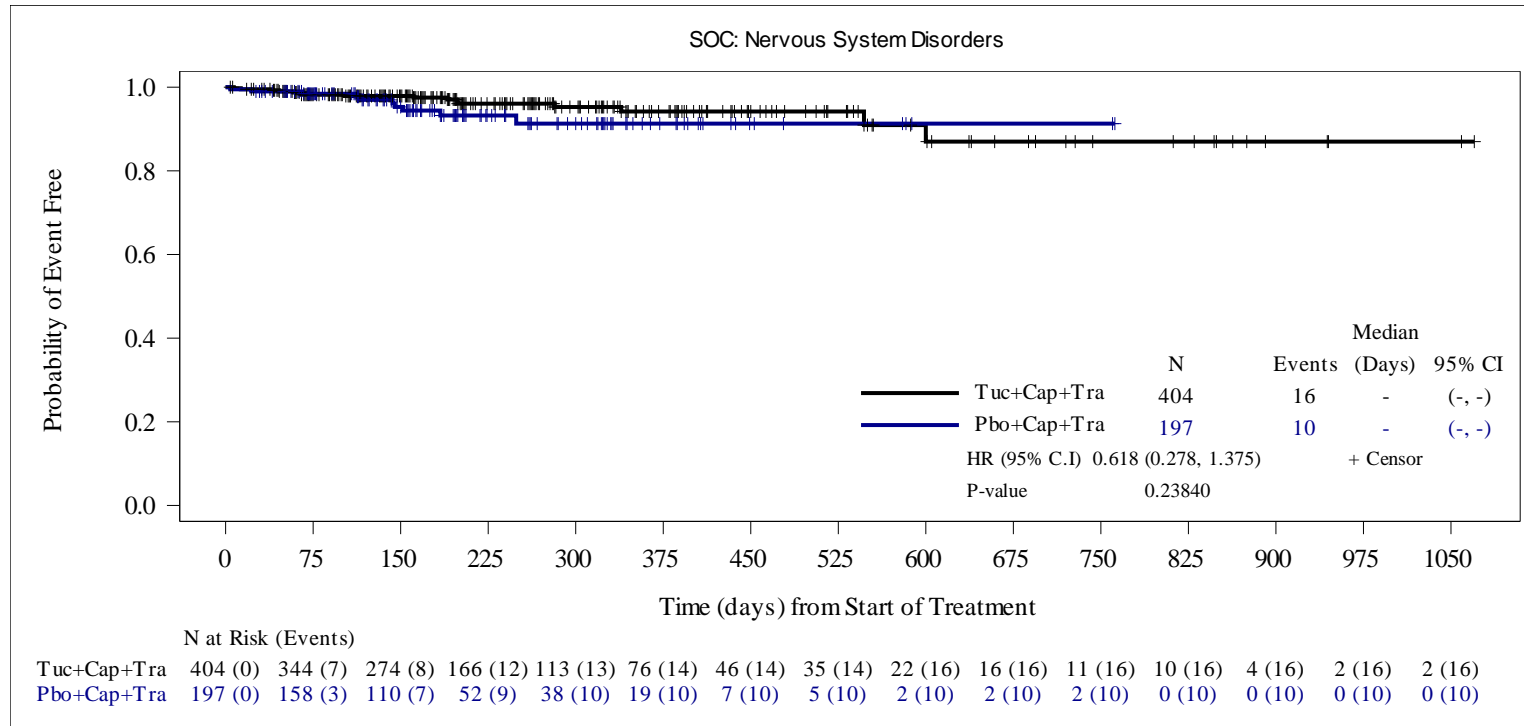
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Data Snapshot: 14OCT2019, Data Cutoff Date: 04SEP2019

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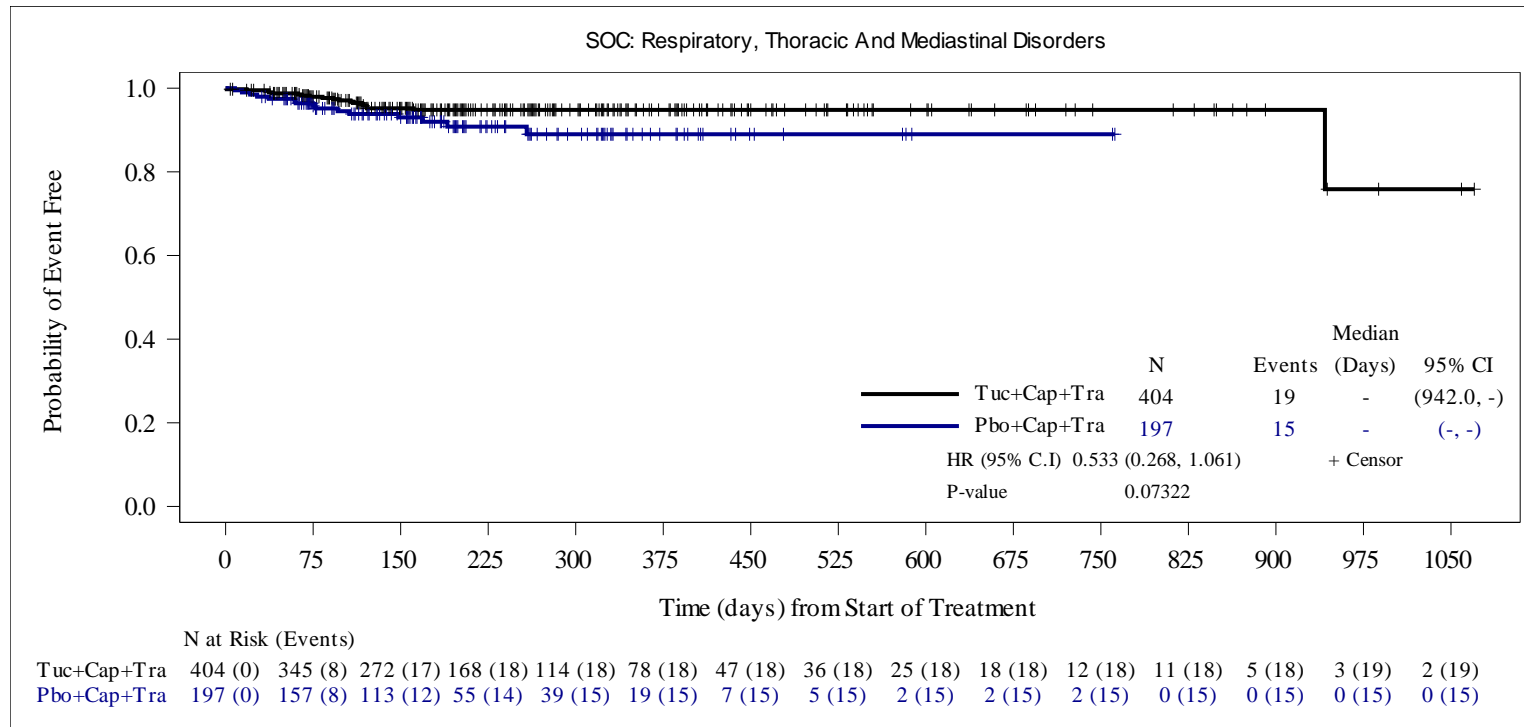
Two-sided p-value calculated from Cox proportional hazards model .

Data Snapshot: 14OCT2019, Data Cutoff Date: 04SEP2019

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Seattle Genetics Protocol ONT-380-206

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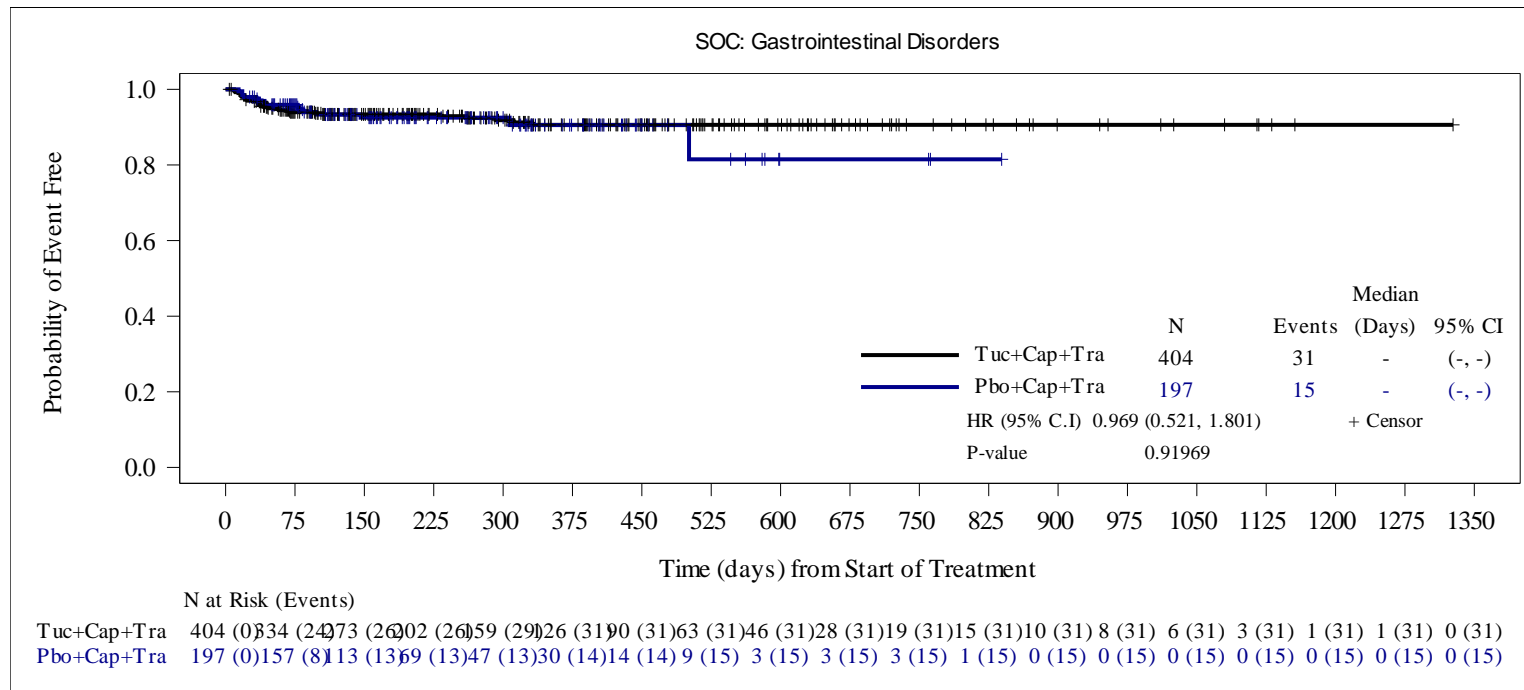
Two-sided p-value calculated from Cox proportional hazards model .

Data Snapshot: 14OCT2019, Data Cutoff Date: 04SEP2019

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Seagen Protocol ONT-380-206

**Figure 2.9.1 Kaplan-Meier Estimate of Time to First Onset of Serious Treatment-Emergent Adverse Events by System Organ Class and Preferred Term
Safety Analysis Set**



HR is computed from the Cox proportional hazards model using stratification factors (Presence or history of brain metastases: Yes/No, ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization. When the number of subjects with at least one event was ≤ 30 , an unstratified Cox model was run.

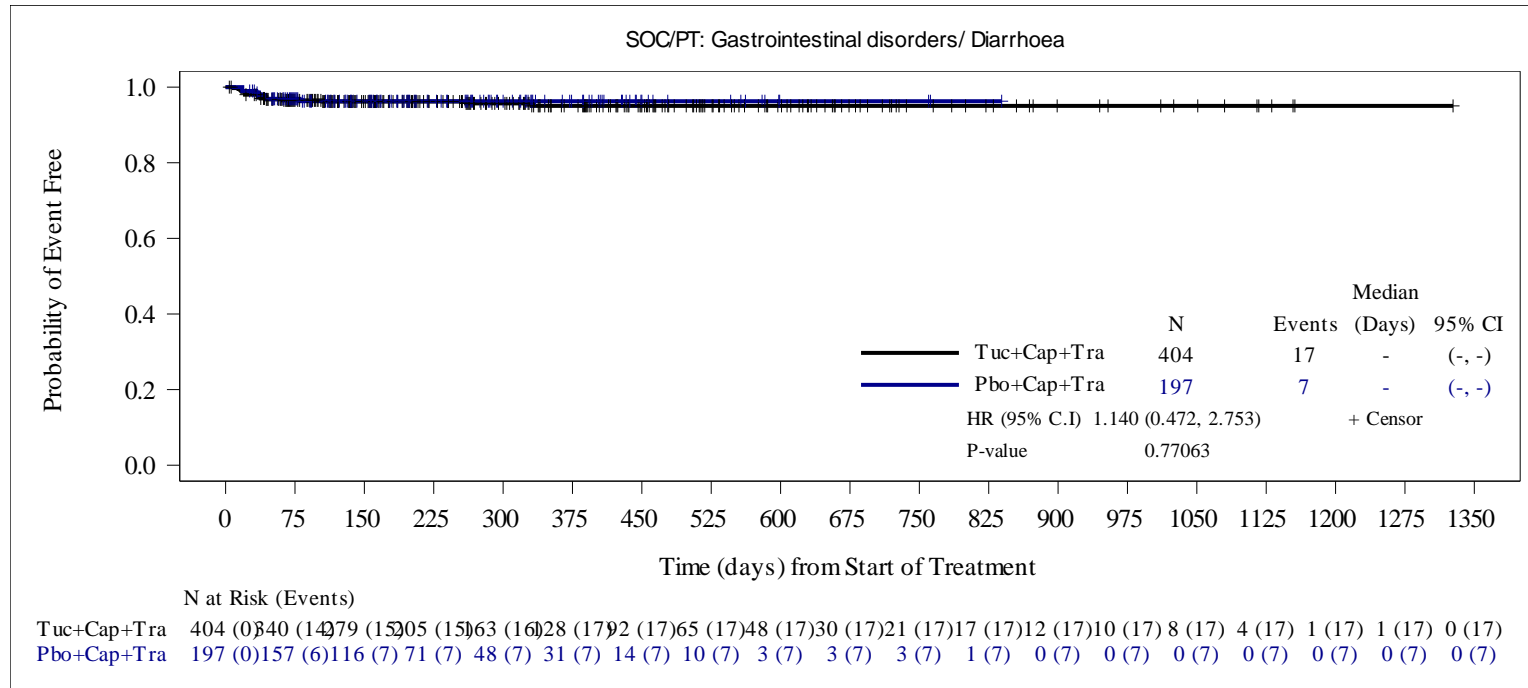
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Snapshot date: 10SEP2020, data cutoff date: 29MAY2020.

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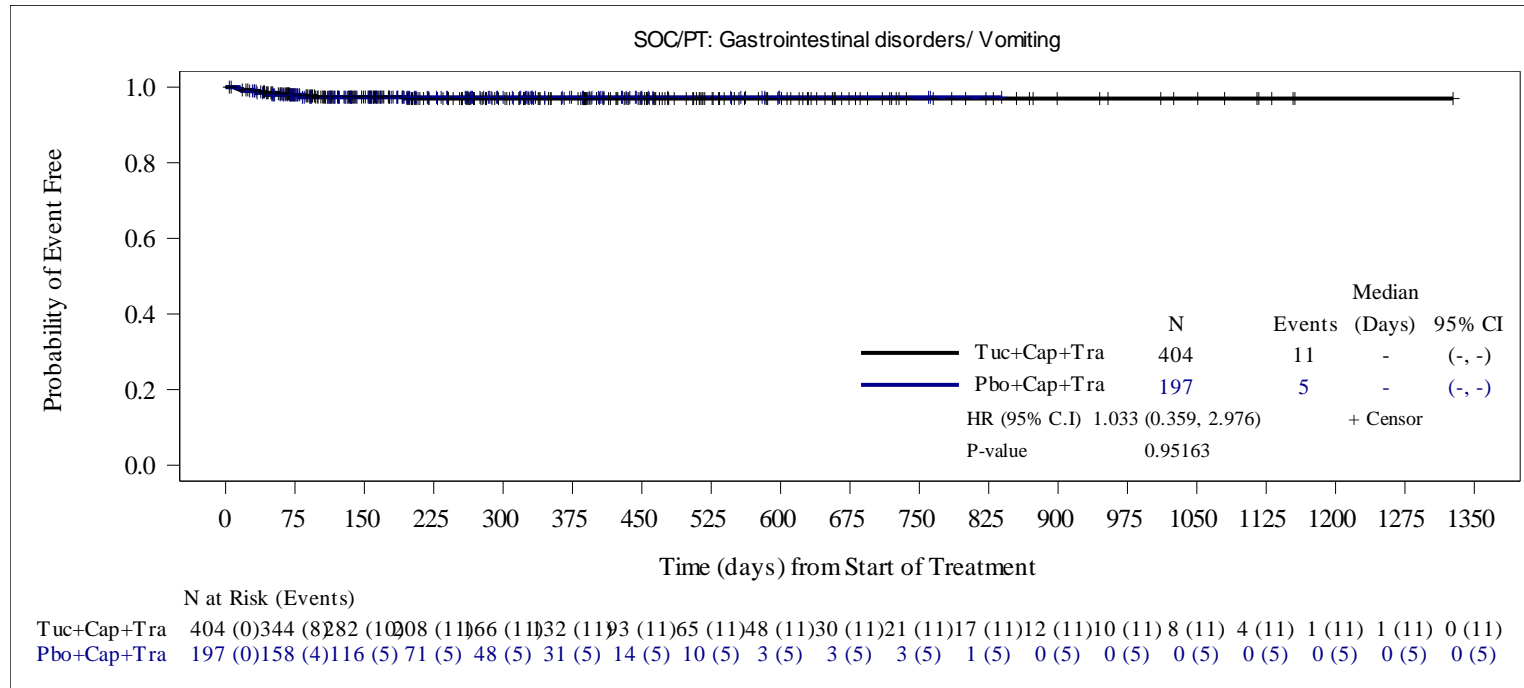
Two-sided p-value calculated from Cox proportional hazards model .

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Seagen Protocol ONT-380-206

**Figure 2.9.1 Kaplan-Meier Estimate of Time to First Onset of Serious Treatment-Emergent Adverse Events by System Organ Class and Preferred Term
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HR is computed from the Cox proportional hazards model using stratification factors (Presence or history of brain metastases: Yes/No, ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization. When the number of subjects with at least one event was ≤ 30 , an unstratified Cox model was run.

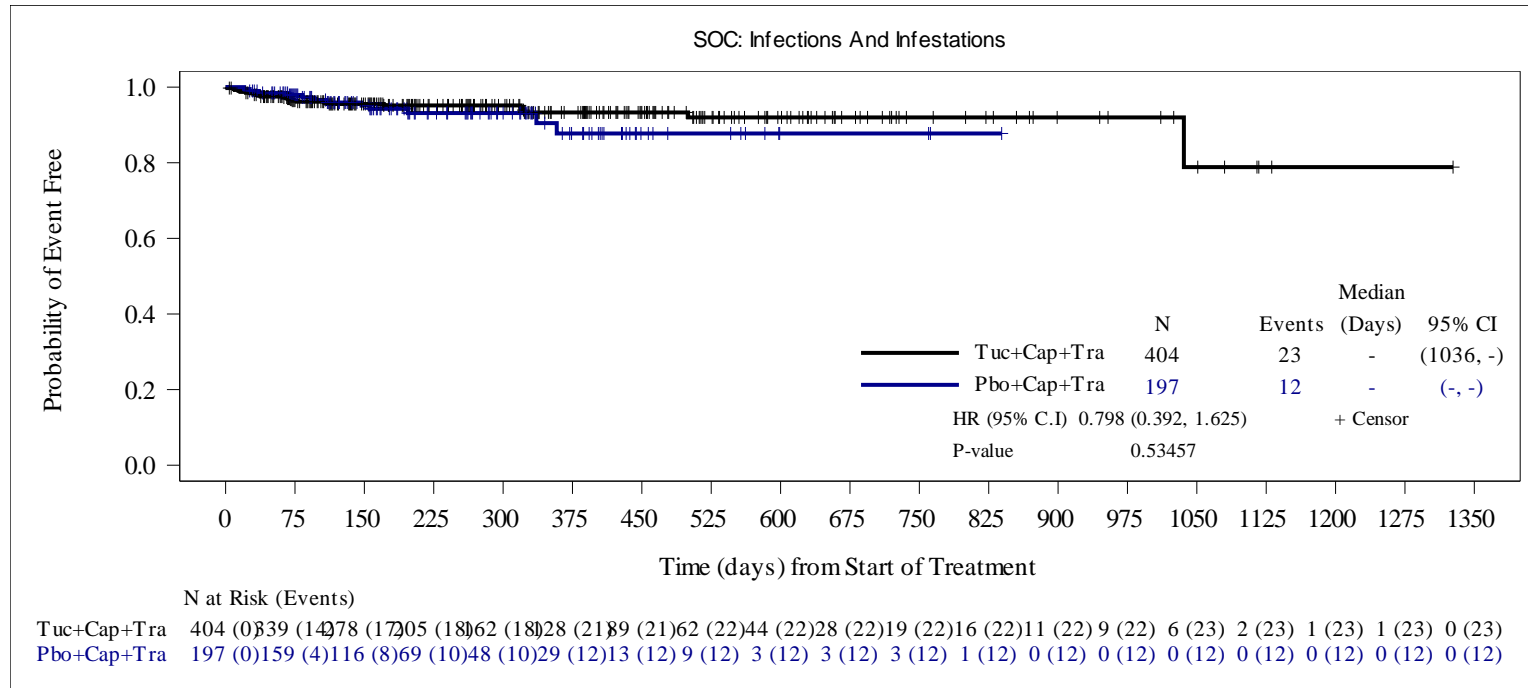
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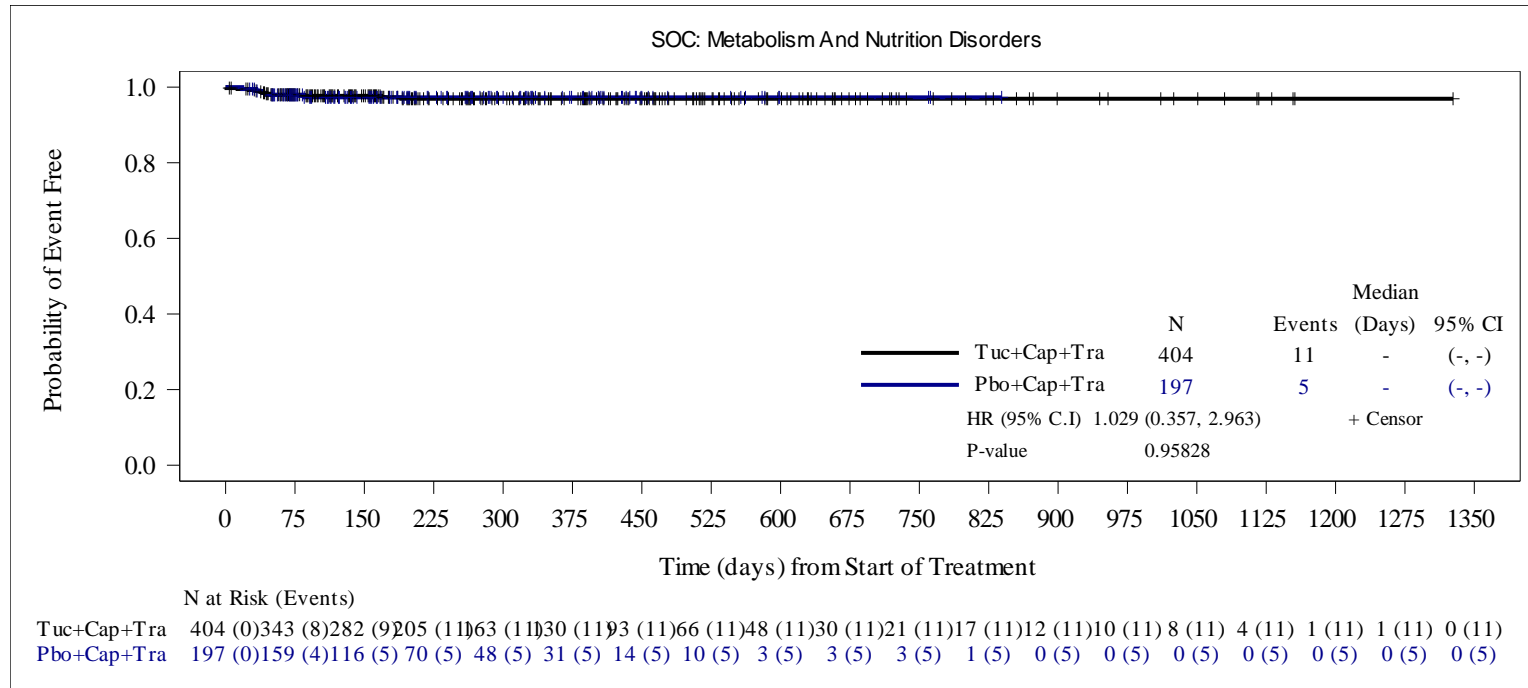
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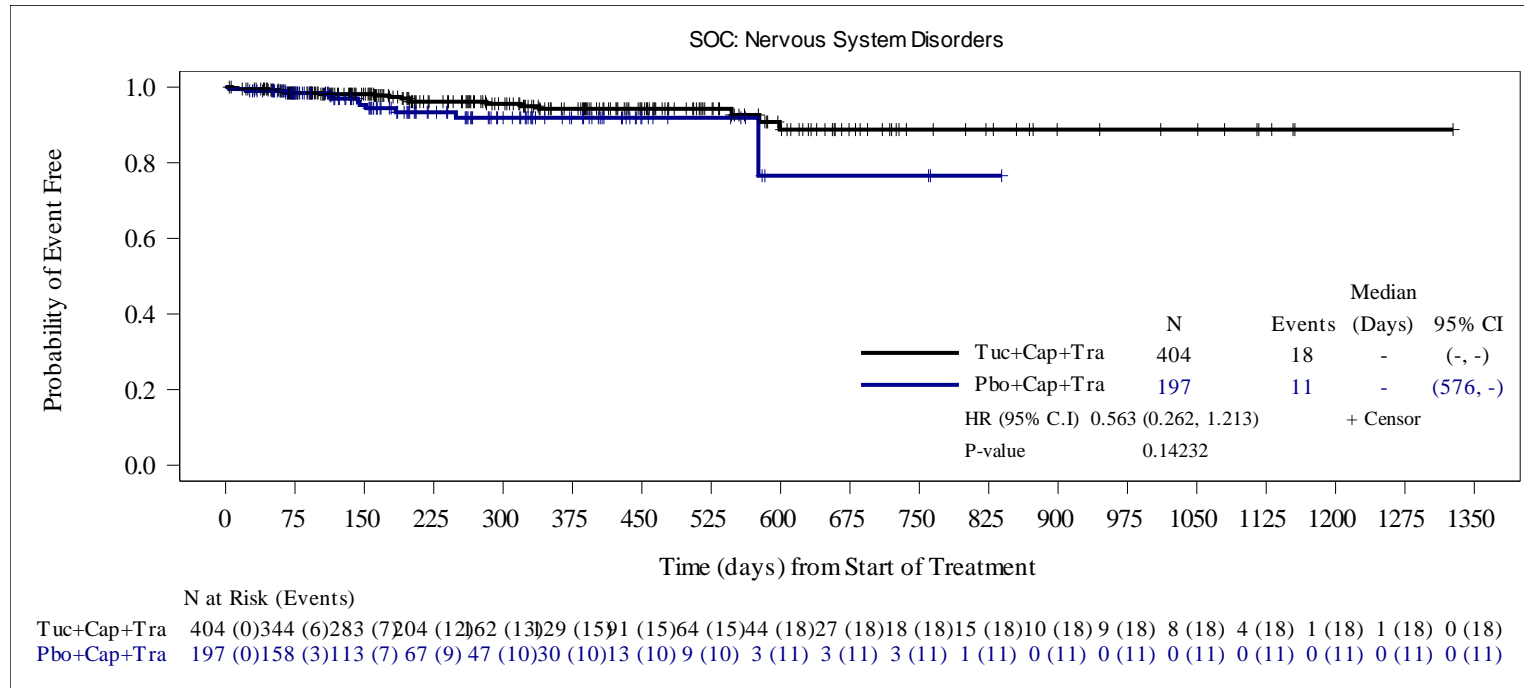
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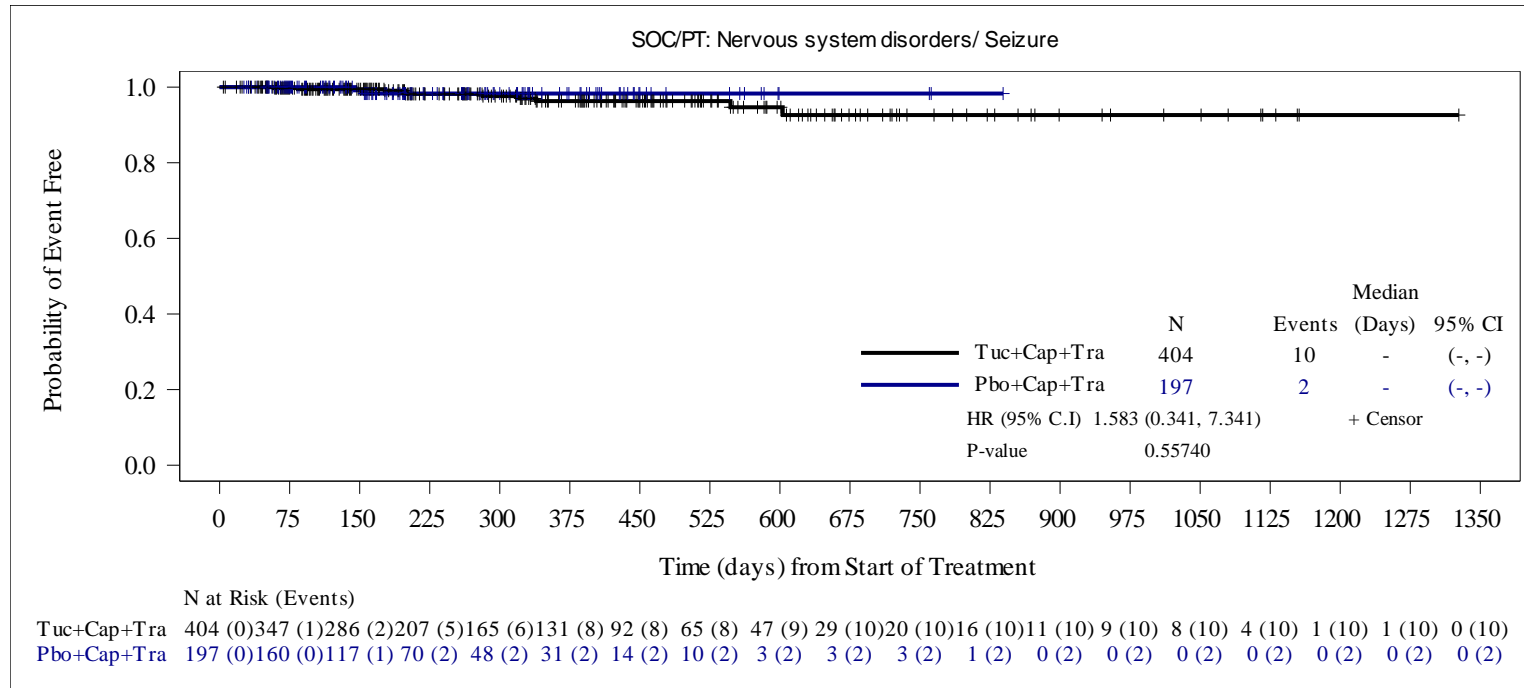
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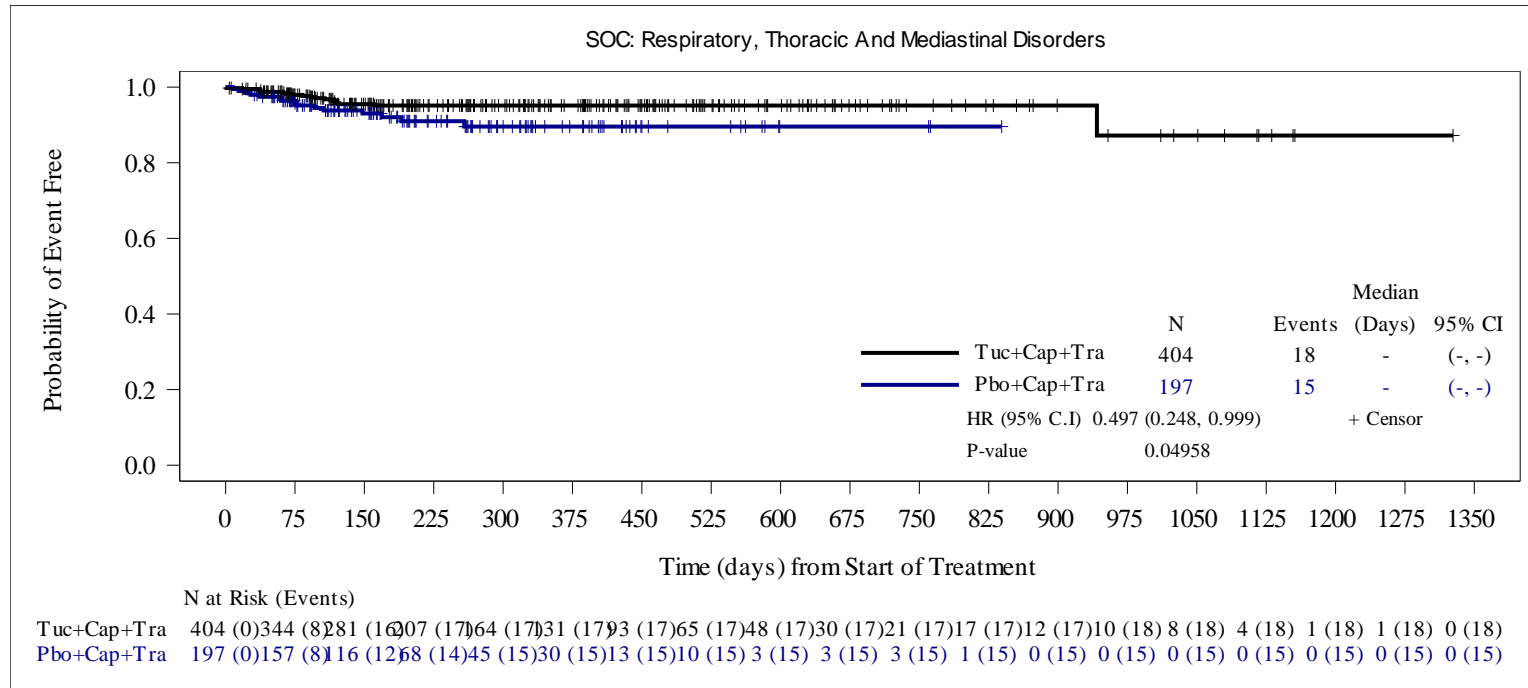
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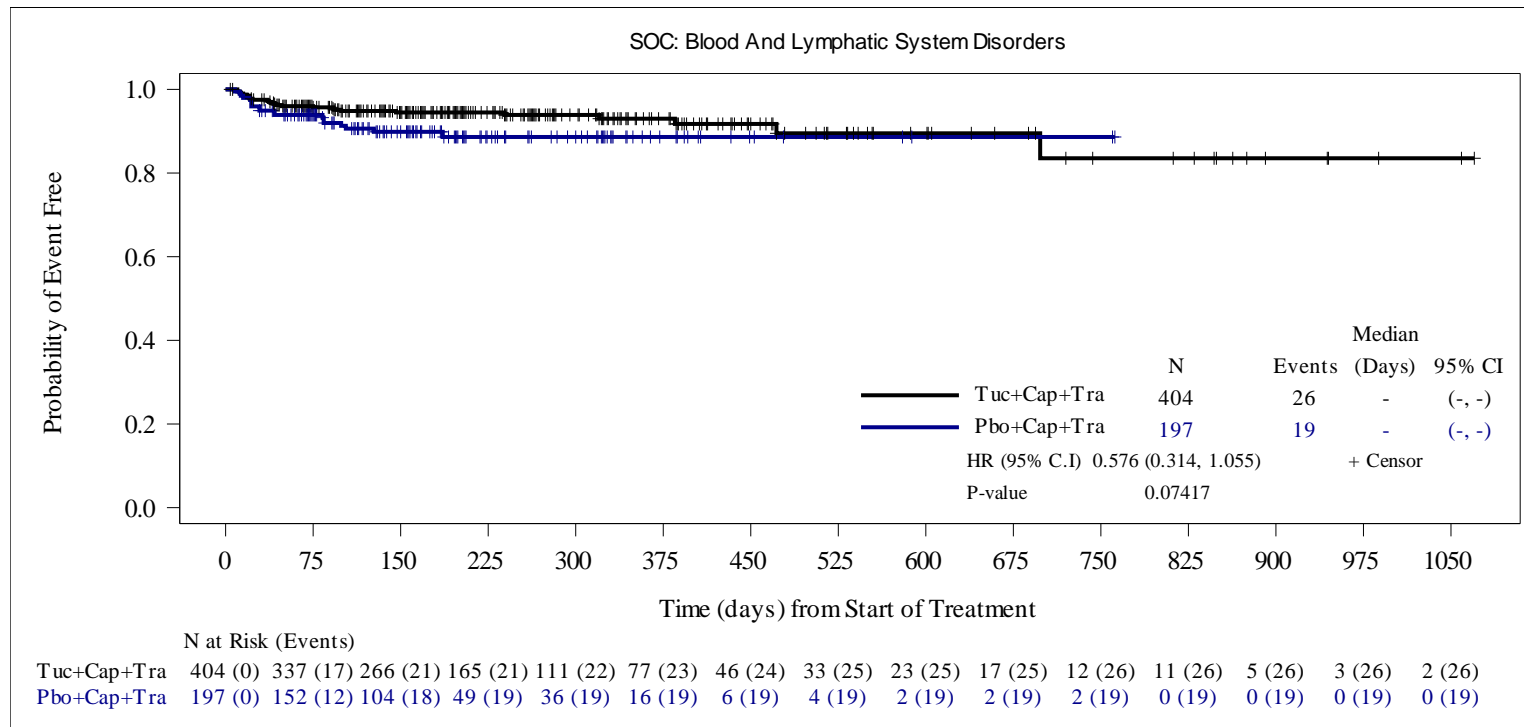
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Seattle Genetics Protocol ONT-380-206

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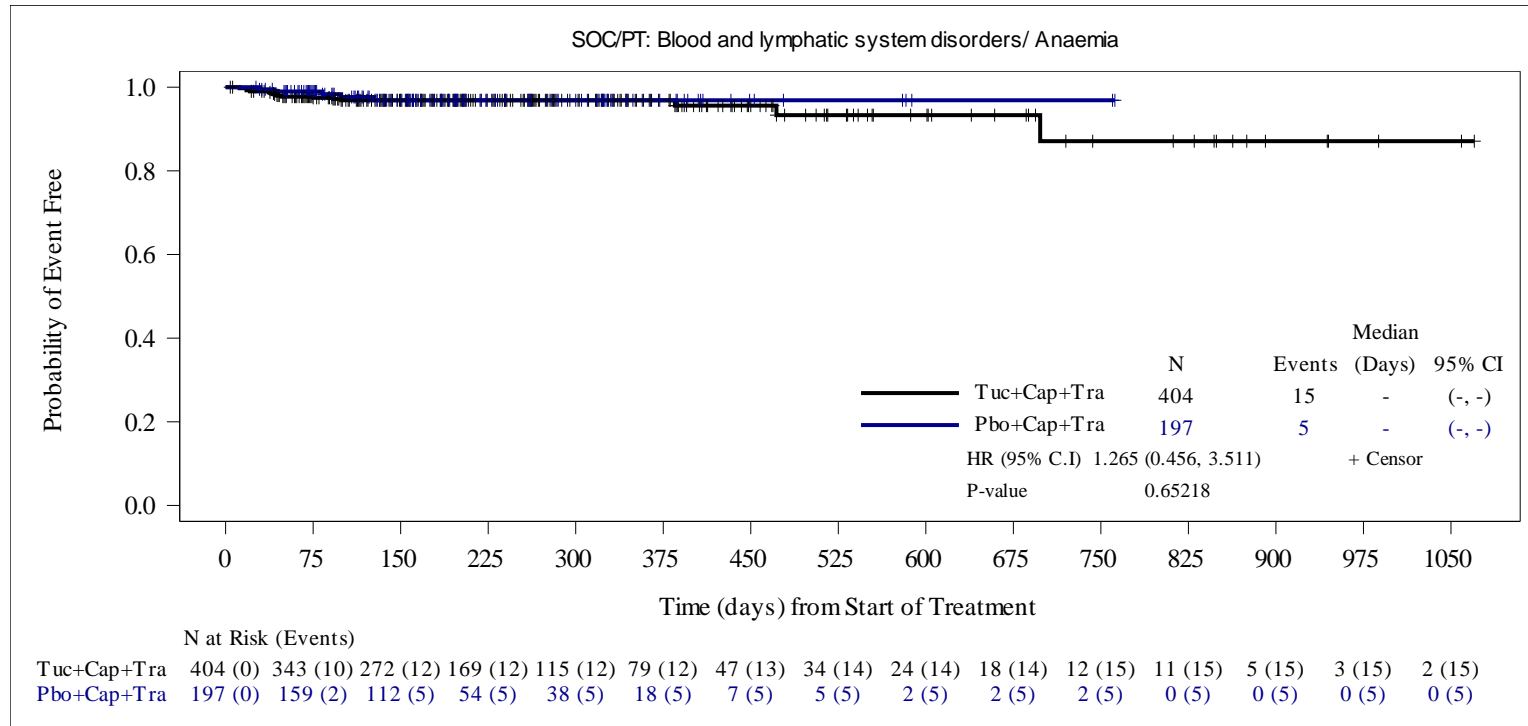
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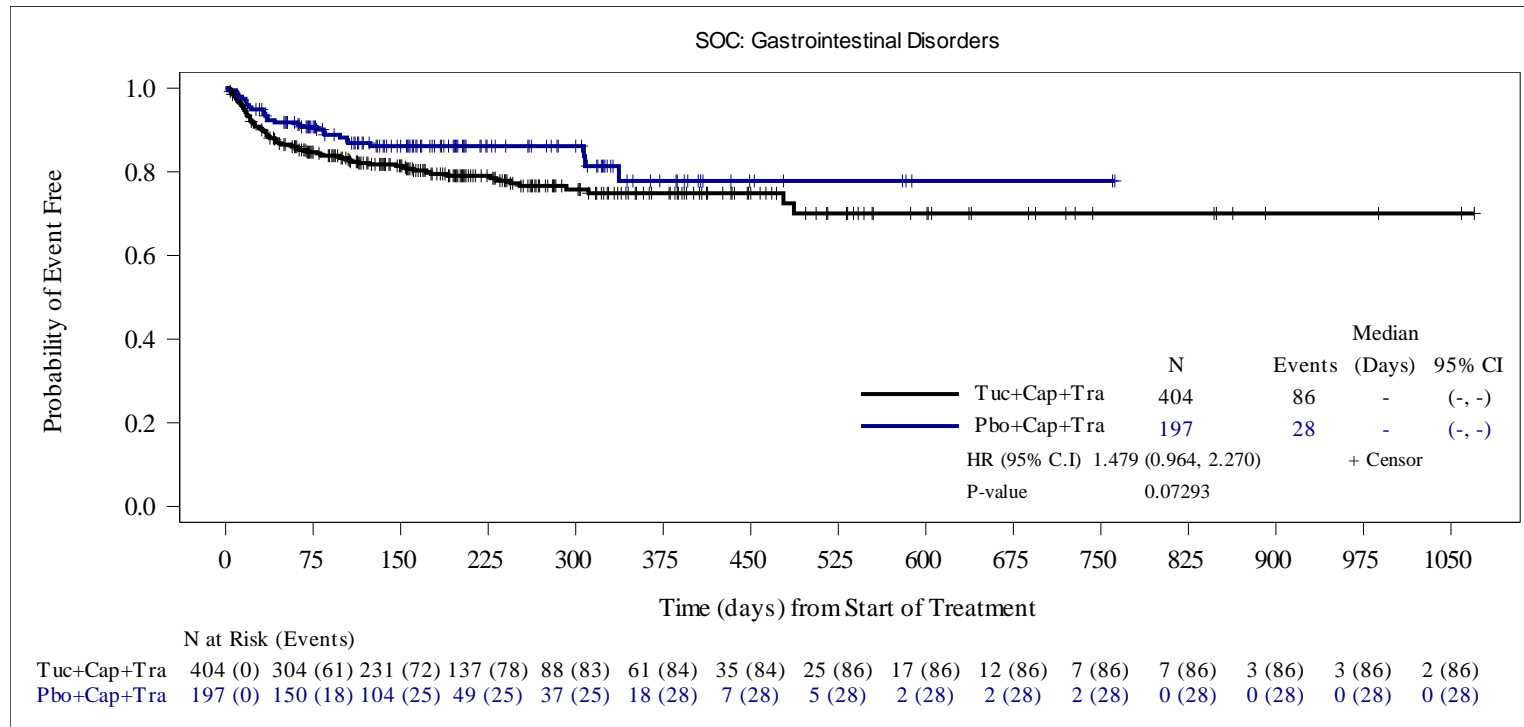
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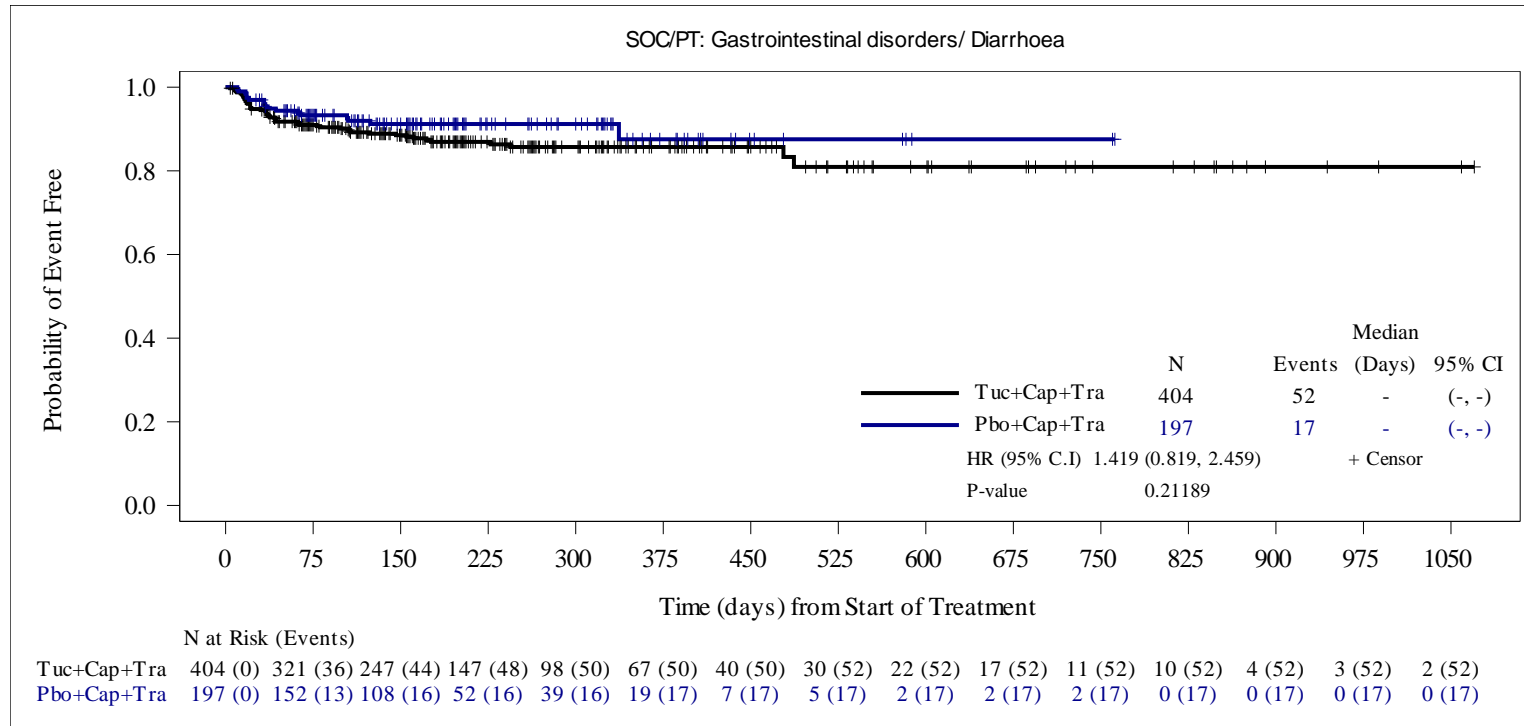
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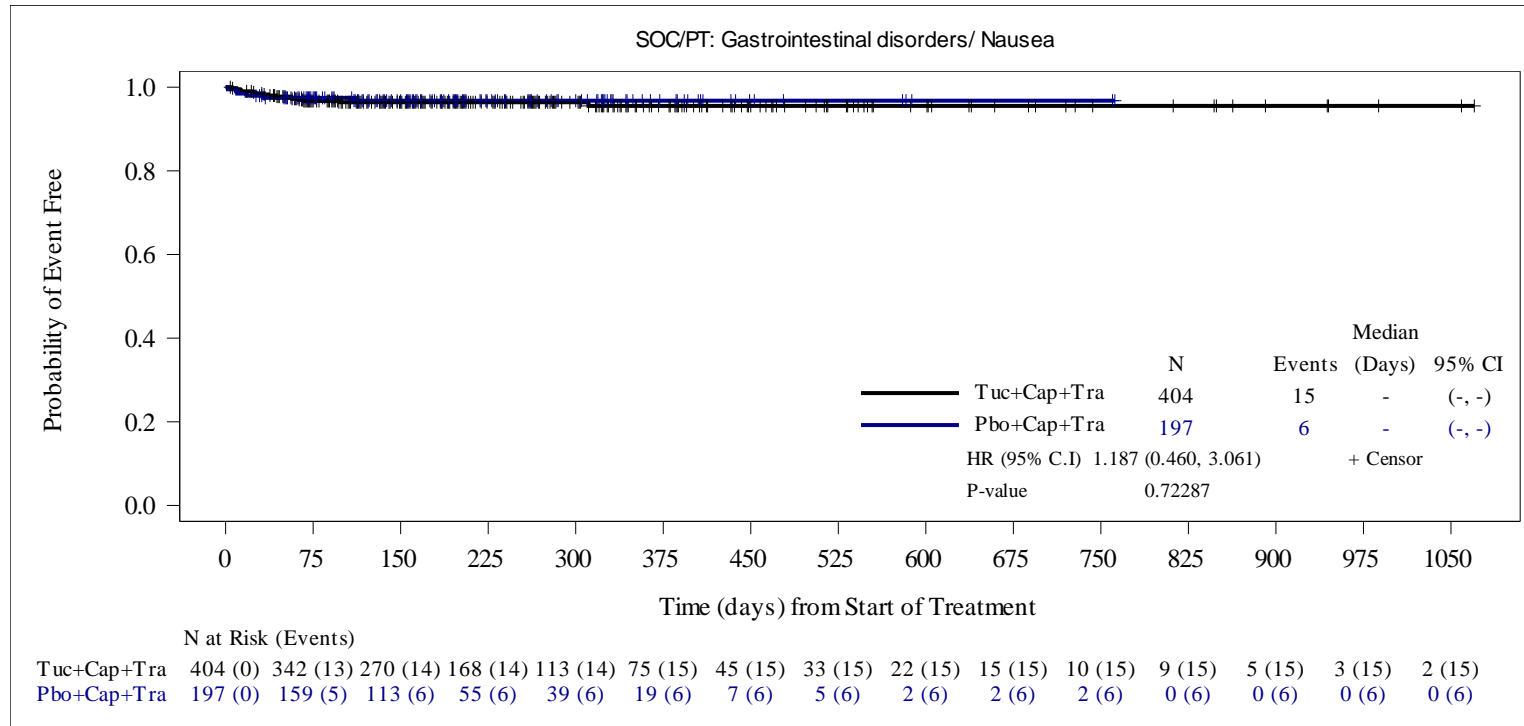
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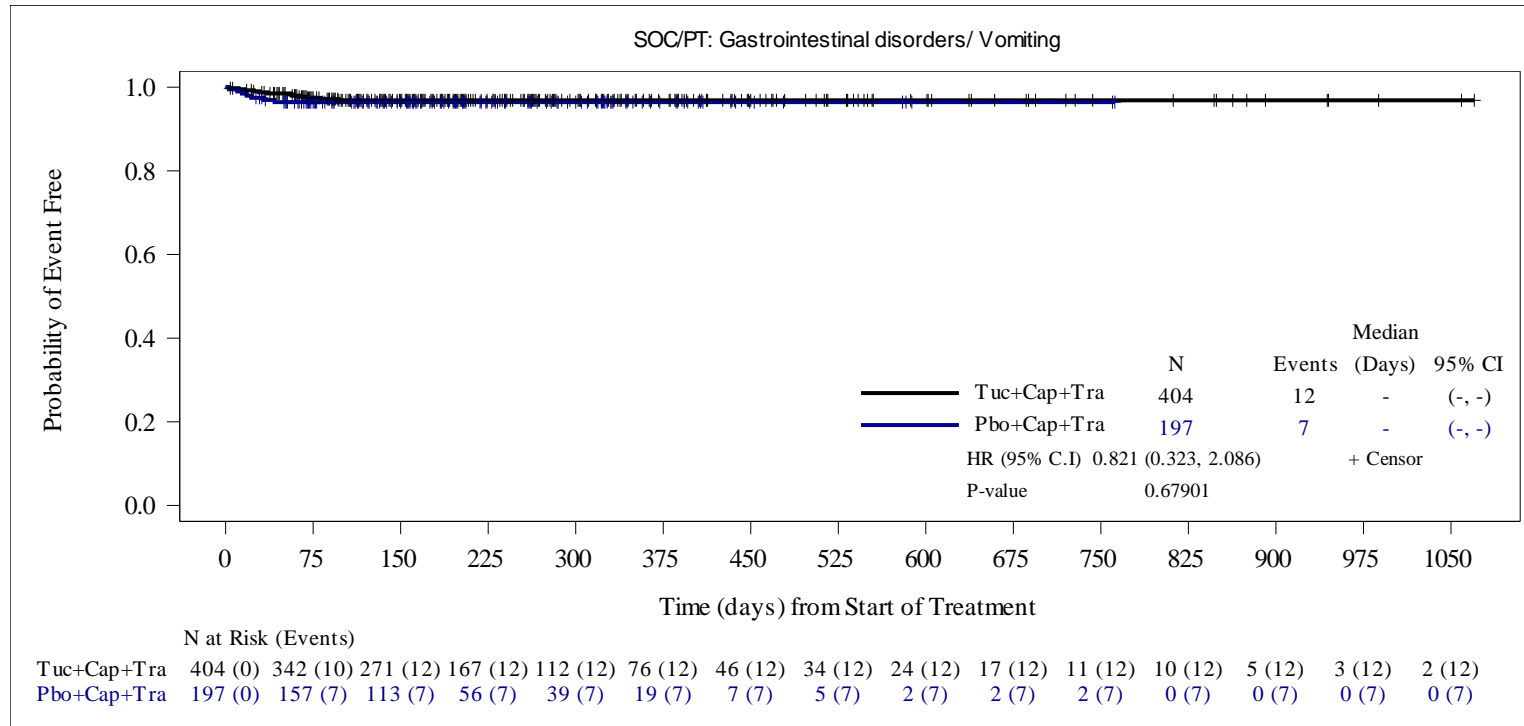
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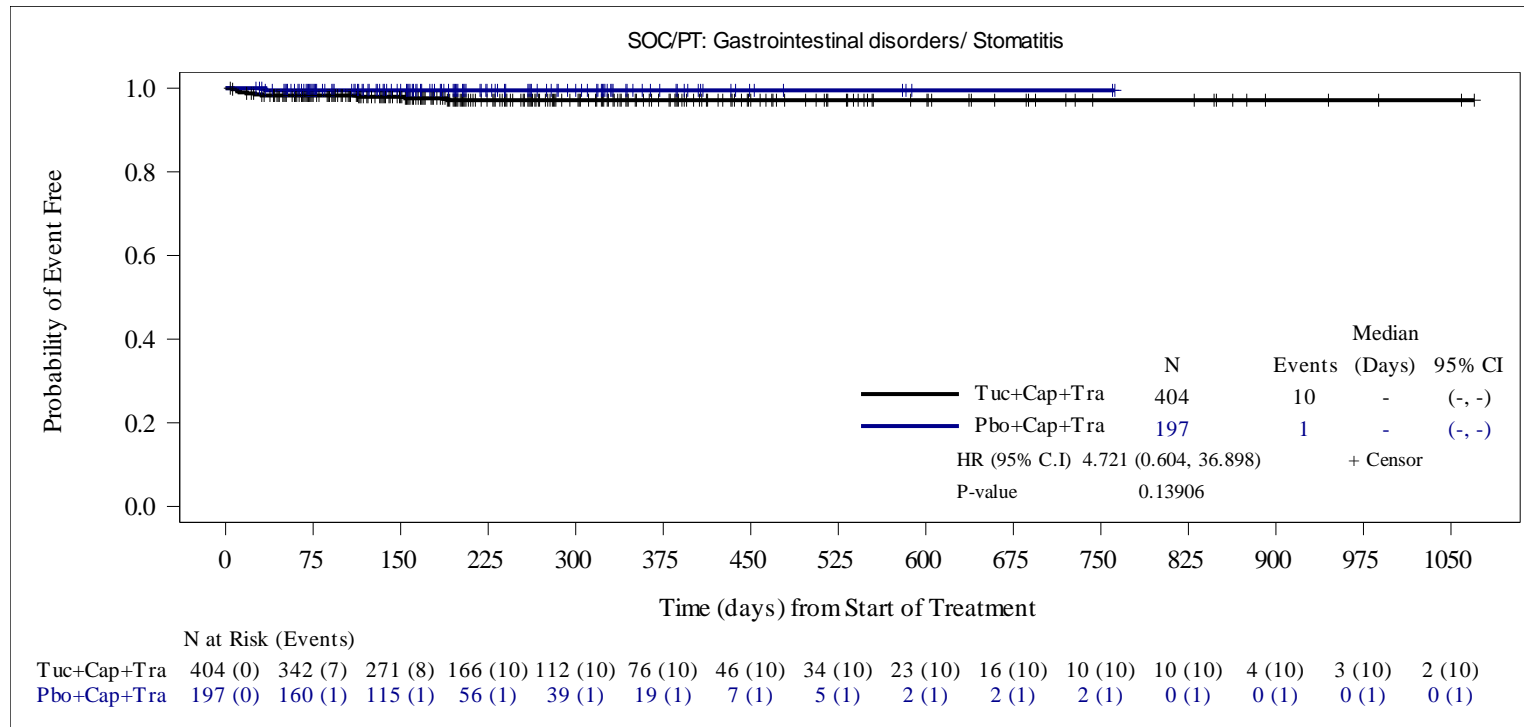
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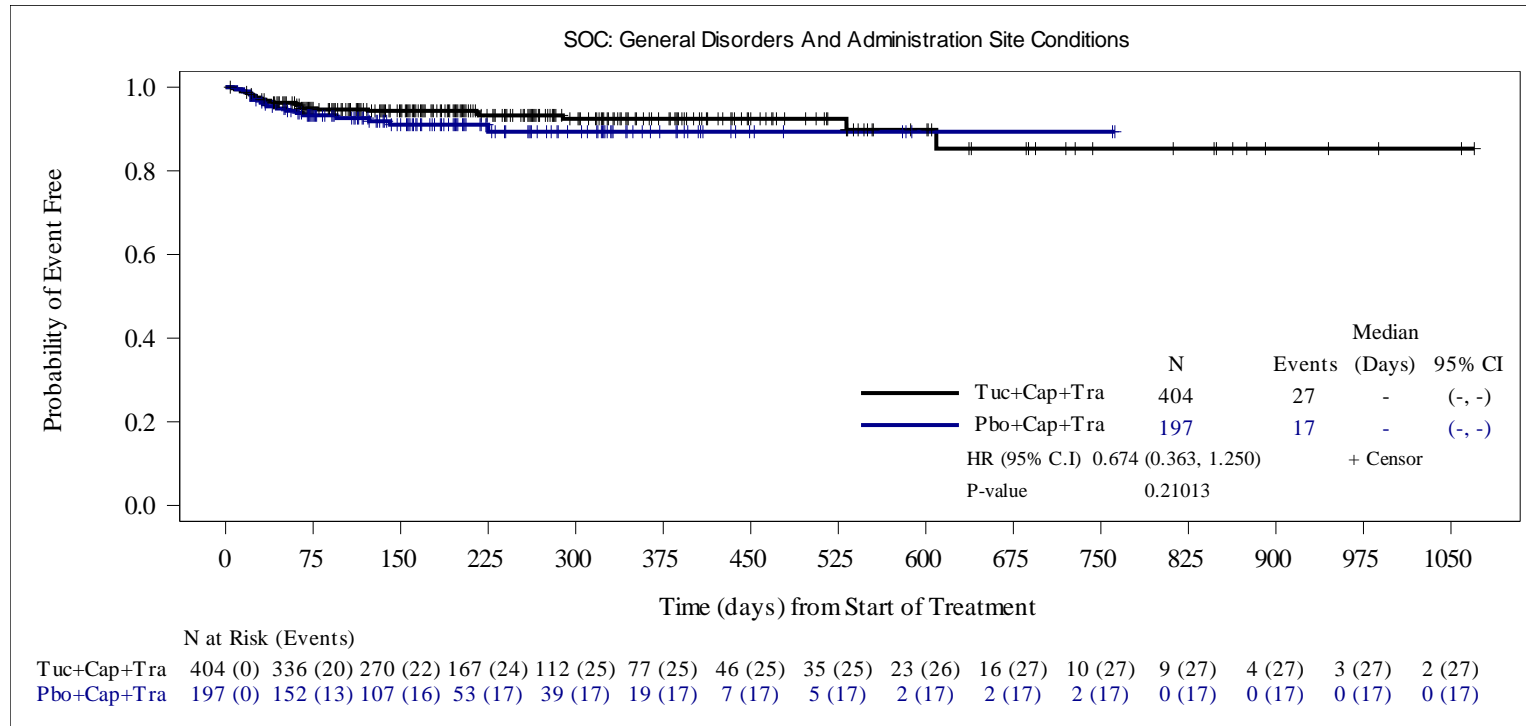
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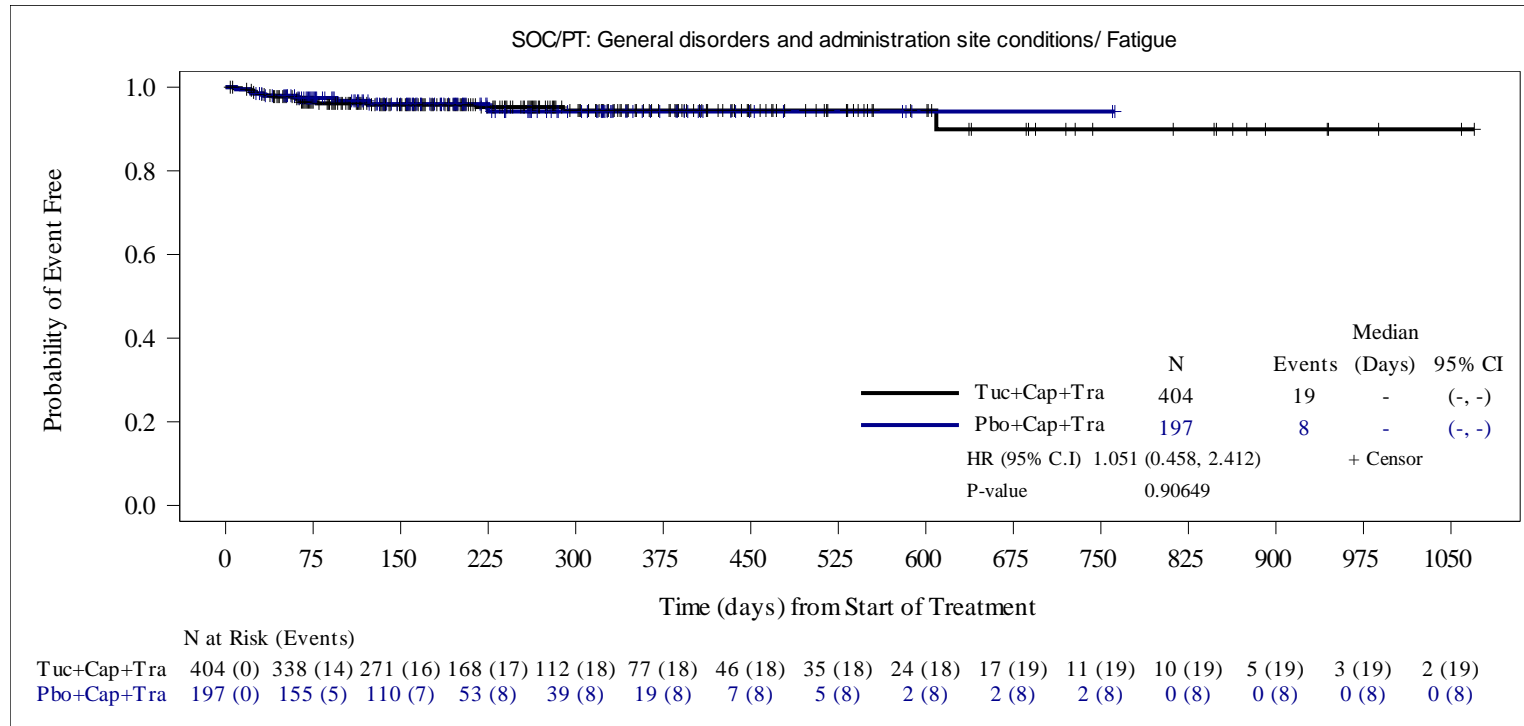
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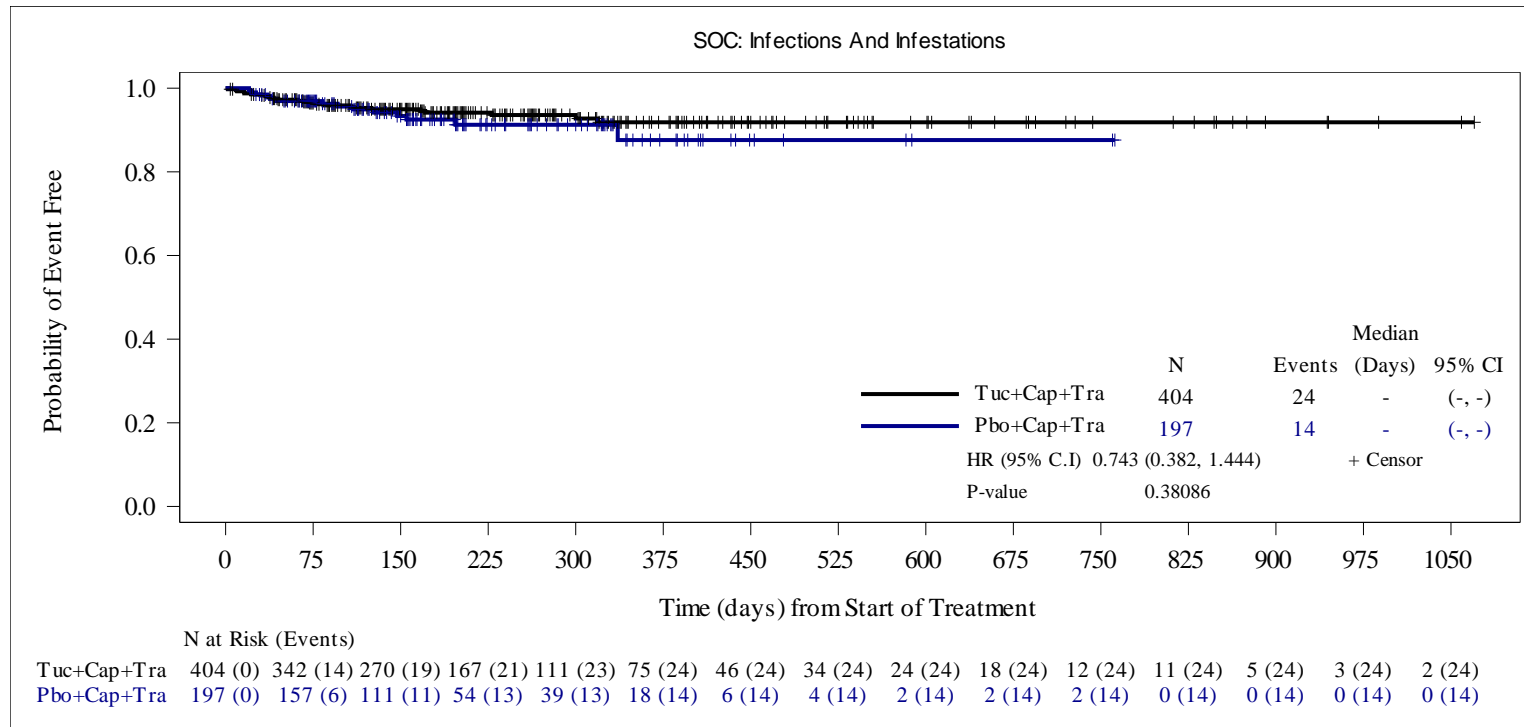
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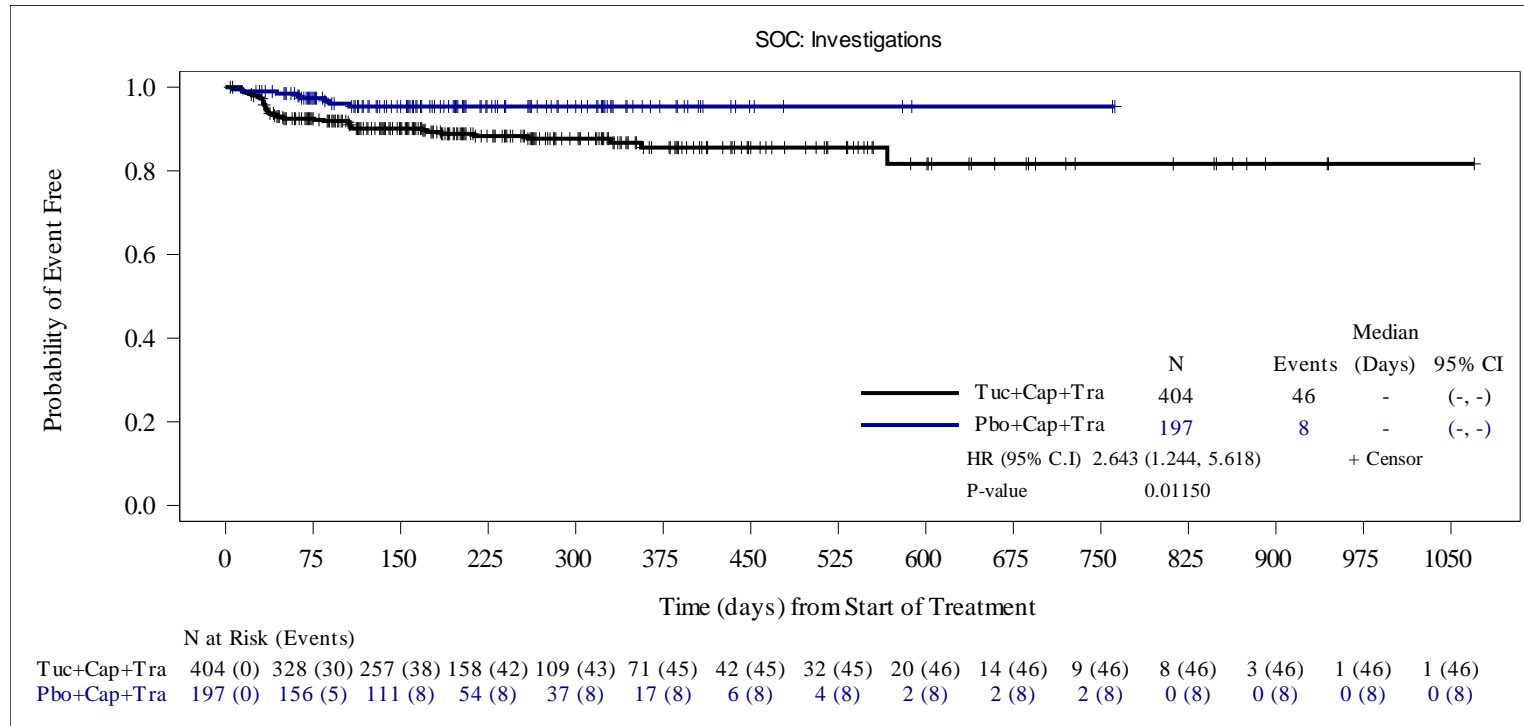
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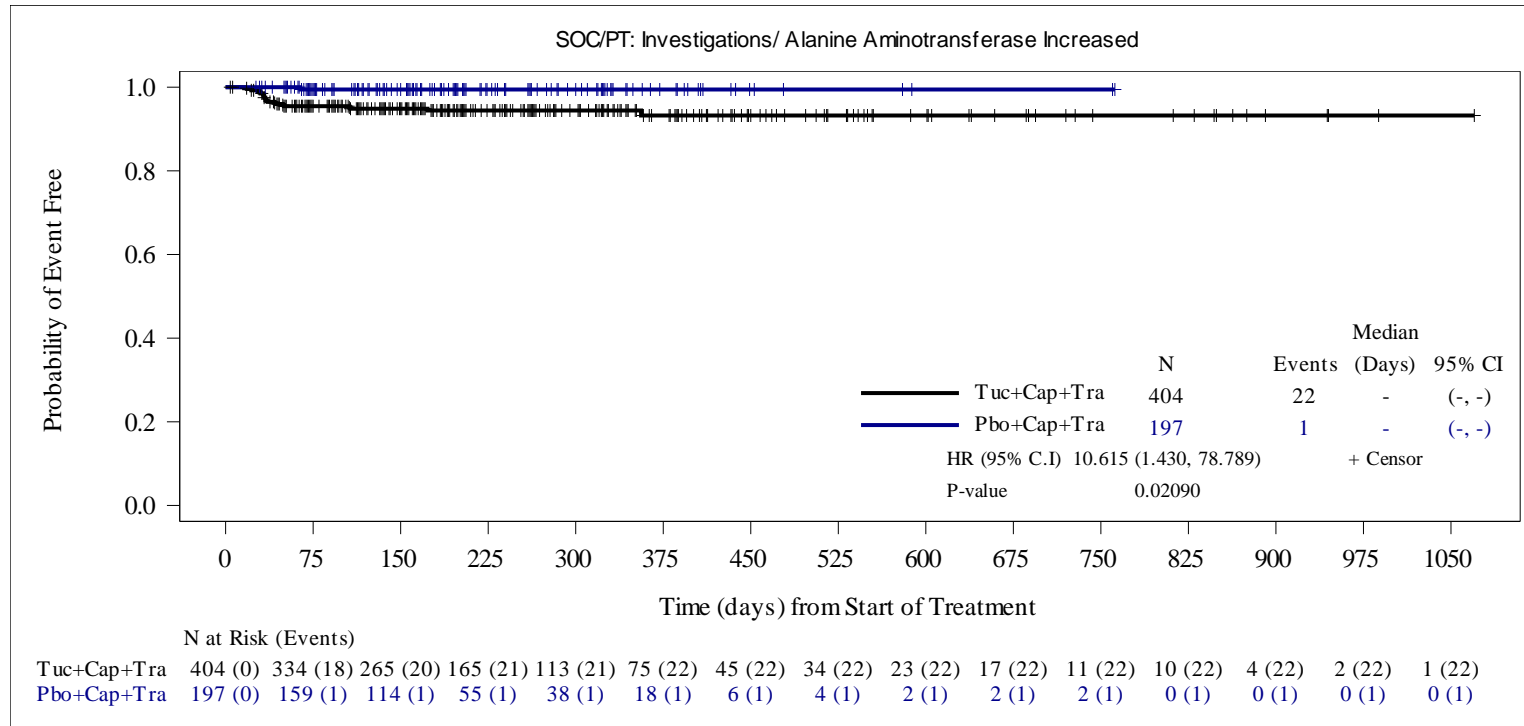
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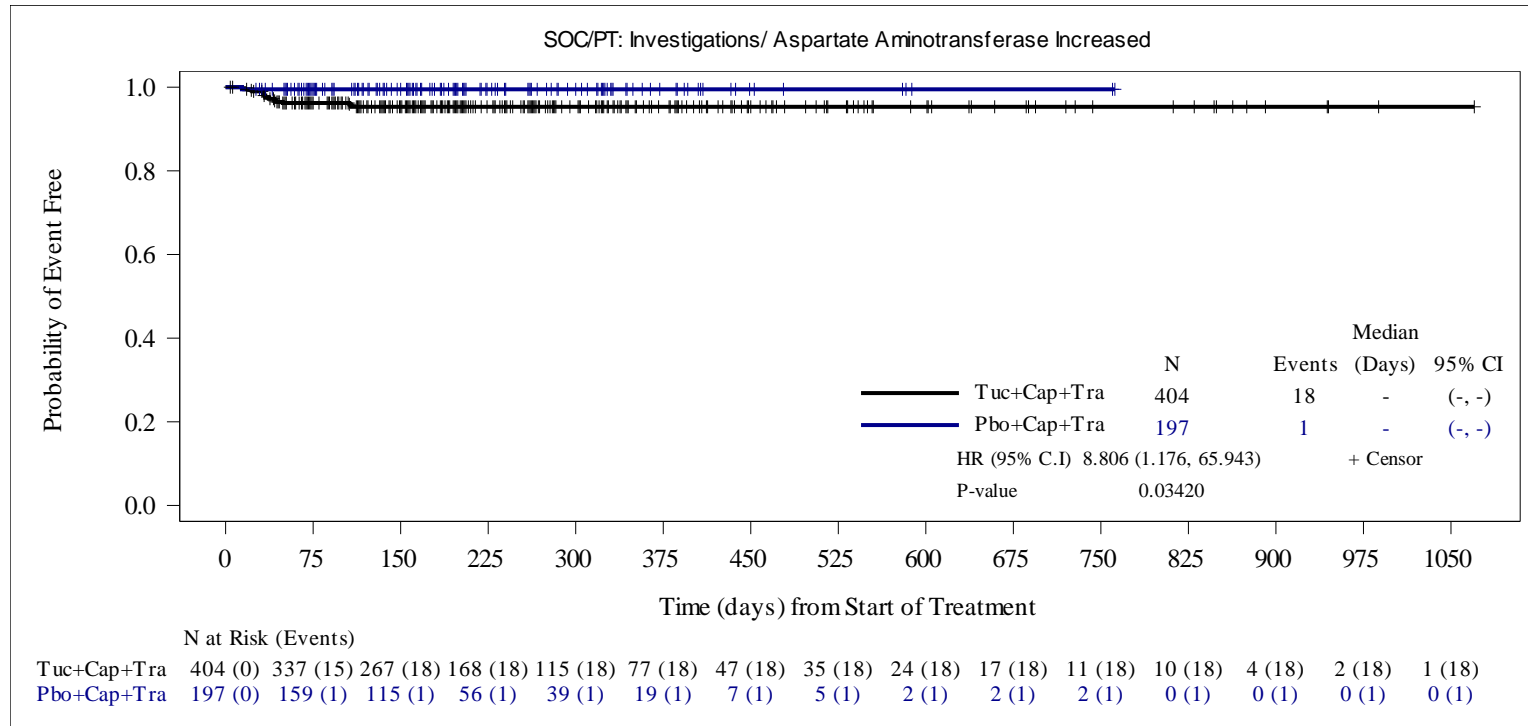
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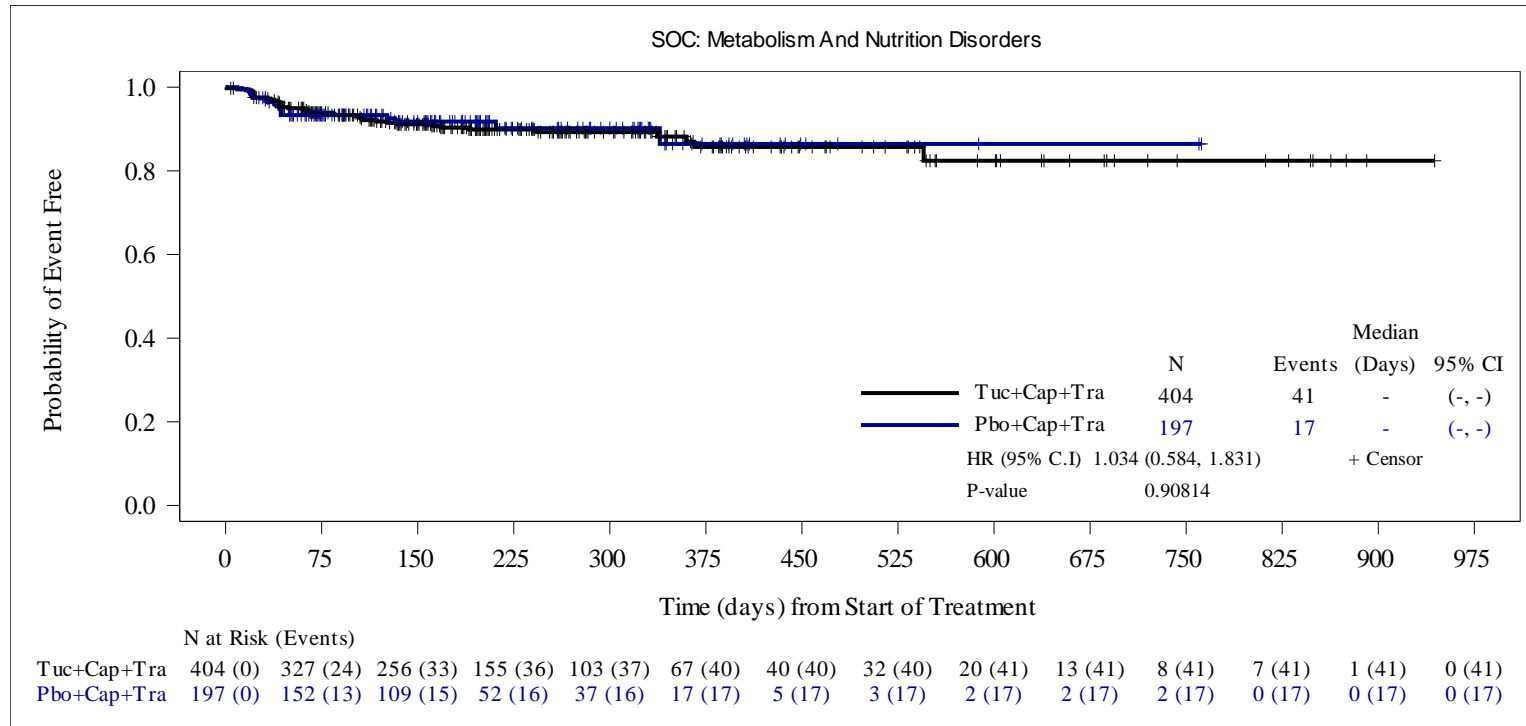
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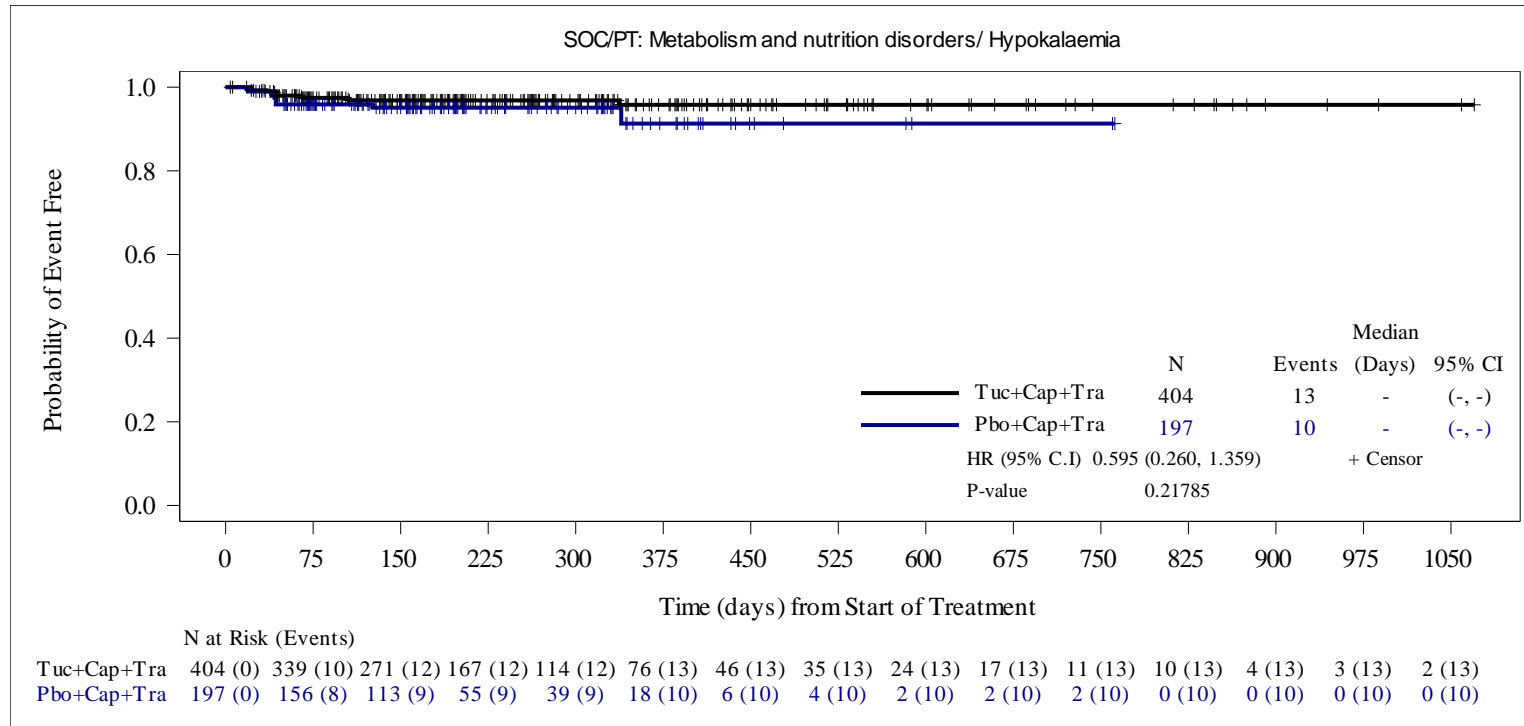
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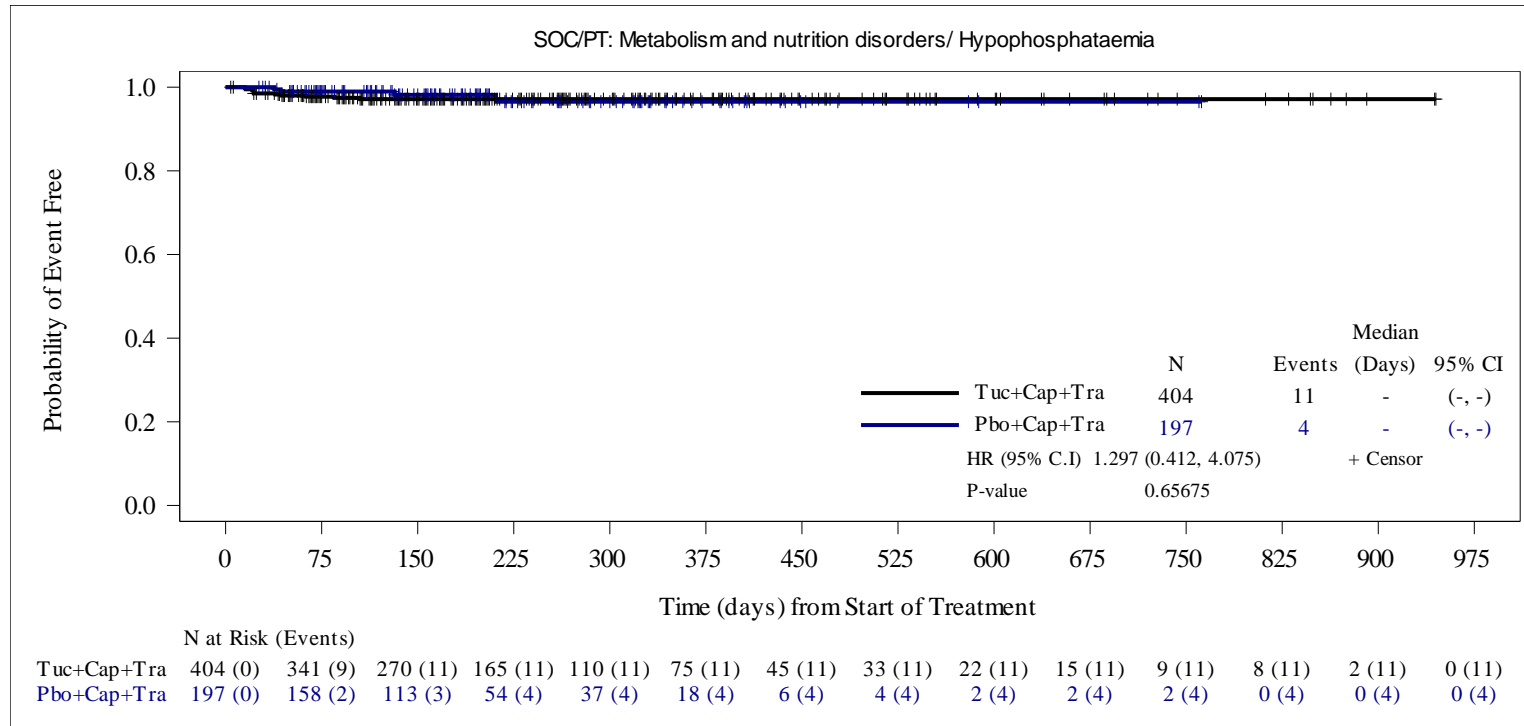
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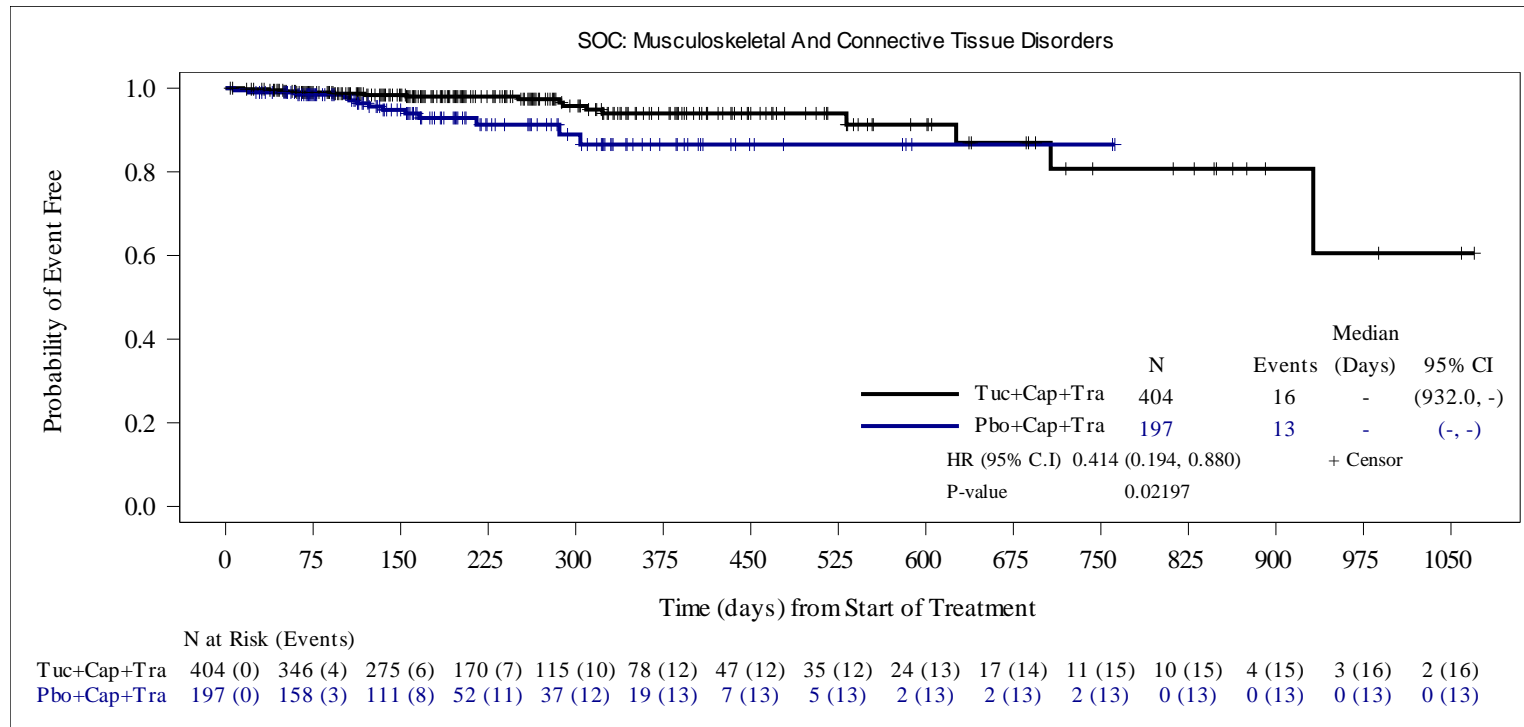
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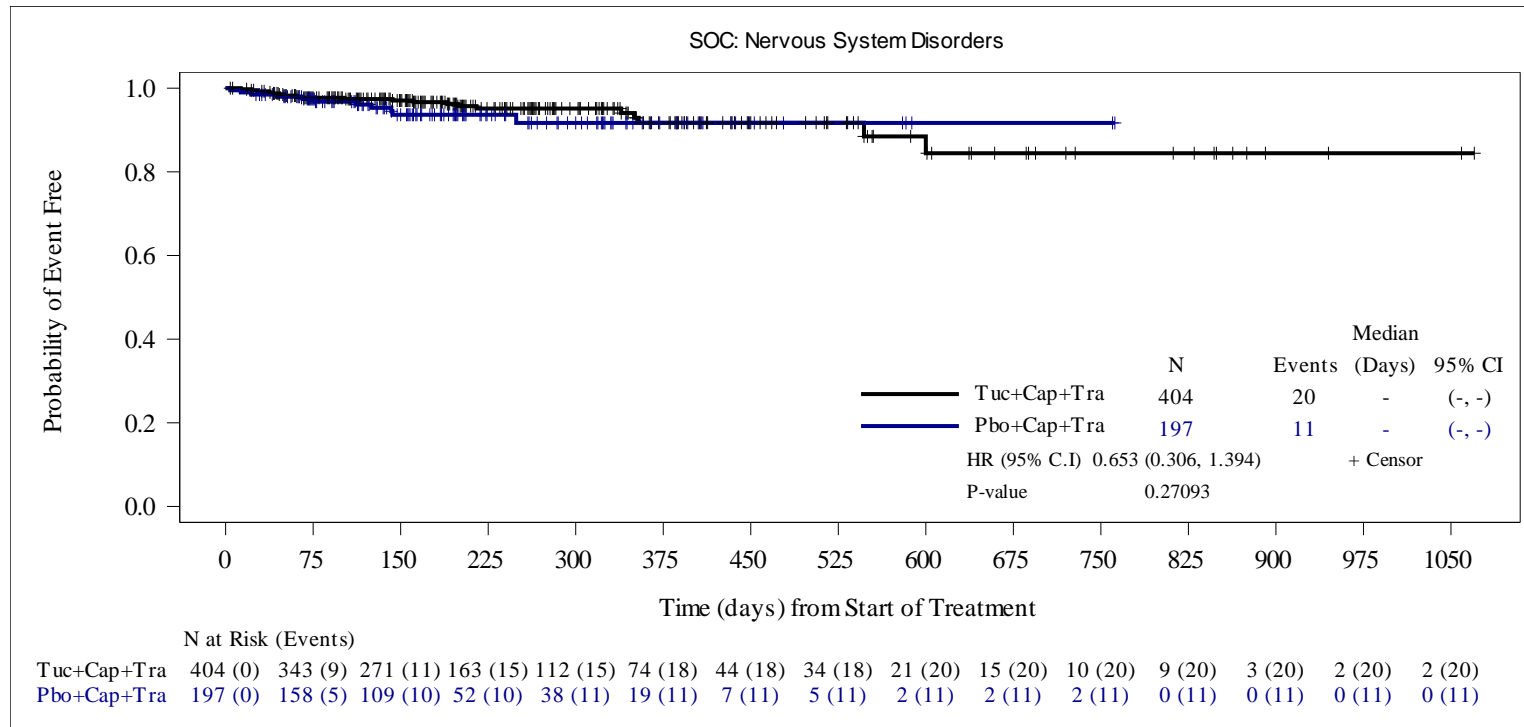
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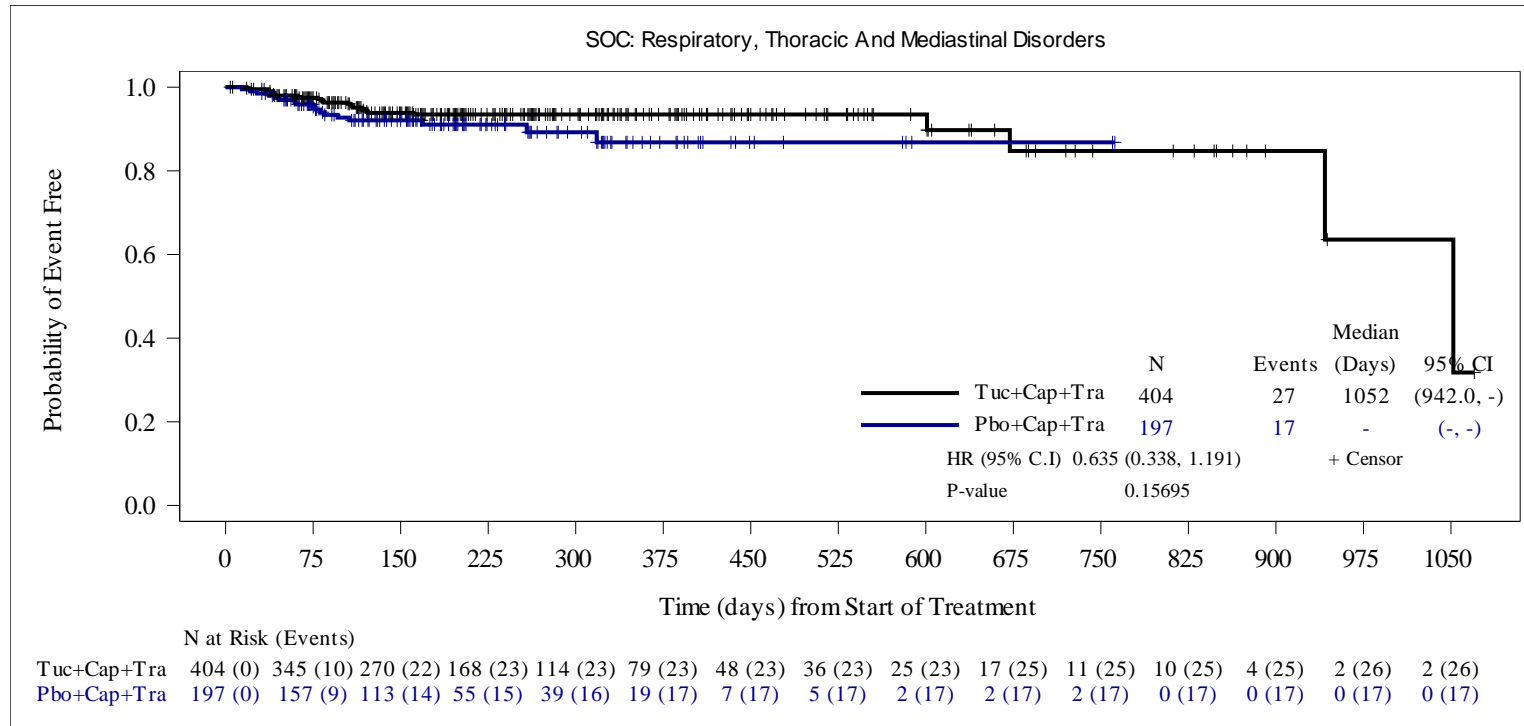
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Figure 2.11.1 Kaplan-Meier Estimate of Time to First Onset of Severe (\geq Grade 3) Treatment-Emergent Adverse Events by System Organ Class and Preferred Term Safety Analysis Set



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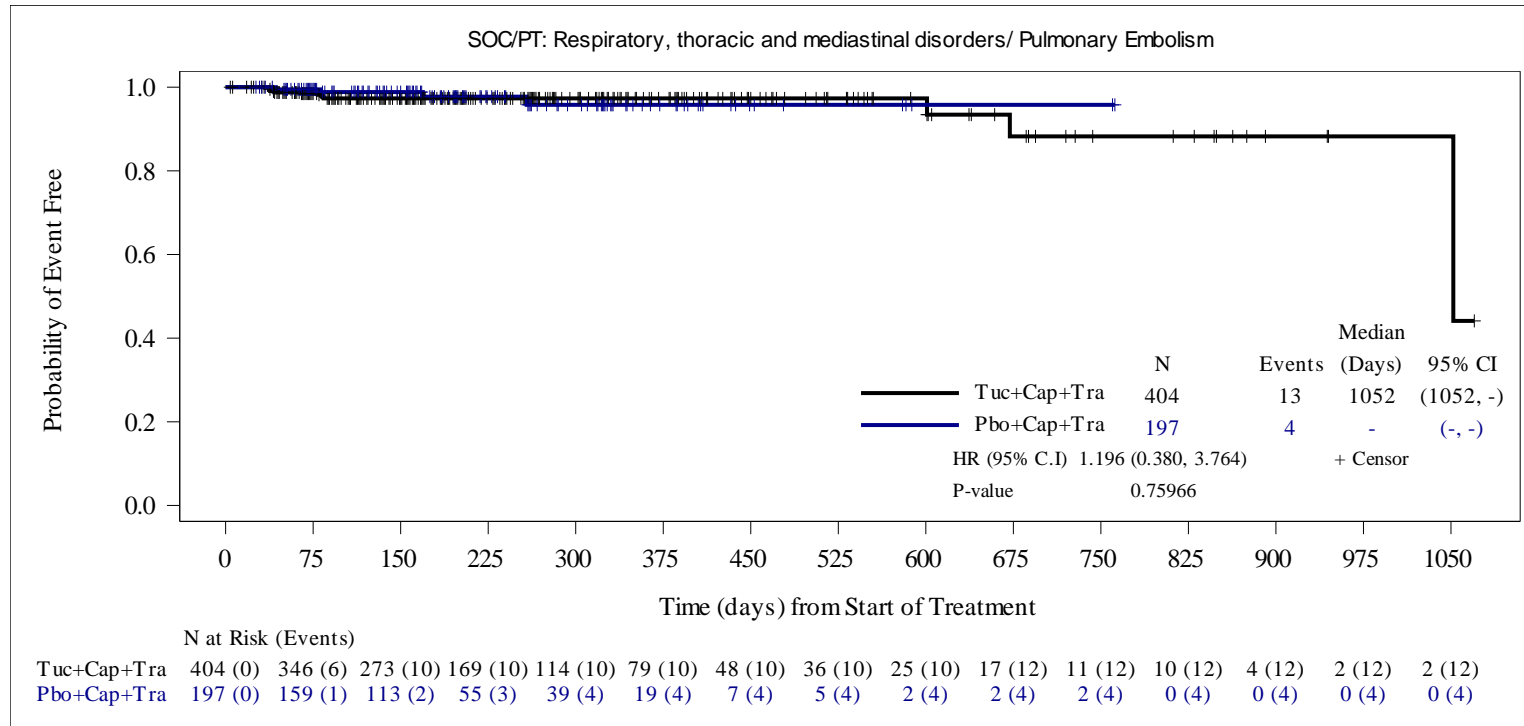
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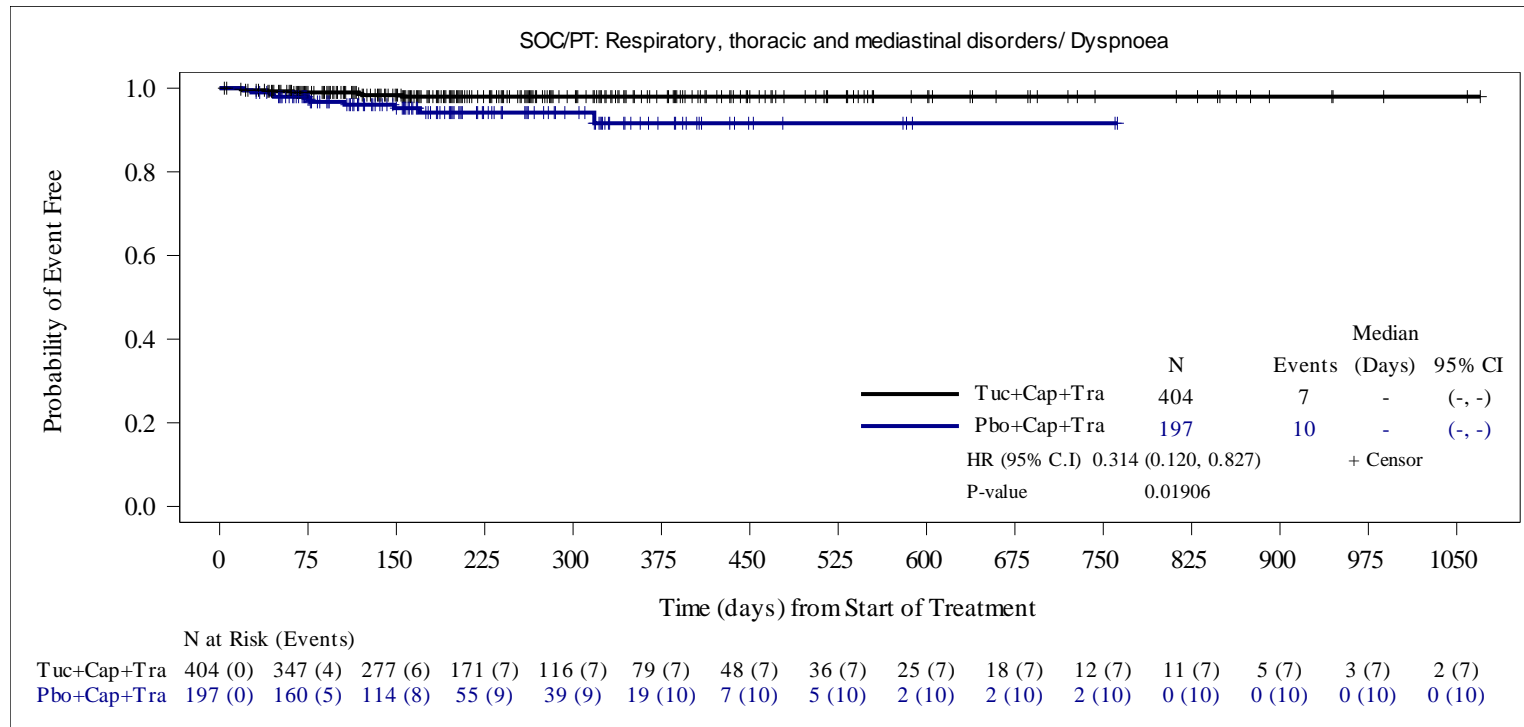
Two-sided p-value calculated from Cox proportional hazards model .

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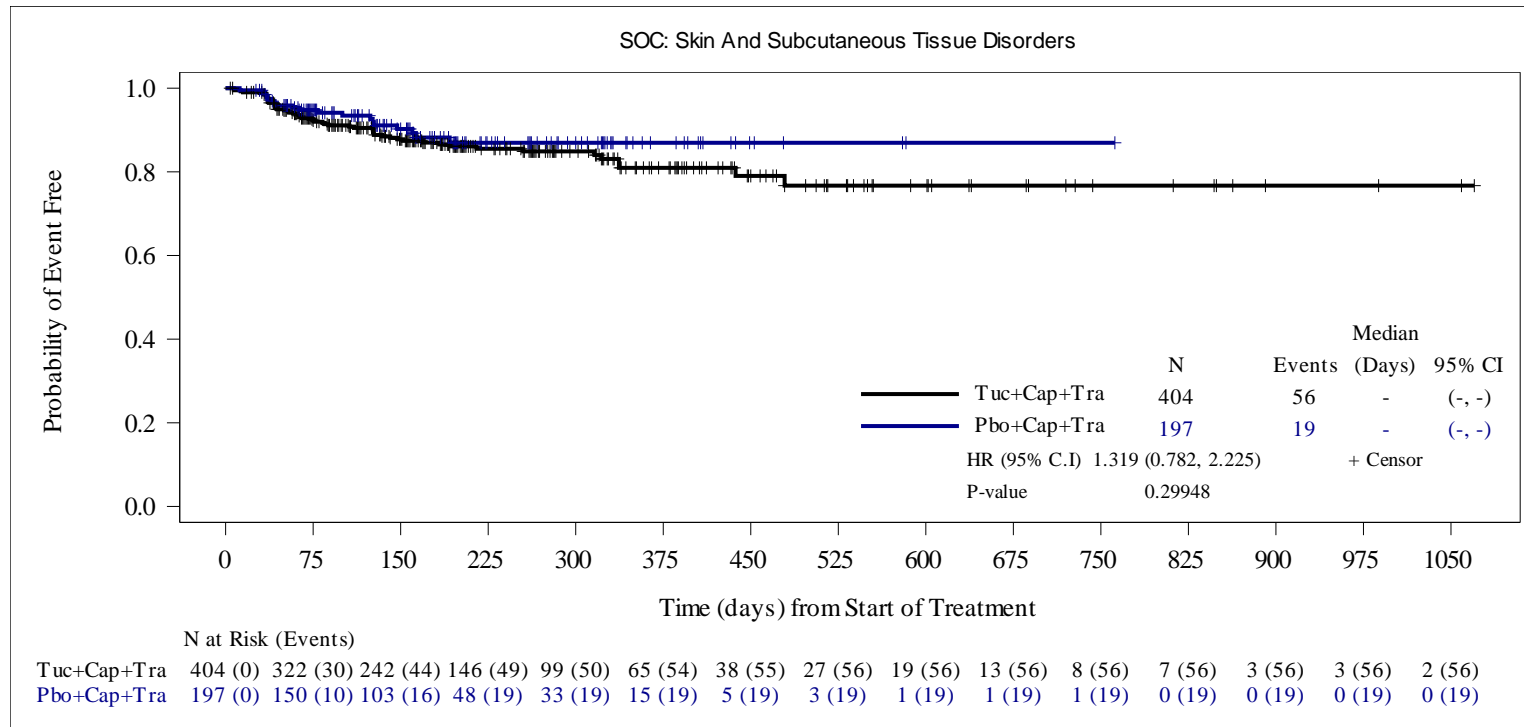
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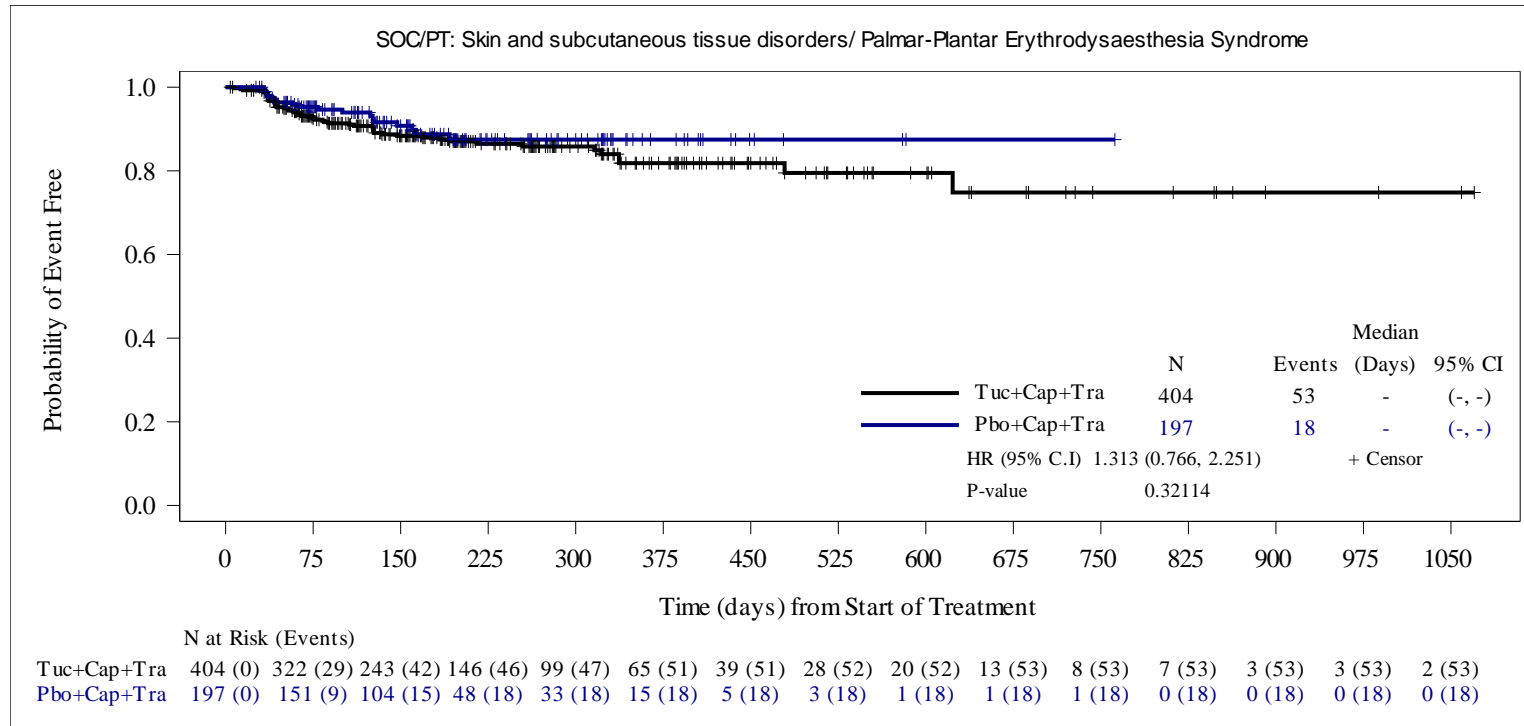
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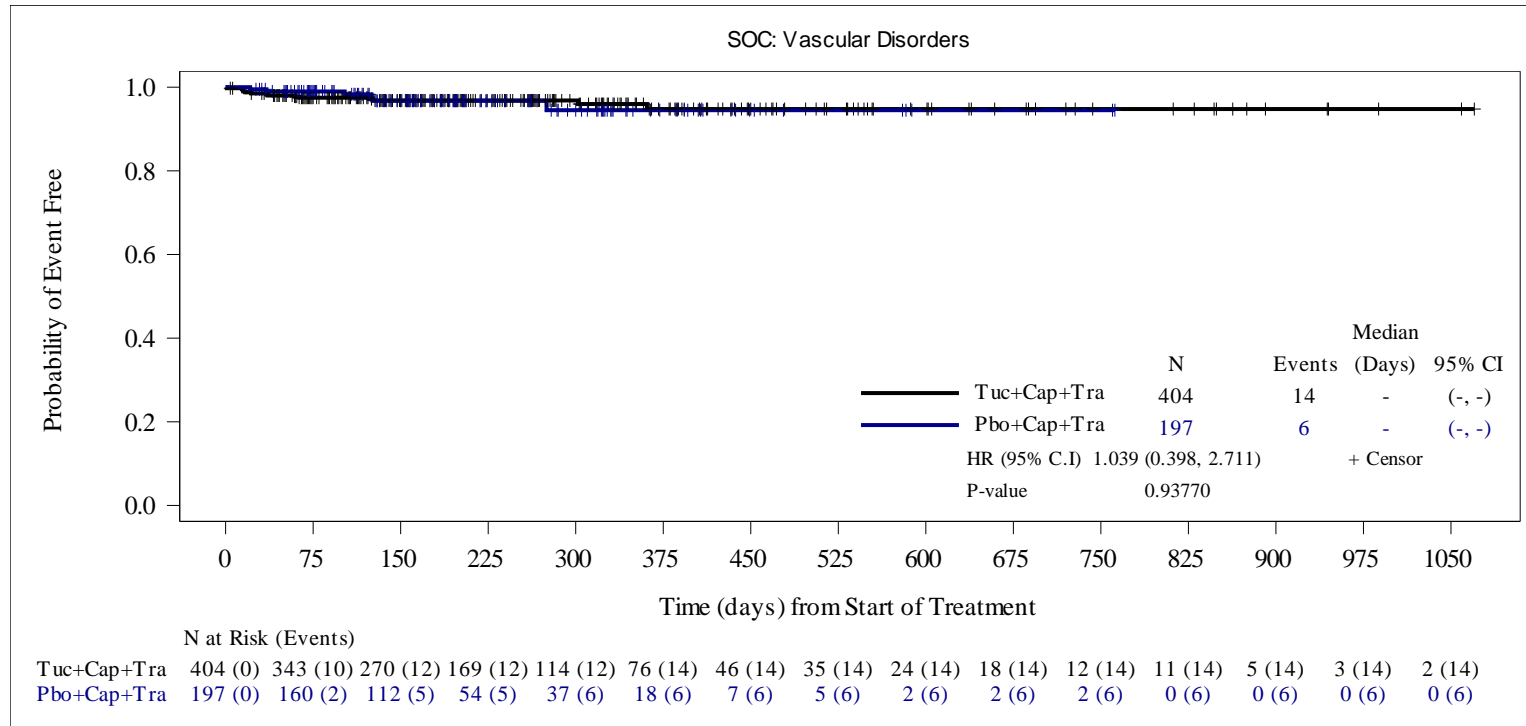
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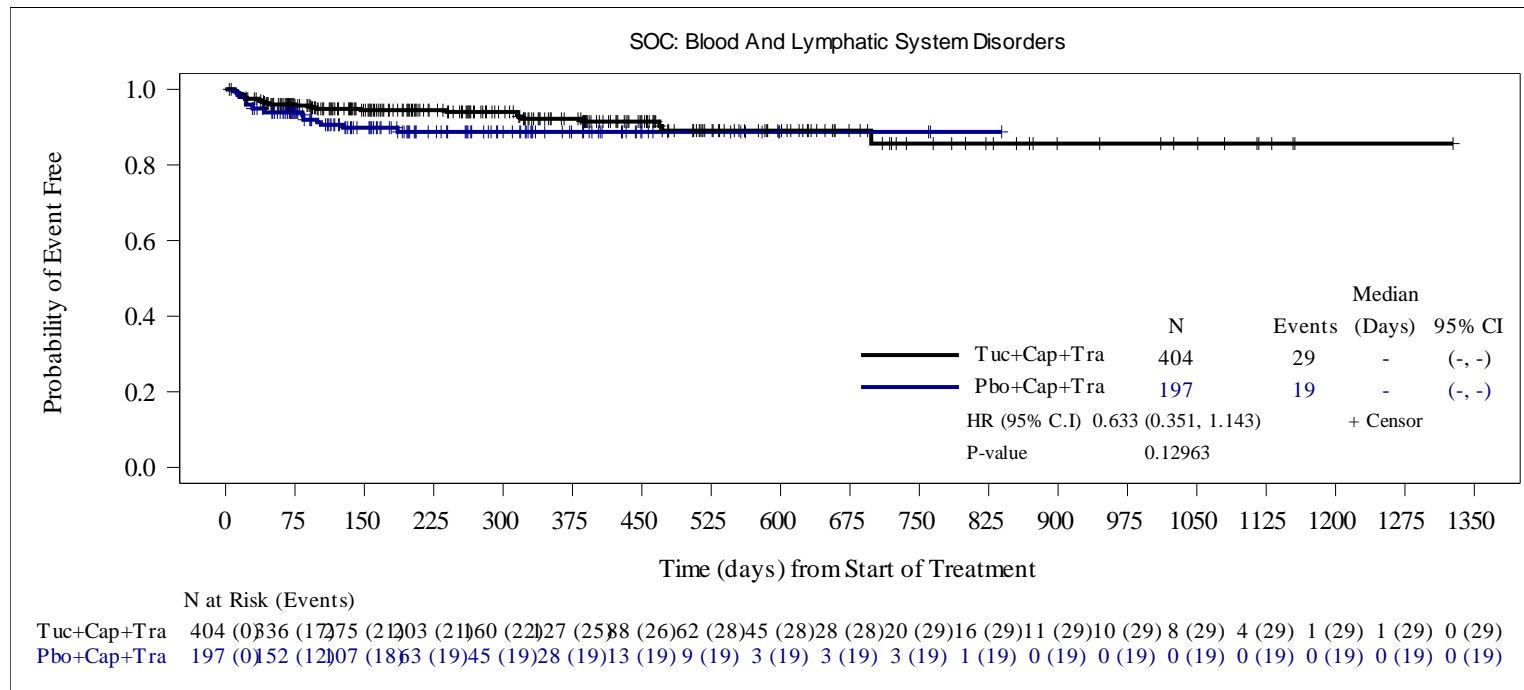
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Data Snapshot: 14OCT2019, Data Cutoff Date: 04SEP2019

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Seagen Protocol ONT-380-206

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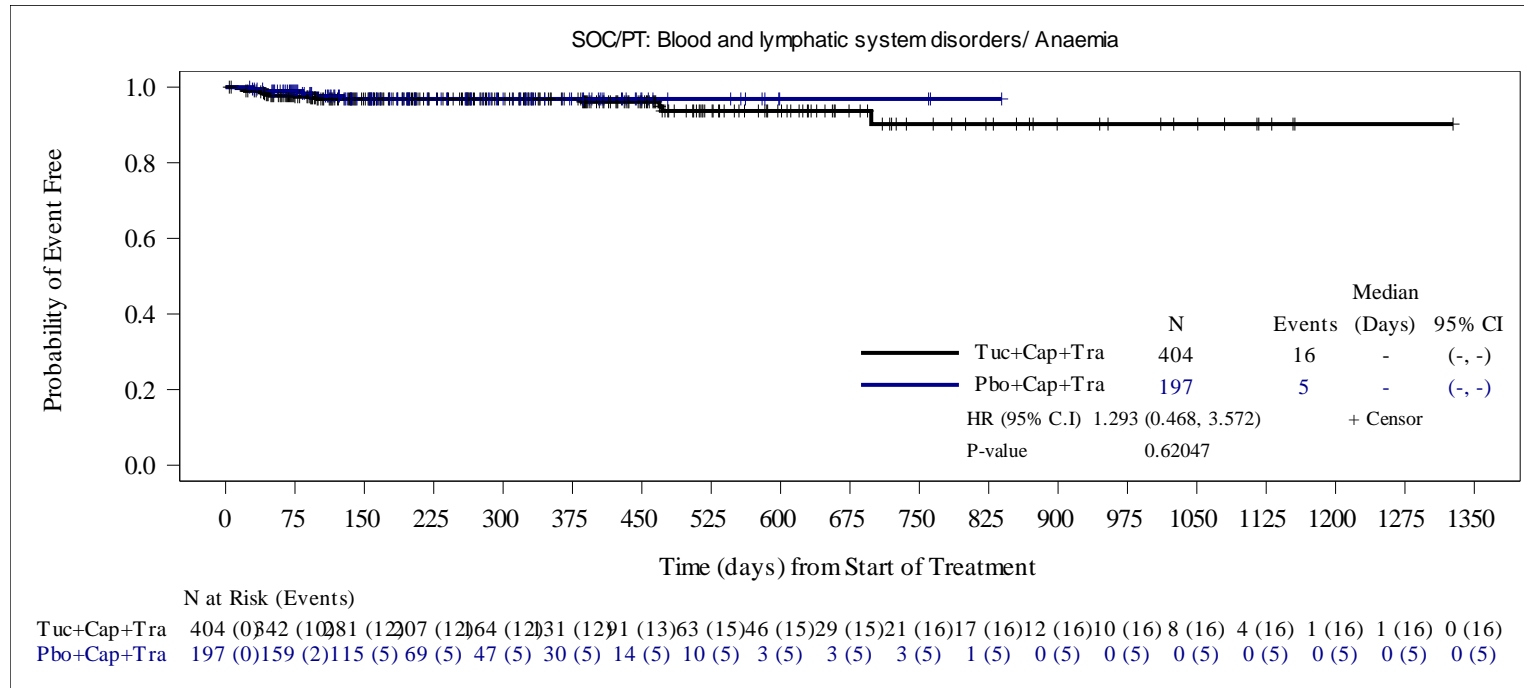
Two-sided p-value calculated from Cox proportional hazards model .

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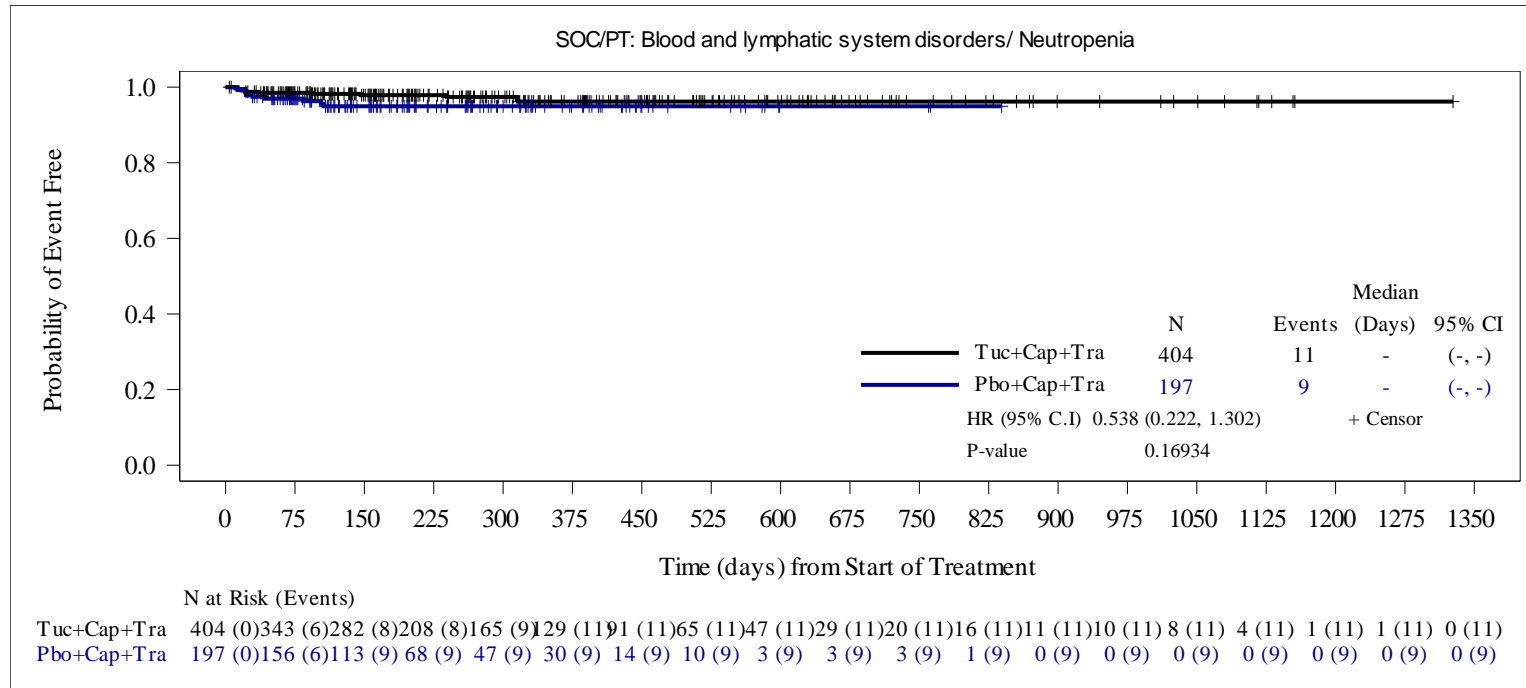
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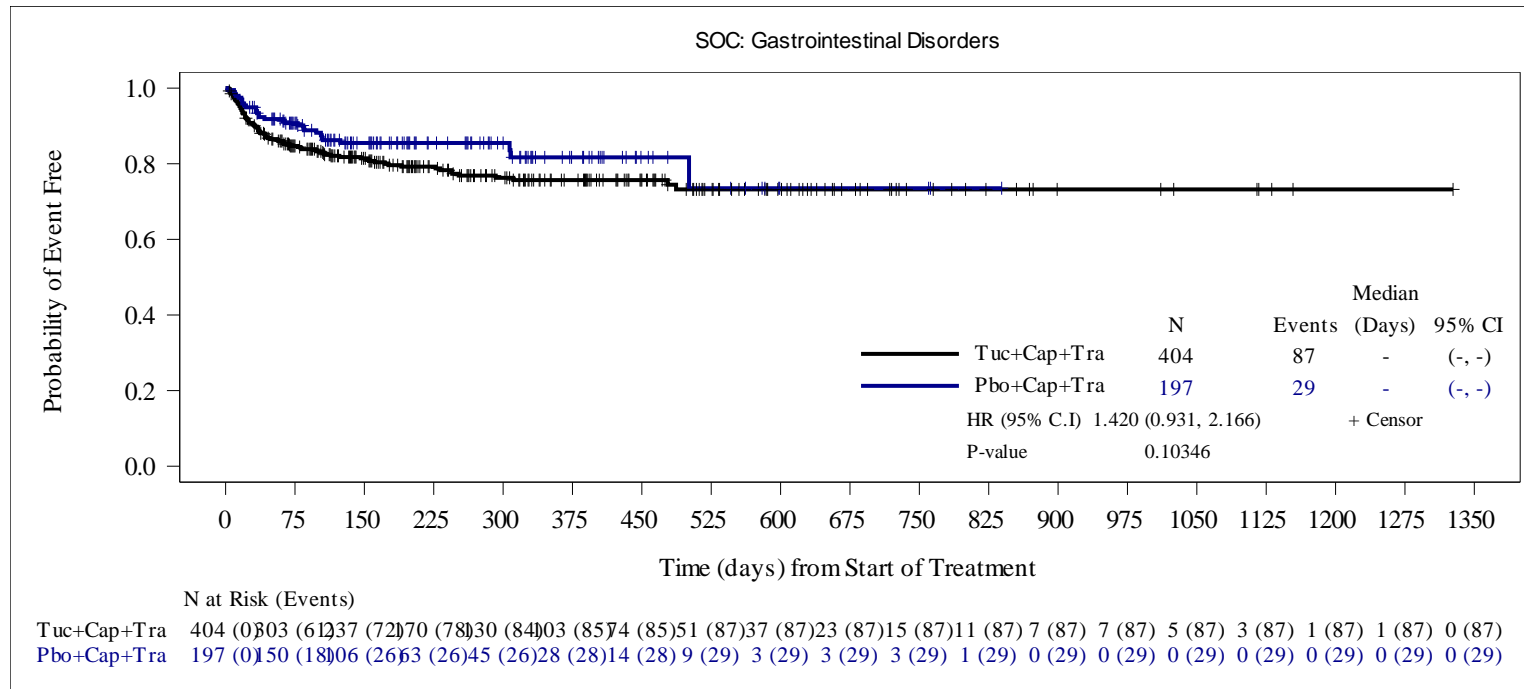
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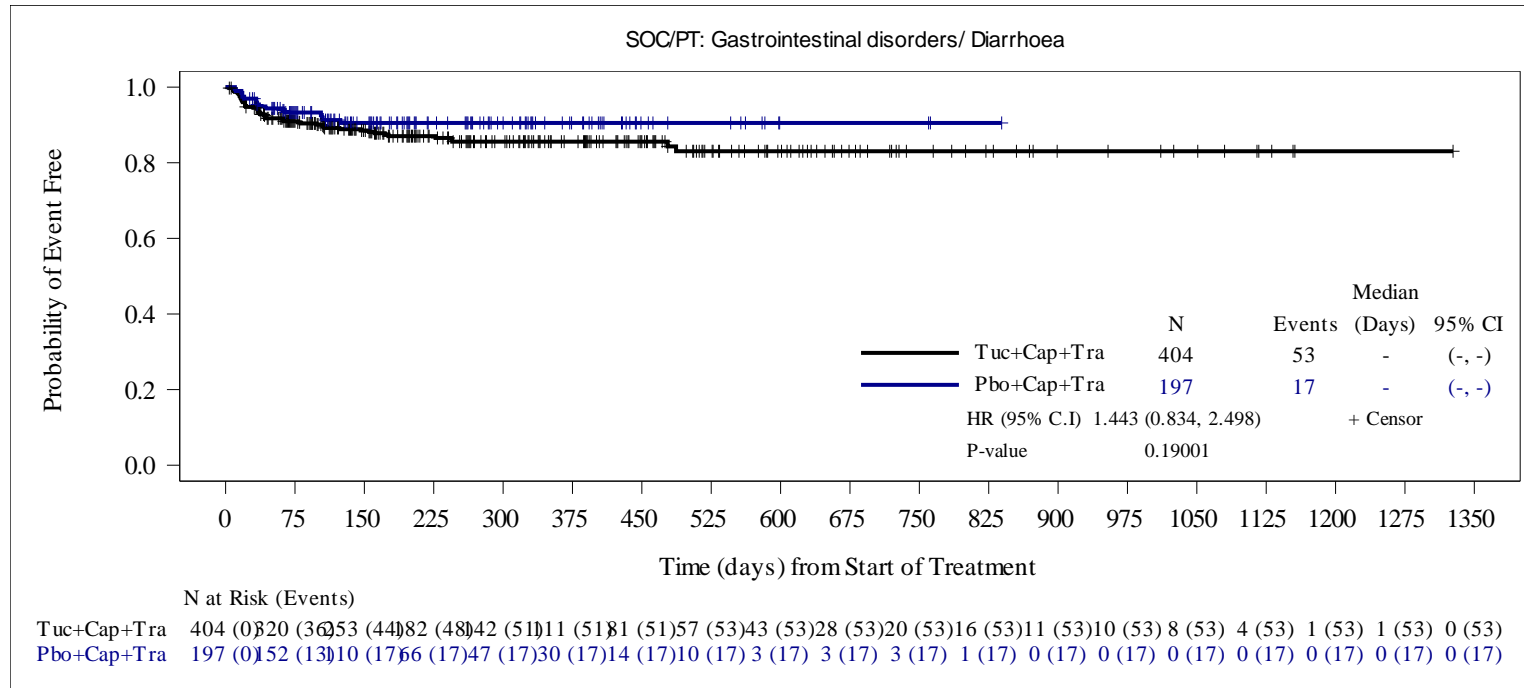
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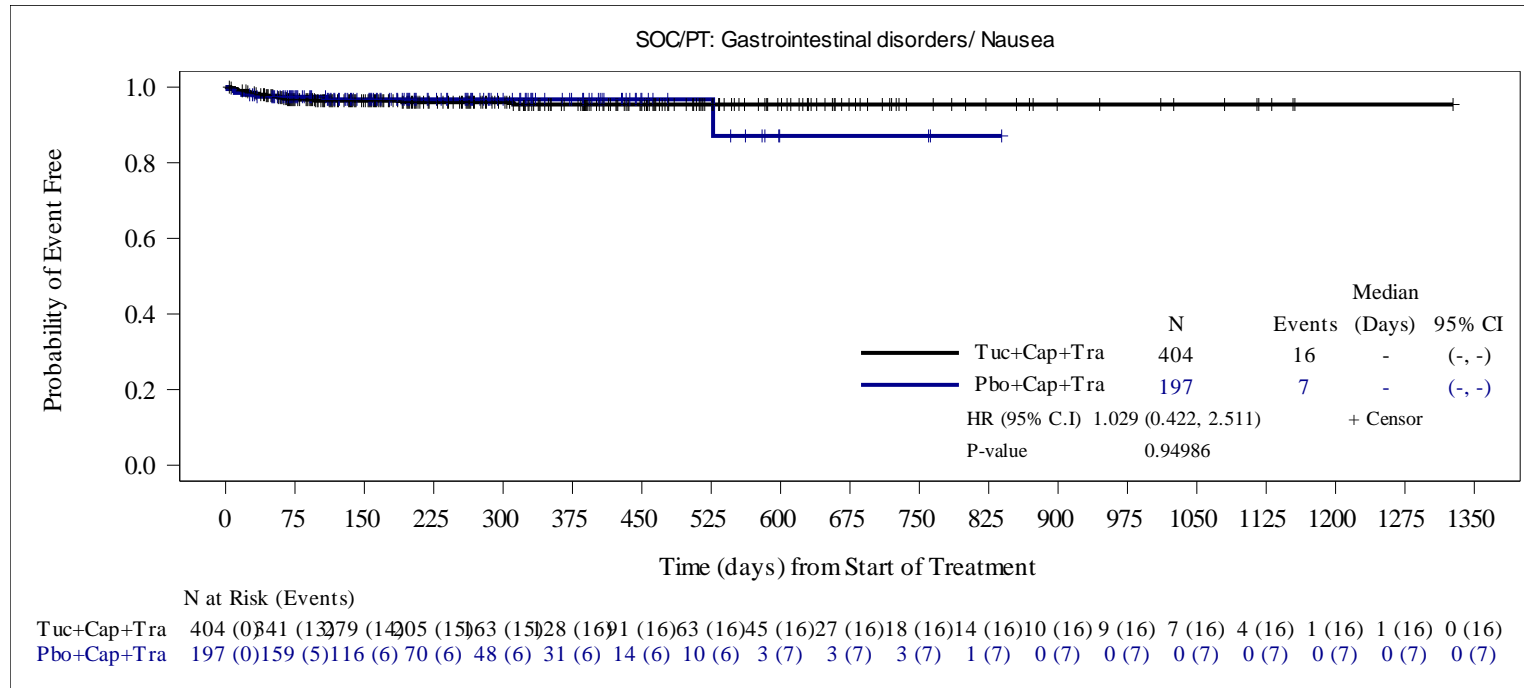
Two-sided p-value calculated from Cox proportional hazards model.

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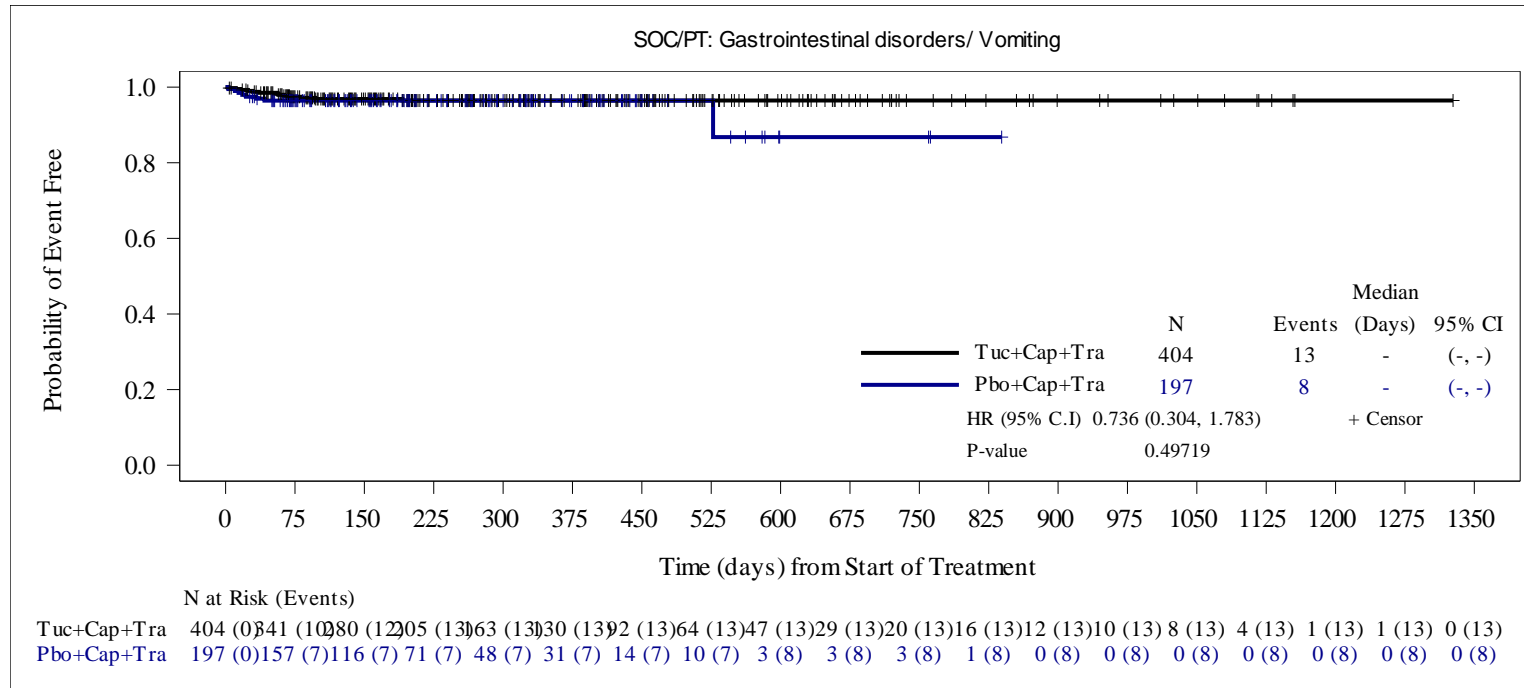
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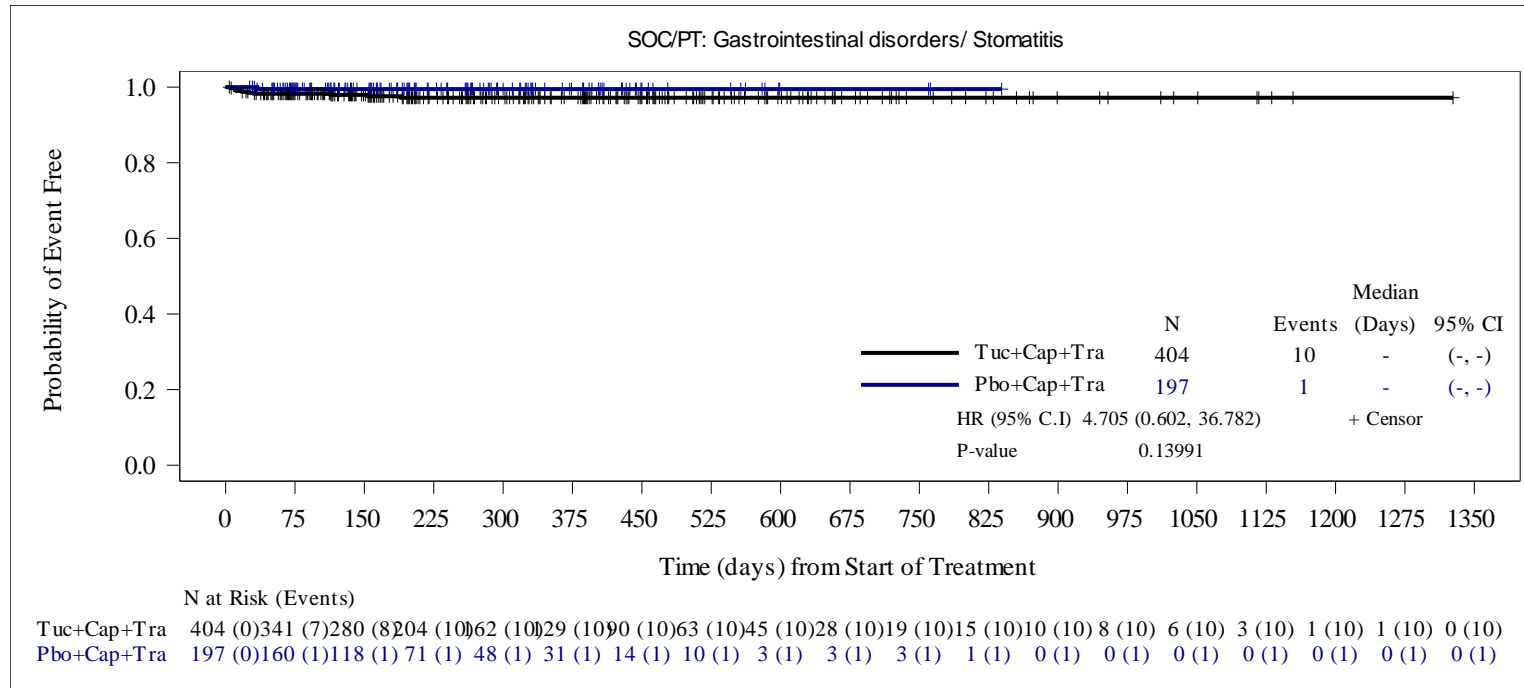
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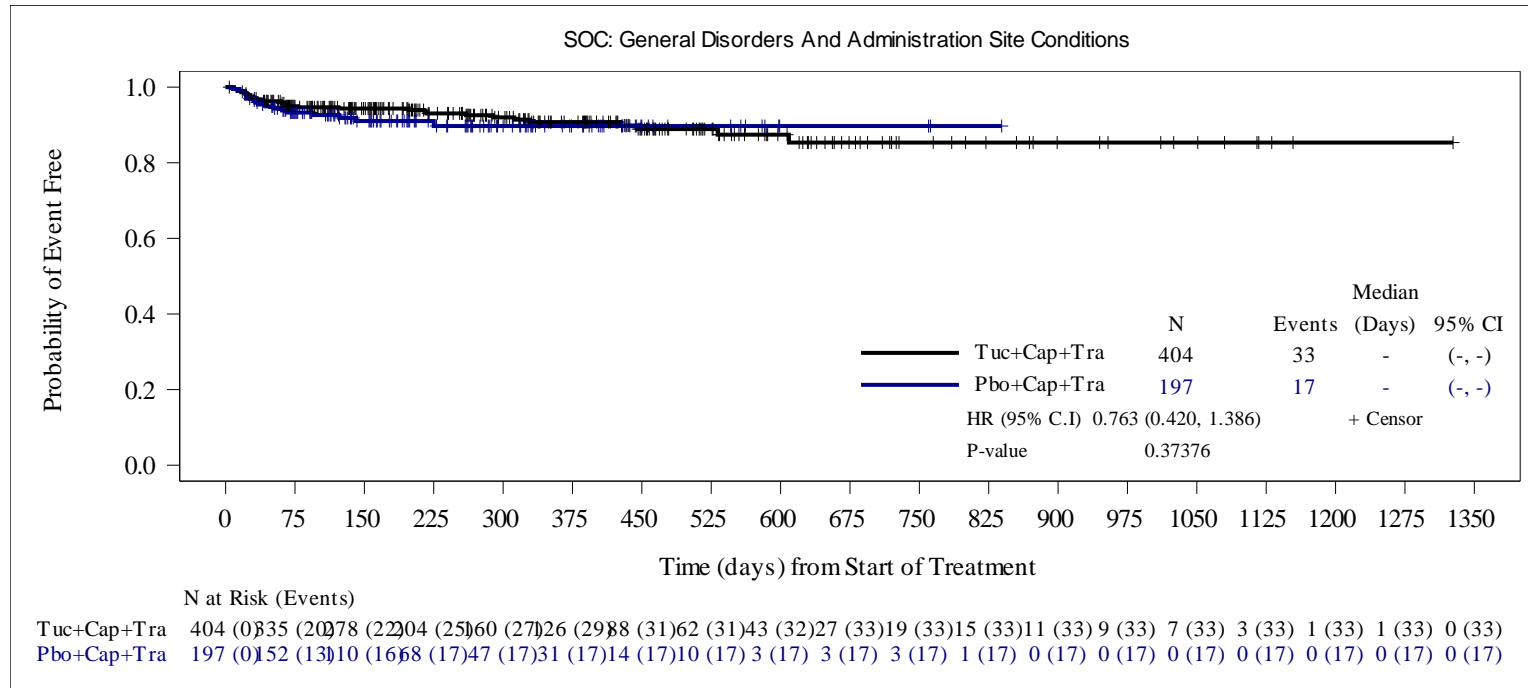
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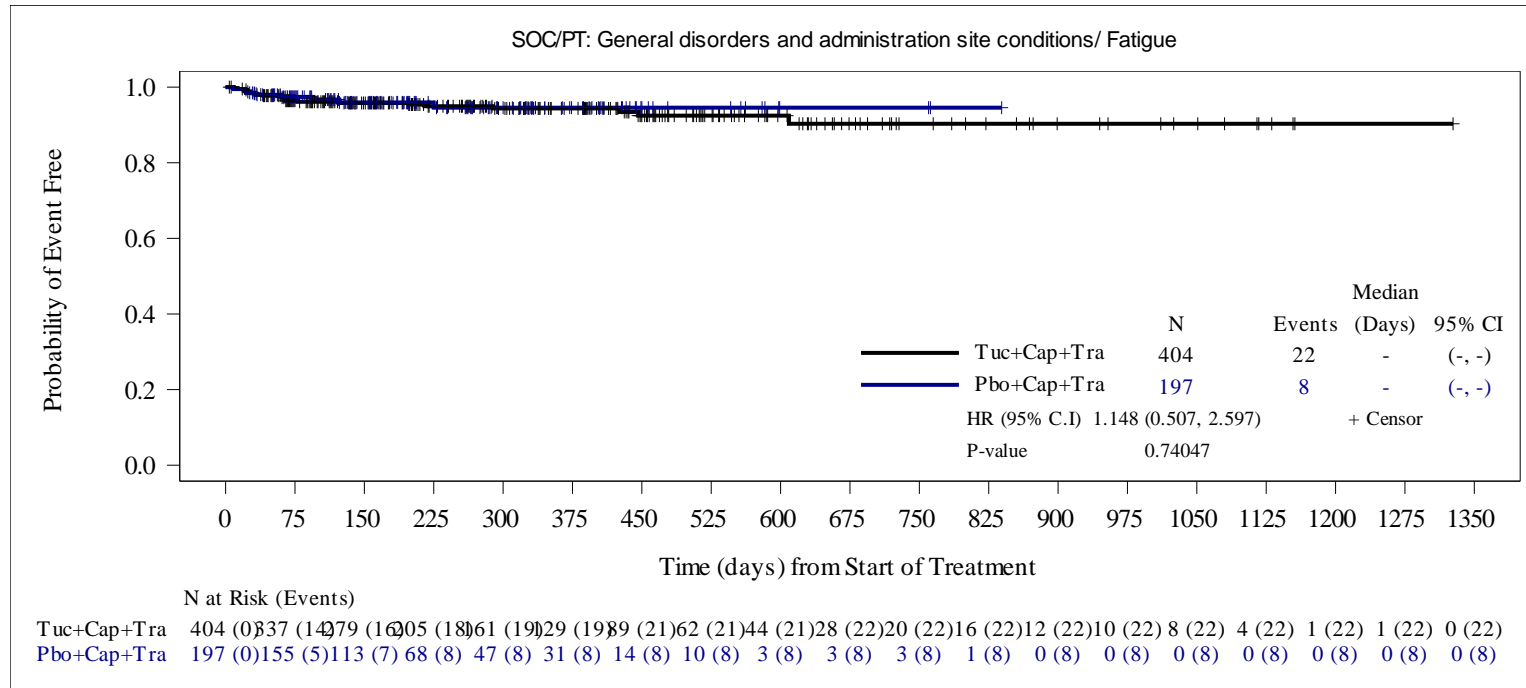
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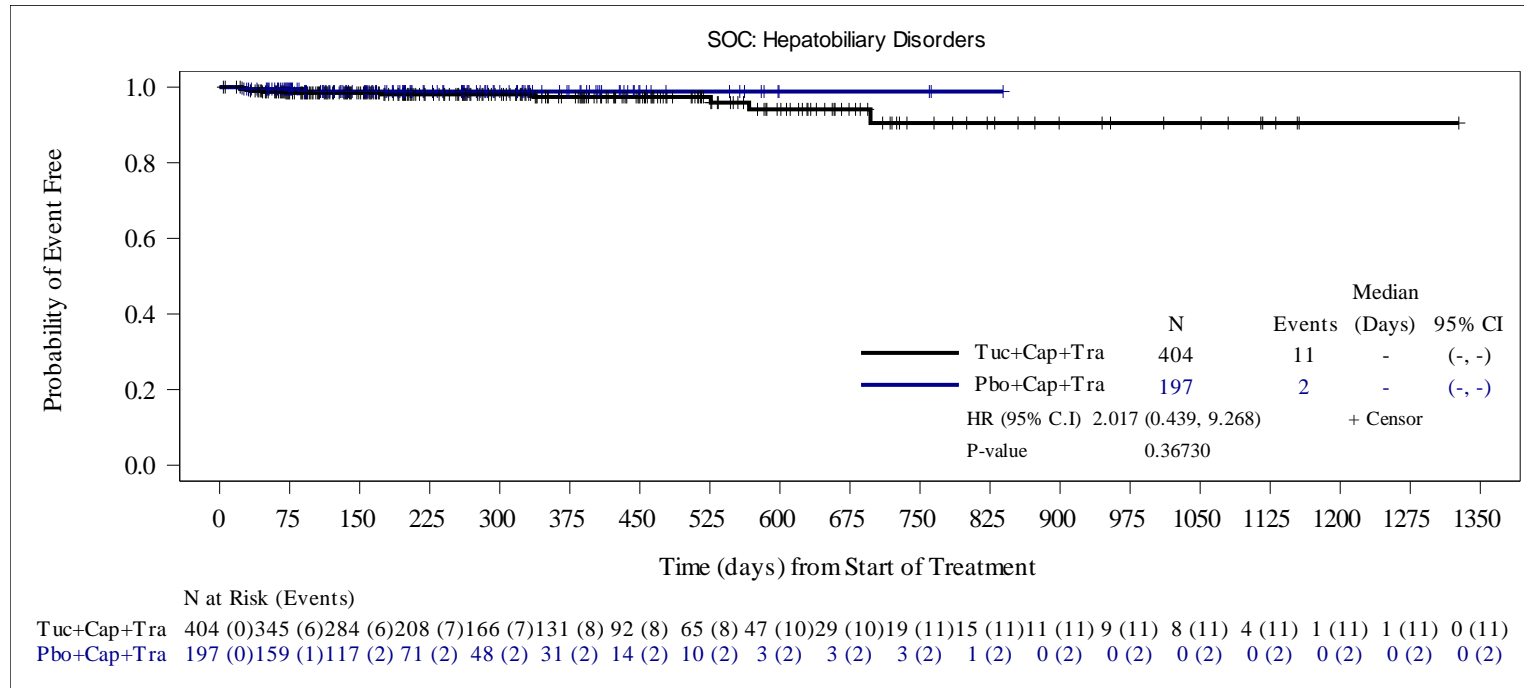
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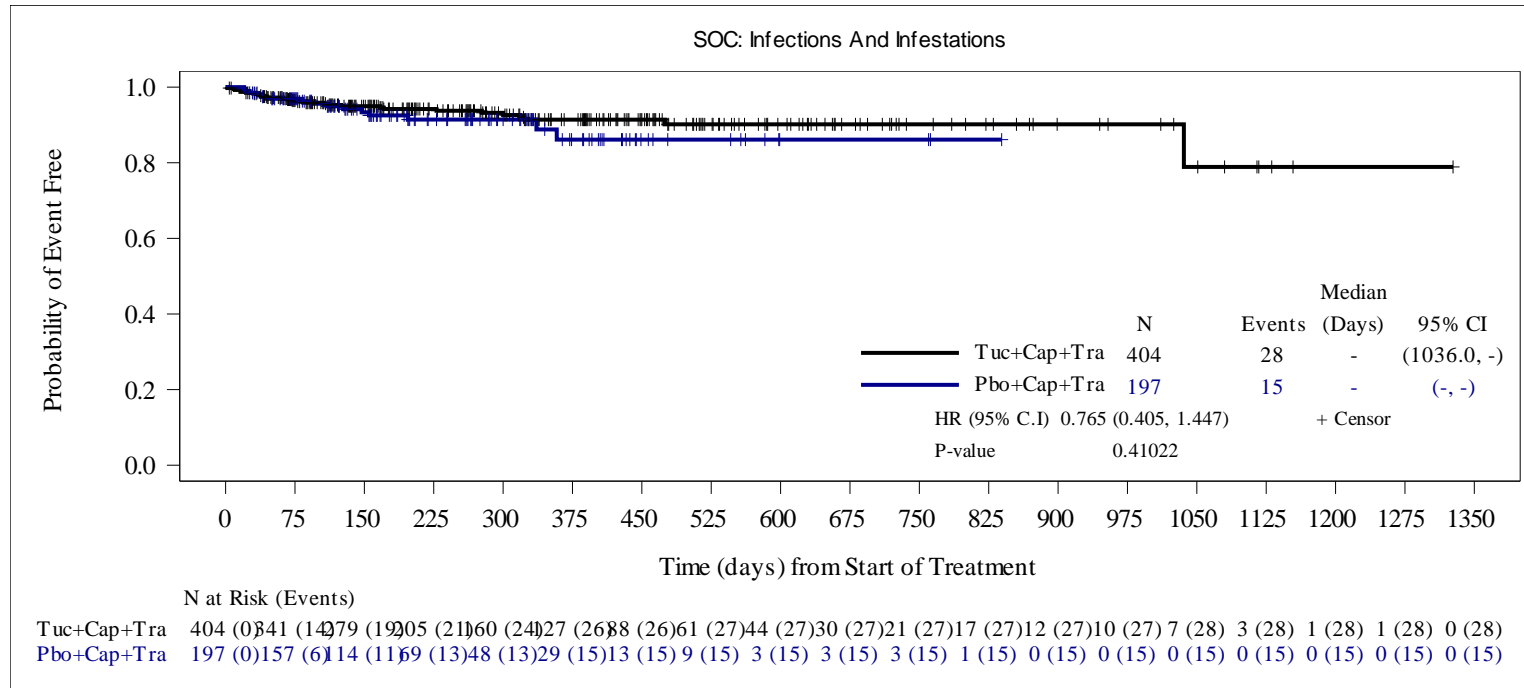
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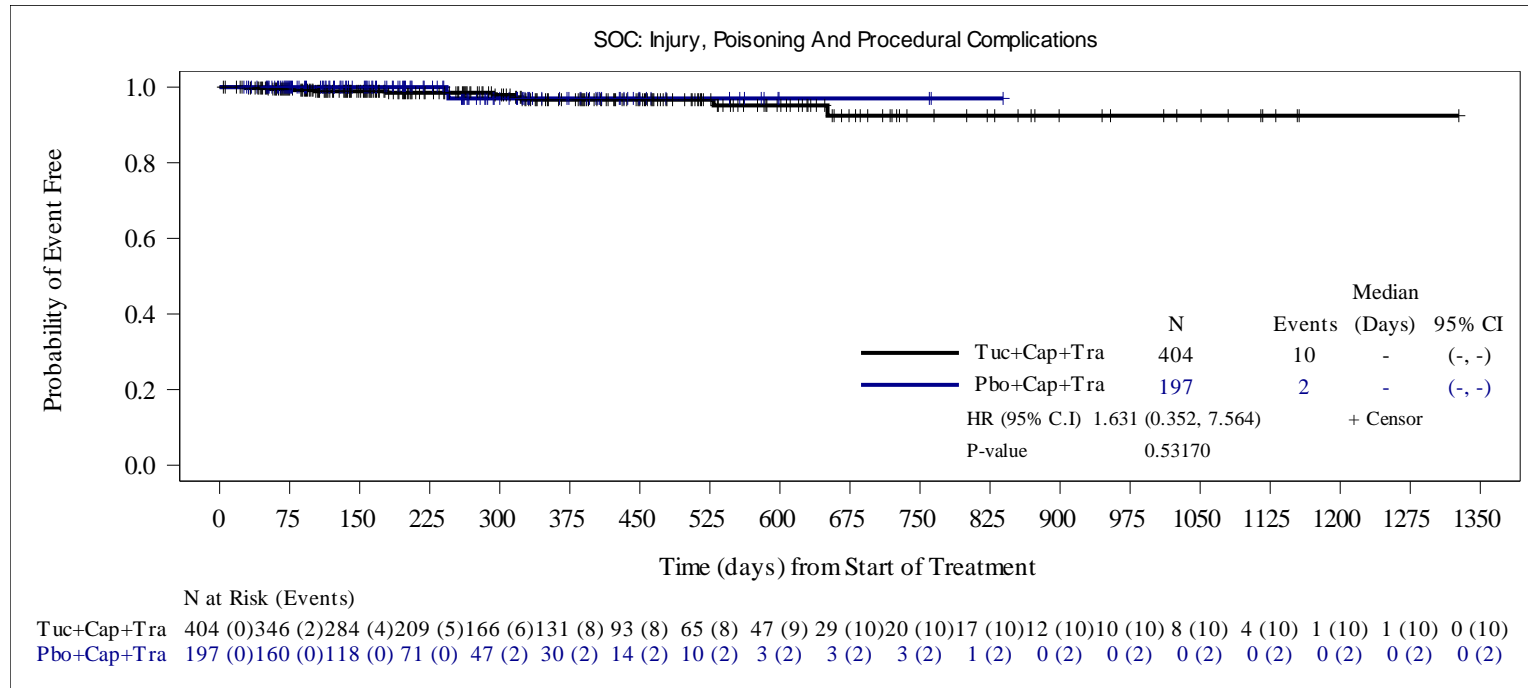
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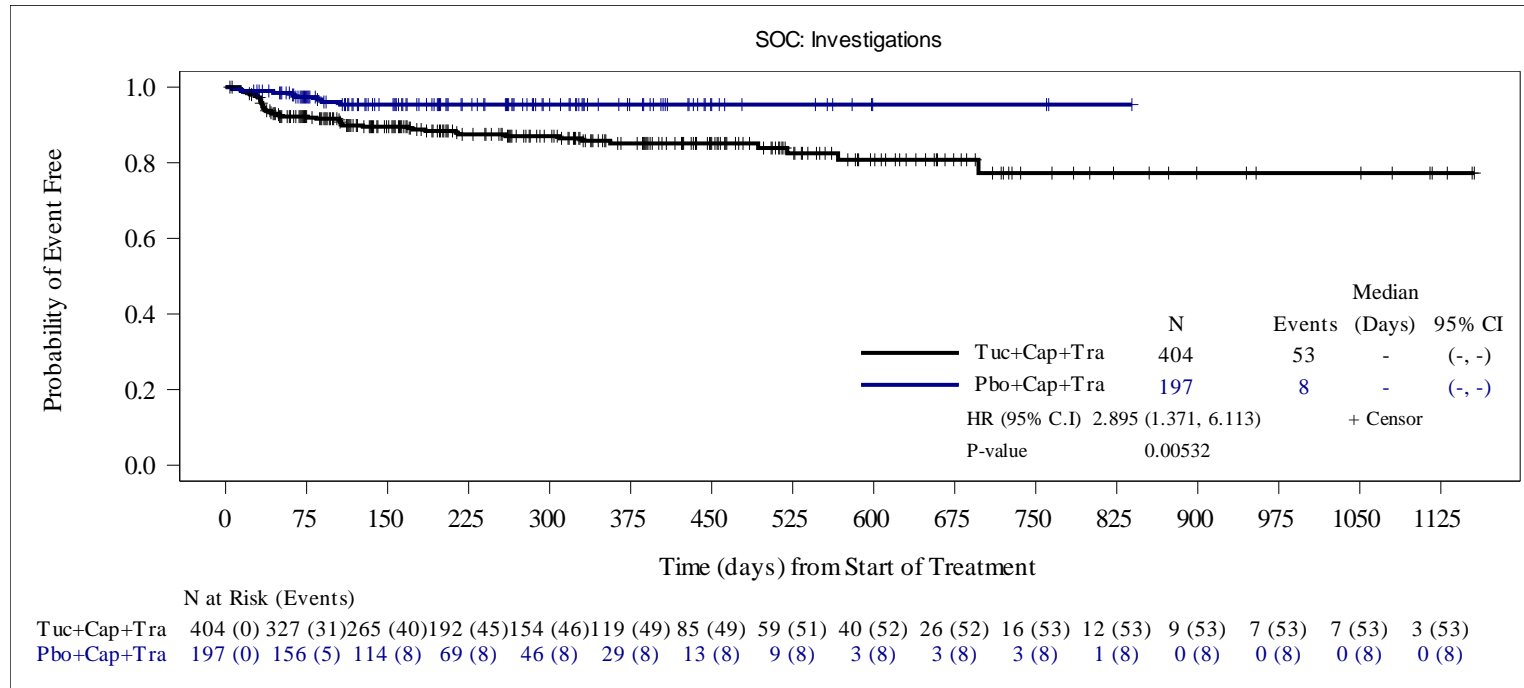
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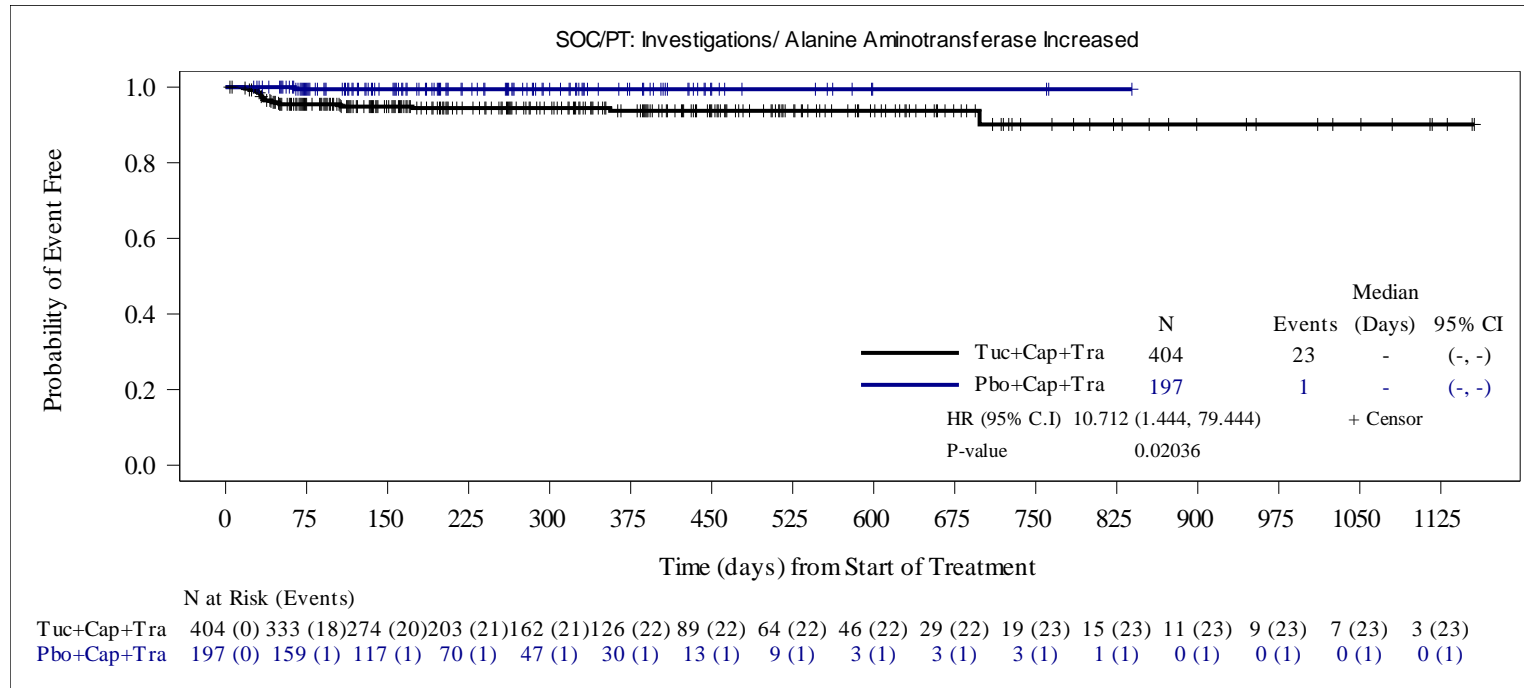
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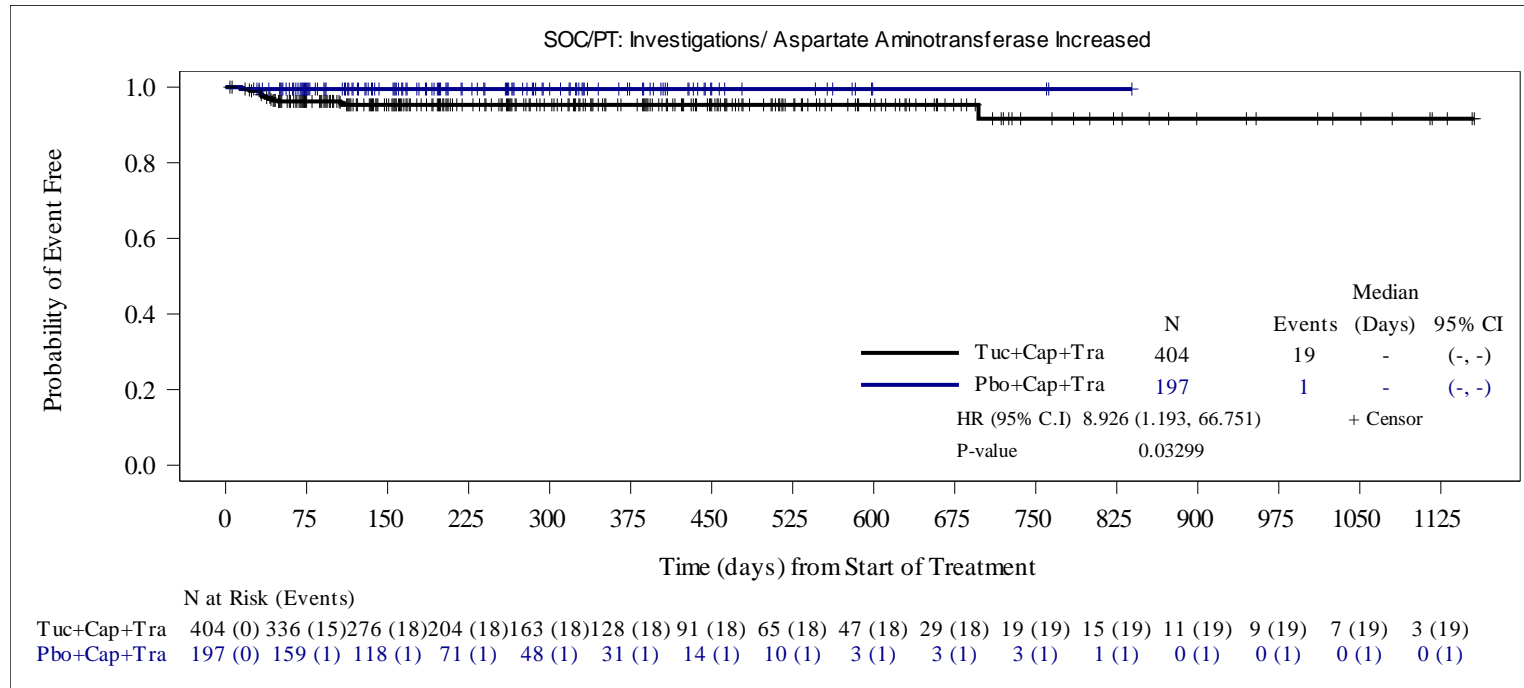
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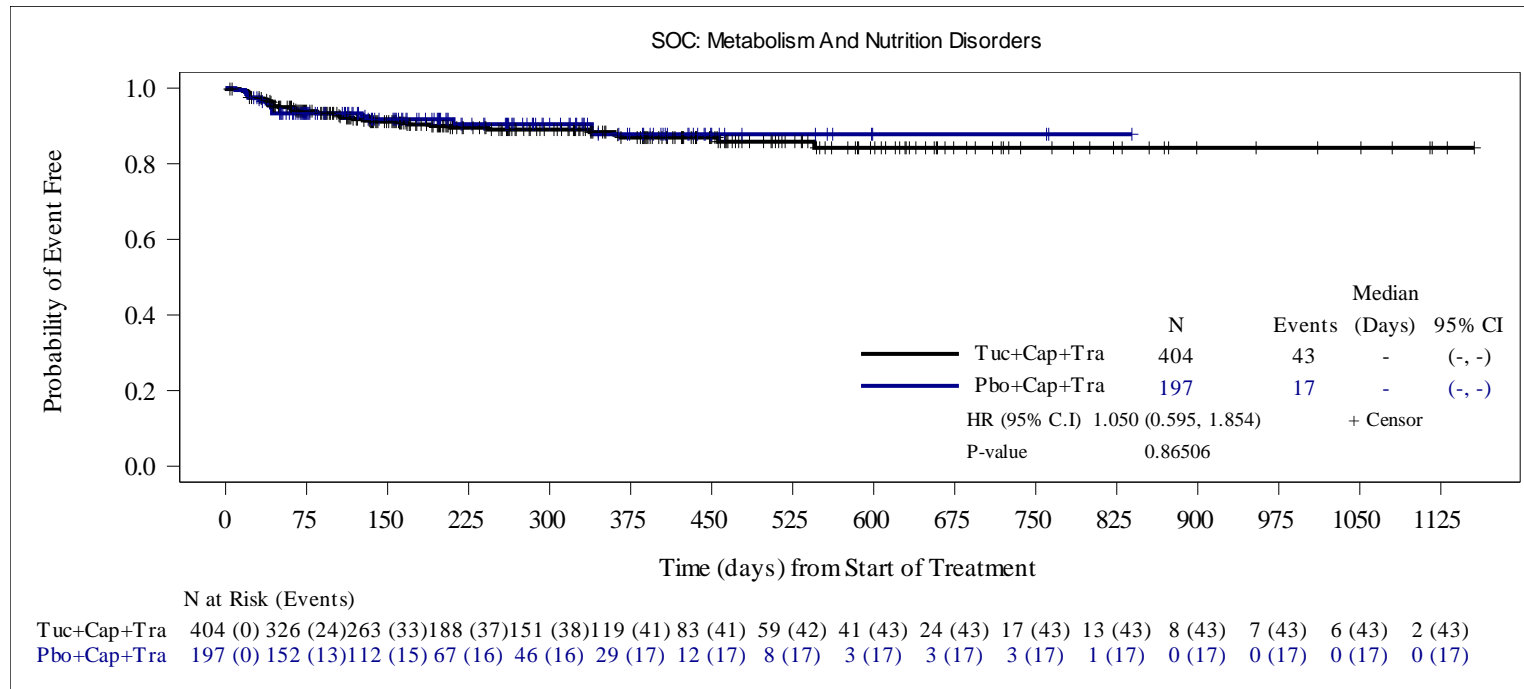
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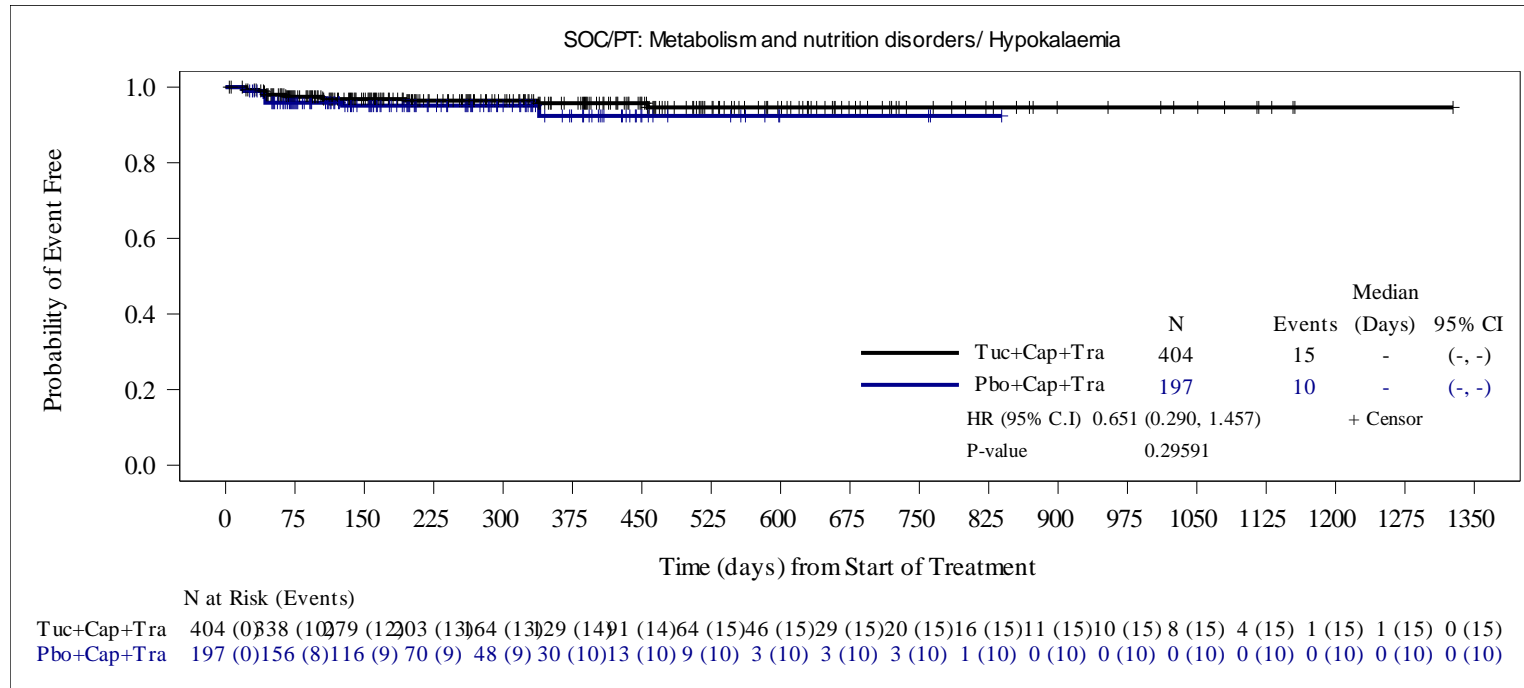
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Figure 2.11.1 Kaplan-Meier Estimate of Time to First Onset of Severe (\geq Grade 3) Treatment-Emergent Adverse Events by System Organ Class and Preferred Term Safety Analysis Set



HR is computed from the Cox proportional hazards model using stratification factors (Presence or history of brain metastases: Yes/No, ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization. When the number of subjects with at least one event was \leq 30, an unstratified Cox model was run.

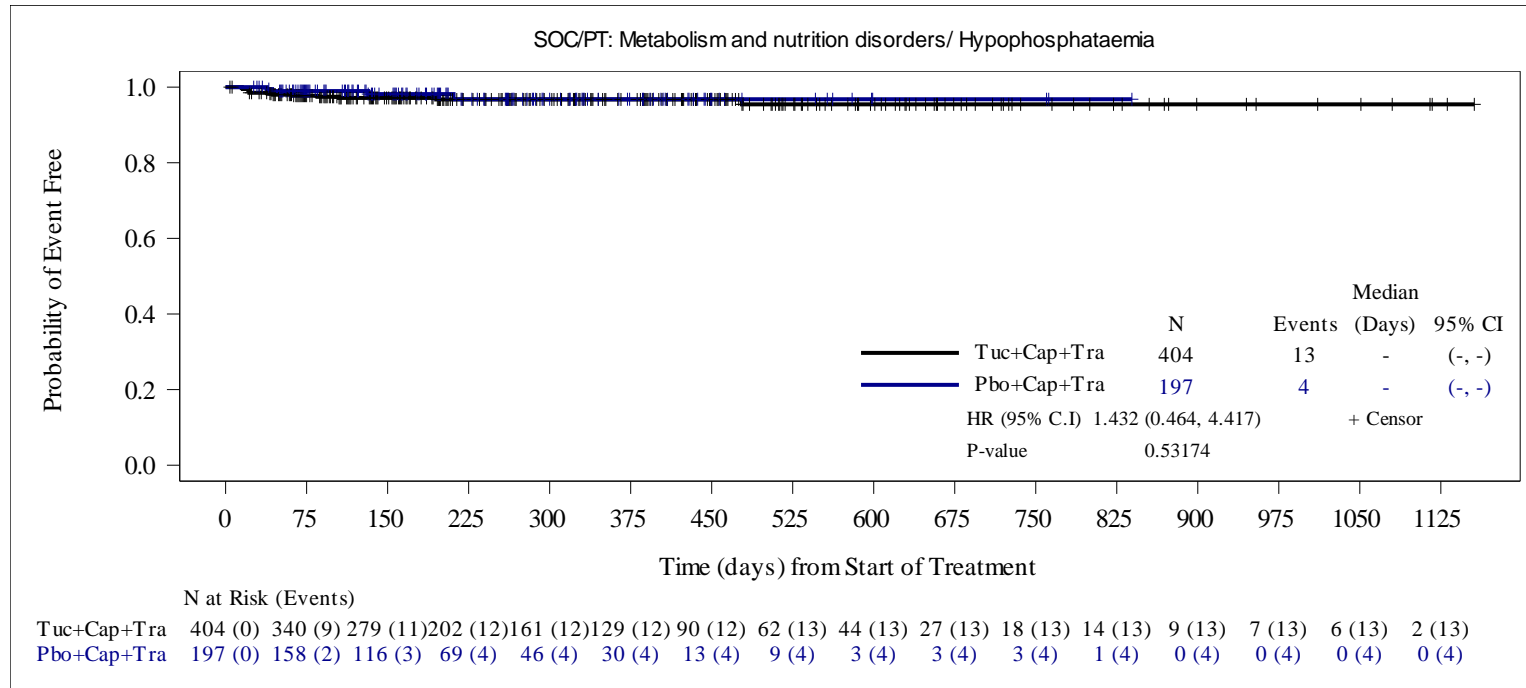
Two-sided p-value calculated from Cox proportional hazards model .

Snapshot date: 10SEP2020, data cutoff date: 29MAY2020.

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Seagen Protocol ONT-380-206

**Figure 2.11.1 Kaplan-Meier Estimate of Time to First Onset of Severe (\geq Grade 3) Treatment-Emergent Adverse Events by System Organ Class and Preferred Term
Safety Analysis Set**



HR is computed from the Cox proportional hazards model using stratification factors (Presence or history of brain metastases: Yes/No, ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization. When the number of subjects with at least one event was \leq 30, an unstratified Cox model was run.

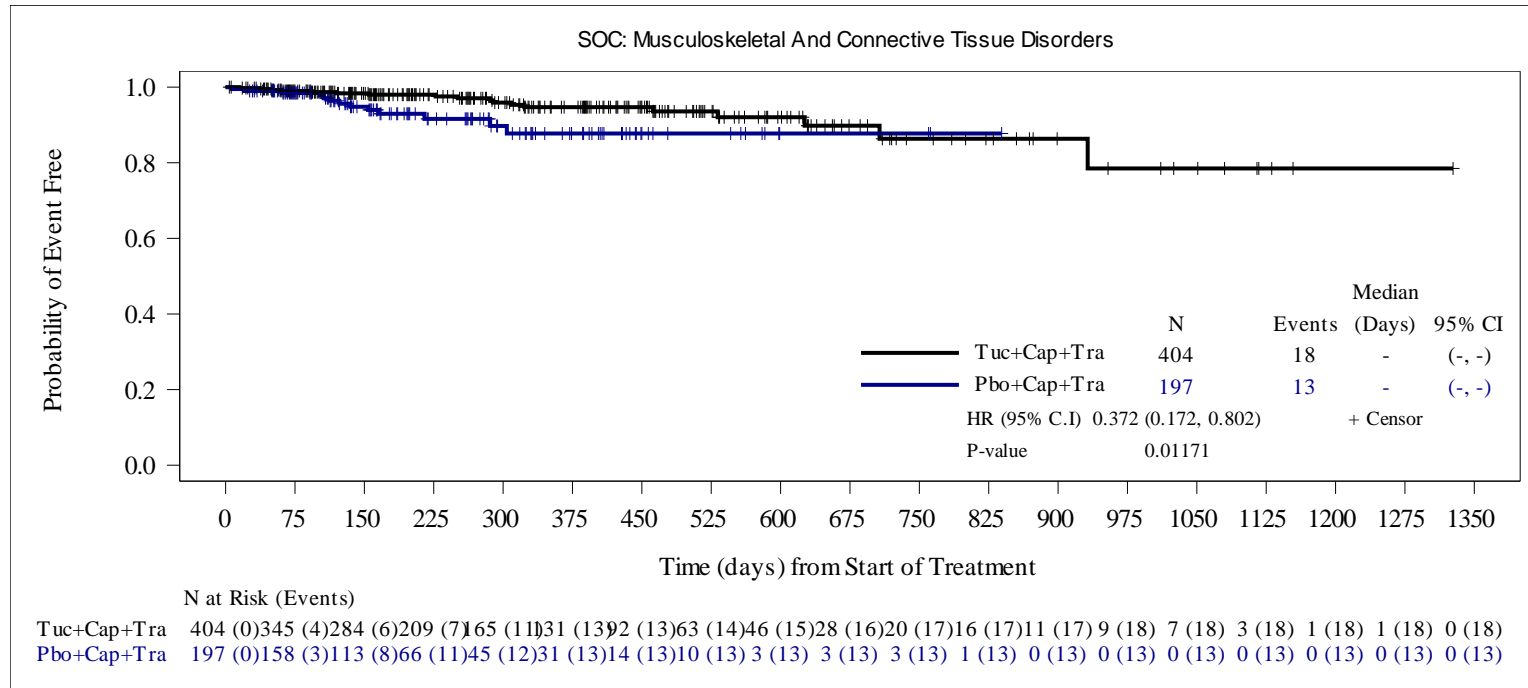
Two-sided p-value calculated from Cox proportional hazards model .

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Figure 2.11.1 Kaplan-Meier Estimate of Time to First Onset of Severe (≥ Grade 3) Treatment-Emergent Adverse Events by System Organ Class and Preferred Term Safety Analysis Set



HR is computed from the Cox proportional hazards model using stratification factors (Presence or history of brain metastases: Yes/No, ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization. When the number of subjects with at least one event was ≤ 30, an unstratified Cox model was run.

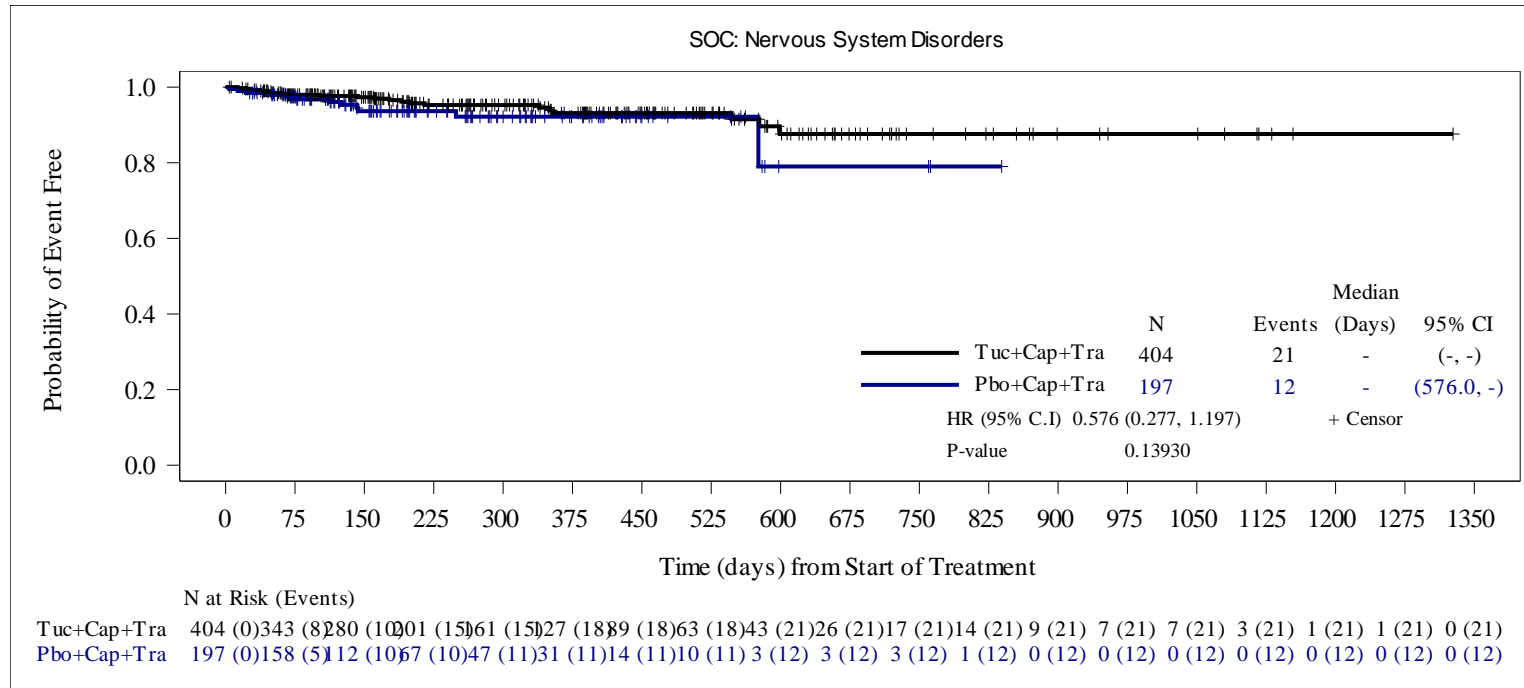
Two-sided p-value calculated from Cox proportional hazards model .

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Figure 2.11.1 Kaplan-Meier Estimate of Time to First Onset of Severe (\geq Grade 3) Treatment-Emergent Adverse Events by System Organ Class and Preferred Term Safety Analysis Set



HR is computed from the Cox proportional hazards model using stratification factors (Presence or history of brain metastases: Yes/No, ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization. When the number of subjects with at least one event was \leq 30, an unstratified Cox model was run.

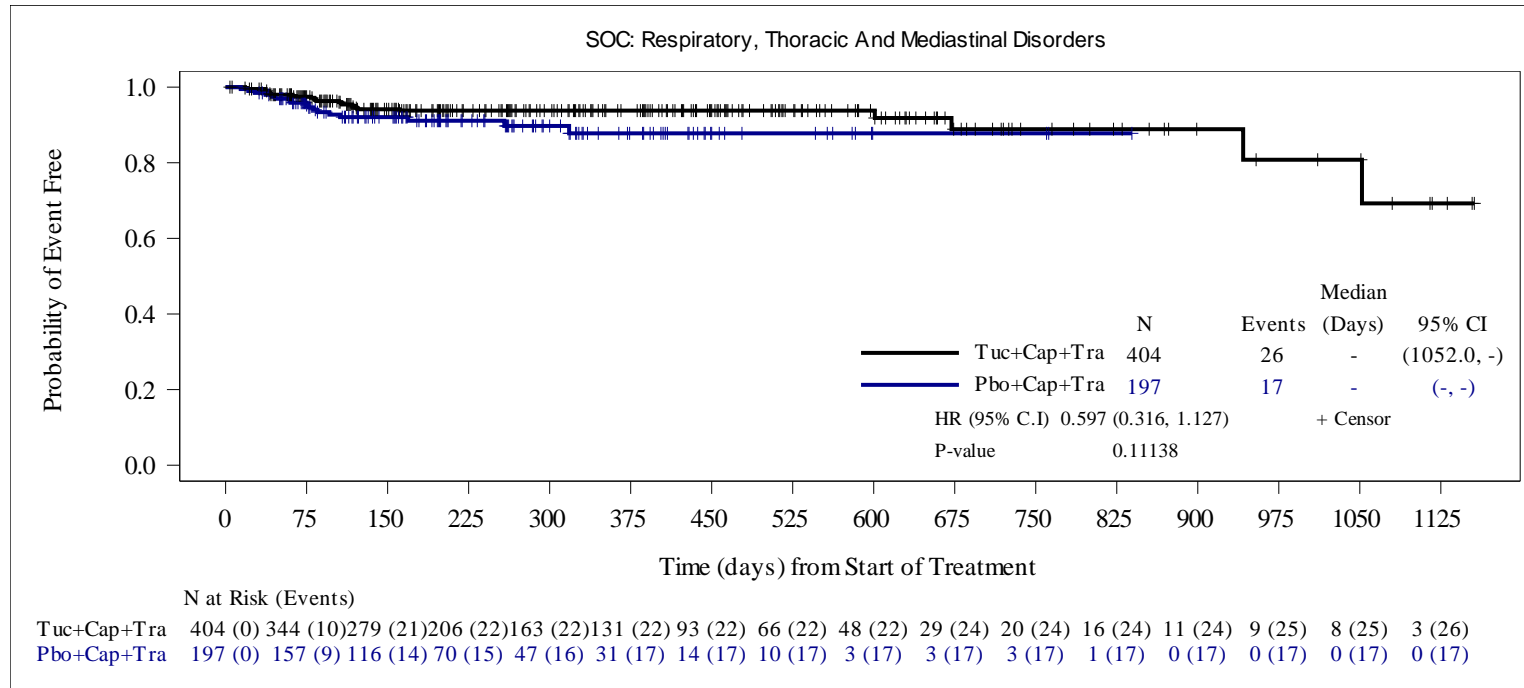
Two-sided p-value calculated from Cox proportional hazards model .

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**Figure 2.11.1 Kaplan-Meier Estimate of Time to First Onset of Severe (\geq Grade 3) Treatment-Emergent Adverse Events by System Organ Class and Preferred Term
Safety Analysis Set**



HR is computed from the Cox proportional hazards model using stratification factors (Presence or history of brain metastases: Yes/No, ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization. When the number of subjects with at least one event was \leq 30, an unstratified Cox model was run.

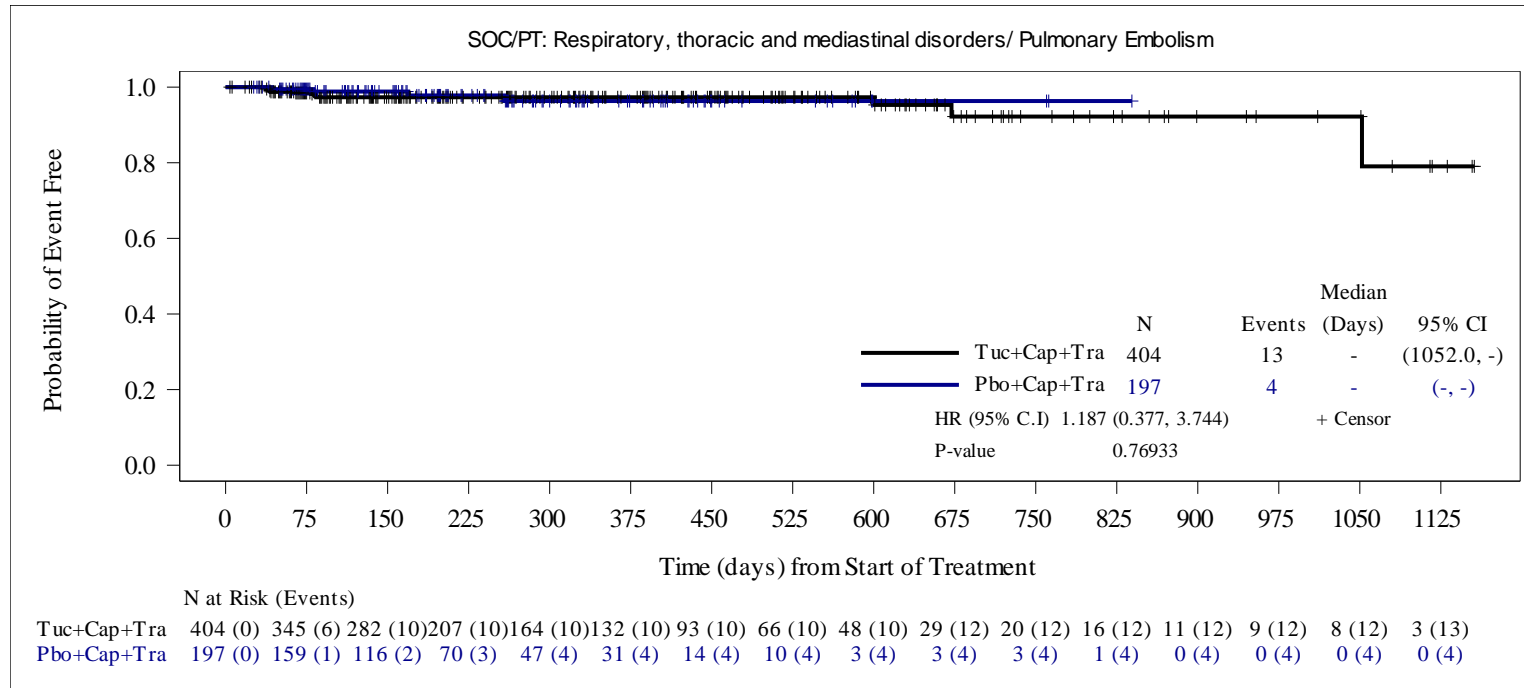
Two-sided p-value calculated from Cox proportional hazards model .

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**Figure 2.11.1 Kaplan-Meier Estimate of Time to First Onset of Severe (\geq Grade 3) Treatment-Emergent Adverse Events by System Organ Class and Preferred Term
Safety Analysis Set**



HR is computed from the Cox proportional hazards model using stratification factors (Presence or history of brain metastases: Yes/No, ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization. When the number of subjects with at least one event was \leq 30, an unstratified Cox model was run.

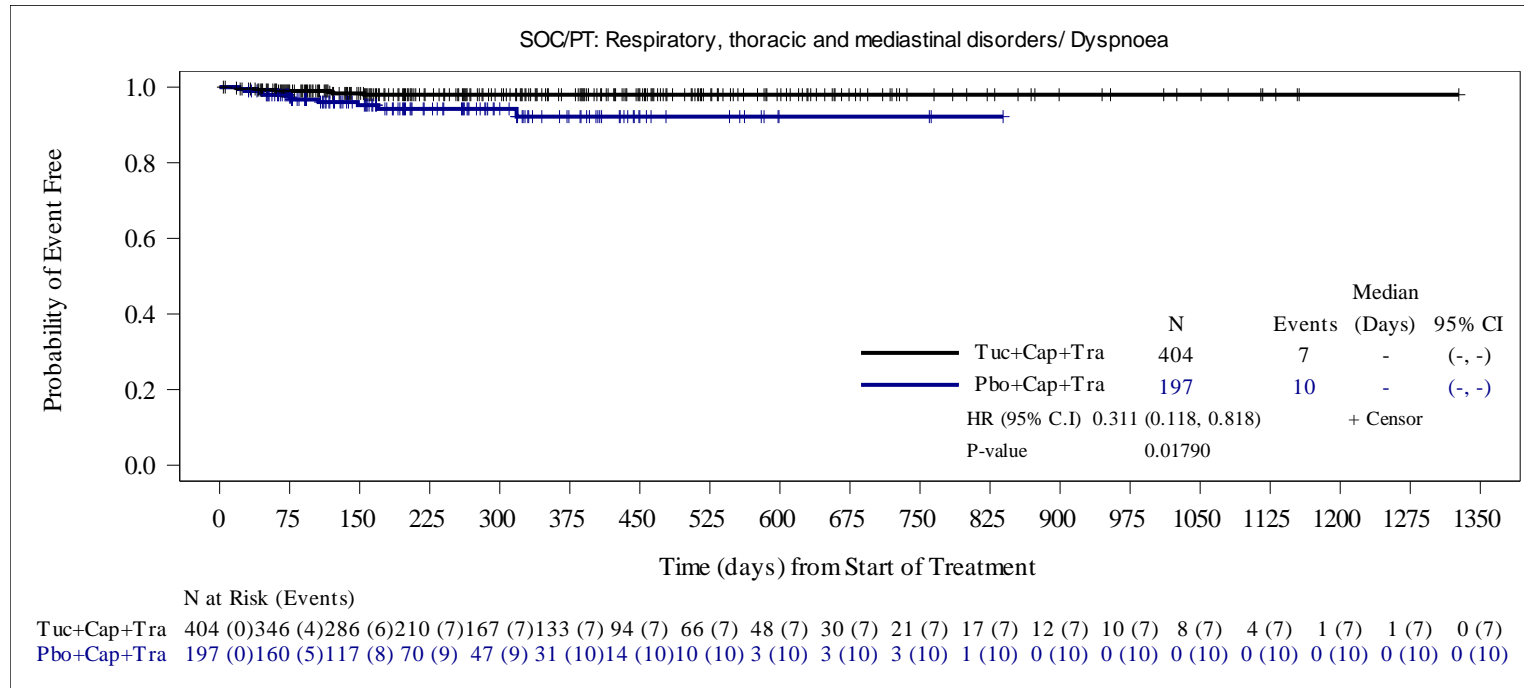
Two-sided p-value calculated from Cox proportional hazards model .

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**Figure 2.11.1 Kaplan-Meier Estimate of Time to First Onset of Severe (\geq Grade 3) Treatment-Emergent Adverse Events by System Organ Class and Preferred Term
Safety Analysis Set**



HR is computed from the Cox proportional hazards model using stratification factors (Presence or history of brain metastases: Yes/No, ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization. When the number of subjects with at least one event was ≤ 30 , an unstratified Cox model was run.

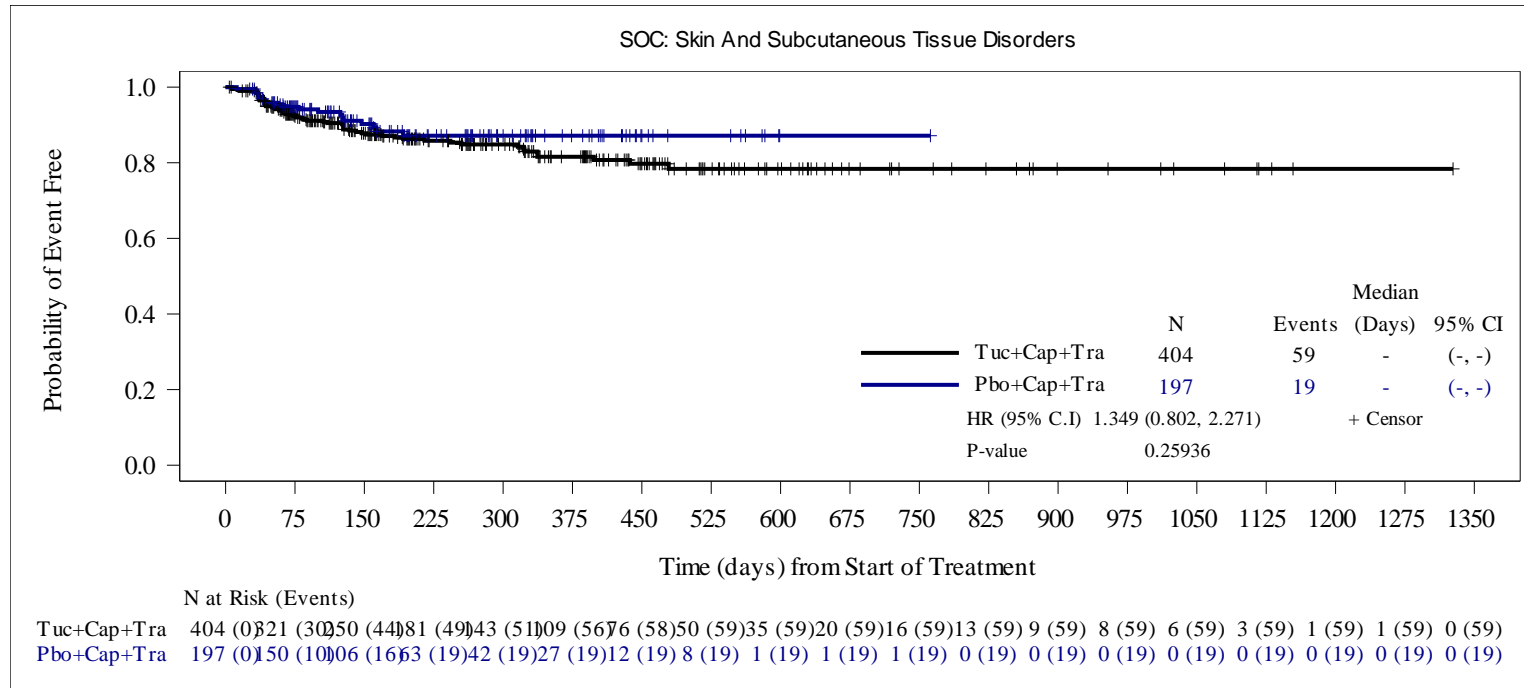
Two-sided p-value calculated from Cox proportional hazards model .

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Figure 2.11.1 Kaplan-Meier Estimate of Time to First Onset of Severe (\geq Grade 3) Treatment-Emergent Adverse Events by System Organ Class and Preferred Term Safety Analysis Set



HR is computed from the Cox proportional hazards model using stratification factors (Presence or history of brain metastases: Yes/No, ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization. When the number of subjects with at least one event was ≤ 30 , an unstratified Cox model was run.

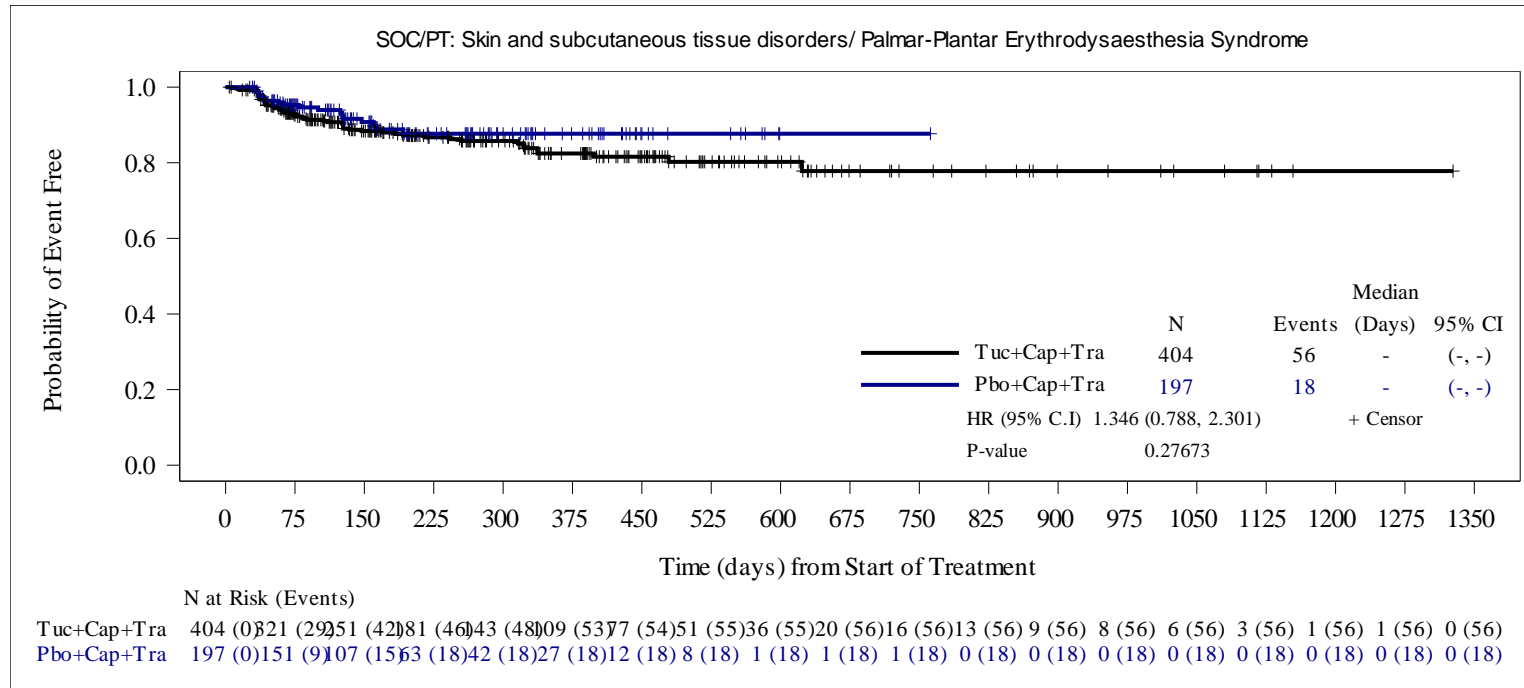
Two-sided p-value calculated from Cox proportional hazards model .

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Figure 2.11.1 Kaplan-Meier Estimate of Time to First Onset of Severe (\geq Grade 3) Treatment-Emergent Adverse Events by System Organ Class and Preferred Term Safety Analysis Set



HR is computed from the Cox proportional hazards model using stratification factors (Presence or history of brain metastases: Yes/No, ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization. When the number of subjects with at least one event was ≤ 30 , an unstratified Cox model was run.

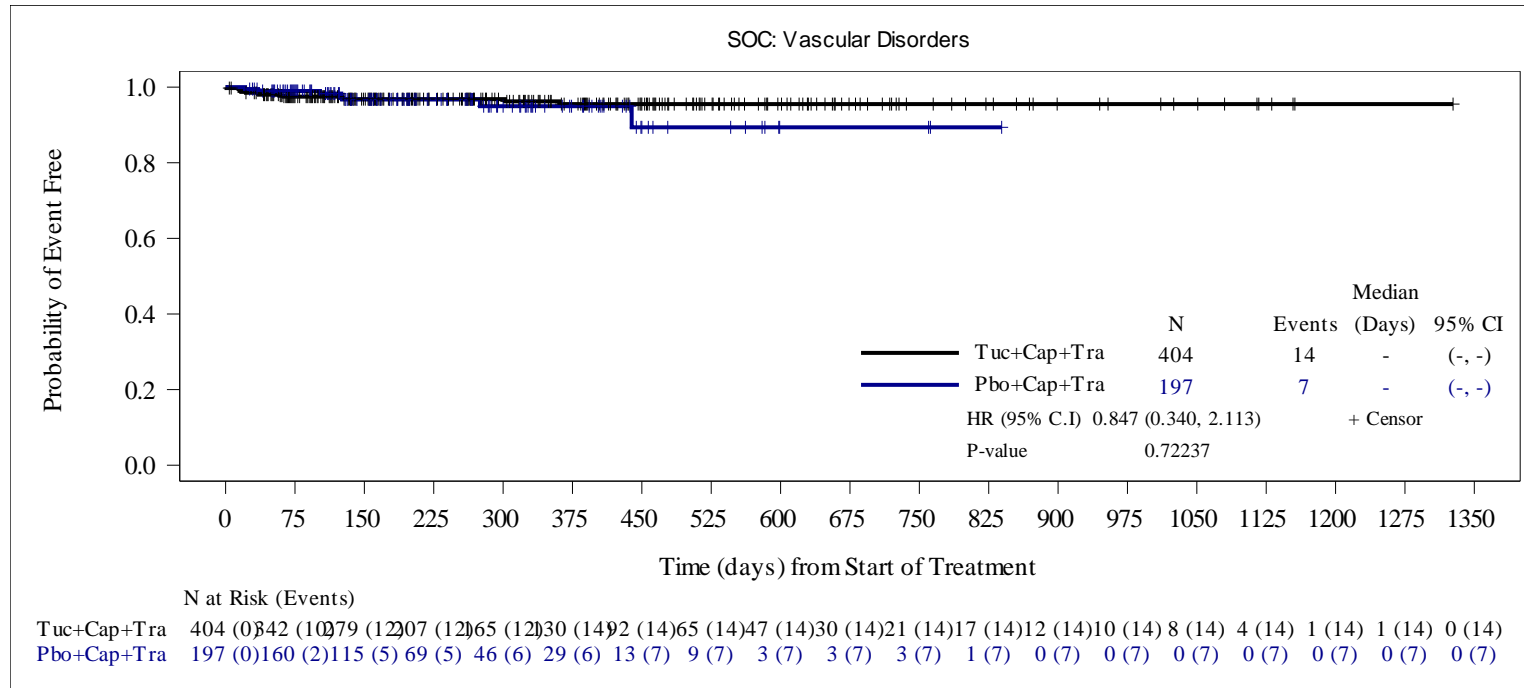
Two-sided p-value calculated from Cox proportional hazards model .

Snapshot date: 10SEP2020, data cutoff date: 29MAY2020.

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Figure 2.11.1 Kaplan-Meier Estimate of Time to First Onset of Severe (\geq Grade 3) Treatment-Emergent Adverse Events by System Organ Class and Preferred Term Safety Analysis Set



HR is computed from the Cox proportional hazards model using stratification factors (Presence or history of brain metastases: Yes/No, ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization. When the number of subjects with at least one event was \leq 30, an unstratified Cox model was run.

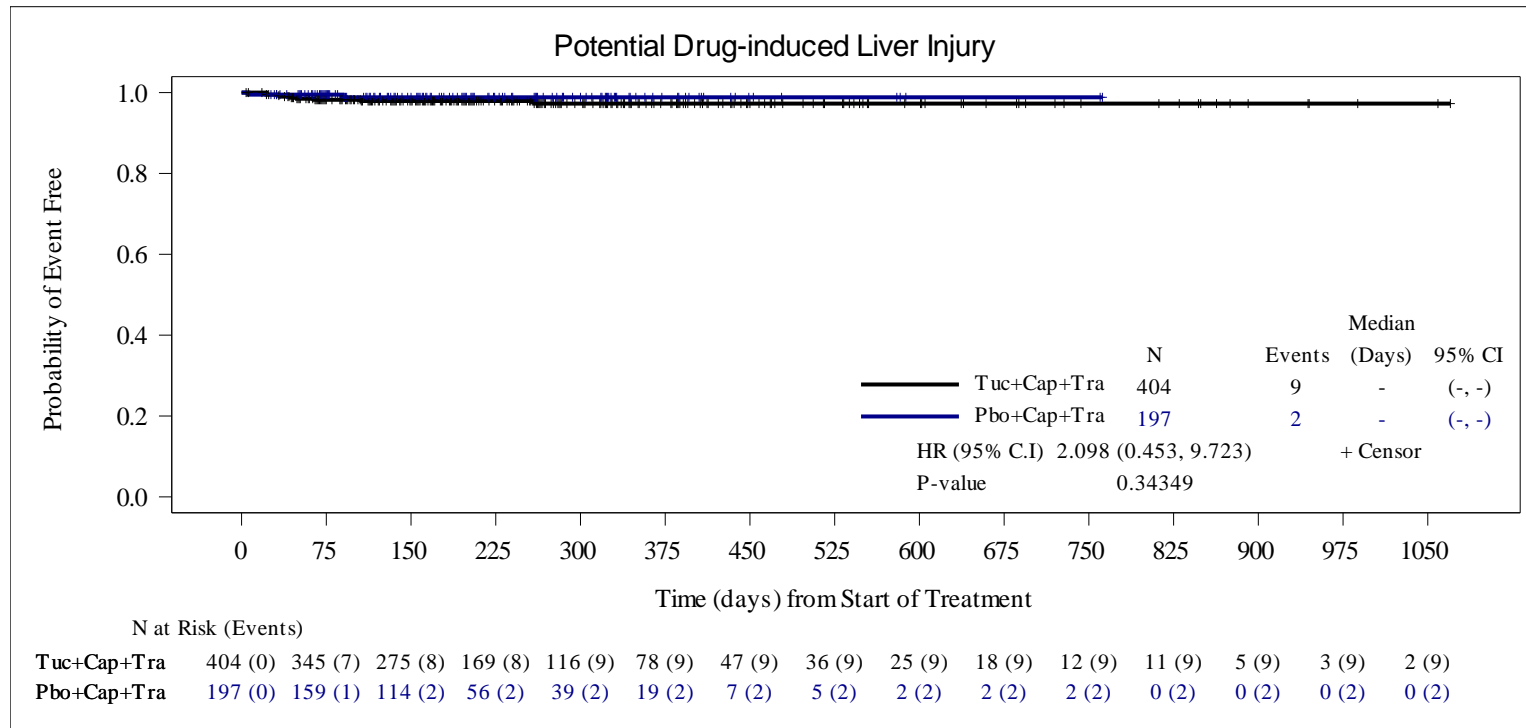
Two-sided p-value calculated from Cox proportional hazards model .

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**Figure 2.14.1 Kaplan-Meier Estimate of Time to First Onset of Treatment-Emergent Adverse Events of Special Interest (AESI)
Safety Analysis Set**



HR is computed from the Cox proportional hazards model using stratification factors (Presence or history of brain metastases: Yes/No, ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization. When the number of subjects with at least one event was ≤ 30 , an unstratified Cox model was run.

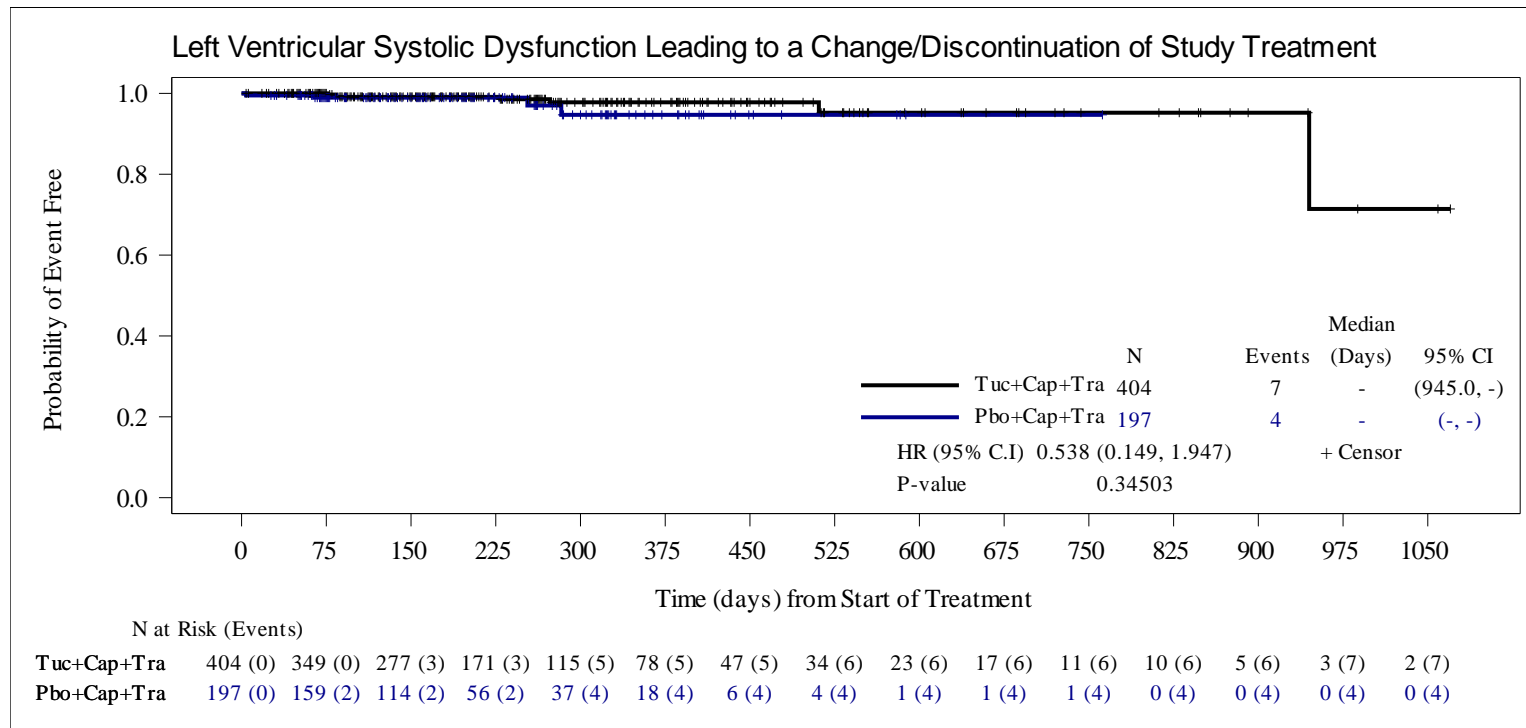
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Figure 2.14.1 Kaplan-Meier Estimate of Time to First Onset of Treatment-Emergent Adverse Events of Special Interest (AESI) Safety Analysis Set



HR is computed from the Cox proportional hazards model using stratification factors (Presence or history of brain metastases: Yes/No, ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization. When the number of subjects with at least one event was ≤ 30 , an unstratified Cox model was run.

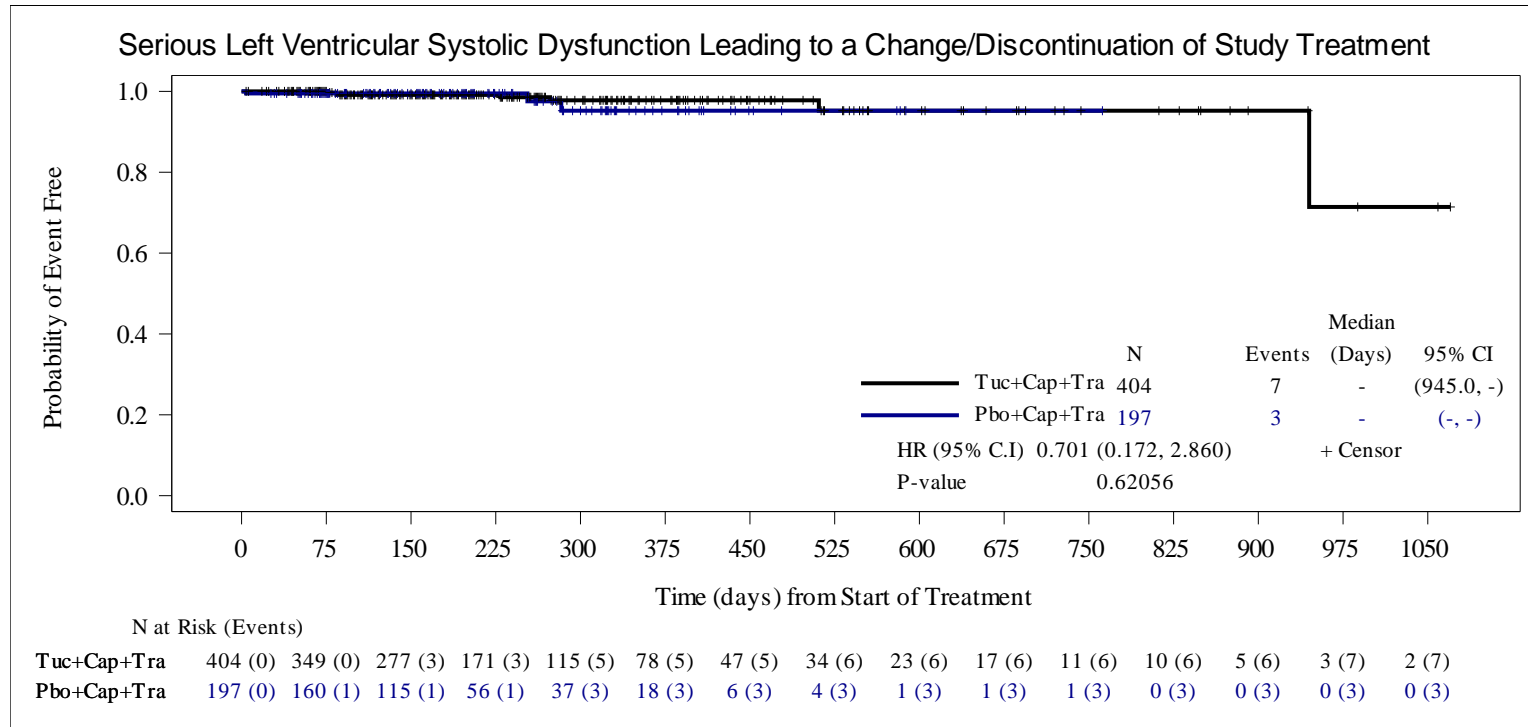
Two-sided p-value calculated from Cox proportional hazards model .

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Figure 2.14.1 Kaplan-Meier Estimate of Time to First Onset of Treatment-Emergent Adverse Events of Special Interest (AESI)
Safety Analysis Set



HR is computed from the Cox proportional hazards model using stratification factors (Presence or history of brain metastases: Yes/No, ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization. When the number of subjects with at least one event was ≤ 30 , an unstratified Cox model was run.

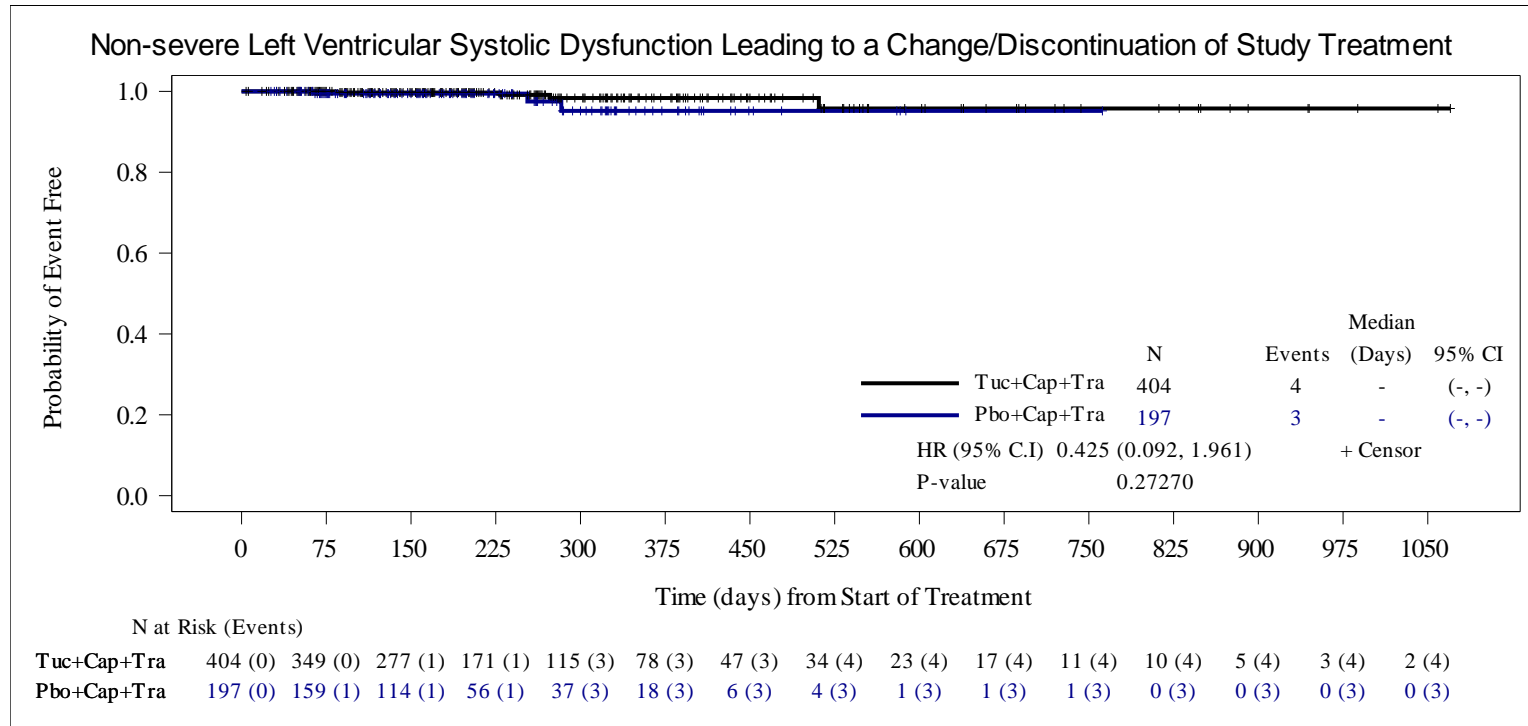
Two-sided p-value calculated from Cox proportional hazards model .

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**Figure 2.14.1 Kaplan-Meier Estimate of Time to First Onset of Treatment-Emergent Adverse Events of Special Interest (AESI)
Safety Analysis Set**



HR is computed from the Cox proportional hazards model using stratification factors (Presence or history of brain metastases: Yes/No, ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization. When the number of subjects with at least one event was ≤ 30 , an unstratified Cox model was run.

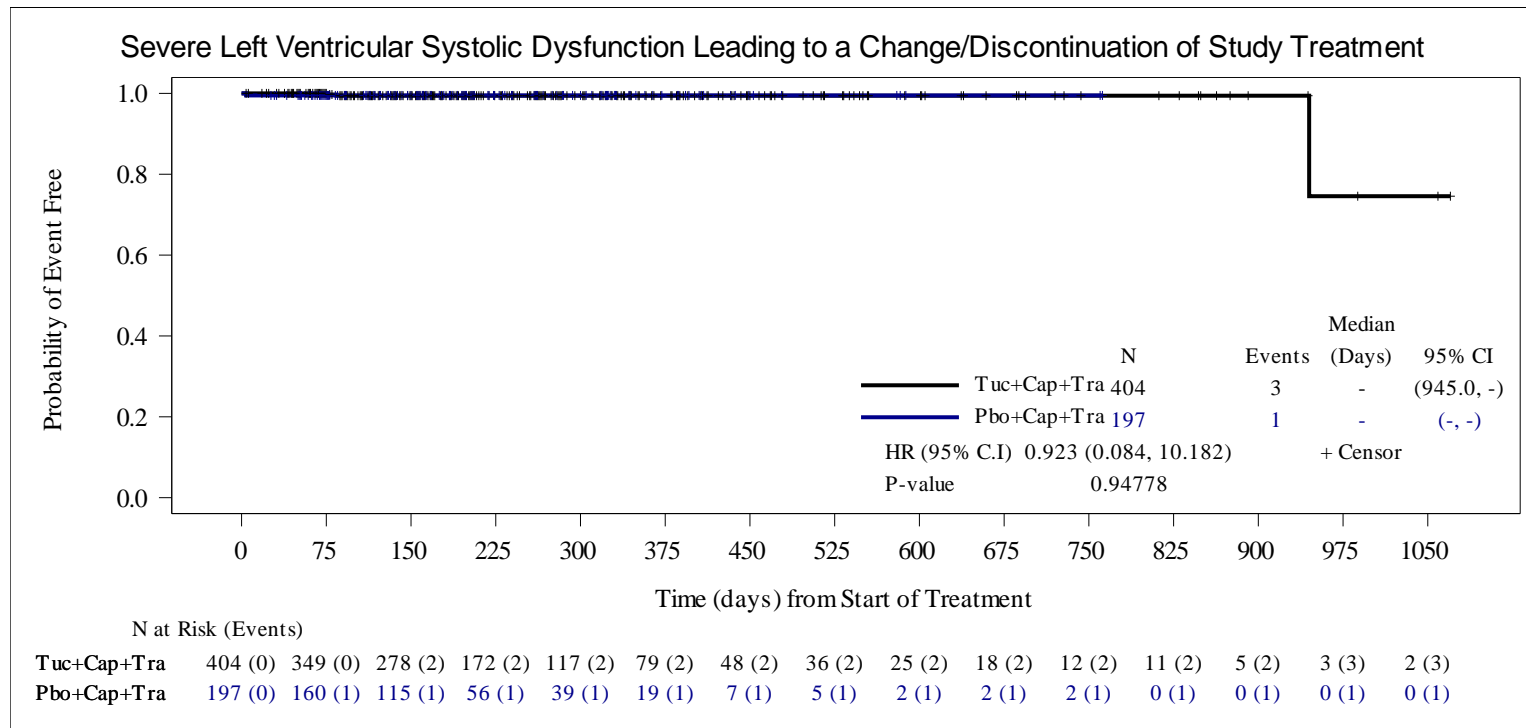
Two-sided p-value calculated from Cox proportional hazards model .

Data Snapshot: 14OCT2019, Data Cutoff Date: 04SEP2019

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**Figure 2.14.1 Kaplan-Meier Estimate of Time to First Onset of Treatment-Emergent Adverse Events of Special Interest (AESI)
Safety Analysis Set**



HR is computed from the Cox proportional hazards model using stratification factors (Presence or history of brain metastases: Yes/No, ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization. When the number of subjects with at least one event was ≤ 30 , an unstratified Cox model was run.

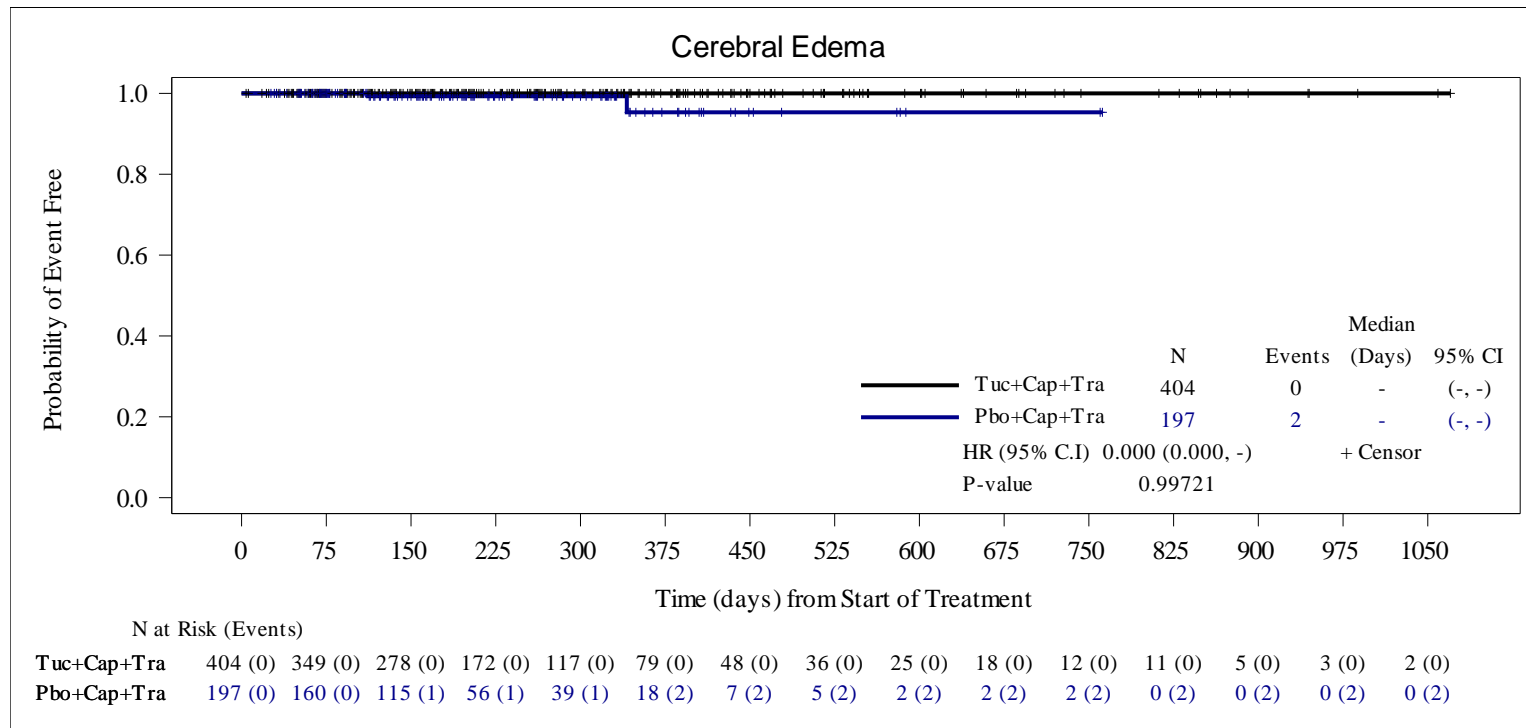
Two-sided p-value calculated from Cox proportional hazards model .

Data Snapshot: 14OCT2019, Data Cutoff Date: 04SEP2019

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Seattle Genetics Protocol ONT-380-206

Figure 2.14.1 Kaplan-Meier Estimate of Time to First Onset of Treatment-Emergent Adverse Events of Special Interest (AESI) Safety Analysis Set



HR is computed from the Cox proportional hazards model using stratification factors (Presence or history of brain metastases: Yes/No, ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization. When the number of subjects with at least one event was ≤ 30 , an unstratified Cox model was run.

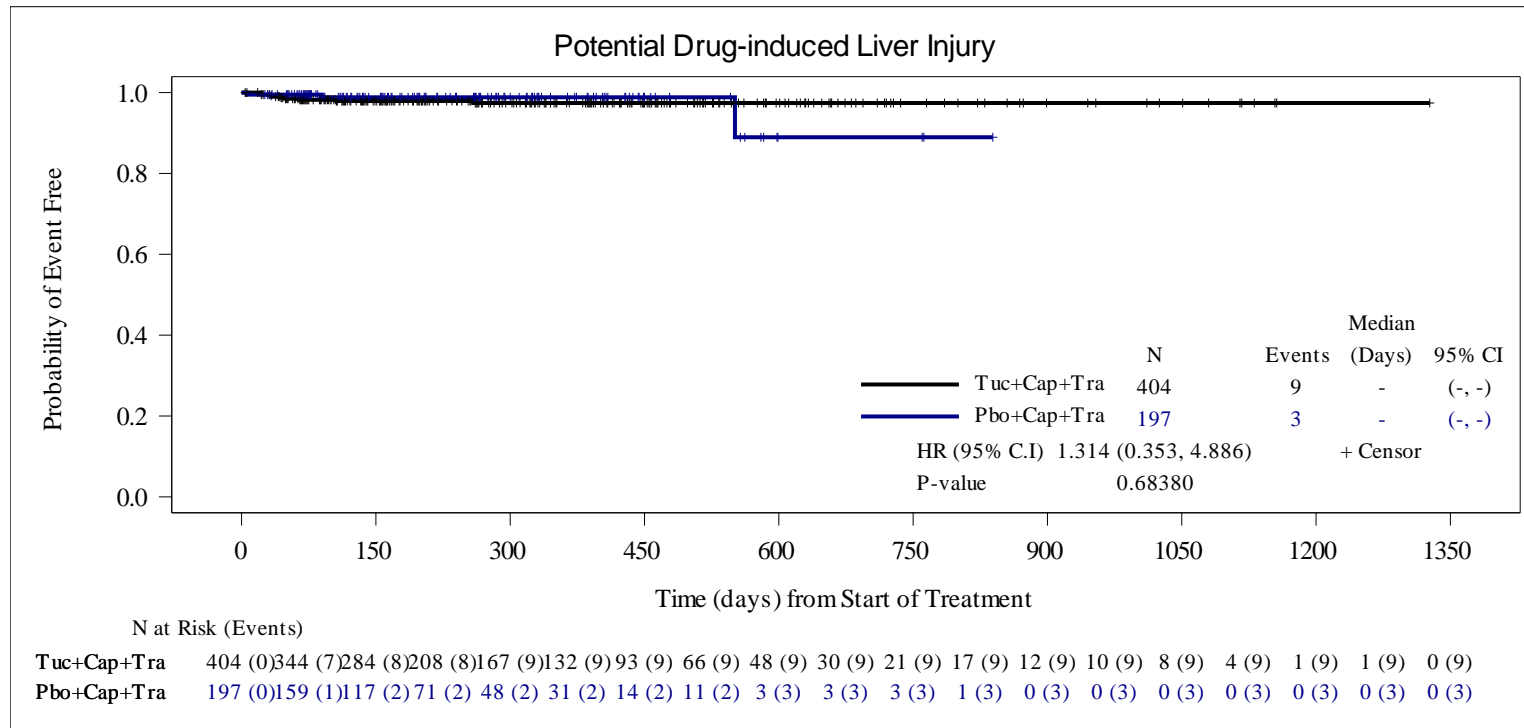
Two-sided p-value calculated from Cox proportional hazards model .

Data Snapshot: 14OCT2019, Data Cutoff Date: 04SEP2019

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**Figure 2.14.1 Kaplan-Meier Estimate of Time to First Onset of Treatment-Emergent Adverse Events of Special Interest (AESI)
Safety Analysis Set**



HR is computed from the Cox proportional hazards model using stratification factors (Presence or history of brain metastases: Yes/No, ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization. When the number of subjects with at least one event was ≤ 30, an unstratified Cox model was run.

Two-sided p-value calculated from Cox proportional hazards model .

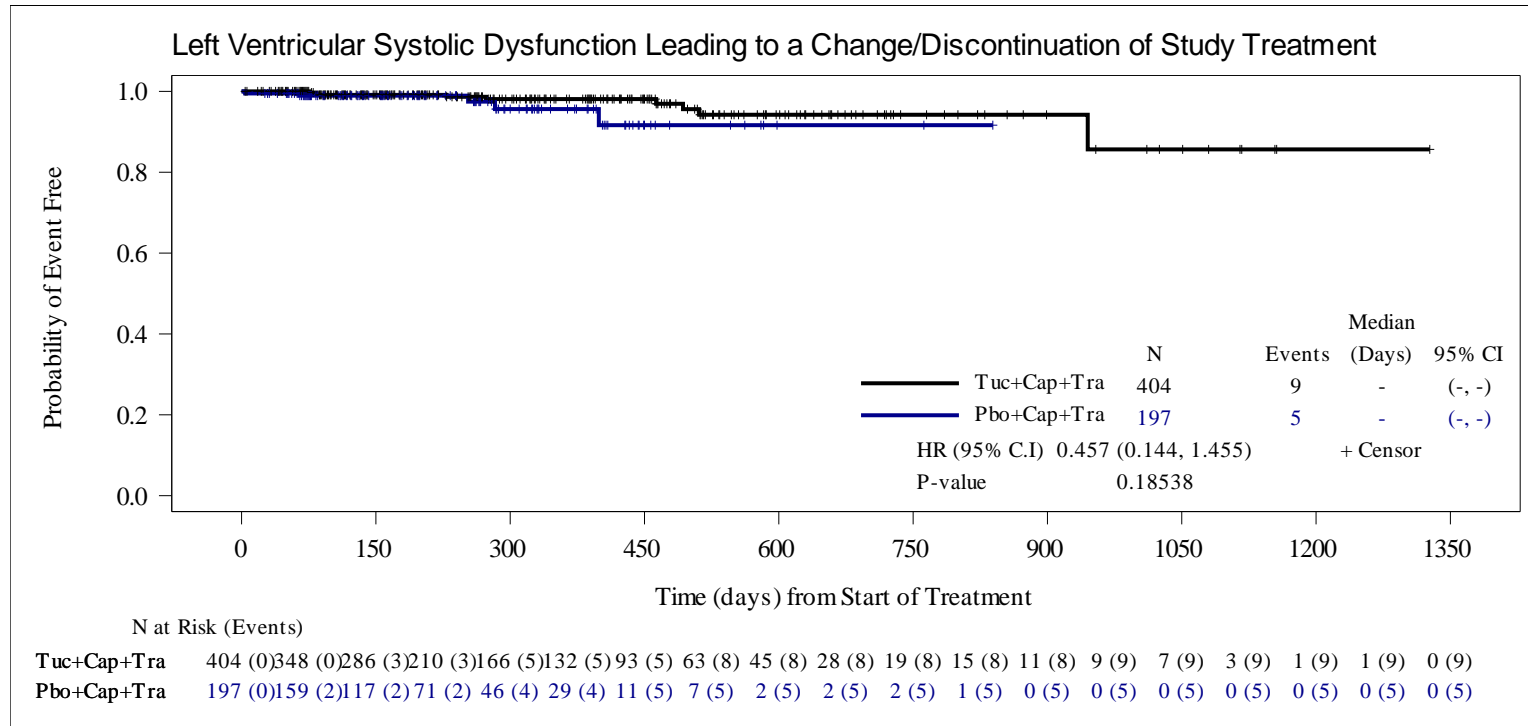
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Data: adsl, adbl, adttesaf

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**Figure 2.14.1 Kaplan-Meier Estimate of Time to First Onset of Treatment-Emergent Adverse Events of Special Interest (AESI)
Safety Analysis Set**



HR is computed from the Cox proportional hazards model using stratification factors (Presence or history of brain metastases: Yes/No, ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization. When the number of subjects with at least one event was ≤ 30 , an unstratified Cox model was run.

Two-sided p-value calculated from Cox proportional hazards model .

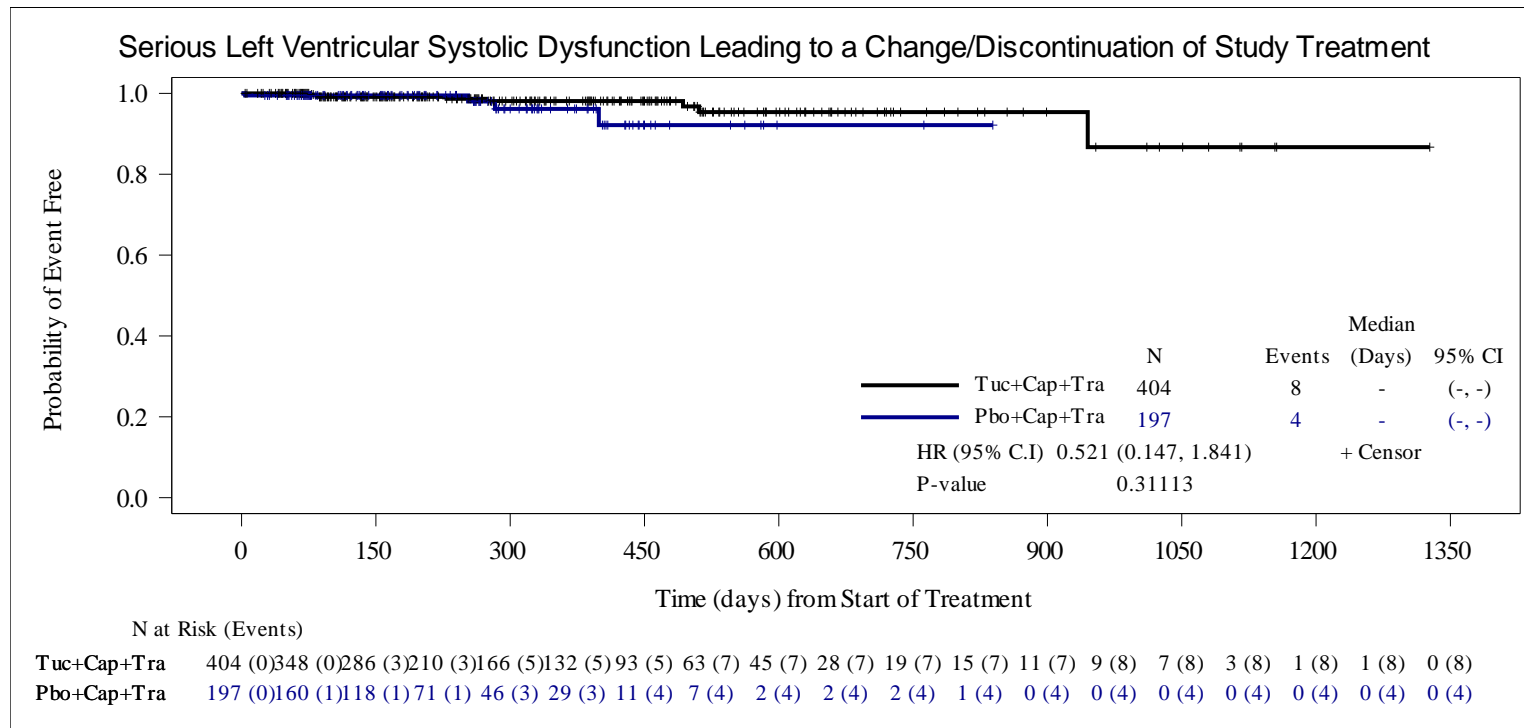
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Data: adsl, adbl, adttesaf

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**Figure 2.14.1 Kaplan-Meier Estimate of Time to First Onset of Treatment-Emergent Adverse Events of Special Interest (AESI)
Safety Analysis Set**



HR is computed from the Cox proportional hazards model using stratification factors (Presence or history of brain metastases: Yes/No, ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization. When the number of subjects with at least one event was ≤ 30 , an unstratified Cox model was run.

Two-sided p-value calculated from Cox proportional hazards model .

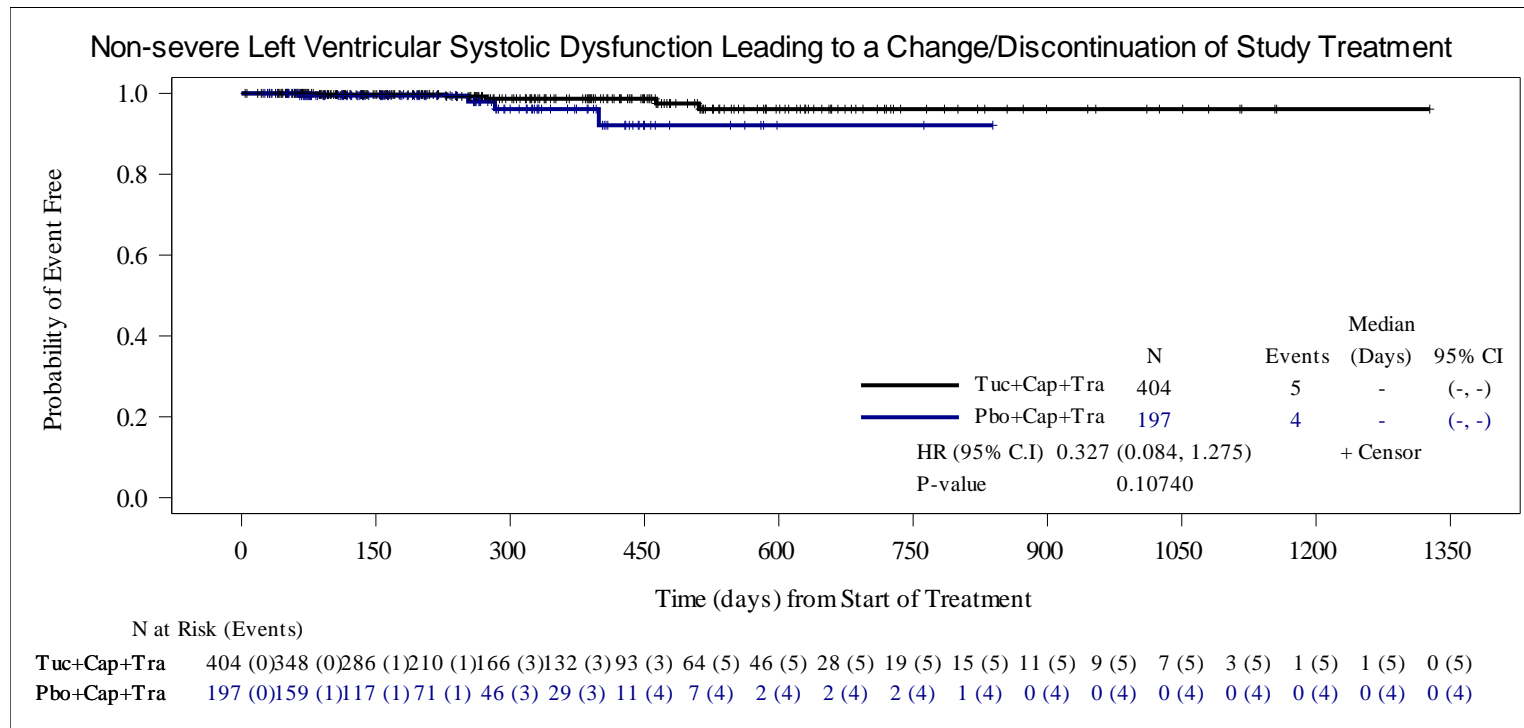
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Data: adsl, adbl, adttesaf

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**Figure 2.14.1 Kaplan-Meier Estimate of Time to First Onset of Treatment-Emergent Adverse Events of Special Interest (AESI)
Safety Analysis Set**



HR is computed from the Cox proportional hazards model using stratification factors (Presence or history of brain metastases: Yes/No, ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization. When the number of subjects with at least one event was ≤ 30 , an unstratified Cox model was run.

Two-sided p-value calculated from Cox proportional hazards model .

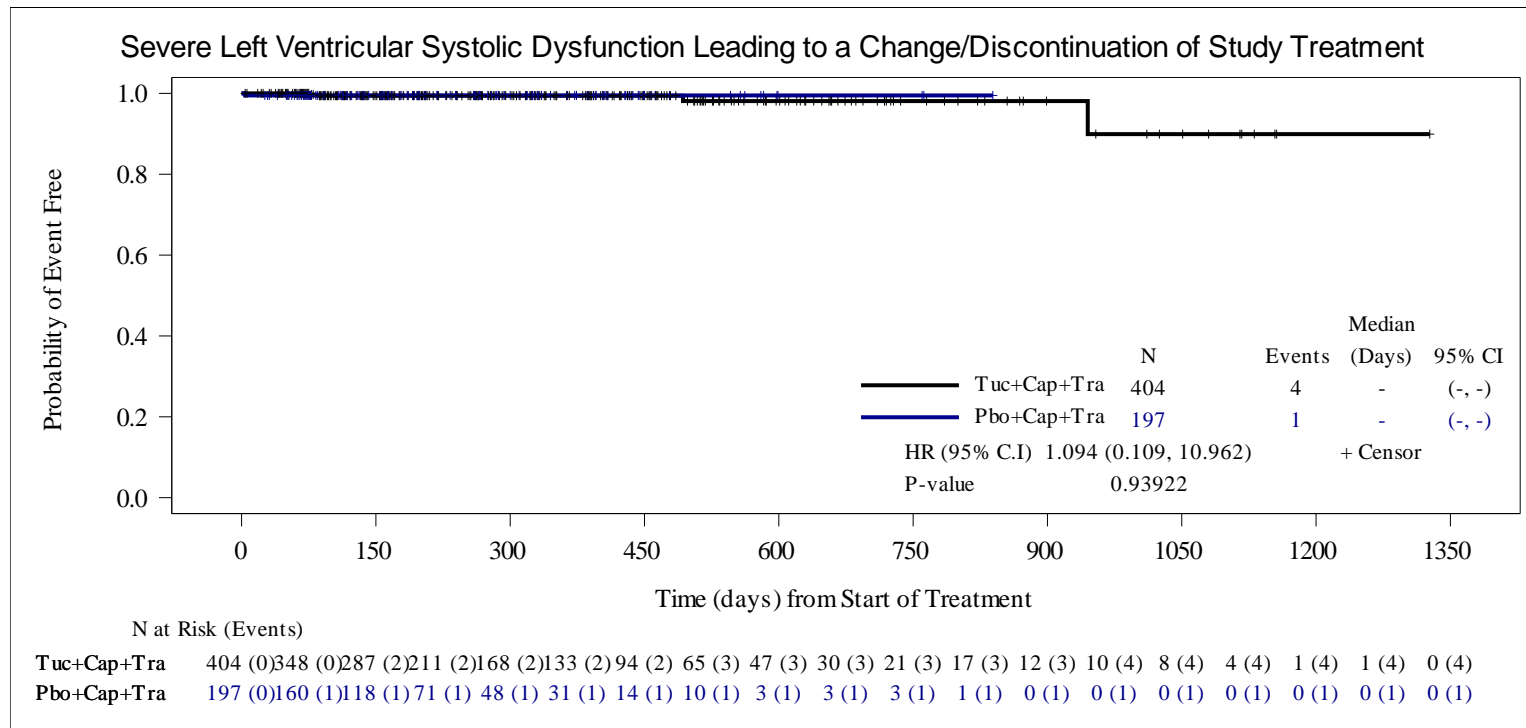
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Data: adsl, adbl, adttesaf

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**Figure 2.14.1 Kaplan-Meier Estimate of Time to First Onset of Treatment-Emergent Adverse Events of Special Interest (AESI)
Safety Analysis Set**



HR is computed from the Cox proportional hazards model using stratification factors (Presence or history of brain metastases: Yes/No, ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization. When the number of subjects with at least one event was ≤ 30 , an unstratified Cox model was run.

Two-sided p-value calculated from Cox proportional hazards model .

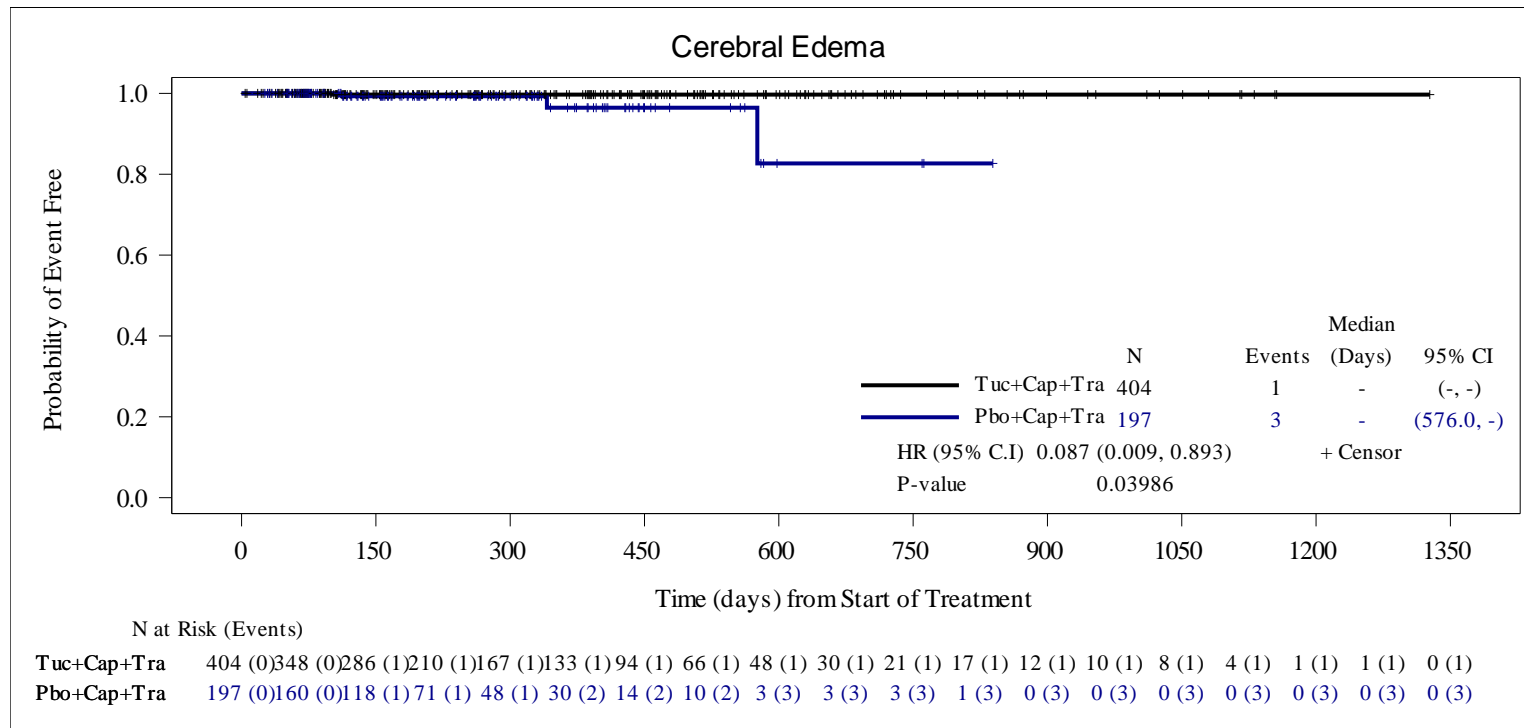
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Data: adsl, adbl, adttesaf

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**Figure 2.14.1 Kaplan-Meier Estimate of Time to First Onset of Treatment-Emergent Adverse Events of Special Interest (AESI)
Safety Analysis Set**



HR is computed from the Cox proportional hazards model using stratification factors (Presence or history of brain metastases: Yes/No, ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization. When the number of subjects with at least one event was ≤ 30 , an unstratified Cox model was run.

Two-sided p-value calculated from Cox proportional hazards model .

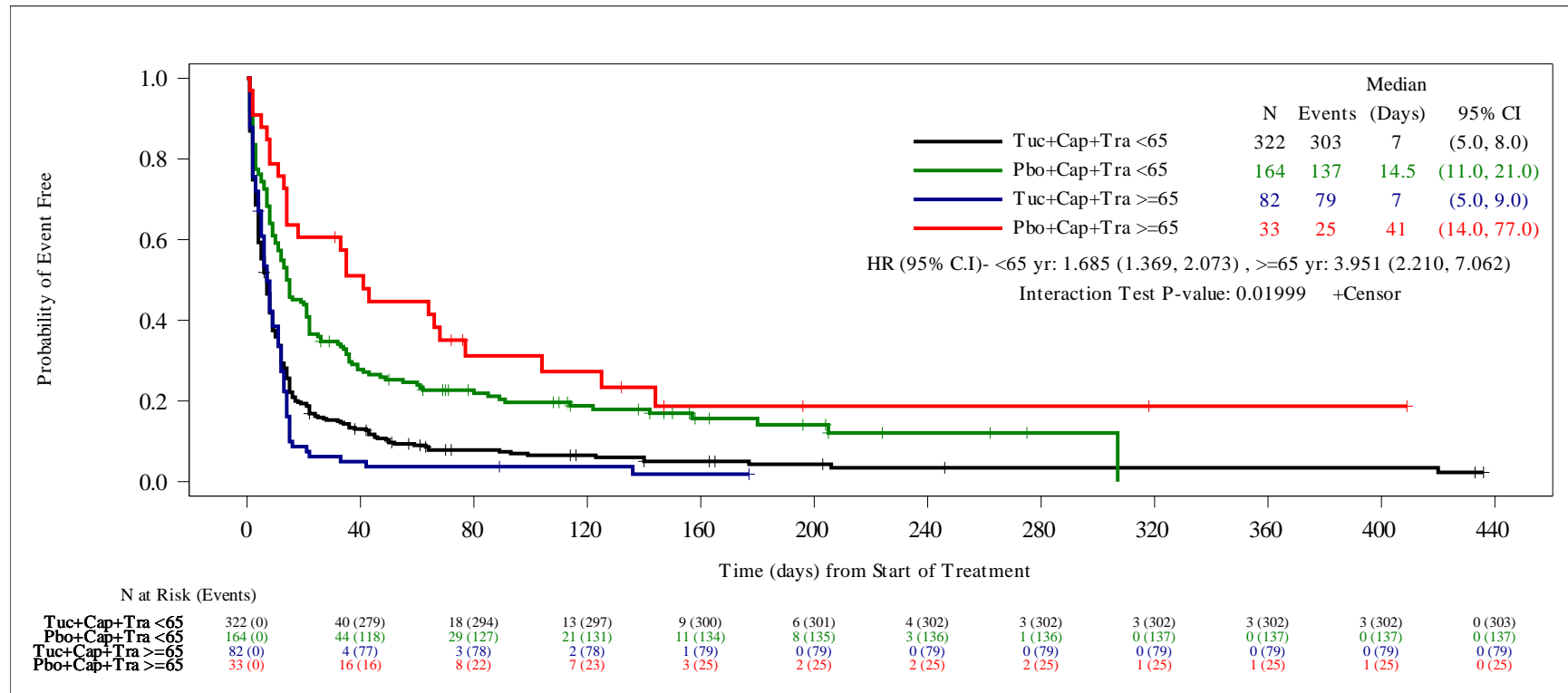
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Data: adsl, adbl, adttesaf

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Figure 2.4.1 Kaplan-Meier Estimate of Time to First Onset of Adverse Events by Age - Gastrointestinal Disorder Safety Analysis Set



HR is computed from the Cox proportional hazards model using stratification factors (Presence or history of brain metastases: Yes/No, ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization.

Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and age.

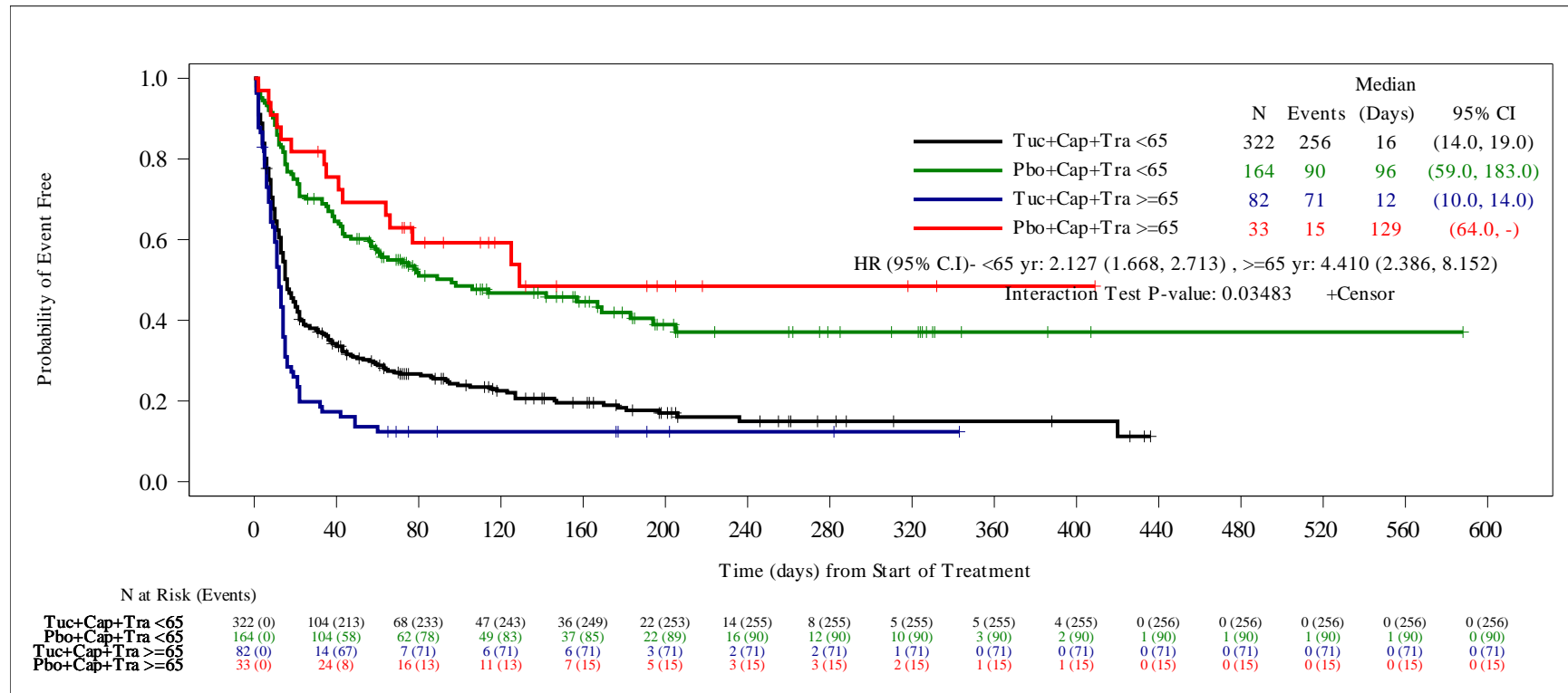
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Data: adsl, adae, adtesaf

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Figure 2.4.2 Kaplan-Meier Estimate of Time to First Onset of Adverse Events by Age - Diarrhoea Safety Analysis Set



HR is computed from the Cox proportional hazards model using stratification factors (Presence or history of brain metastases: Yes/No, ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization.

Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and age.

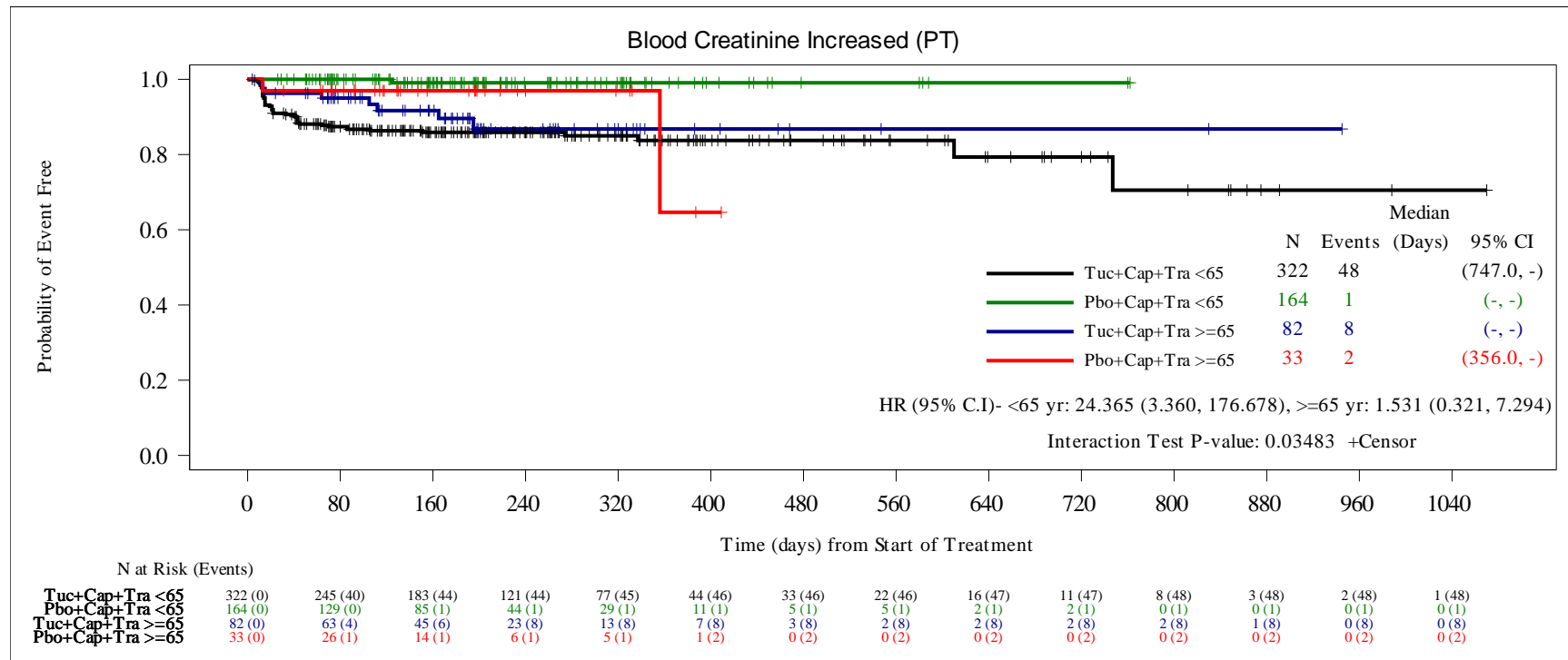
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Data: adsl, adae, adtesaf

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**Figure 2.7.3 Kaplan-Meier Estimate of Time to First Onset of Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Age
Safety Analysis Set**



HR is computed from the Cox proportional hazards model using stratification factors (Presence or history of brain metastases: Yes/No, ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.

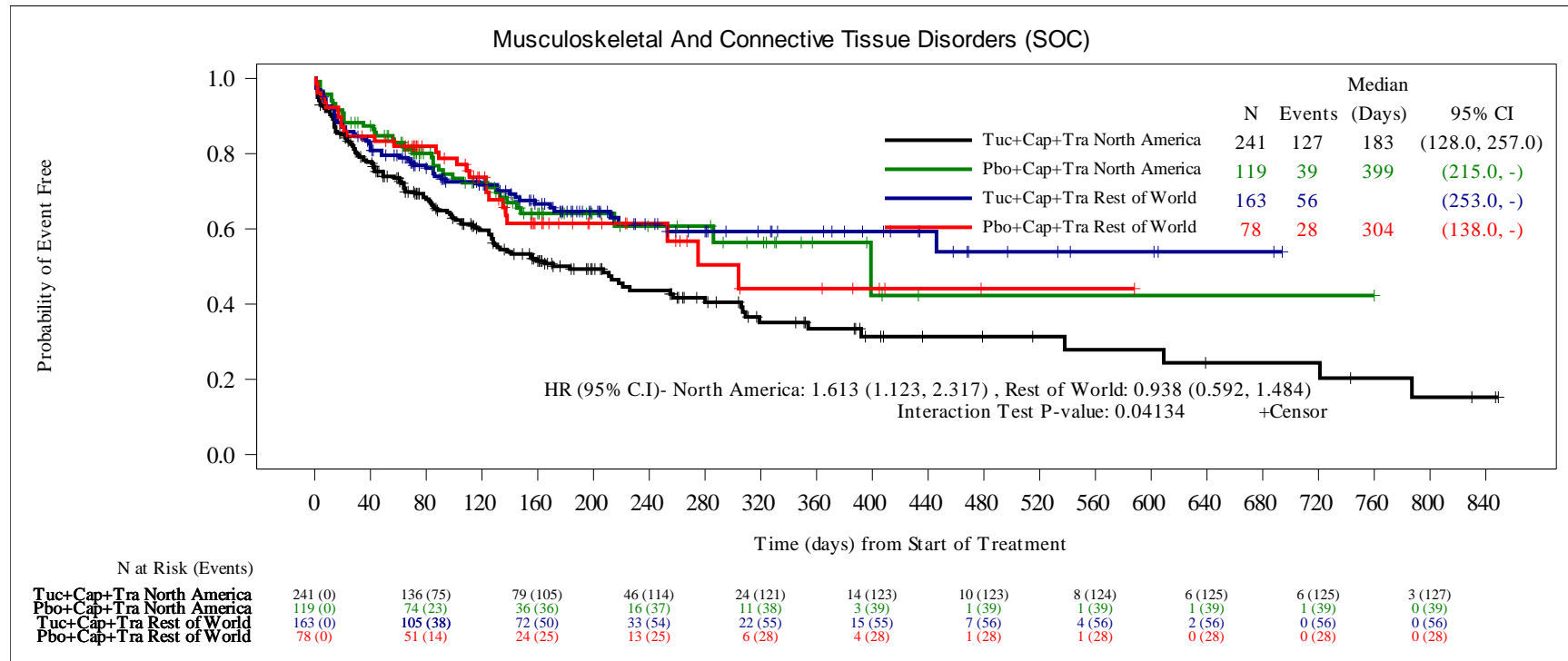
Two-sided p-value calculated from Cox proportional hazards model .

Data Snapshot: 14OCT2019, Data Cutoff Date: 04SEP2019

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_1753\v01\outputs\tlfs\pgms\f-ae-socpt-sub4.sas Output: f-ae-km-socpt-sub-4-age-safs.rtf(17JUL20:16:07) Data: adsl, adae, addtesaf

Seattle Genetics Protocol ONT-380-206

**Figure 2.7.2 Kaplan-Meier Estimate of Time to First Onset of Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Geographic Region
Safety Analysis Set**



HR is computed from the Cox proportional hazards model using stratification factors (Presence or history of brain metastases: Yes/No and ECOG performance status: 0/1) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.

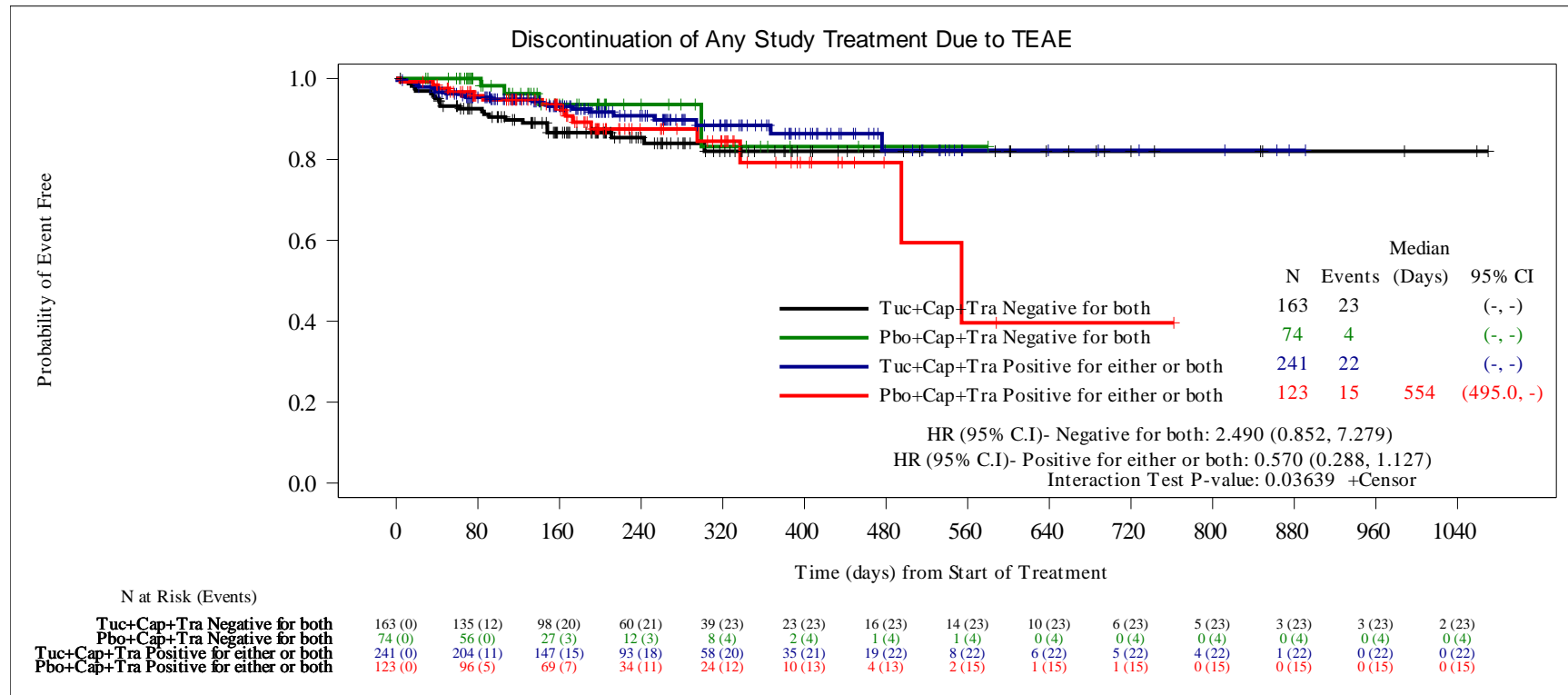
Two-sided p-value calculated from Cox proportional hazards model .

Data Snapshot: 14OCT2019, Data Cutoff Date: 04SEP2019

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_1753\v01\outputs\tlfs\pgms\f-ae-socpt-sub2.sas Output: f-ae-km-socpt-sub-2-reg-safs.rtf(17JUL20:16:07) Data: adsl, adae, addtesaf

Seattle Genetics Protocol ONT-380-206

Figure 2.5.3 Kaplan-Meier Estimate of Time to First Onset of Treatment-Emergent Adverse Events by Hormone Receptor Status Safety Analysis Set



HR is computed from the Cox proportional hazards model using stratification factors (Presence or history of brain metastases: Yes/No, ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.

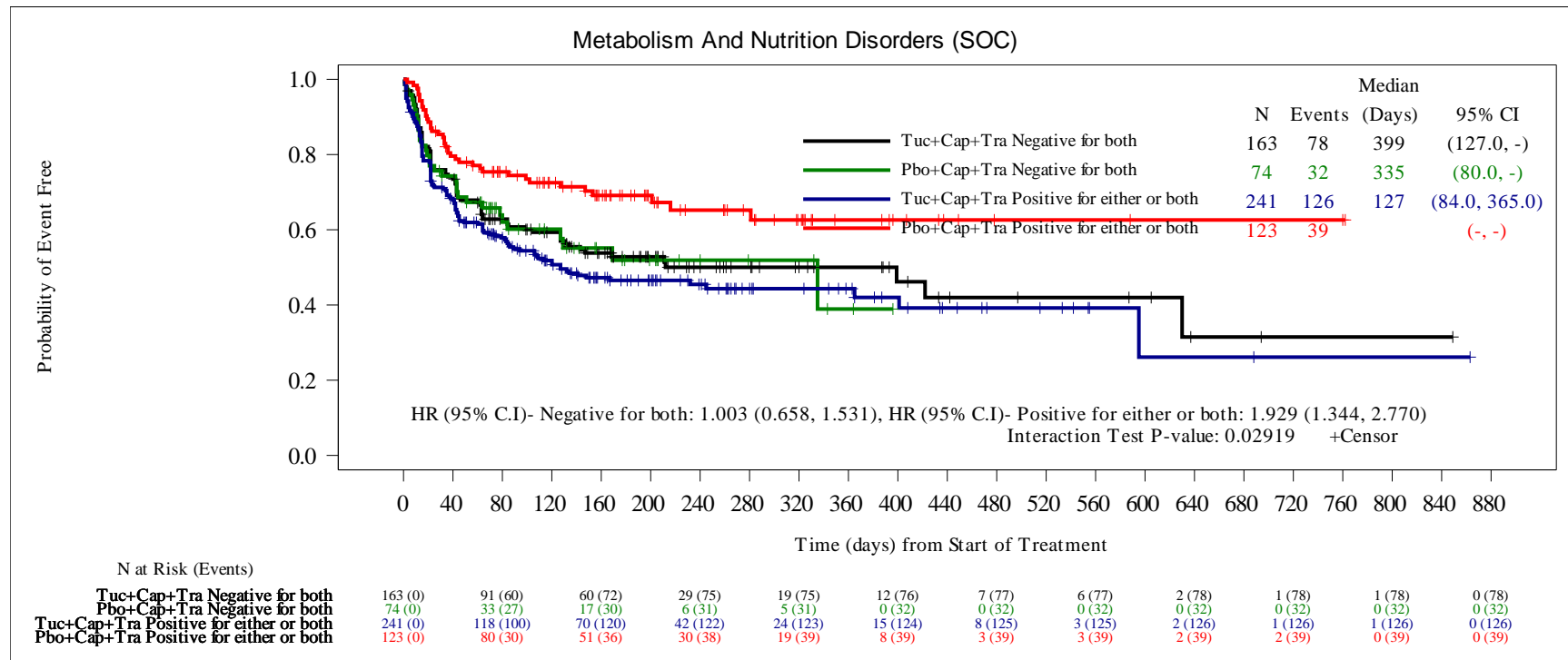
Two-sided p-value calculated from Cox proportional hazards model .

Data Snapshot: 14OCT2019, Data Cutoff Date: 04SEP2019

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_1753\v01\outputs\tlfs\pgms\f-ae-km-oval-sub6.sas Output: f-ae-km-oval-sub-6-hr-safs.rtf(17JUL20:16:07) Data: adsl, adae, addtesaf

Seattle Genetics Protocol ONT-380-206

**Figure 2.7.4 Kaplan-Meier Estimate of Time to First Onset of Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Hormone Receptor Status
Safety Analysis Set**



HR is computed from the Cox proportional hazards model using stratification factors (Presence or history of brain metastases: Yes/No, ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.

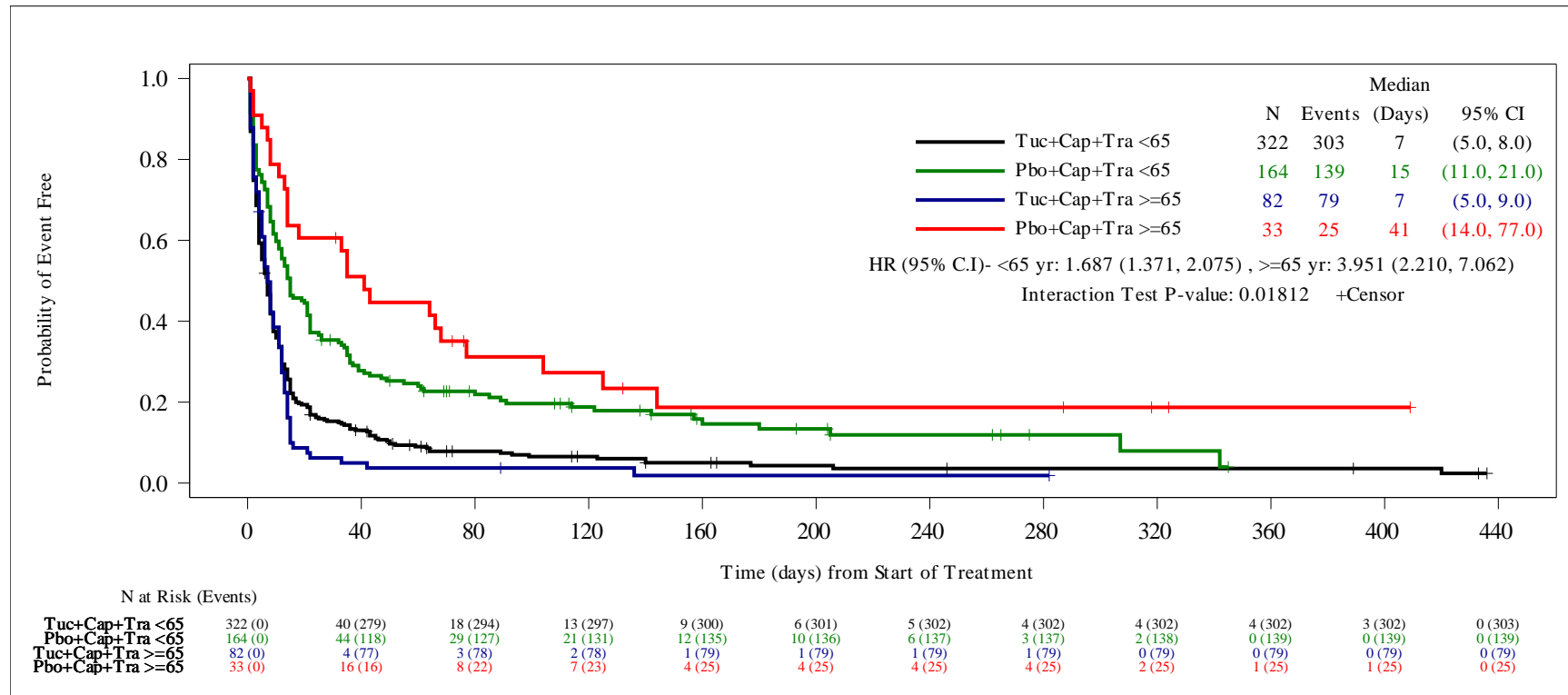
Two-sided p-value calculated from Cox proportional hazards model .

Data Snapshot: 14OCT2019, Data Cutoff Date: 04SEP2019

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_1753\v01\outputs\tlfs\pgms\f-ae-km-socpt-sub6.sas Output: f-ae-km-socpt-sub-6-hr-safs.rtf(17JUL20:16:07) Data: adsl, adae, addtesaf

Seagen Protocol ONT-380-206

Figure 2.4.1 Kaplan-Meier Estimate of Time to First Onset of Adverse Events by Age - Gastrointestinal Disorder Safety Analysis Set



HR is computed from the Cox proportional hazards model using stratification factors (Presence or history of brain metastases: Yes/No, ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.

Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and age.

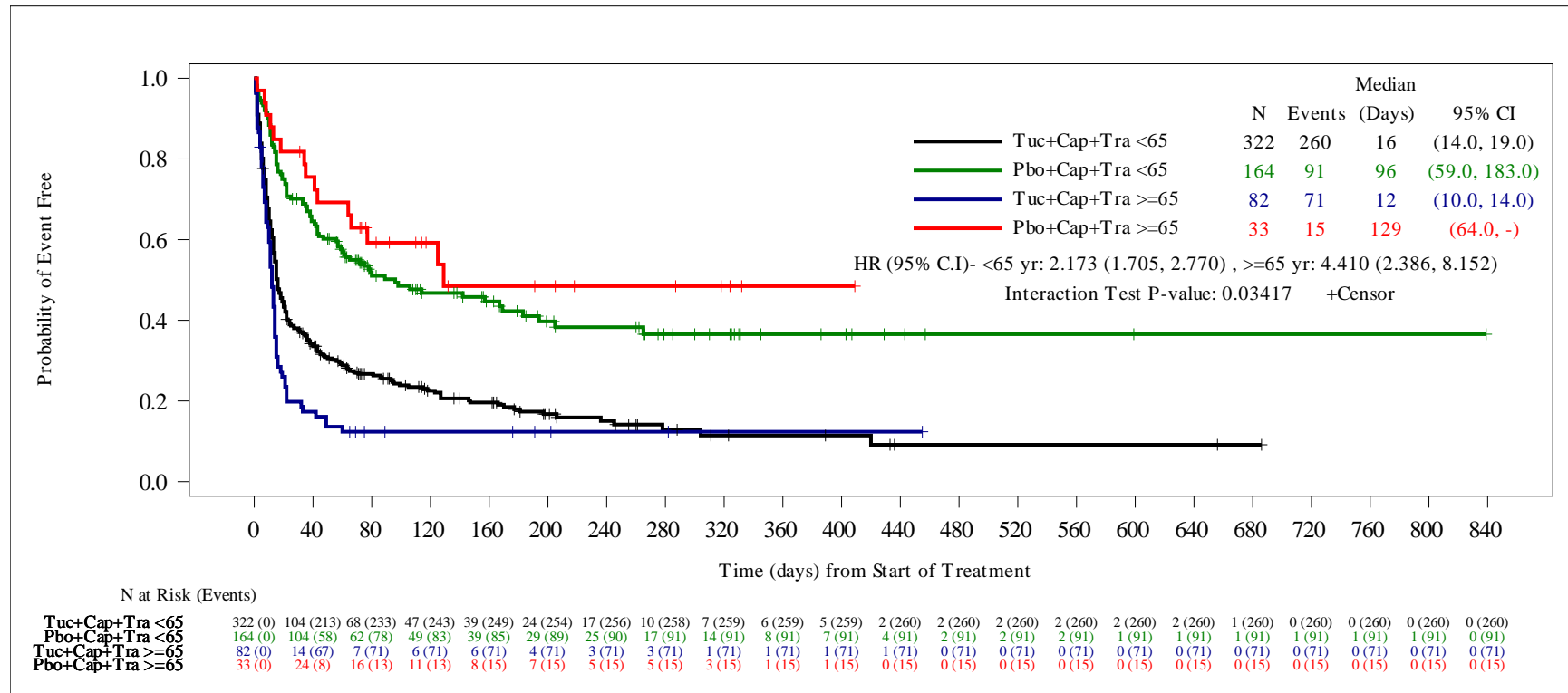
Snapshot date: 10SEP2020, data cutoff date: 29MAY2020.

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_may2020_dco_1943\v01\outputs\tlfs\pgms\f-ae-onset-gastro-sub4.sas Output:

f02-04-01-ae-km-gisoc-sub4-age-safs.rtf(14DEC20:17:11) Data: adsl, adae, adttesaf

Seagen Protocol ONT-380-206

**Figure 2.4.2 Kaplan-Meier Estimate of Time to First Onset of Adverse Events by Age - Diarrhoea
Safety Analysis Set**



HR is computed from the Cox proportional hazards model using stratification factors (Presence or history of brain metastases: Yes/No, ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization.

Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and age.

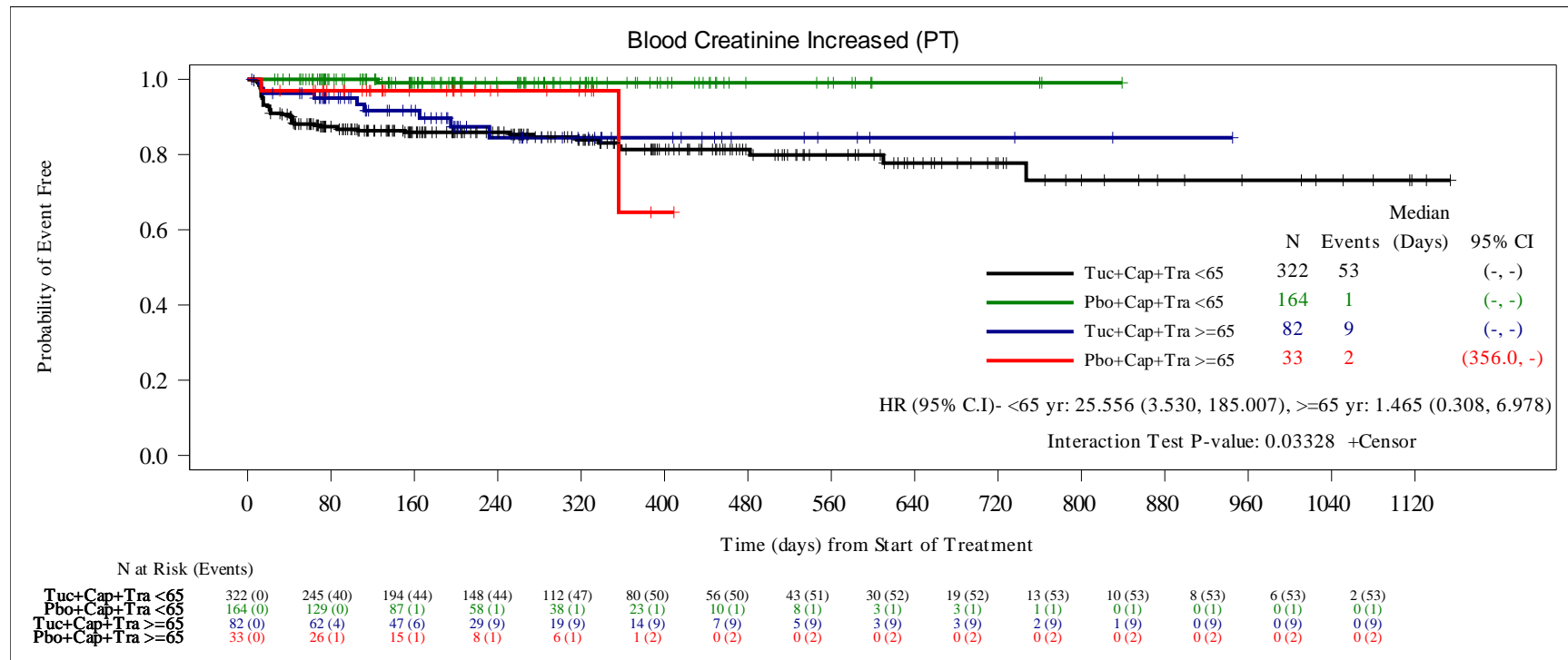
Snapshot date: 10SEP2020, data cutoff date: 29MAY2020.

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_may2020_dco_1943\v01\outputs\tlfs\pgms\f-ae-onset-gastro-sub4.sas Output:

f02-04-02-ae-km-gi-dia-sub4-age-safs.rtf(14DEC20:17:11) Data: adsl, adae, adtesaf

Seagen Protocol ONT-380-206

Figure 2.7.3 Kaplan-Meier Estimate of Time to First Onset of Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Age
Safety Analysis Set



HR is computed from the Cox proportional hazards model using stratification factors (Presence or history of brain metastases: Yes/No, ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.

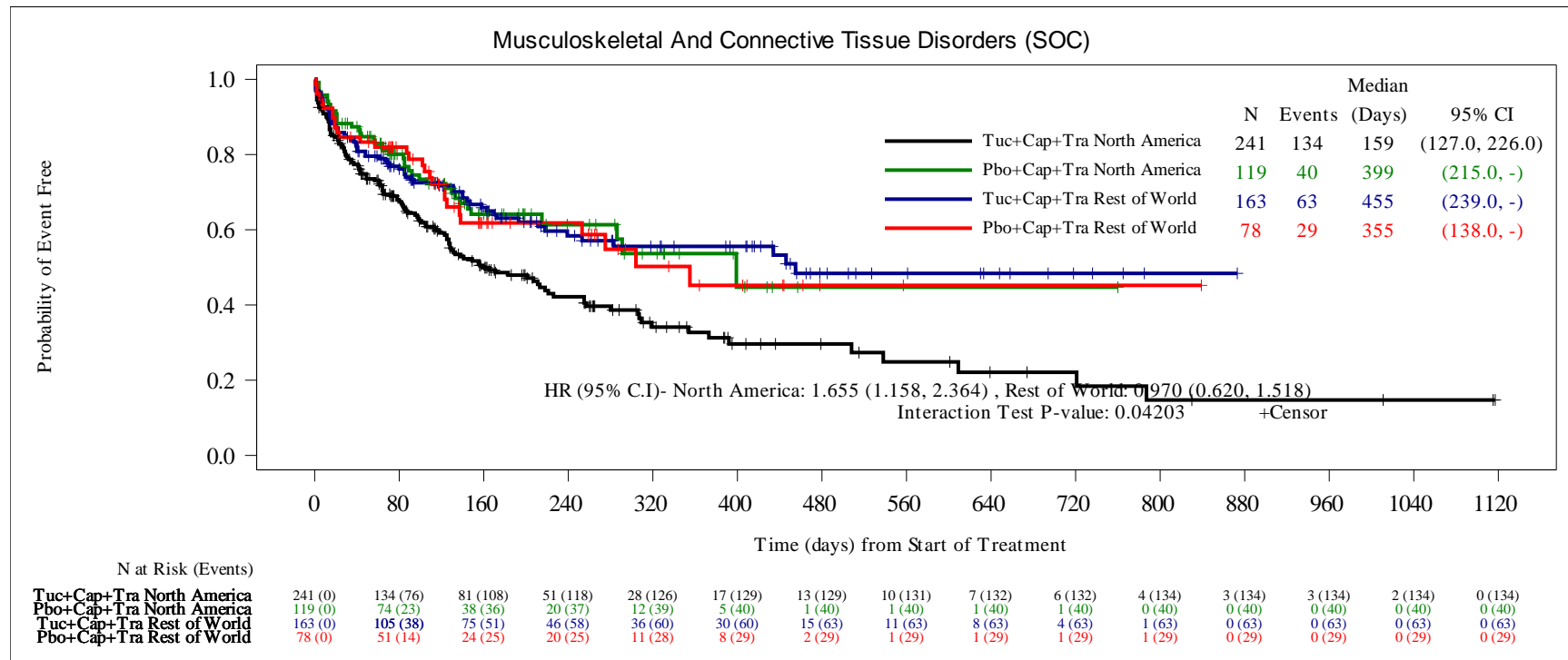
Two-sided p-value calculated from Cox proportional hazards model.

Snapshot date: 10SEP2020, data cutoff date: 29MAY2020.

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_may2020_dco_1943\v01\outputs\tlfs\pgms\ae-socpt-sub4.sas Output: f02-07-03-ae-km-socpt-sub-4-age-safs.rtf(14DEC20:17:12) Data: adsl, adae, addtesaf

Seagen Protocol ONT-380-206

**Figure 2.7.2 Kaplan-Meier Estimate of Time to First Onset of Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Geographic Region
Safety Analysis Set**



HR is computed from the Cox proportional hazards model using stratification factors (Presence or history of brain metastases: Yes/No and ECOG performance status: 0/1) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.

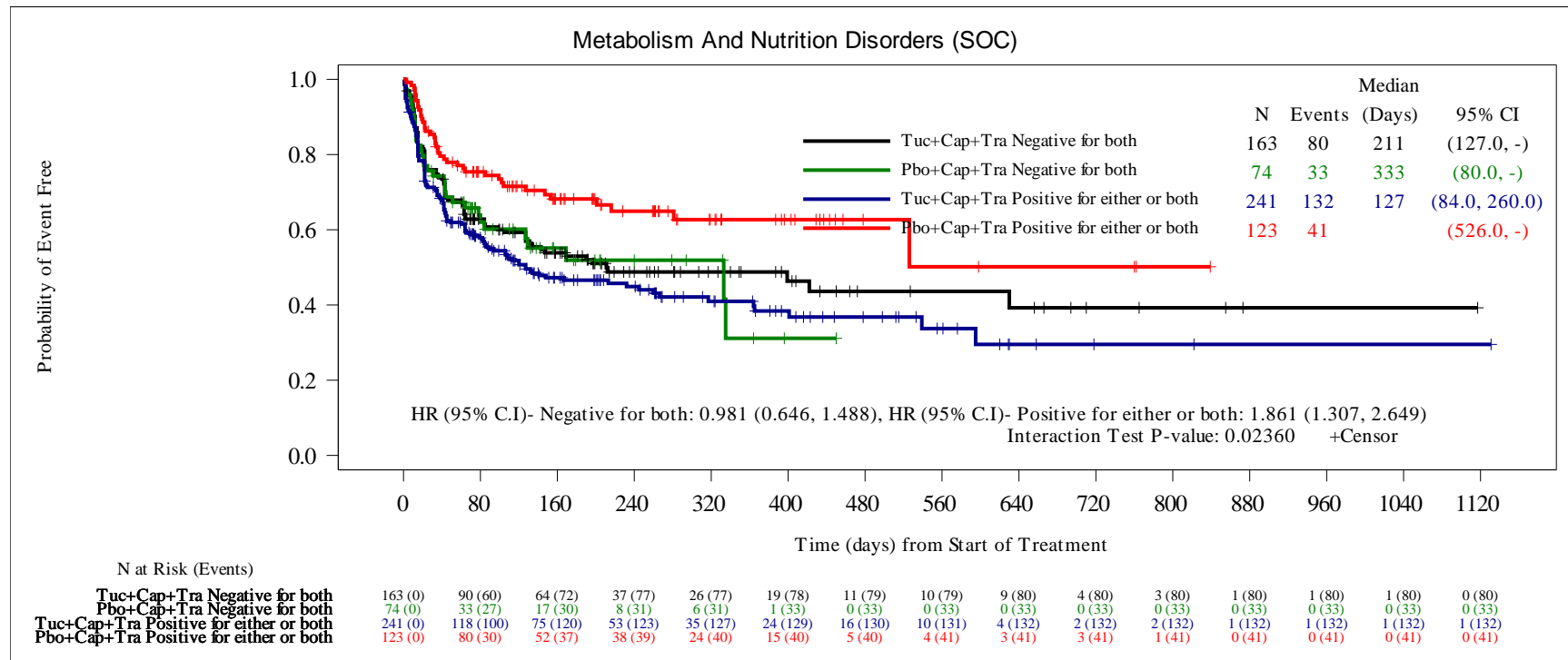
Two-sided p-value calculated from Cox proportional hazards model .

Snapshot date: 10SEP2020, data cutoff date: 29MAY2020.

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_may2020_dco_1943\v01\outputs\tlfs\pgms\fae-socpt-sub2.sas Output: f02-07-02-ae-km-socpt-sub-2-reg-safs.rtf(14DEC20:17:12) Data: adsl, adae, adtesaf

Seagen Protocol ONT-380-206

**Figure 2.7.4 Kaplan-Meier Estimate of Time to First Onset of Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Hormone Receptor Status
Safety Analysis Set**



HR is computed from the Cox proportional hazards model using stratification factors (Presence or history of brain metastases: Yes/No, ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.

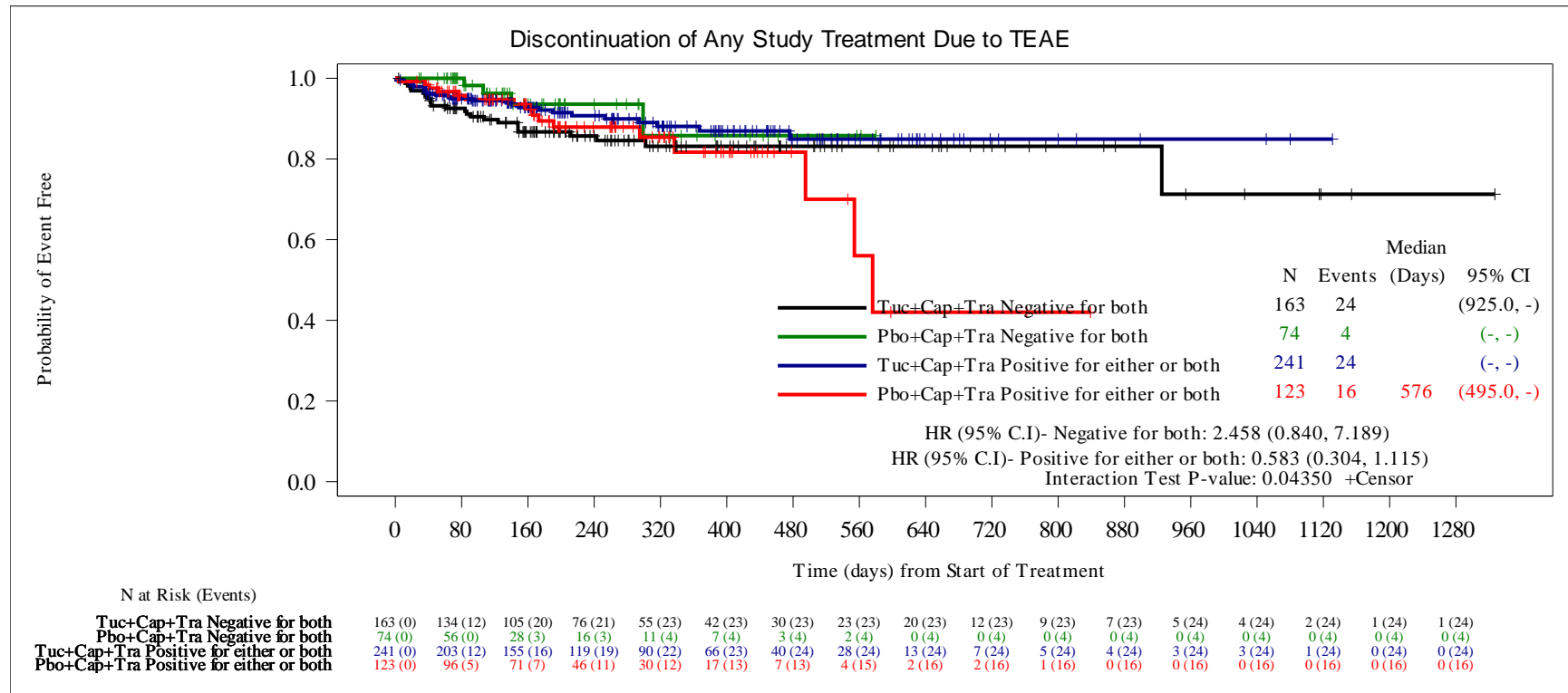
Two-sided p-value calculated from Cox proportional hazards model .

Snapshot date: 10SEP2020, data cutoff date: 29MAY2020.

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_may2020_dco_1943\v01\outputs\tlfs\pgms\ae-km-socpt-sub6.sas Output:
f02-07-04-ae-km-socpt-sub-6-hr-safs.rtf(14DEC20:17:11) Data: adsl, adae, adttesaf

Seagen Protocol ONT-380-206

**Figure 2.5.3 Kaplan-Meier Estimate of Time to First Onset of Treatment-Emergent Adverse Events by Hormone Receptor Status
Safety Analysis Set**



HR is computed from the Cox proportional hazards model using stratification factors (Presence or history of brain metastases: Yes/No, ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.

Two-sided p-value calculated from Cox proportional hazards model .

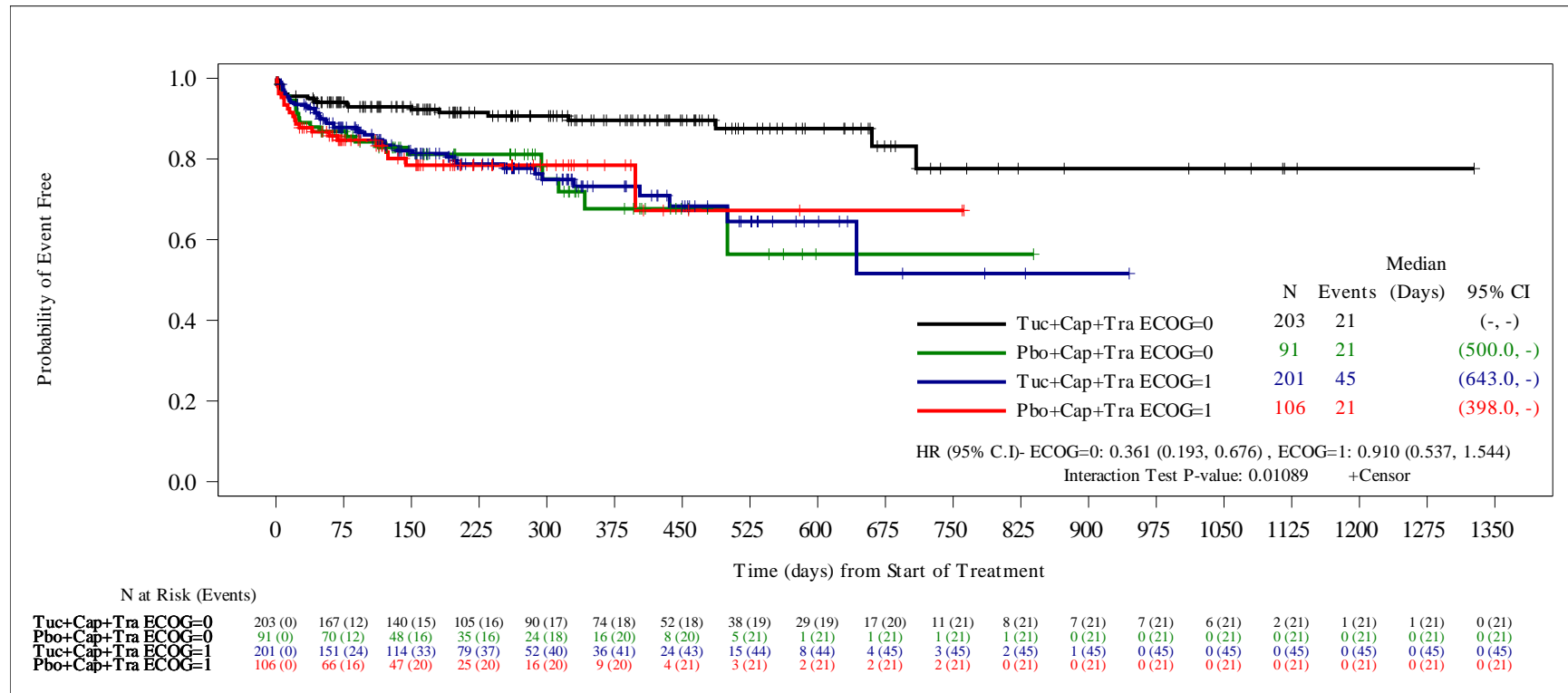
Snapshot date: 10SEP2020, data cutoff date: 29MAY2020.

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_may2020_dco_1943\v01\outputs\tlfs\pgms\ae-km-oval-sub6.sas Output:

f02-05-03-ae-km-oval-sub-6-hr-safs.rtf(14DEC20:17:08) Data: adsl, adae, adttesaf

Seagen Protocol ONT-380-206

Figure 2.4.5 Kaplan-Meier Estimate of Time to First Onset of Adverse Events by ECOG - Constipation
Safety Analysis Set



HR is computed from the Cox proportional hazards model using stratification factors (Presence or history of brain metastases: Yes/No and Region of world: North America /Rest of World) at randomization.

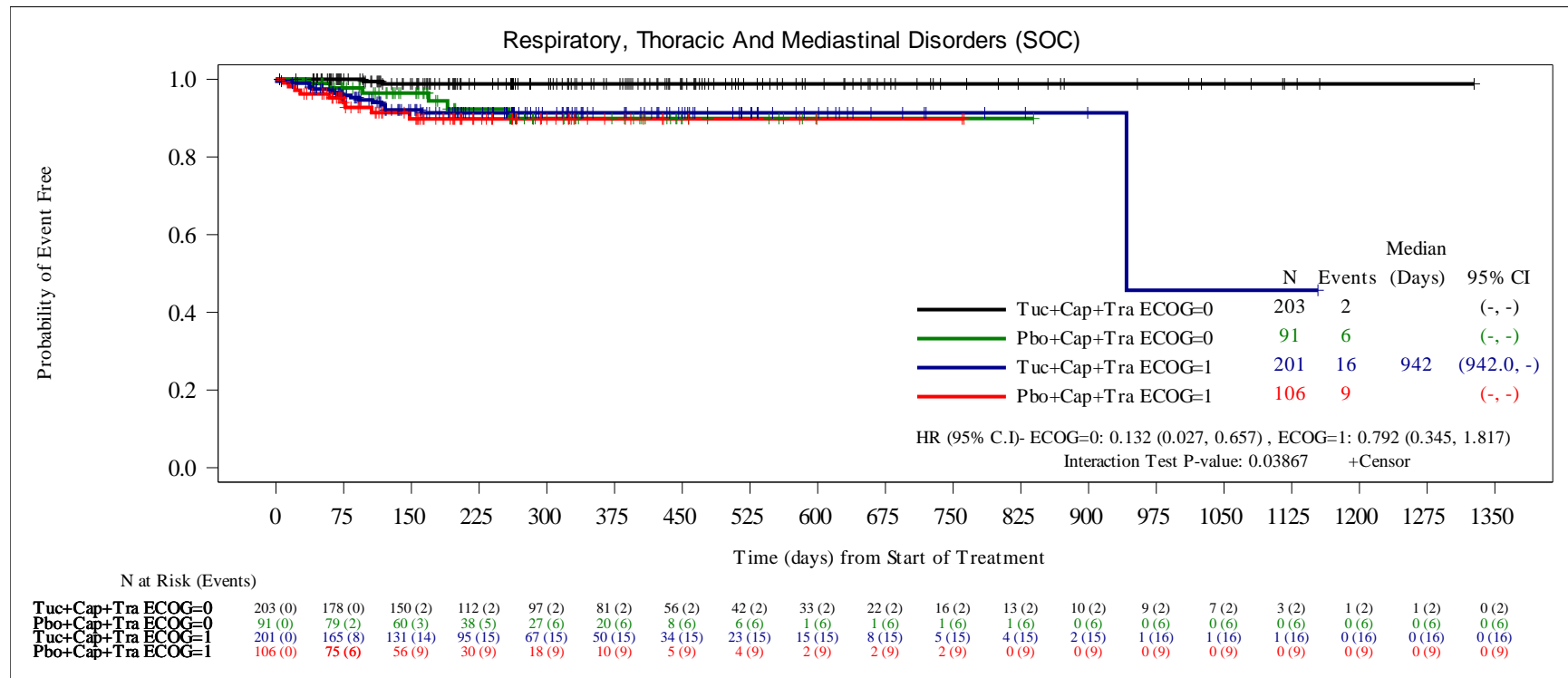
Two-sided p-value calculated from Cox proportional hazards model .

Snapshot date: 10SEP2020, data cutoff date: 29MAY2020.

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_may2020_dco_1943\v01\outputs\tlfs\pgms\f-ae-km-gi-con-sub3-ecog-safs.sas Output: f02-04-05-ae-km-gi-con-sub3-ecog-safs.rtf(17DEC20:09:55) Data: adsl, adae, adttesaf

Seagen Protocol ONT-380-206

**Figure 2.9.2 Kaplan-Meier Estimate of Time to First Onset of Serious Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Baseline ECOG Score
Safety Analysis Set**



HR is computed from the Cox proportional hazards model using stratification factors (Presence or history of brain metastases: Yes/No and Region of world: North America /Rest of World) at randomization. When the number of subjects with at least one event was ≤ 30, an unstratified Cox model was run.

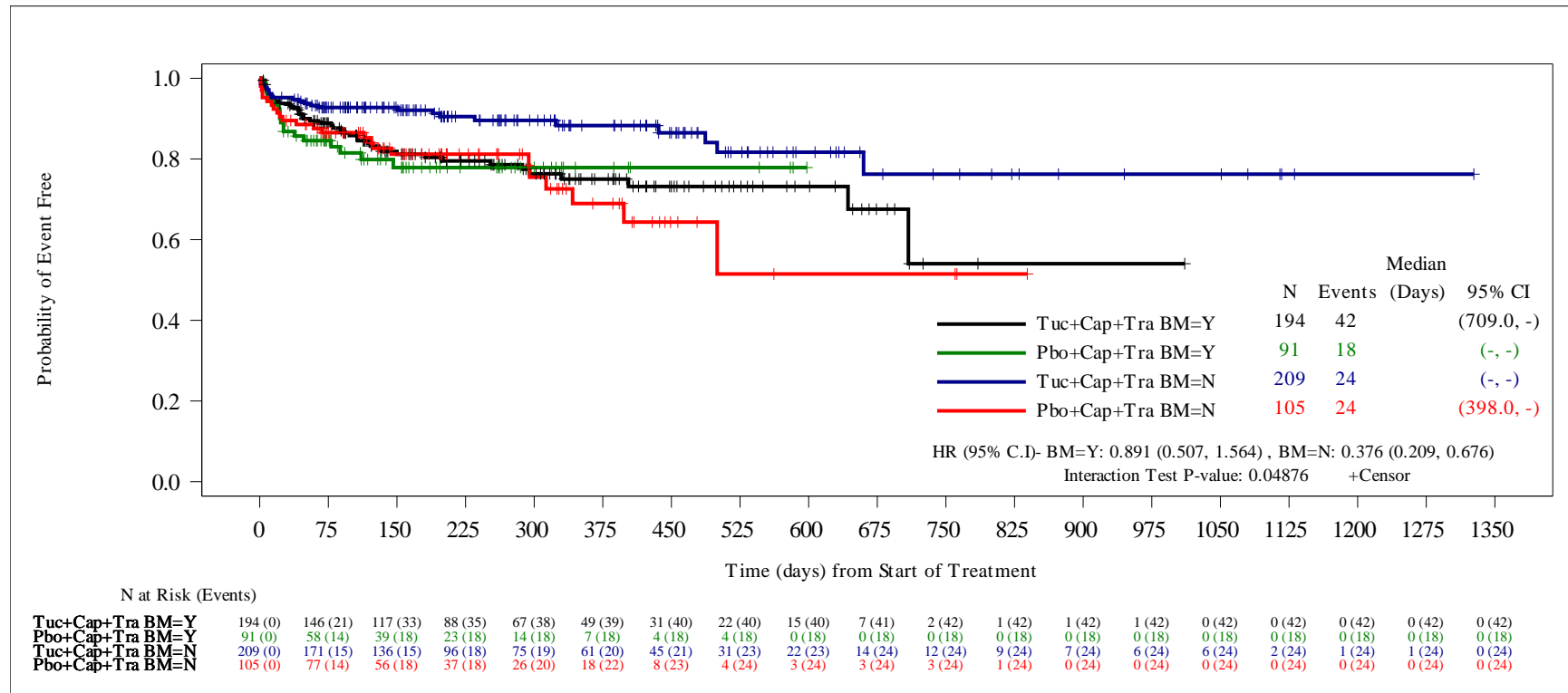
Two-sided p-value calculated from Cox proportional hazards model .

Snapshot date: 10SEP2020, data cutoff date: 29MAY2020.

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_may2020_dco_1943\v01\outputs\tlfs\pgms\f-sae-km-socpt-sub-3-ecog-safs.sas Output: f02-09-02-sae-km-socpt-sub-3-ecog-safs.rtf(17DEC20:16:57) Data: adsl, adae, adttesaf

Seagen Protocol ONT-380-206

**Figure 2.4.4 Kaplan-Meier Estimate of Time to First Onset of Adverse Events by BM - Constipation
Safety Analysis Set**



HR is computed from the Cox proportional hazards model using stratification factors (ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization.

Two-sided p-value calculated from Cox proportional hazards model .

Snapshot date: 10SEP2020, data cutoff date: 29MAY2020.

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_may2020_dco_1943\01\outputs\tlfs\pgms\f-ae-km-gi-con-sub1-bm-safs.sas Output:

f02-04-04-ae-km-gi-con-sub1-bm-safs.rtf(17DEC20:09:55) Data: adsl, adae, adttesaf

Seattle Genetics Protocol ONT-380-206**Table 14.2.3.6.5.1 Summary of Overall Survival (OS), Subgroup 5 (Race)
Subset of Subjects Who Are White Among ITT - OS Population**

| | Tuc+Cap+Tra (N=287) | Pbo+Cap+Tra (N=157) |
|--|------------------------|------------------------|
| Number of deaths, n (%) | 94 (32.8) | 66 (42.0) |
| Stratified Hazard Ratio ^{a, b} (95% C.I.) | | 0.694 (0.504, 0.956) |
| Stratified Log-rank p-value ^{b, c} | | 0.02446 |
| Median OS (Months) (95% C.I.) ^d | 22.2 (18.1, 31.1) | 17.5 (12.8, 20.0) |
| 25 th , 75 th percentile | 12.4, - | 10.4, 23.4 |
| Observed min, max ^e | 0.2, 35.9+ | 0.1+, 33.9+ |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (Presence or history of brain metastases: Yes/No, ECOG performance status: 0/1, Region of world: North America /Rest of World) at randomization.

c. Two-sided p-value calculated from stratified log-rank test.

d. Calculated using the complementary log-log transformation method (Collett, 1994).

e. '+' means the observed time is from censored subject.

Data Snapshot: 14OCT2019, Data Cutoff Date: 04SEP2019

Source: O:\Projects\Tucatinib\ONT380-206\csr_1354\v02\outputs\tlfs\pgms\t-eff-os-subgp.sas Output: t-eff-os-sub-5-white-itrs.rtf (04NOV19:23:54) Data: adsl, adtte

Seattle Genetics Protocol ONT-380-206**Table 14.2.3.6.5.2 Summary of Overall Survival (OS), Subgroup 5 (Race)
Subset of Subjects Who Are Non-White Among ITT - OS Population**

| | Tuc+Cap+Tra (N=123) | Pbo+Cap+Tra (N=45) |
|--|------------------------|-----------------------|
| Number of deaths, n (%) | 36 (29.3) | 19 (42.2) |
| Stratified Hazard Ratio ^{a, b} (95% C.I.) | 0.511 (0.282, 0.925) | |
| Stratified Log-rank p-value ^{b, c} | 0.02427 | |
| Median OS (Months) (95% C.I.) ^d | 21.7 (16.8, -) | 15.2 (12.0, -) |
| 25 th , 75 th percentile | 12.2, - | 9.6, - |
| Observed min, max ^e | 0.1+, 35.2+ | 1.7, 29.9+ |

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Subjects with races other than white are included.

a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (Presence or history of brain metastases: Yes/No, ECOG performance status: 0/1, Region of world: North America /Rest of World) at randomization.

c. Two-sided p-value calculated from stratified log-rank test.

d. Calculated using the complementary log-log transformation method (Collett, 1994).

e. '+' means the observed time is from censored subject.

Data Snapshot: 14OCT2019, Data Cutoff Date: 04SEP2019

Source: O:\Projects\Tucatinib\ONT380-206\csr_1354\v02\outputs\tlfs\pgms\t-eff-os-subgp.sas Output: t-eff-os-sub-5-non-white-itts.rtf (04NOV19:23:54) Data: adsl, adtte

Seattle Genetics Protocol ONT-380-206**Table 14.2.3.6.6.2 Summary of Overall Survival (OS), Subgroup 6 (Hormone Receptor Status)
Subset of Subjects Without Positive Estrogen/Progesterone Receptor Among ITT - OS Population**

| | Tuc+Cap+Tra (N=167) | Pbo+Cap+Tra (N=75) |
|--|------------------------|-----------------------|
| Number of deaths, n (%) | 52 (31.1) | 35 (46.7) |
| Stratified Hazard Ratio ^{a, b} (95% C.I.) | | 0.501 (0.314, 0.799) |
| Stratified Log-rank p-value ^{b, c} | | 0.00312 |
| Median OS (Months) (95% C.I.) ^d | 31.1 (16.5, -) | 14.1 (11.5, 19.0) |
| 25 th , 75 th percentile | 11.4, - | 8.8, 22.2 |
| Observed min, max ^e | 0.1+, 35.2+ | 1.0, 28.5+ |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (Presence or history of brain metastases: Yes/No, ECOG performance status: 0/1, Region of world: North America /Rest of World) at randomization.

c. Two-sided p-value calculated from stratified log-rank test.

d. Calculated using the complementary log-log transformation method (Collett, 1994).

e. '+' means the observed time is from censored subject.

Data Snapshot: 14OCT2019, Data Cutoff Date: 04SEP2019

Source: O:\Projects\Tucatinib\ONT380-206\csr_1354\v02\outputs\tlfs\pgms\t-eff-os-subgp.sas Output: t-eff-os-sub-6-neg-itts.rtf (04NOV19:23:54) Data: adsl, adtte

Seattle Genetics Protocol ONT-380-206**Table 14.2.3.6.6.1 Summary of Overall Survival (OS), Subgroup 6 (Hormone Receptor Status)
Subset of Subjects With Estrogen/Progesterone Receptor Either or Both Positive Among ITT - OS Population**

| | Tuc+Cap+Tra (N=243) | Pbo+Cap+Tra (N=127) |
|--|------------------------|------------------------|
| Number of deaths, n (%) | 78 (32.1) | 50 (39.4) |
| Stratified Hazard Ratio ^{a, b} (95% C.I.) | 0.854 (0.594, 1.230) | |
| Stratified Log-rank p-value ^{b, c} | 0.39609 | |
| Median OS (Months) (95% C.I.) ^d | 21.7 (18.1, 26.4) | 18.2 (13.6, 22.5) |
| 25 th , 75 th percentile | 13.2, 31.0 | 10.6, - |
| Observed min, max ^e | 0.2, 35.9+ | 0.1+, 33.9+ |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (Presence or history of brain metastases: Yes/No, ECOG performance status: 0/1, Region of world: North America /Rest of World) at randomization.

c. Two-sided p-value calculated from stratified log-rank test.

d. Calculated using the complementary log-log transformation method (Collett, 1994).

e. '+' means the observed time is from censored subject.

Data Snapshot: 14OCT2019, Data Cutoff Date: 04SEP2019

Source: O:\Projects\Tucatinib\ONT380-206\csr_1354\v02\outputs\tlfs\pgms\t-eff-os-subgp.sas Output: t-eff-os-sub-6-pos-itts.rtf (04NOV19:23:54) Data: adsl, adtte

Seattle Genetics Protocol ONT-380-206**Table 14.2.3.6.3.1 Summary of Overall Survival (OS), Subgroup 3 (ECOG)
Subset of Subjects With Baseline ECOG Score=0 Among ITT - OS Population**

| | Tuc+Cap+Tra (N=204) | Pbo+Cap+Tra (N=94) |
|--|------------------------|-----------------------|
| Number of deaths, n (%) | 45 (22.1) | 36 (38.3) |
| Stratified Hazard Ratio ^{a, b} (95% C.I.) | 0.513 (0.329, 0.800) | |
| Stratified Log-rank p-value ^{b, c} | 0.00274 | |
| Median OS (Months) (95% C.I.) ^d | 31.0 (24.0, -) | 19.0 (13.8, -) |
| 25 th , 75 th percentile | 17.6, - | 11.5, - |
| Observed min, max ^e | 0.1+, 35.9+ | 0.1+, 29.9+ |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (Presence or history of brain metastases: Yes/No and Region of world (North America /Rest of World)) at randomization.

c. Two-sided p-value calculated from stratified log-rank test.

d. Calculated using the complementary log-log transformation method (Collett, 1994).

e. '+' means the observed time is from censored subject.

Data Snapshot: 14OCT2019, Data Cutoff Date: 04SEP2019

Source: O:\Projects\Tucatinib\ONT380-206\csr_1354\v02\outputs\tlfs\pgms\t-eff-os-subgp.sas Output: t-eff-os-sub-3-ecog0-itts.rtf
(04NOV19:23:54) Data: adsl, adtte

Seattle Genetics Protocol ONT-380-206**Table 14.2.3.6.3.2 Summary of Overall Survival (OS), Subgroup 3 (ECOG)
Subset of Subjects With Baseline ECOG Score=1 Among ITT - OS Population**

| | Tuc+Cap+Tra (N=206) | Pbo+Cap+Tra (N=108) |
|--|------------------------|------------------------|
| Number of deaths, n (%) | 85 (41.3) | 49 (45.4) |
| Stratified Hazard Ratio ^{a, b} (95% C.I.) | | 0.841 (0.589, 1.200) |
| Stratified Log-rank p-value ^{b, c} | | 0.33816 |
| Median OS (Months) (95% C.I.) ^d | 16.5 (14.5, 21.7) | 14.1 (12.0, 18.5) |
| 25 th , 75 th percentile | 10.5, 31.1 | 8.8, 22.2 |
| Observed min, max ^e | 0.2, 35.2+ | 0.9, 33.9+ |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (Presence or history of brain metastases: Yes/No and Region of world (North America /Rest of World)) at randomization.

c. Two-sided p-value calculated from stratified log-rank test.

d. Calculated using the complementary log-log transformation method (Collett, 1994).

e. '+' means the observed time is from censored subject.

Data Snapshot: 14OCT2019, Data Cutoff Date: 04SEP2019

Source: O:\Projects\Tucatinib\ONT380-206\csr_1354\v02\outputs\tlfs\pgms\t-eff-os-subgp.sas Output: t-eff-os-sub-3-ecog1-itts.rtf
(04NOV19:23:54) Data: adsl, adtte

Seattle Genetics Protocol ONT-380-206**Table 14.2.3.6.1.1 Summary of Overall Survival (OS), Subgroup 1 (Baseline Brain Metastases Status)
Subset of Subjects With Brain Mets Among ITT - OS Population**

| | Tuc+Cap+Tra (N=198) | Pbo+Cap+Tra (N=93) |
|--|------------------------|-----------------------|
| Number of deaths, n (%) | 68 (34.3) | 46 (49.5) |
| Stratified Hazard Ratio ^{a, b} (95% C.I.) | 0.583 (0.398, 0.853) | |
| Stratified Log-rank p-value ^{b, c} | 0.00497 | |
| Median OS (Months) (95% C.I.) ^d | 18.1 (15.5, -) | 12.0 (11.2, 15.2) |
| 25 th , 75 th percentile | 10.5, - | 8.8, 19.9 |
| Observed min, max ^e | 0.1+, 35.2+ | 0.1+, 23.3+ |

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Brain Mets Subgroup: subset of subjects with a history of brain metastases or presence of brain metastases or brain lesions of equivocal significance on screening MRI.

a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (ECOG performance status: 0/1, and Region of world: North America/Rest of World) at randomization.

c. Two-sided p-value calculated from stratified log-rank test.

d. Calculated using the complementary log-log transformation method (Collett, 1994).

e. '+' means the observed time is from censored subject.

Data Snapshot: 14OCT2019, Data Cutoff Date: 04SEP2019

Source: O:\Projects\Tucatinib\ONT380-206\csr_1354\v02\outputs\tlfs\pgms\t-topline-eff-os-subgp.sas Output: t-eff-os-sub-1-bm-itss.rtf
(04NOV19:23:47) Data: adsl, adtte

Seattle Genetics Protocol ONT-380-206**Table 14.2.3.6.1.2 Summary of Overall Survival (OS), Subgroup 1 (Baseline Brain Metastases Status)
Subset of Subjects Without Brain Mets Among ITT - OS Population**

| | Tuc+Cap+Tra (N=211) | Pbo+Cap+Tra (N=108) |
|--|------------------------|------------------------|
| Number of deaths, n (%) | 62 (29.4) | 39 (36.1) |
| Stratified Hazard Ratio ^{a, b} (95% C.I.) | 0.716 (0.476, 1.079) | |
| Stratified Log-rank p-value ^{b, c} | 0.10867 | |
| Median OS (Months) (95% C.I.) ^d | 22.8 (21.7, 31.1) | 20.0 (17.0, -) |
| 25 th , 75 th percentile | 14.5, 31.1 | 12.0, - |
| Observed min, max ^e | 0.8, 35.9+ | 1.0, 33.9+ |

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Non-Brain Mets Subgroup: subset of subjects without a history of brain metastases or presence of brain metastases or brain lesions of equivocal significance on screening MRI.

a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (ECOG performance status: 0/1, and Region of world: North America/Rest of World) at randomization.

c. Two-sided p-value calculated from stratified log-rank test.

d. Calculated using the complementary log-log transformation method (Collett, 1994).

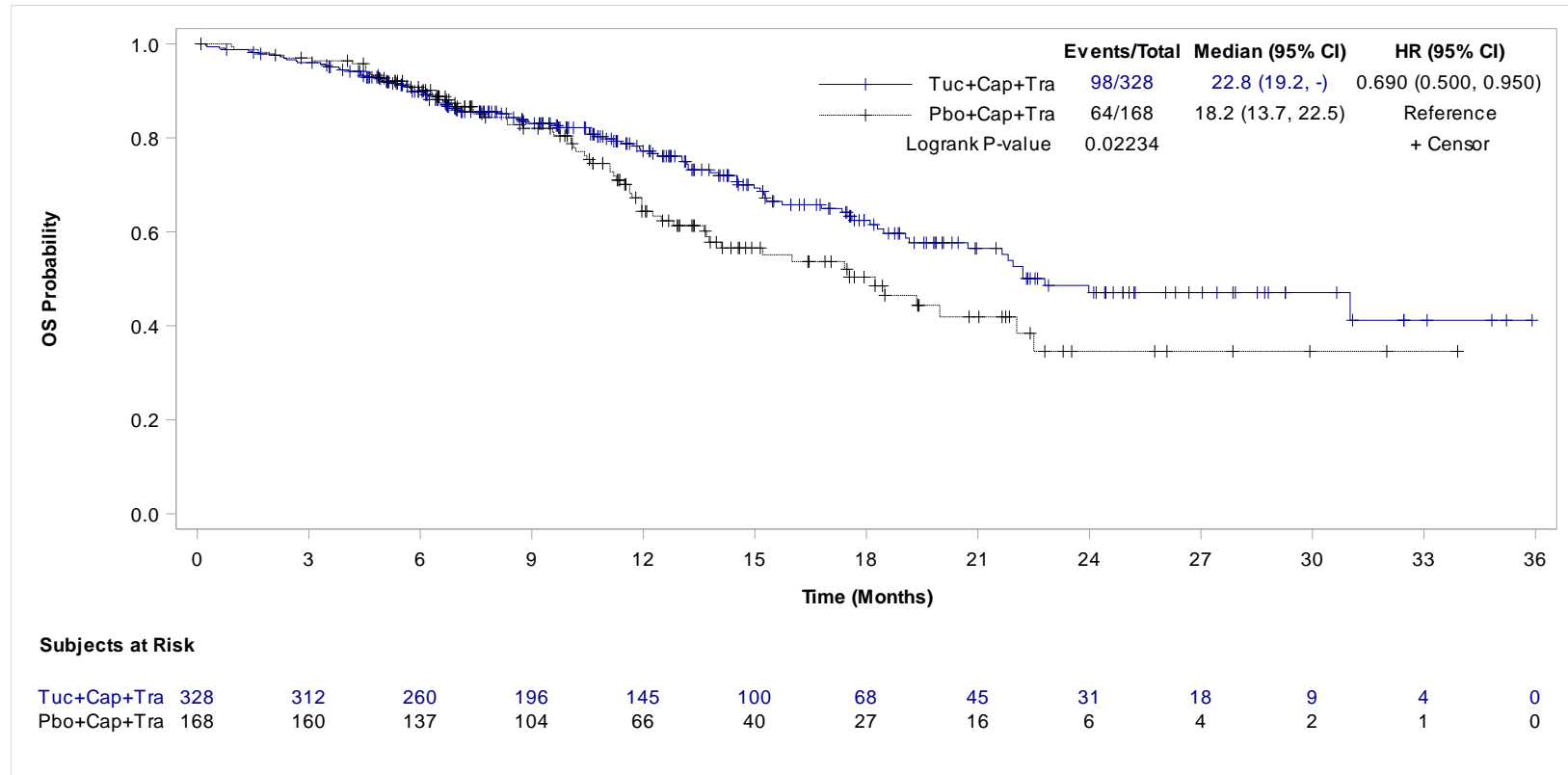
e. '+' means the observed time is from censored subject.

Data Snapshot: 14OCT2019, Data Cutoff Date: 04SEP2019

Source: O:\Projects\Tucatinib\ONT380-206\csr_1354\v02\outputs\tlfs\pgms\t-topline-eff-os-subgp.sas Output: t-eff-os-sub-1-nbm-itts.rtf
(04NOV19:23:47) Data: adsl, adtte

Seattle Genetics Protocol ONT-380-206

**Figure 1.1.8 Overall Survival by Treatment Arm
Subset of Subjects <65 Years Old Among ITT - OS Population**



HR is computed from the Cox proportional hazards model using stratification factors (Presence or history of brain metastases: Yes/No, ECOG performance status: 0/1, and Region of world: North America /Rest of World) at randomization.

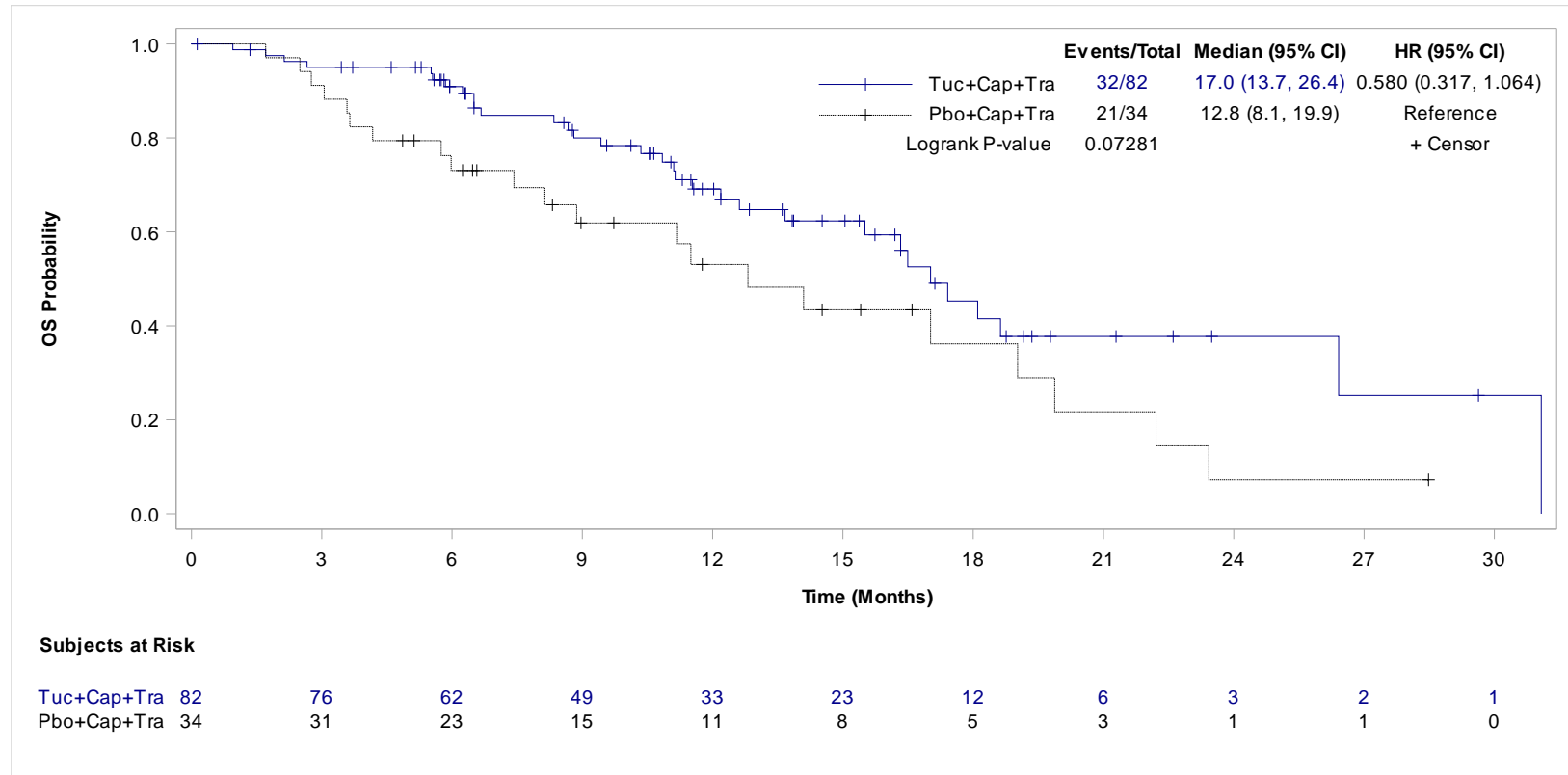
Two-sided p-value calculated from stratified log-rank test.

Data Snapshot: 14OCT2019, Data Cutoff Date: 04SEP2019

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_1753\v01\outputs\tlfs\pgms\f-eff-km.sas Output: f-eff-km-os-lt65-itts.rtf(14APR20:22:33) Data: adsl, adtte

Seattle Genetics Protocol ONT-380-206

**Figure 1.1.9 Overall Survival by Treatment Arm
Subset of Subjects ≥ 65 Years Old Among ITT - OS Population**



HR is computed from the Cox proportional hazards model using stratification factors (Presence or history of brain metastases: Yes/No, ECOG performance status: 0/1, and Region of world: North America /Rest of World) at randomization.

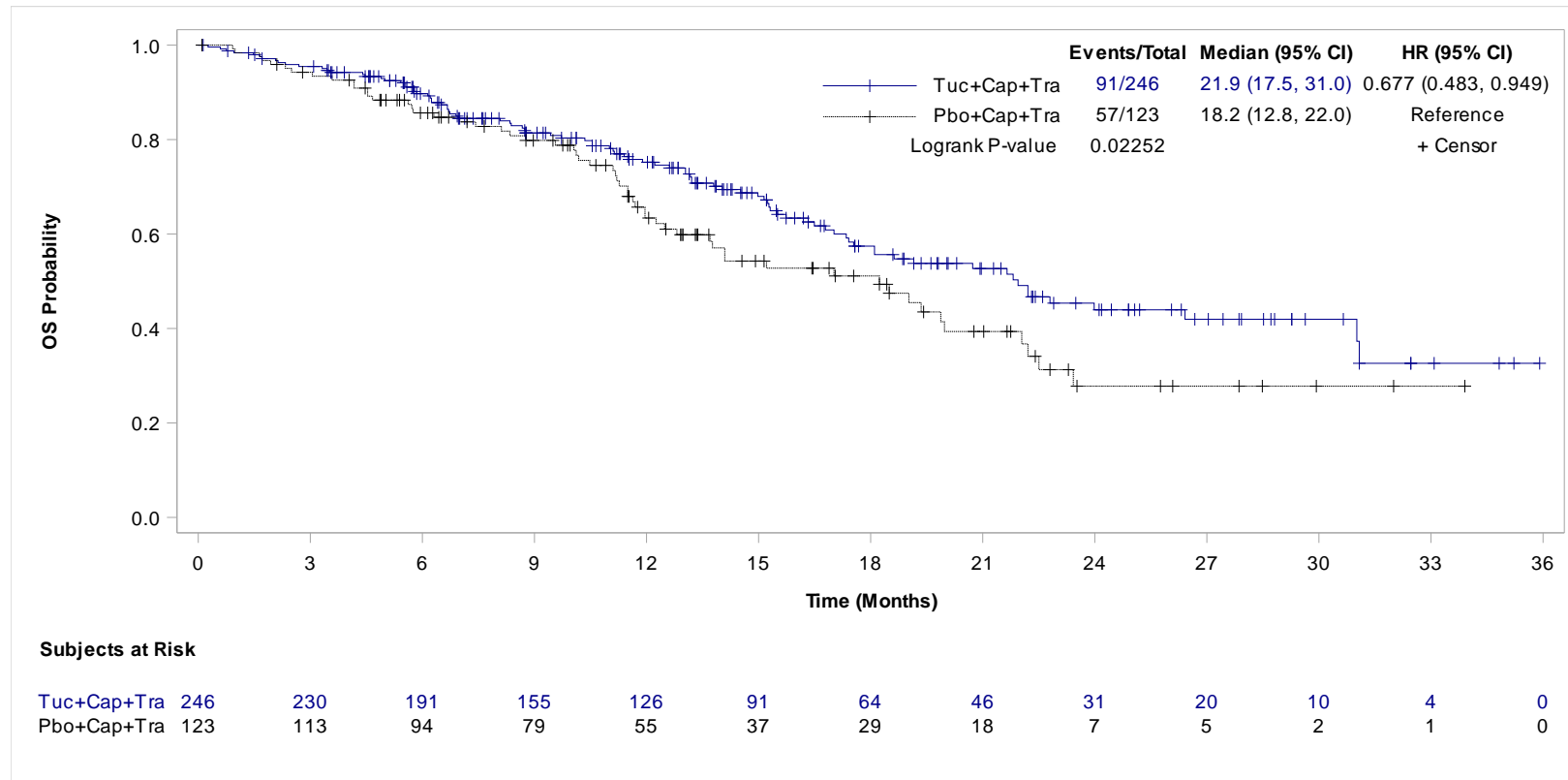
Two-sided p-value calculated from stratified log-rank test.

Data Snapshot: 14OCT2019, Data Cutoff Date: 04SEP2019

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_1753\v01\outputs\tlfs\pgms\f-eff-km.sas Output: f-eff-km-os-ge65-itts.rtf(14APR20:22:33) Data: adsl, adtte

Seattle Genetics Protocol ONT-380-206

Figure 1.1.17 Overall Survival by Treatment Arm
Subset of Subjects in North America Among ITT - OS Population



HR is computed from the Cox proportional hazards model using stratification factors (Presence or history of brain metastases: Yes/No, and ECOG performance status: 0/1) at randomization.

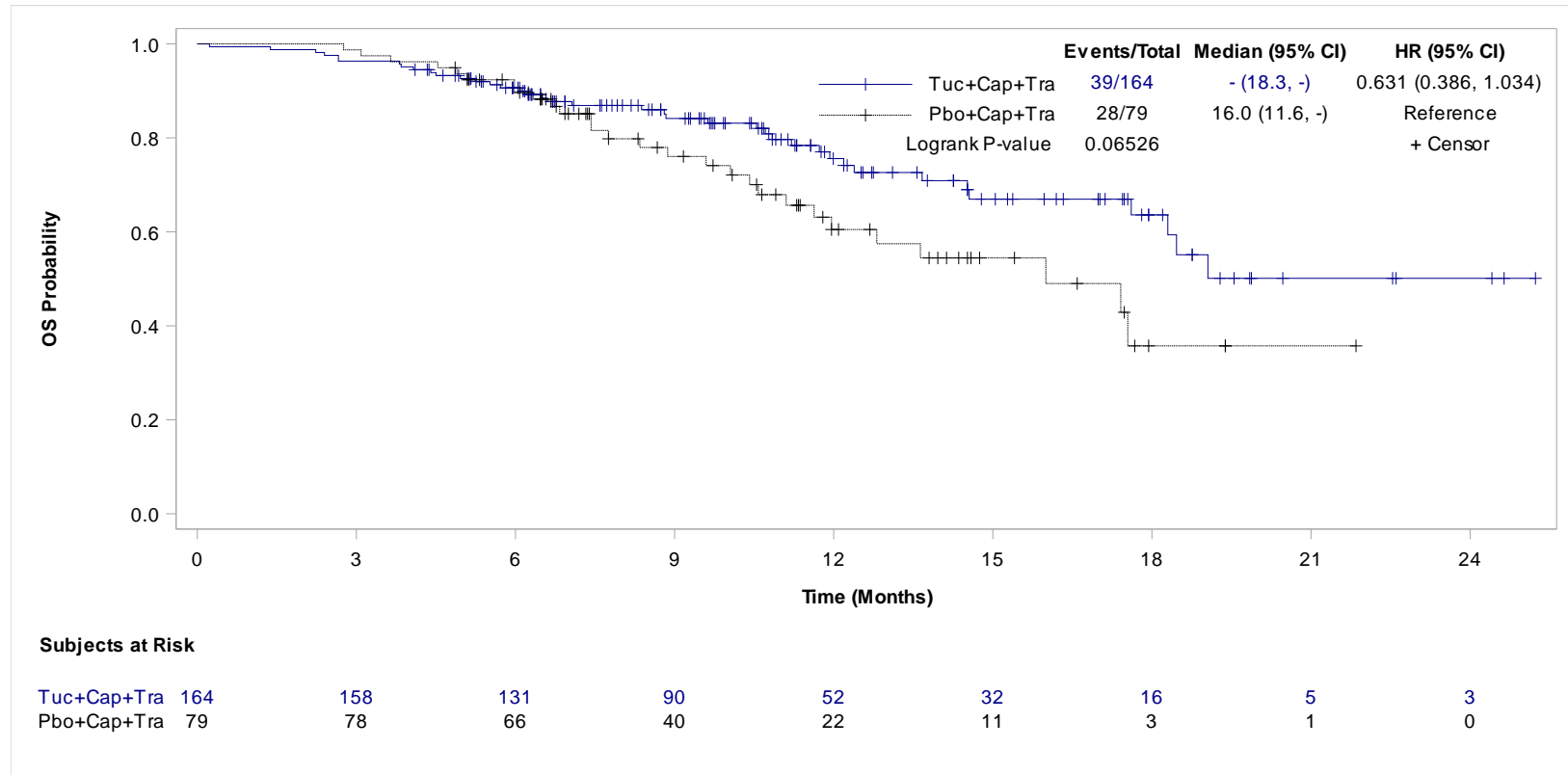
Two-sided p-value calculated from stratified log-rank test.

Data Snapshot: 14OCT2019, Data Cutoff Date: 04SEP2019

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_1753\v01\outputs\tlfs\pgms\f-eff-km.sas Output: f-eff-km-os-na-itts.rtf(14APR20:22:33) Data: adsl, adtte

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**Figure 1.1.18 Overall Survival by Treatment Arm
Subset of Subjects in the Rest of World Among ITT - OS Population**



HR is computed from the Cox proportional hazards model using stratification factors (Presence or history of brain metastases: Yes/No, and ECOG performance status: 0/1) at randomization.

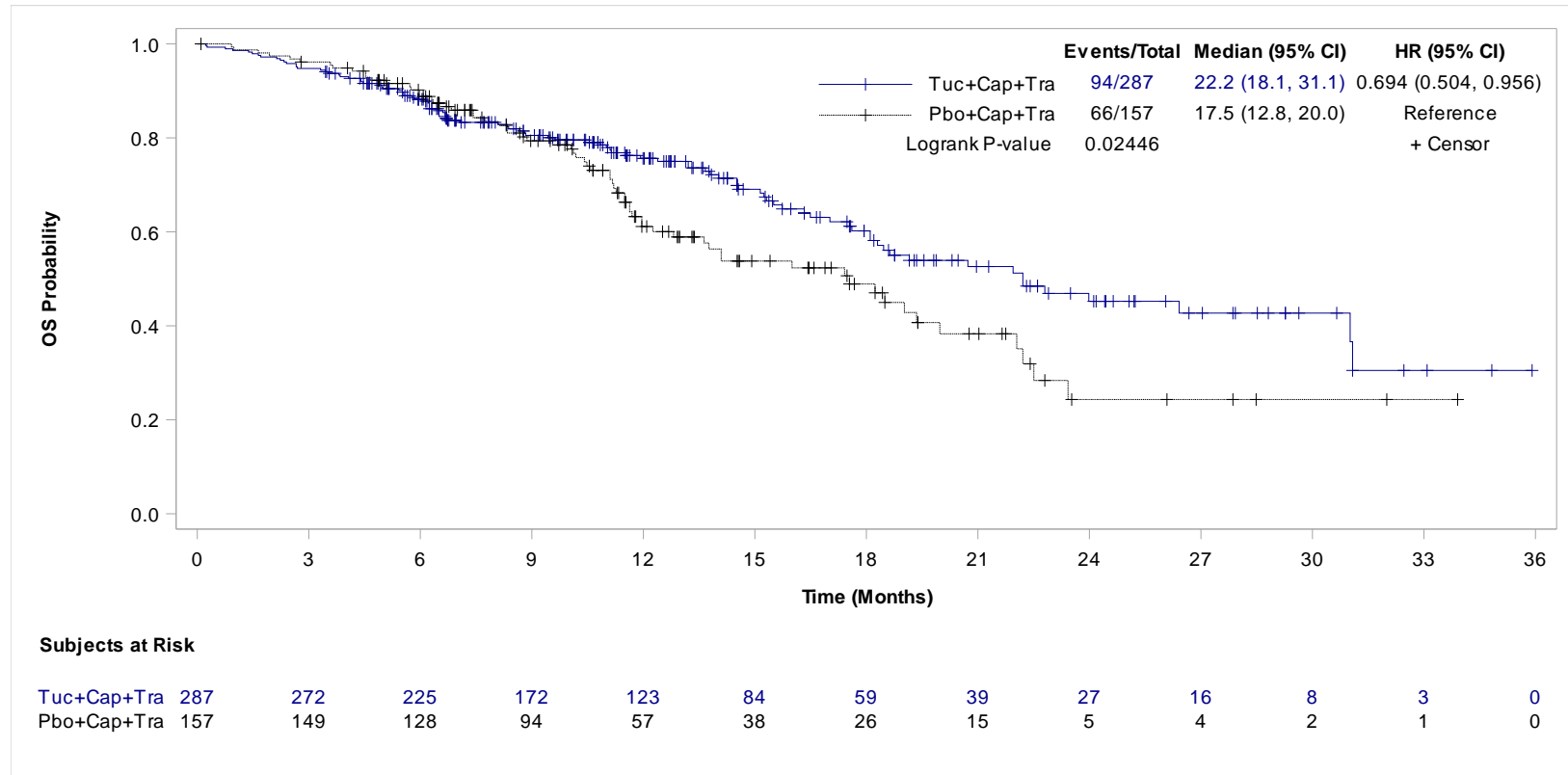
Two-sided p-value calculated from stratified log-rank test.

Data Snapshot: 14OCT2019, Data Cutoff Date: 04SEP2019

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_1753\v01\outputs\tlfs\pgms\f-eff-km.sas Output: f-eff-km-os-row-itts.rtf(14APR20:22:33) Data: adsl, adtte

Seattle Genetics Protocol ONT-380-206

**Figure 1.1.15 Overall Survival by Treatment Arm
Subset of Subjects Who Are White Among ITT - OS Population**



HR is computed from the Cox proportional hazards model using stratification factors (Presence or history of brain metastases: Yes/No, ECOG performance status: 0/1, and Region of world: North America /Rest of World) at randomization.

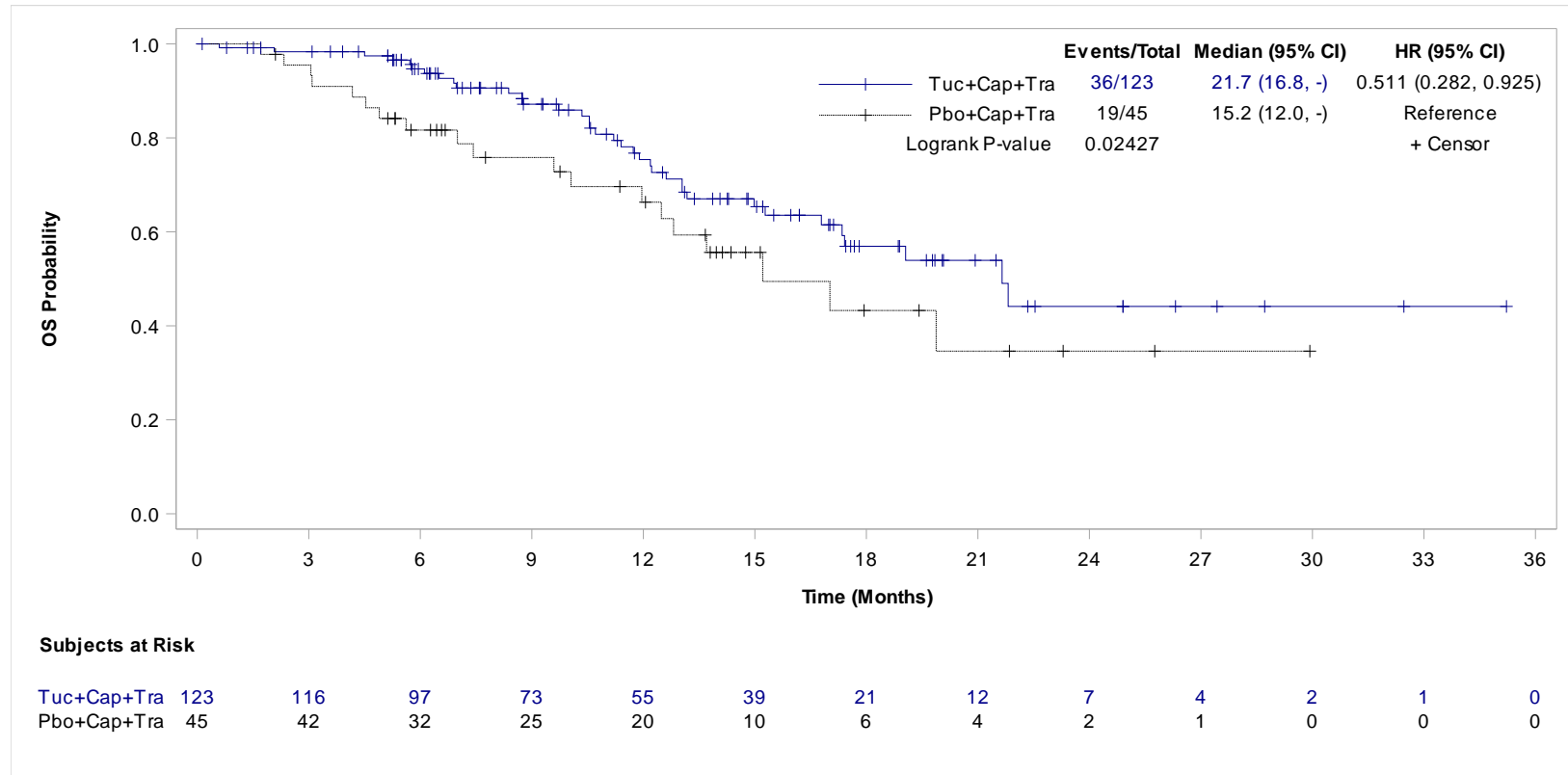
Two-sided p-value calculated from stratified log-rank test.

Data Snapshot: 14OCT2019, Data Cutoff Date: 04SEP2019

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_1753\v01\outputs\tlfs\pgms\f-eff-km.sas Output: f-eff-km-os-white-itts.rtf(14APR20:22:33) Data: adsl, adtte

Seattle Genetics Protocol ONT-380-206

**Figure 1.1.16 Overall Survival by Treatment Arm
Subset of Subjects Who Are Non-White Among ITT - OS Population**



HR is computed from the Cox proportional hazards model using stratification factors (Presence or history of brain metastases: Yes/No, ECOG performance status: 0/1, and Region of world: North America /Rest of World) at randomization.

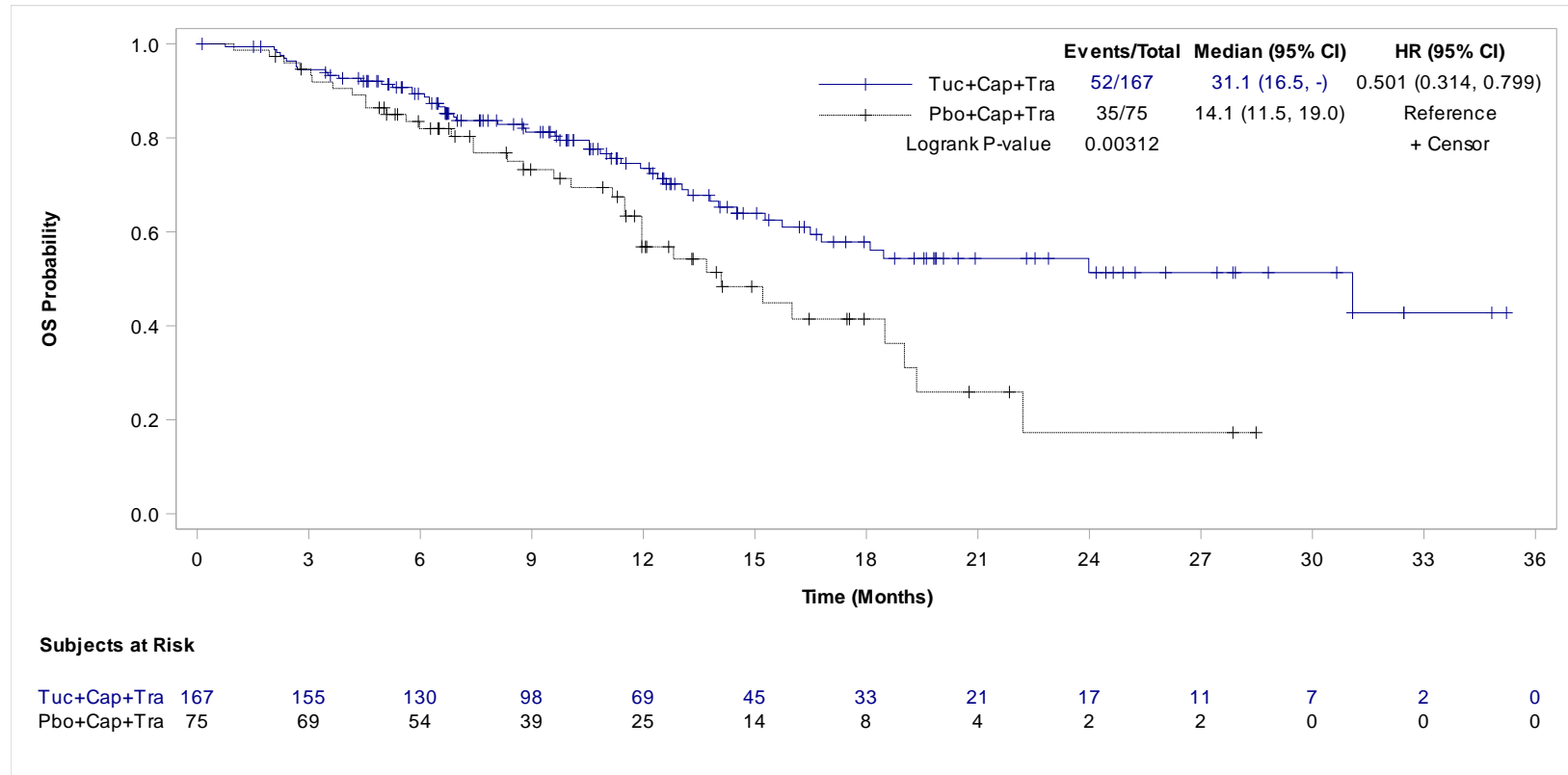
Two-sided p-value calculated from stratified log-rank test.

Data Snapshot: 14OCT2019, Data Cutoff Date: 04SEP2019

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_1753\v01\outputs\tlfs\pgms\f-eff-km.sas Output: f-eff-km-os-nwhite-itts.rtf(14APR20:22:33) Data: adsl, adtte

Seattle Genetics Protocol ONT-380-206

Figure 1.1.14 Overall Survival by Treatment Arm
Subset of Subjects Without Positive Estrogen/Progesterone Receptor Among ITT - OS Population



HR is computed from the Cox proportional hazards model using stratification factors (Presence or history of brain metastases: Yes/No, ECOG performance status: 0/1, and Region of world: North America /Rest of World) at randomization.

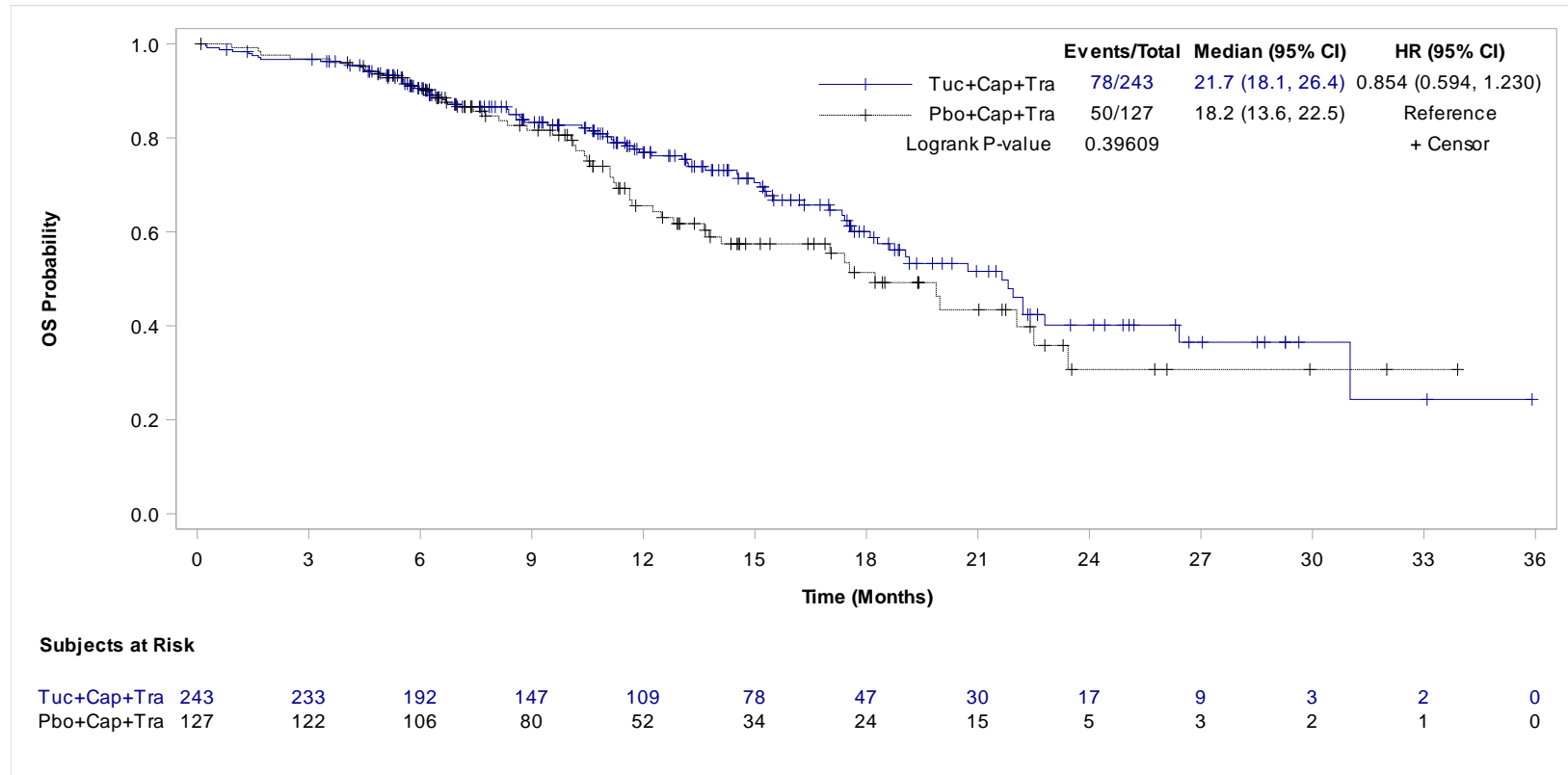
Two-sided p-value calculated from stratified log-rank test.

Data Snapshot: 14OCT2019, Data Cutoff Date: 04SEP2019

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_1753\v01\outputs\tlfs\pgms\f-eff-km.sas Output: f-eff-km-os-negerpr-itts.rtf(14APR20:22:33) Data: adsl, adtte

Seattle Genetics Protocol ONT-380-206

Figure 1.1.13 Overall Survival by Treatment Arm
Subset of Subjects With Estrogen/Progesterone Receptor Either or Both Positive Among ITT - OS Population



HR is computed from the Cox proportional hazards model using stratification factors (Presence or history of brain metastases: Yes/No, ECOG performance status: 0/1, and Region of world: North America /Rest of World) at randomization.

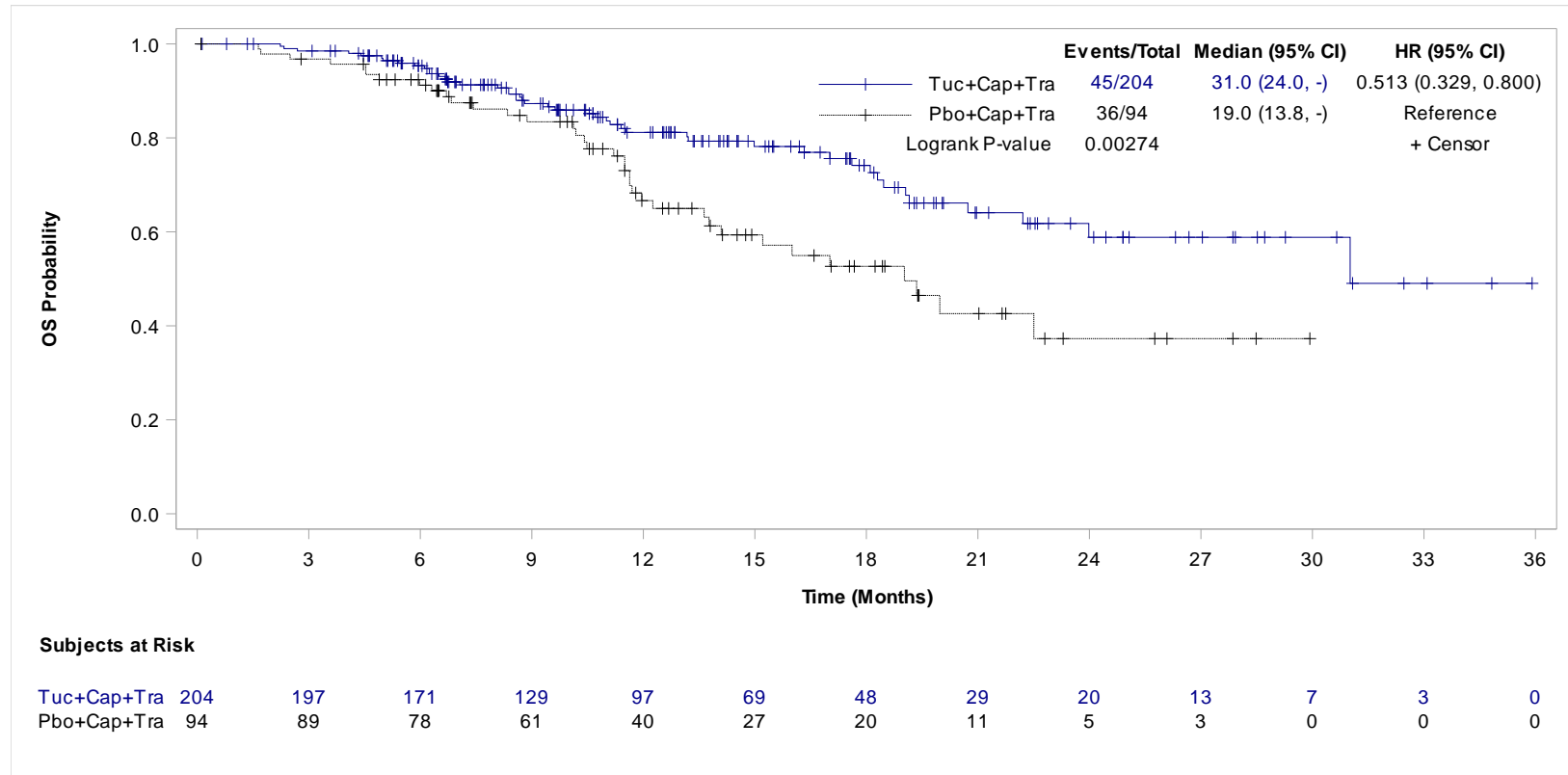
Two-sided p-value calculated from stratified log-rank test.

Data Snapshot: 14OCT2019, Data Cutoff Date: 04SEP2019

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_1753\v01\outputs\tlfs\pgms\f-eff-km.sas Output: f-eff-km-os-posrpr-itss.rtf(14APR20:22:33) Data: adsl, adtte

Seattle Genetics Protocol ONT-380-206

Figure 1.1.6 Overall Survival by Treatment Arm
Subset of Subjects With Baseline ECOG Score=0 Among ITT - OS Population



HR is computed from the Cox proportional hazards model using stratification factors (Presence or history of brain metastases: Yes/No, and Region of world: North America /Rest of World) at randomization.

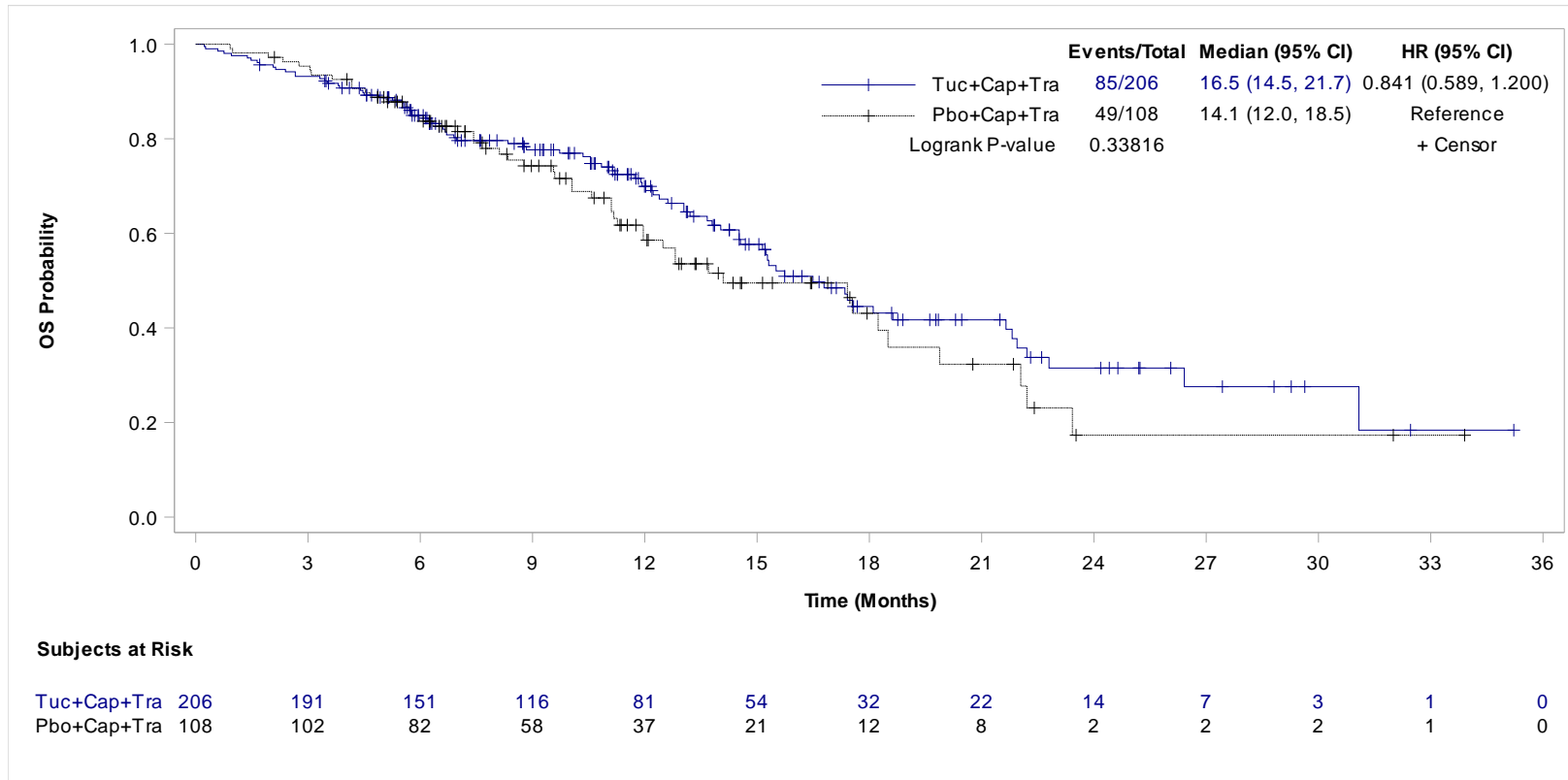
Two-sided p-value calculated from stratified log-rank test.

Data Snapshot: 14OCT2019, Data Cutoff Date: 04SEP2019

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_1753\v01\outputs\tlfs\pgms\f-eff-km.sas Output: f-eff-km-os-ecog0-itts.rtf(14APR20:22:33) Data: adsl, adtte

Seattle Genetics Protocol ONT-380-206

Figure 1.1.7 Overall Survival by Treatment Arm
Subset of Subjects With Baseline ECOG Score=1 Among ITT - OS Population



HR is computed from the Cox proportional hazards model using stratification factors (Presence or history of brain metastases: Yes/No, and Region of world: North America /Rest of World) at randomization.

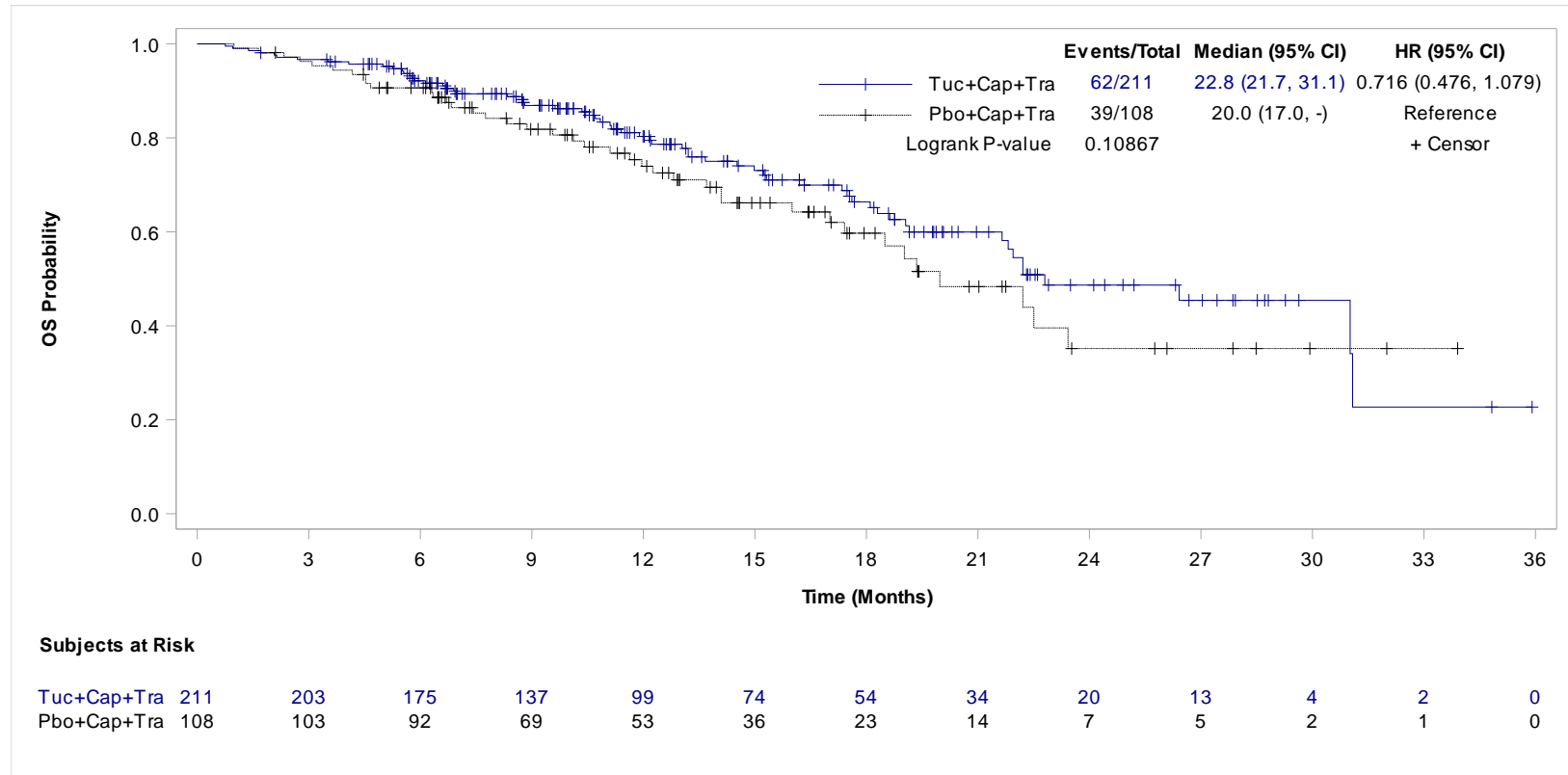
Two-sided p-value calculated from stratified log-rank test.

Data Snapshot: 14OCT2019, Data Cutoff Date: 04SEP2019

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_1753\v01\outputs\tlfs\pgms\f-eff-km.sas Output: f-eff-km-os-ecog1-itts.rtf(14APR20:22:33) Data: adsl, adtte

Seattle Genetics Protocol ONT-380-206

**Figure 1.1.12 Overall Survival by Treatment Arm
Subset of Subjects Without Brain Mets Among ITT - OS Population**



HR is computed from the Cox proportional hazards model using stratification factors (ECOG performance status: 0/1, and Region of world: North America /Rest of World) at randomization.

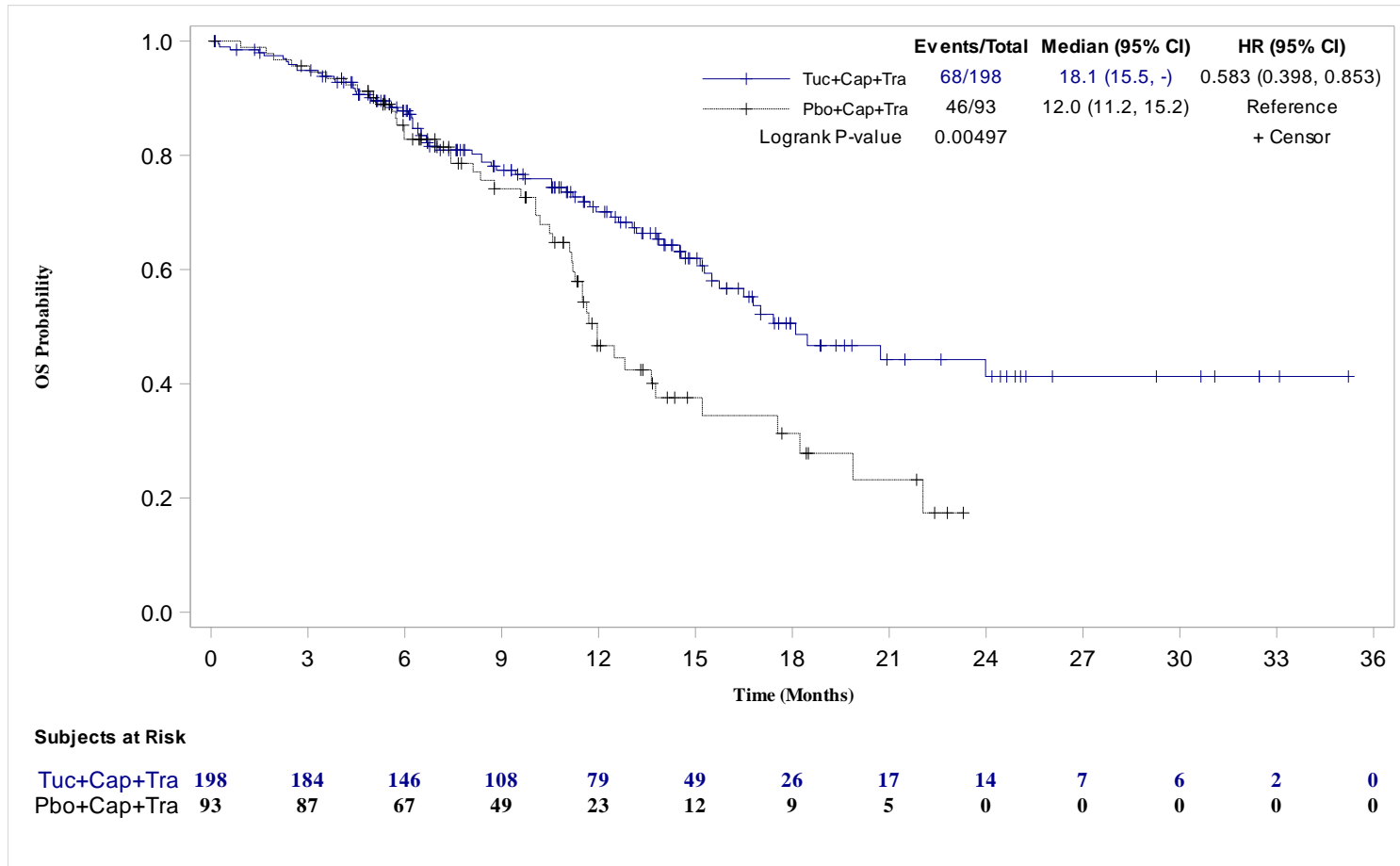
Two-sided p-value calculated from stratified log-rank test.

Data Snapshot: 14OCT2019, Data Cutoff Date: 04SEP2019

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_1753\v01\outputs\tlfs\pgms\f-eff-km.sas Output: f-eff-km-os-nbmitts.rtf(14APR20:22:33) Data: adsl, adtte

Seattle Genetics ONT380-206

Figure <Insert Table Num> Overall Survival by Treatment Arm
Subset of Subjects With Brain Mets Among ITT - OS Population



HR is computed from the Cox proportional hazards model using stratification factors (ECOG performance status: 0/1, and Region of world: North America/Rest of World) at randomization.
 Data Snapshot: 14OCT2019, Data Cutoff Date: 04SEP2019
 Source: O:\Projects\Tucatinib\ONT380-206\202001_asco_1687\v01\outputs\tlfs\pgms\f-eff-km.sas Output: f-eff-km-os-bmitts.rtf(30JAN20:22:40) Data: adsl, adtte

Seattle Genetics Protocol ONT-380-206**Table 14.2.3.6.4.2 Summary of Overall Survival (OS), Subgroup 4 (Age)
Subset of Subjects <65 Years Old Among ITT - OS Population**

| | Tuc+Cap+Tra (N=328) | Pbo+Cap+Tra (N=168) |
|--|------------------------|------------------------|
| Number of deaths, n (%) | 98 (29.9) | 64 (38.1) |
| Stratified Hazard Ratio ^{a, b} (95% C.I.) | | 0.690 (0.500, 0.950) |
| Stratified Log-rank p-value ^{b, c} | | 0.02234 |
| Median OS (Months) (95% C.I.) ^d | 22.8 (19.2, -) | 18.2 (13.7, 22.5) |
| 25 th , 75 th percentile | 13.0, - | 10.6, - |
| Observed min, max ^e | 0.2, 35.9+ | 0.1+, 33.9+ |

Page 1 of 1

a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (Presence or history of brain metastases: Yes/No, ECOG performance status: 0/1, Region of world: North America /Rest of World) at randomization.

c. Two-sided p-value calculated from stratified log-rank test.

d. Calculated using the complementary log-log transformation method (Collett, 1994).

e. '+' means the observed time is from censored subject.

Data Snapshot: 14OCT2019, Data Cutoff Date: 04SEP2019

Source: O:\Projects\Tucatinib\ONT380-206\csr_1354\v02\outputs\tlfs\pgms\t-eff-os-subgp.sas Output: t-eff-os-sub-4-age165-itte.rtf (04NOV19:23:54) Data: adsl, adtte

Seattle Genetics Protocol ONT-380-206**Table 14.2.3.6.4.1 Summary of Overall Survival (OS), Subgroup 4 (Age)
Subset of Subjects ≥65 Years Old Among ITT - OS Population**

| | Tuc+Cap+Tra (N=82) | Pbo+Cap+Tra (N=34) |
|--|-----------------------|-----------------------|
| Number of deaths, n (%) | 32 (39.0) | 21 (61.8) |
| Stratified Hazard Ratio ^{a, b} (95% C.I.) | | 0.580 (0.317, 1.064) |
| Stratified Log-rank p-value ^{b, c} | | 0.07281 |
| Median OS (Months) (95% C.I.) ^d | 17.0 (13.7, 26.4) | 12.8 (8.1, 19.9) |
| 25 th , 75 th percentile | 10.8, 31.1 | 6.0, 19.9 |
| Observed min, max ^e | 0.1+, 31.1 | 1.7, 28.5+ |

Page 1 of 1

a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (Presence or history of brain metastases: Yes/No, ECOG performance status: 0/1, Region of world: North America /Rest of World) at randomization.

c. Two-sided p-value calculated from stratified log-rank test.

d. Calculated using the complementary log-log transformation method (Collett, 1994).

e. '+' means the observed time is from censored subject.

Data Snapshot: 14OCT2019, Data Cutoff Date: 04SEP2019

Source: O:\Projects\Tucatinib\ONT380-206\csr_1354\v02\outputs\tlfs\pgms\t-eff-os-subgp.sas Output: t-eff-os-sub-4-agege65-itts.rtf (04NOV19:23:54) Data: adsl, adtte

Seattle Genetics Protocol ONT-380-206**Table 14.2.3.6.2.1 Summary of Overall Survival (OS), Subgroup 2 (Geographic Region)
Subset of Subjects in North America Among ITT - OS Population**

| | Tuc+Cap+Tra (N=246) | Pbo+Cap+Tra (N=123) |
|--|------------------------|------------------------|
| Number of deaths, n (%) | 91 (37.0) | 57 (46.3) |
| Stratified Hazard Ratio ^{a, b} (95% C.I.) | 0.677 (0.483, 0.949) | |
| Stratified Log-rank p-value ^{b, c} | 0.02252 | |
| Median OS (Months) (95% C.I.) ^d | 21.9 (17.5, 31.0) | 18.2 (12.8, 22.0) |
| 25 th , 75 th percentile | 12.2, - | 10.5, - |
| Observed min, max ^e | 0.1+, 35.9+ | 0.1+, 33.9+ |

Page 1 of 1

a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (Presence or history of brain metastases: Yes/No and ECOG performance status: 0/1) at randomization.

c. Two-sided p-value calculated from stratified log-rank test.

d. Calculated using the complementary log-log transformation method (Collett, 1994).

e. '+' means the observed time is from censored subject.

Data Snapshot: 14OCT2019, Data Cutoff Date: 04SEP2019

Source: O:\Projects\Tucatinib\ONT380-206\csr_1354\v02\outputs\tlfs\pgms\t-eff-os-subgp.sas Output: t-eff-os-sub-2-na-itts.rtf (04NOV19:23:54) Data: adsl, adtte

Seattle Genetics Protocol ONT-380-206**Table 14.2.3.6.2.2 Summary of Overall Survival (OS), Subgroup 2 (Geographic Region)
Subset of Subjects in the Rest of World Among ITT - OS Population**

| | Tuc+Cap+Tra (N=164) | Pbo+Cap+Tra (N=79) |
|--|------------------------|-----------------------|
| Number of deaths, n (%) | 39 (23.8) | 28 (35.4) |
| Stratified Hazard Ratio ^{a, b} (95% C.I.) | 0.631 (0.386, 1.034) | |
| Stratified Log-rank p-value ^{b, c} | 0.06526 | |
| Median OS (Months) (95% C.I.) ^d | - (18.3, -) | 16.0 (11.6, -) |
| 25 th , 75 th percentile | 12.2, - | 9.6, - |
| Observed min, max ^e | 0.2, 25.2+ | 2.8, 21.8+ |

Page 1 of 1

a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (Presence or history of brain metastases: Yes/No and ECOG performance status: 0/1) at randomization.

c. Two-sided p-value calculated from stratified log-rank test.

d. Calculated using the complementary log-log transformation method (Collett, 1994).

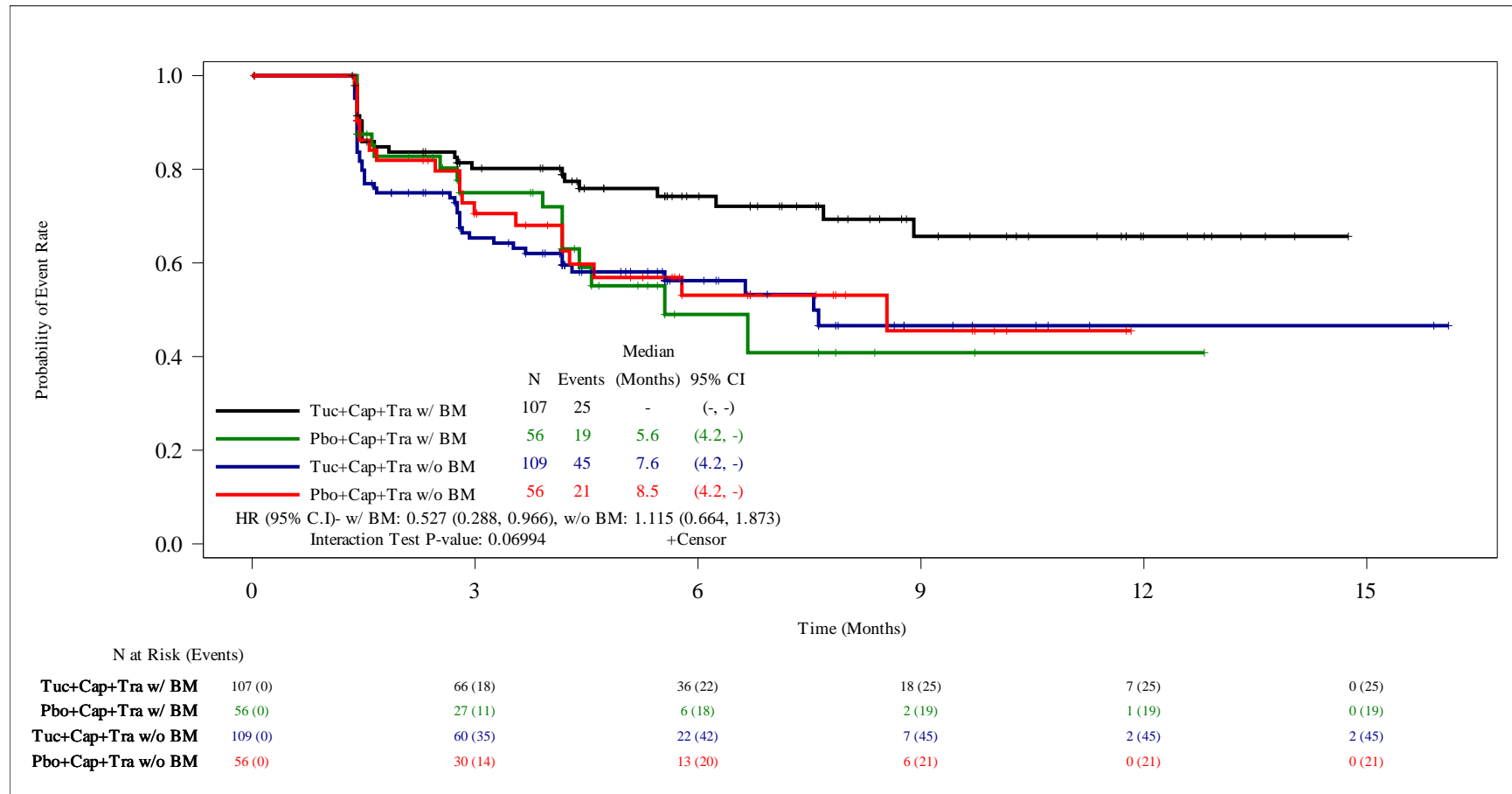
e. '+' means the observed time is from censored subject.

Data Snapshot: 14OCT2019, Data Cutoff Date: 04SEP2019

Source: O:\Projects\Tucatinib\ONT380-206\csr_1354\v02\outputs\tlfs\pgms\t-eff-os-subgp.sas Output: t-eff-os-sub-2-row-itrs.rtf (04NOV19:23:54) Data: adsl, adtte

Seattle Genetics Protocol ONT-380-206

**Figure <Insert Table Num> Time to Worsening ≥ 10 in EQ-5D-5L Health Score by Treatment Arm and Brain Metastases Status
ITT - OS Population**



Time to first worsening ≥ 10 in EQ-5D-5L Health Score.

Subjects without worsening ≥ 10 are censored to the last EQ-5D-5L assessment date with non-missing health score.

HR is computed from the unstratified Cox proportional hazards model.

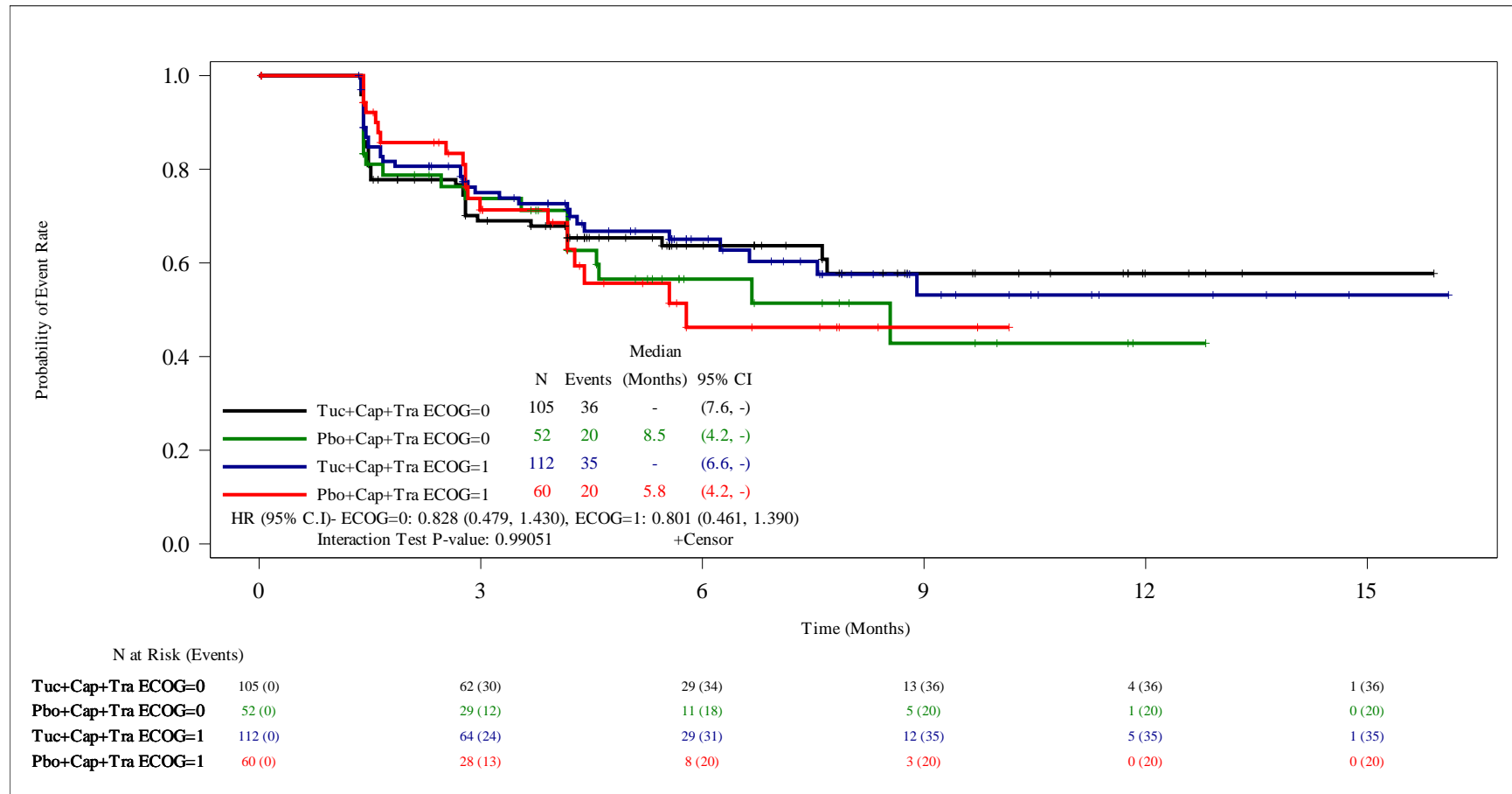
Interaction test p-value calculated from unstratified Cox proportional hazards model for the interaction term of treatment and brain metastases status.

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_1753\v01\outputs\tlfs\pgms\f-pro-km-ttw-tx.sas Output: f-pro-km-ttw10-txbm-itts.rtf(11MAY20:15:36)

Data: adsl,adcm,adttepro

Seattle Genetics Protocol ONT-380-206

**Figure <Insert Table Num> Time to Worsening ≥ 10 in EQ-5D-5L Health Score by Treatment Arm and Baseline ECOG Status
ITT - OS Population**



Time to first worsening ≥ 10 in EQ-5D-5L Health Score.

Subjects without worsening ≥ 10 are censored to the last EQ-5D-5L assessment date with non-missing health score.

HR is computed from the unstratified Cox proportional hazards model.

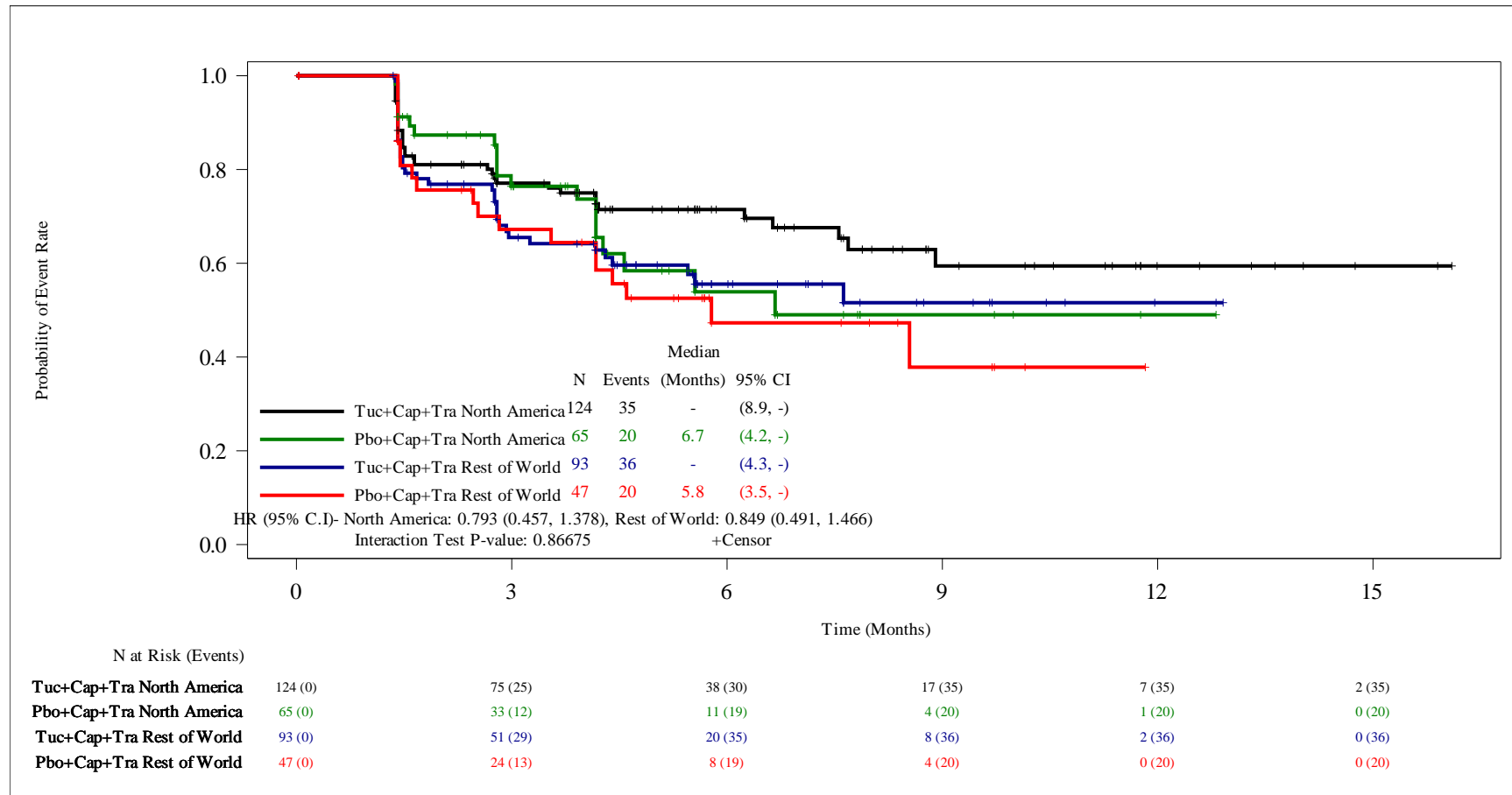
Interaction test p-value calculated from unstratified Cox proportional hazards model for the interaction term of treatment and baseline ECOG status.

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_1753\v01\outputs\tlfs\pgms\f-pro-km-ttw-tx.sas Output: f-pro-km-ttw10-txecog-itts.rtf(11MAY20:15:36)

Data: adsl,adcm,adttepro

Seattle Genetics Protocol ONT-380-206

**Figure <Insert Table Num> Time to Worsening ≥ 10 in EQ-5D-5L Health Score by Treatment Arm and Geographic Region
ITT - OS Population**



Time to first worsening ≥ 10 in EQ-5D-5L Health Score.

Subjects without worsening ≥ 10 are censored to the last EQ-5D-5L assessment date with non-missing health score.

HR is computed from the unstratified Cox proportional hazards model.

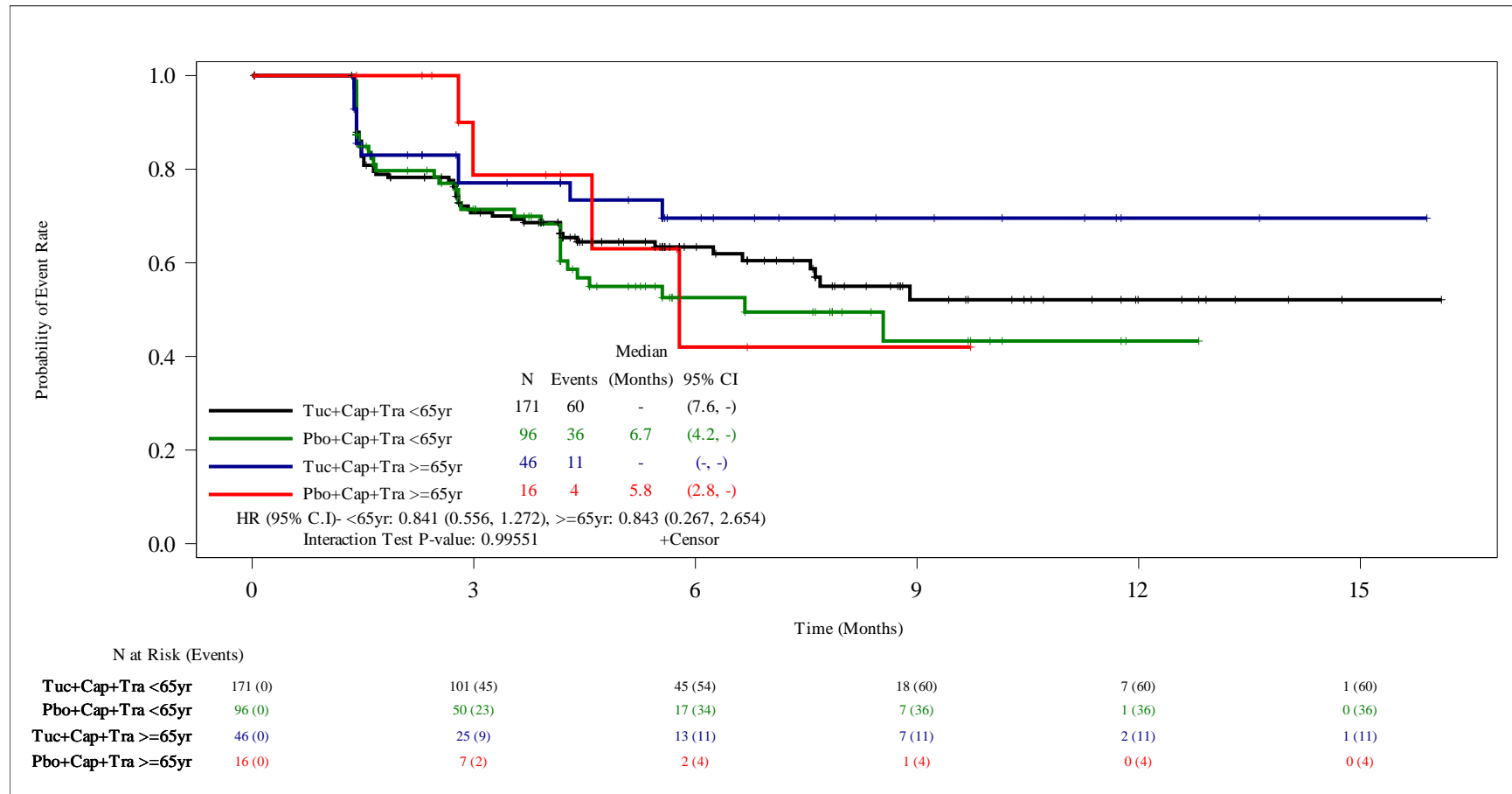
Interaction test p-value calculated from unstratified Cox proportional hazards model for the interaction term of treatment and geographic region.

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_1753\v01\outputs\tlfs\pgms\f-pro-km-ttw-tx.sas Output: f-pro-km-ttw10-txgr-itts.rtf(11MAY20:15:36)

Data: adsl,adcm,adttepro

Seattle Genetics Protocol ONT-380-206

**Figure <Insert Table Num> Time to Worsening ≥ 10 in EQ-5D-5L Health Score by Treatment Arm and Age
ITT - OS Population**



Time to first worsening ≥ 10 in EQ-5D-5L Health Score.

Subjects without worsening ≥ 10 are censored to the last EQ-5D-5L assessment date with non-missing health score.

HR is computed from the unstratified Cox proportional hazards model.

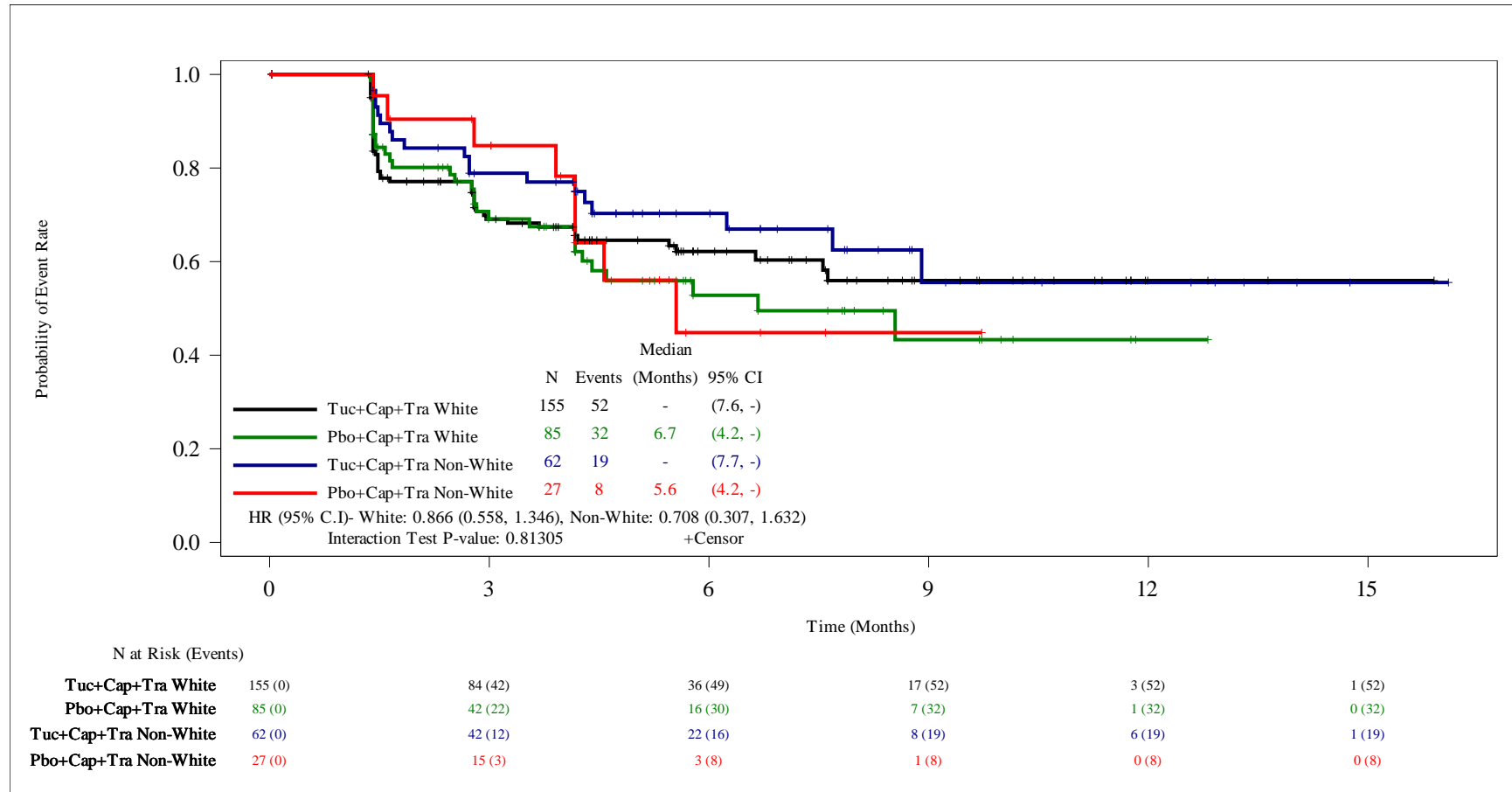
Interaction test p-value calculated from unstratified Cox proportional hazards model for the interaction term of treatment and age.

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_1753\v01\outputs\tlfs\pgms\f-pro-km-ttw-tx.sas Output: f-pro-km-ttw10-txage-itts.rtf(11MAY20:15:36)

Data: adsl,adcm,adttepro

Seattle Genetics Protocol ONT-380-206

**Figure <Insert Table Num> Time to Worsening ≥ 10 in EQ-5D-5L Health Score by Treatment Arm and Race
ITT - OS Population**



Time to first worsening ≥ 10 in EQ-5D-5L Health Score.

Subjects without worsening ≥ 10 are censored to the last EQ-5D-5L assessment date with non-missing health score.

HR is computed from the unstratified Cox proportional hazards model.

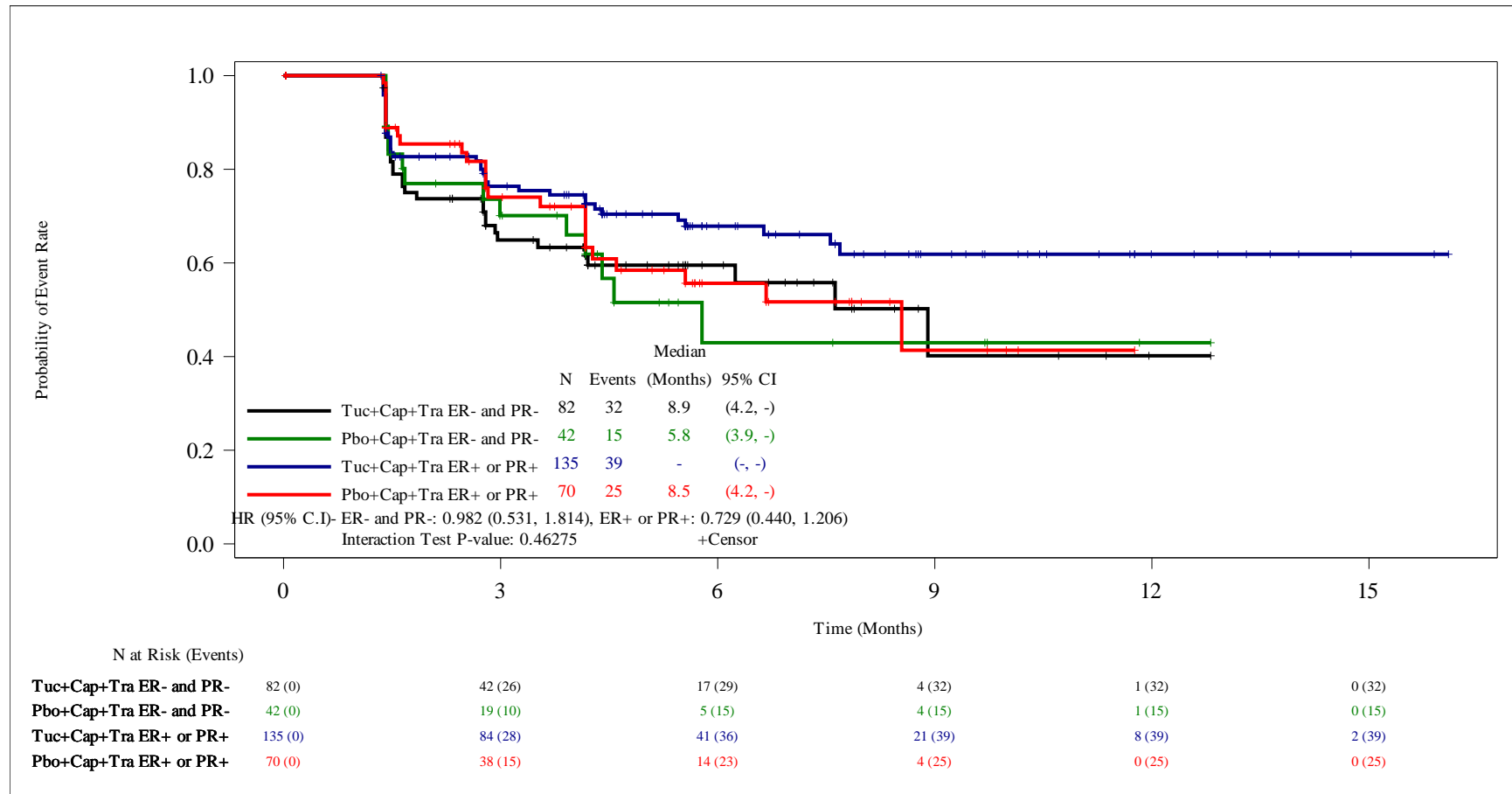
Interaction test p-value calculated from unstratified Cox proportional hazards model for the interaction term of treatment and race.

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_1753\v01\outputs\tlfs\pgms\f-pro-km-ttw-tx.sas Output: f-pro-km-ttw10-txrace-itts.rtf(11MAY20:15:36)

Data: adsl,adcm,adttepro

Seattle Genetics Protocol ONT-380-206

**Figure <Insert Table Num> Time to Worsening ≥ 10 in EQ-5D-5L Health Score by Treatment Arm and Hormone Receptor Status
ITT - OS Population**



Time to first worsening ≥ 10 in EQ-5D-5L Health Score.

Subjects without worsening ≥ 10 are censored to the last EQ-5D-5L assessment date with non-missing health score.

HR is computed from the unstratified Cox proportional hazards model.

Interaction test p-value calculated from unstratified Cox proportional hazards model for the interaction term of treatment and hormone receptor status.

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_1753\v01\outputs\tlfs\pgms\f-pro-km-ttw-tx.sas Output: f-pro-km-ttw10-tx-hr-itss.rtf(11MAY20:15:36)

Data: adsl,adcm,adttepro

Seattle Genetics Protocol ONT-380-206**Time to Worsening in EQ-5D-5L Health Score by Treatment Arm and Brain Metastases Status
ITT - OS Population**

| Event | With Brian Metastases | | Without Brain Metastases | | |
|----------------------------|--|-----------------------|--------------------------|-----------------------|-------------------|
| | Tuc+Cap+Tra (N=107) | Pbo+Cap+Tra (N=56) | Tuc+Cap+Tra (N=109) | Pbo+Cap+Tra (N=56) | |
| Time to Worsening \geq 7 | Number of Events ^a , n (%) | 26 (24.3) | 20 (35.7) | 46 (42.2) | 22 (39.3) |
| | Number of Censored ^a , n (%) | 81 (75.7) | 36 (64.3) | 63 (57.8) | 34 (60.7) |
| | Hazard Ratio ^b (95% C.I.) | 0.513 (0.284, 0.927) | | 1.098 (0.660, 1.826) | |
| | P-value ^c | 0.02234 | | 0.71320 | |
| | Interaction Test P-value ^d | 0.06451 | | | |
| | Median Time to Onset of the First Event (Days) (95% C.I.) ^e | - (-, -) | 5.5 (4.2, -) | 7.6 (4.2, -) | 8.5 (4.2, -) |
| | 25 th , 75 th Percentile | 4.4025, - | 2.7926, - | 1.6427, - | 2.8255, - |
| | Observed Min, Max ^f | 0.0329+, 14.7515+ | 0.0329+, 12.8131+ | 0.0329+, 16.0986+ | 0.0329+, 11.8275+ |

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Only subjects with baseline health scores are included.

a. Event is defined as the first worsening \geq 7 in EQ-5D-5L health score. Subjects without worsening \geq 7 are censored to the last EQ5D assessment date with non-missing health score.

b. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the unstratified Cox proportional hazards model. A hazard ratio $<$ 1.0 favors the Tuc+Cap+Tra arm.

c. Two-sided p-value calculated from unstratified log-rank test.

d. Interaction test p-value calculated from unstratified Cox proportional hazards model for the interaction term of treatment and brain metastases status at baseline.

e. Calculated using the complementary log-log transformation method (Collett, 1994).

f. '+' means the observed time is from censored subjects.

g. Event is defined as the first worsening \geq 10 in EQ-5D-5L health score. Subjects without worsening \geq 10 are censored to the last EQ5D assessment date with non-missing health score.

Data Snapshot: 14OCT2019, Data Cutoff Date: 04SEP2019

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_1753\v01\outputs\tlfs\pgms\t-pro-ttw.sas Output: t-pro-ttw-bm-itts.rtf (14MAY20:14:35) Data: adsl, adcm, adttepro

Seattle Genetics Protocol ONT-380-206**Time to Worsening in EQ-5D-5L Health Score by Treatment Arm and Brain Metastases Status****ITT - OS Population**

| Event | | With Brain Metastases | | Without Brain Metastases | |
|--------------------------------|---|-------------------------|-----------------------|--------------------------|-----------------------|
| | | Tuc+Cap+Tra (N=107) | Pbo+Cap+Tra (N=56) | Tuc+Cap+Tra (N=109) | Pbo+Cap+Tra (N=56) |
| Time to Worsening \geq 10 | Number of Events ^g , n (%) | 25 (23.4) | 19 (33.9) | 45 (41.3) | 21 (37.5) |
| | Number of Censored ^g , n (%) | 82 (76.6) | 37 (66.1) | 64 (58.7) | 35 (62.5) |
| | Hazard Ratio ^b (95% C.I.) | 0.527 (0.288, 0.966) | | 1.115 (0.664, 1.873) | |
| | P-value ^c | 0.03235 | | 0.67370 | |
| | Interaction Test P-value ^d | 0.06994 | | | |
| | Median Time to Onset of the First Event (Days) (95% C.I.) ^e | - (-, -) | 5.6 (4.2, -) | 7.6 (4.2, -) | 8.5 (4.2, -) |
| | 25 th , 75 th Percentile | 5.4538, - | 2.7926, - | 1.6756, - | 2.8255, - |
| Observed Min, Max ^f | 0.0329+, 14.7515+ | 0.0329+, 12.8131+ | 0.0329+, 16.0986+ | 0.0329+, 11.8275+ | |

| Event | With Brain Metastases | | Without Brain Metastases | |
|-------|------------------------|-----------------------|--------------------------|-----------------------|
| | Tuc+Cap+Tra (N=107) | Pbo+Cap+Tra (N=56) | Tuc+Cap+Tra (N=109) | Pbo+Cap+Tra (N=56) |

Only subjects with baseline health scores are included.

- Event is defined as the first worsening ≥ 7 in EQ-5D-5L health score. Subjects without worsening ≥ 7 are censored to the last EQ5D assessment date with non-missing health score.
- Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the unstratified Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.
- Two-sided p-value calculated from unstratified log-rank test.
- Interaction test p-value calculated from unstratified Cox proportional hazards model for the interaction term of treatment and brain metastases status at baseline.
- Calculated using the complementary log-log transformation method (Collett, 1994).
- '+' means the observed time is from censored subjects.
- Event is defined as the first worsening ≥ 10 in EQ-5D-5L health score. Subjects without worsening ≥ 10 are censored to the last EQ5D assessment date with non-missing health score.

Data Snapshot: 14OCT2019, Data Cutoff Date: 04SEP2019

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_1753\v01\outputs\tlfs\pgms\t-pro-ttw.sas Output: t-pro-ttw-bm-itts.rtf (14MAY20:14:35) Data: adsl, adcm, adttepro

Seattle Genetics Protocol ONT-380-206**Time to Worsening in EQ-5D-5L Health Score by Treatment Arm and Baseline ECOG Status
ITT - OS Population**

| Event | ECOG=0 | | ECOG=1 | | |
|----------------------------|--|-----------------------|------------------------|-----------------------|-------------------|
| | Tuc+Cap+Tra (N=105) | Pbo+Cap+Tra (N=52) | Tuc+Cap+Tra (N=112) | Pbo+Cap+Tra (N=60) | |
| Time to Worsening \geq 7 | Number of Events ^a , n (%) | 38 (36.2) | 21 (40.4) | 35 (31.3) | 21 (35.0) |
| | Number of Censored ^a , n (%) | 67 (63.8) | 31 (59.6) | 77 (68.8) | 39 (65.0) |
| | Hazard Ratio ^b (95% C.I.) | 0.838 (0.492, 1.429) | | 0.763 (0.443, 1.313) | |
| | P-value ^c | 0.50583 | | 0.32132 | |
| | Interaction Test P-value ^d | 0.86911 | | | |
| | Median Time to Onset of the First Event (Days) (95% C.I.) ^e | - (7.6, -) | 6.7 (4.2, -) | - (6.6, -) | 5.6 (4.2, -) |
| | 25 th , 75 th Percentile | 2.7598, - | 2.7926, - | 3.2526, - | 2.8255, - |
| | Observed Min, Max ^f | 0.0329+, 15.9014+ | 0.0329+, 12.8131+ | 0.0329+, 16.0986+ | 0.0329+, 10.1520+ |

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Only subjects with baseline health scores are included.

a. Event is defined as the first worsening \geq 7 in EQ-5D-5L health score. Subjects without worsening \geq 7 are censored to the last EQ5D assessment date with non-missing health score.

b. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the unstratified Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

c. Two-sided p-value calculated from unstratified log-rank test.

d. Interaction test p-value calculated from unstratified Cox proportional hazards model for the interaction term of treatment and baseline ECOG status.

e. Calculated using the complementary log-log transformation method (Collett, 1994).

f. '+' means the observed time is from censored subjects.

g. Event is defined as the first worsening \geq 10 in EQ-5D-5L health score. Subjects without worsening \geq 10 are censored to the last EQ5D assessment date with non-missing health score.

Data Snapshot: 14OCT2019, Data Cutoff Date: 04SEP2019

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_1753\v01\outputs\tlfs\pgms\t-pro-ttw.sas Output: t-pro-ttw-ecog-itts.rtf (14MAY20:14:35) Data: adsl, adcm, adttepro

Seattle Genetics Protocol ONT-380-206**Time to Worsening in EQ-5D-5L Health Score by Treatment Arm and Baseline ECOG Status
ITT - OS Population**

| Event | | ECOG=0 | | ECOG=1 | |
|-----------------------------|--|------------------------|-----------------------|------------------------|-----------------------|
| | | Tuc+Cap+Tra (N=105) | Pbo+Cap+Tra (N=52) | Tuc+Cap+Tra (N=112) | Pbo+Cap+Tra (N=60) |
| Time to Worsening \geq 10 | Number of Events ^g , n (%) | 36 (34.3) | 20 (38.5) | 35 (31.3) | 20 (33.3) |
| | Number of Censored ^g , n (%) | 69 (65.7) | 32 (61.5) | 77 (68.8) | 40 (66.7) |
| | Hazard Ratio ^b (95% C.I.) | 0.828 (0.479, 1.430) | | 0.801 (0.461, 1.390) | |
| | P-value ^c | 0.48621 | | 0.42359 | |
| | Interaction Test P-value ^d | 0.99051 | | | |
| | Median Time to Onset of the First Event (Days) (95% C.I.) ^e | - (7.6, -) | 8.5 (4.2, -) | - (6.6, -) | 5.8 (4.2, -) |
| | 25 th , 75 th Percentile | 2.7598, - | 2.7926, - | 3.2526, - | 2.8255, - |
| | Observed Min, Max ^f | 0.0329+, 15.9014+ | 0.0329+, 12.8131+ | 0.0329+, 16.0986+ | 0.0329+, 10.1520+ |

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Only subjects with baseline health scores are included.

a. Event is defined as the first worsening ≥ 7 in EQ-5D-5L health score. Subjects without worsening ≥ 7 are censored to the last EQ5D assessment date with non-missing health score.

b. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the unstratified Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

c. Two-sided p-value calculated from unstratified log-rank test.

d. Interaction test p-value calculated from unstratified Cox proportional hazards model for the interaction term of treatment and baseline ECOG status.

e. Calculated using the complementary log-log transformation method (Collett, 1994).

f. '+' means the observed time is from censored subjects.

g. Event is defined as the first worsening ≥ 10 in EQ-5D-5L health score. Subjects without worsening ≥ 10 are censored to the last EQ5D assessment date with non-missing health score.

Data Snapshot: 14OCT2019, Data Cutoff Date: 04SEP2019

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_1753\v01\outputs\tlfs\pgms\t-pro-ttw.sas Output: t-pro-ttw-ecog-itts.rf (14MAY20:14:35) Data: adsl, adcm, adttepro

Seattle Genetics Protocol ONT-380-206**Time to Worsening in EQ-5D-5L Health Score by Treatment Arm and Race
ITT - OS Population**

| Event | White | | Non-White | | |
|----------------------------|--|-----------------------|-----------------------|-----------------------|---------------------|
| | Tuc+Cap+Tra (N=155) | Pbo+Cap+Tra (N=85) | Tuc+Cap+Tra (N=62) | Pbo+Cap+Tra (N=27) | |
| Time to Worsening \geq 7 | Number of Events ^a , n (%) | 53 (34.2) | 33 (38.8) | 20 (32.3) | 9 (33.3) |
| | Number of Censored ^a , n (%) | 102 (65.8) | 52 (61.2) | 42 (67.7) | 18 (66.7) |
| | Hazard Ratio ^b (95% C.I.) | 0.856 (0.554, 1.323) | | 0.673 (0.304, 1.491) | |
| | P-value ^c | 0.47421 | | 0.32437 | |
| | Interaction Test P-value ^d | 0.73422 | | | |
| | Median Time to Onset of the First Event (Days) (95% C.I.) ^e | - (6.6, -) | 6.7 (4.2, -) | - (7.7, -) | 5.5 (4.2, -) |
| | 25 th , 75 th Percentile | 2.7598, - | 2.7926, - | 4.1725, - | 4.1725, - |
| | Observed Min, Max ^f | 0.0329+, 15.9014+ | 0.0329+, 12.8131+ | 0.0329+, 16.0986+ | 0.0329+, 9.7248+ |

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Only subjects with baseline health scores are included.

a. Event is defined as the first worsening \geq 7 in EQ-5D-5L health score. Subjects without worsening \geq 7 are censored to the last EQ5D assessment date with non-missing health score.

b. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the unstratified Cox proportional hazards model. A hazard ratio $<$ 1.0 favors the Tuc+Cap+Tra arm.

c. Two-sided p-value calculated from unstratified log-rank test.

d. Interaction test p-value calculated from unstratified Cox proportional hazards model for the interaction term of treatment and race.

e. Calculated using the complementary log-log transformation method (Collett, 1994).

f. '+' means the observed time is from censored subjects.

g. Event is defined as the first worsening \geq 10 in EQ-5D-5L health score. Subjects without worsening \geq 10 are censored to the last EQ5D assessment date with non-missing health score.

Data Snapshot: 14OCT2019, Data Cutoff Date: 04SEP2019

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_1753\v01\outputs\tlfs\pgms\t-pro-ttw.sas Output: t-pro-ttw-race-itts.rtf (14MAY20:14:35) Data: adsl, adcm, adttepro

Seattle Genetics Protocol ONT-380-206**Time to Worsening in EQ-5D-5L Health Score by Treatment Arm and Race
ITT - OS Population**

| Event | White | | Non-White | | |
|-----------------------------|--|-----------------------|-----------------------|-----------------------|------------------|
| | Tuc+Cap+Tra (N=155) | Pbo+Cap+Tra (N=85) | Tuc+Cap+Tra (N=62) | Pbo+Cap+Tra (N=27) | |
| Time to Worsening \geq 10 | Number of Events ^a , n (%) | 52 (33.5) | 32 (37.6) | 19 (30.6) | 8 (29.6) |
| | Number of Censored ^a , n (%) | 103 (66.5) | 53 (62.4) | 43 (69.4) | 19 (70.4) |
| | Hazard Ratio ^b (95% C.I.) | 0.866 (0.558, 1.346) | | 0.708 (0.307, 1.632) | |
| | P-value ^c | 0.51302 | | 0.41362 | |
| | Interaction Test P-value ^d | 0.81305 | | | |
| | Median Time to Onset of the First Event (Days) (95% C.I.) ^e | - (7.6, -) | 6.7 (4.2, -) | - (7.7, -) | 5.6 (4.2, -) |
| | 25 th , 75 th Percentile | 2.7598, - | 2.7926, - | 4.1725, - | 4.1725, - |
| | Observed Min, Max ^f | 0.0329+, 15.9014+ | 0.0329+, 12.8131+ | 0.0329+, 16.0986+ | 0.0329+, 9.7248+ |

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Only subjects with baseline health scores are included.

a. Event is defined as the first worsening \geq 7 in EQ-5D-5L health score. Subjects without worsening \geq 7 are censored to the last EQ5D assessment date with non-missing health score.

b. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the unstratified Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

c. Two-sided p-value calculated from unstratified log-rank test.

d. Interaction test p-value calculated from unstratified Cox proportional hazards model for the interaction term of treatment and race.

e. Calculated using the complementary log-log transformation method (Collett, 1994).

f. '+' means the observed time is from censored subjects.

g. Event is defined as the first worsening \geq 10 in EQ-5D-5L health score. Subjects without worsening \geq 10 are censored to the last EQ5D assessment date with non-missing health score.

Data Snapshot: 14OCT2019, Data Cutoff Date: 04SEP2019

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_1753\v01\outputs\tlfs\pgms\t-pro-ttw.sas Output: t-pro-ttw-race-itts.rtf (14MAY20:14:35) Data: adsl, adcm, adttepro

Seattle Genetics Protocol ONT-380-206**Time to Worsening in EQ-5D-5L Health Score by Treatment Arm and Hormone Receptor Status
ITT - OS Population**

| Event | | ER- and PR- | | ER+ or PR+ | |
|----------------------------|--|-----------------------|-------------------------|------------------------|-------------------------|
| | | Tuc+Cap+Tra (N=82) | Pbo+Cap+Tra (N=42) | Tuc+Cap+Tra (N=135) | Pbo+Cap+Tra (N=70) |
| Time to Worsening \geq 7 | Number of Events ^a , n (%) | 33 (40.2) | 17 (40.5) | 40 (29.6) | 25 (35.7) |
| | Number of Censored ^a , n (%) | 49 (59.8) | 25 (59.5) | 95 (70.4) | 45 (64.3) |
| | Hazard Ratio ^b (95% C.I.) | | 0.900 (0.501, 1.617) | | 0.747 (0.452, 1.233) |
| | P-value ^c | | 0.71926 | | 0.24385 |
| | Interaction Test P-value ^d | | | 0.63186 | |
| | Median Time to Onset of the First Event (Days) (95% C.I.) ^e | 7.6 (3.5, -) | 4.6 (3.0, -) | - (7.7, -) | 8.5 (4.2, -) |
| | 25 th , 75 th Percentile | 1.6756, - | 2.7598, - | 3.6797, - | 2.8255, - |
| | Observed Min, Max ^f | 0.0329+, 12.8131+ | 0.0329+, 12.8131+ | 0.0329+, 16.0986+ | 0.0329+, 11.7618+ |

| Event | ER- and PR- | | ER+ or PR+ | |
|-------|-----------------------|-----------------------|------------------------|-----------------------|
| | Tuc+Cap+Tra (N=82) | Pbo+Cap+Tra (N=42) | Tuc+Cap+Tra (N=135) | Pbo+Cap+Tra (N=70) |

Only subjects with baseline health scores are included.

- Event is defined as the first worsening ≥ 7 in EQ-5D-5L health score. Subjects without worsening ≥ 7 are censored to the last EQ5D assessment date with non-missing health score.
- Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the unstratified Cox proportional hazards model. A hazard ratio < 1.0 favors the Tuc+Cap+Tra arm.
- Two-sided p-value calculated from unstratified log-rank test.
- Interaction test p-value calculated from unstratified Cox proportional hazards model for the interaction term of treatment and hormone receptor status.
- Calculated using the complementary log-log transformation method (Collett, 1994).
- '+' means the observed time is from censored subjects.
- Event is defined as the first worsening ≥ 10 in EQ-5D-5L health score. Subjects without worsening ≥ 10 are censored to the last EQ5D assessment date with non-missing health score.

Data Snapshot: 14OCT2019, Data Cutoff Date: 04SEP2019

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_1753\v01\outputs\tlfs\pgms\t-pro-ttw.sas Output: t-pro-ttw-hr-itts.rtf (14MAY20:14:35) Data: adsl, adcm, adttepro

Seattle Genetics Protocol ONT-380-206**Time to Worsening in EQ-5D-5L Health Score by Treatment Arm and Hormone Receptor Status
ITT - OS Population**

| Event | | ER- and PR- | | ER+ or PR+ | |
|-----------------------------|--|-----------------------|-------------------------|------------------------|-------------------------|
| | | Tuc+Cap+Tra (N=82) | Pbo+Cap+Tra (N=42) | Tuc+Cap+Tra (N=135) | Pbo+Cap+Tra (N=70) |
| Time to Worsening \geq 10 | Number of Events ^g , n (%) | 32 (39.0) | 15 (35.7) | 39 (28.9) | 25 (35.7) |
| | Number of Censored ^g , n (%) | 50 (61.0) | 27 (64.3) | 96 (71.1) | 45 (64.3) |
| | Hazard Ratio ^b (95% C.I.) | | 0.982 (0.531, 1.814) | | 0.729 (0.440, 1.206) |
| | P-value ^c | | 0.95192 | | 0.20853 |
| | Interaction Test P-value ^d | | | 0.46275 | |
| | Median Time to Onset of the First Event (Days) (95% C.I.) ^e | 8.9 (4.2, -) | 5.8 (3.9, -) | - (-, -) | 8.5 (4.2, -) |
| | 25 th , 75 th Percentile | 1.8398, - | 2.7598, - | 3.6797, - | 2.8255, - |
| | Observed Min, Max ^f | 0.0329+, 12.8131+ | 0.0329+, 12.8131+ | 0.0329+, 16.0986+ | 0.0329+, 11.7618+ |

| Event | ER- and PR- | | ER+ or PR+ | |
|-------|-----------------------|-----------------------|------------------------|-----------------------|
| | Tuc+Cap+Tra (N=82) | Pbo+Cap+Tra (N=42) | Tuc+Cap+Tra (N=135) | Pbo+Cap+Tra (N=70) |

Only subjects with baseline health scores are included.

a. Event is defined as the first worsening ≥ 7 in EQ-5D-5L health score. Subjects without worsening ≥ 7 are censored to the last EQ5D assessment date with non-missing health score.

b. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the unstratified Cox proportional hazards model. A hazard ratio < 1.0 favors the Tuc+Cap+Tra arm.

c. Two-sided p-value calculated from unstratified log-rank test.

d. Interaction test p-value calculated from unstratified Cox proportional hazards model for the interaction term of treatment and hormone receptor status.

e. Calculated using the complementary log-log transformation method (Collett, 1994).

f. '+' means the observed time is from censored subjects.

g. Event is defined as the first worsening ≥ 10 in EQ-5D-5L health score. Subjects without worsening ≥ 10 are censored to the last EQ5D assessment date with non-missing health score.

Data Snapshot: 14OCT2019, Data Cutoff Date: 04SEP2019

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_1753\v01\outputs\tlfs\pgms\t-pro-ttw.sas Output: t-pro-ttw-hr-itts.rtf (14MAY20:14:35) Data: adsl, adcm, adttepro

Seattle Genetics Protocol ONT-380-206**Time to Worsening in EQ-5D-5L Health Score by Treatment Arm and Geographic Region
ITT - OS Population**

| Event | North America | | Rest of World | | |
|----------------------------|--|-----------------------|-----------------------|-----------------------|-------------------|
| | Tuc+Cap+Tra (N=124) | Pbo+Cap+Tra (N=65) | Tuc+Cap+Tra (N=93) | Pbo+Cap+Tra (N=47) | |
| Time to Worsening \geq 7 | Number of Events ^a , n (%) | 36 (29.0) | 22 (33.8) | 37 (39.8) | 20 (42.6) |
| | Number of Censored ^a , n (%) | 88 (71.0) | 43 (66.2) | 56 (60.2) | 27 (57.4) |
| | Hazard Ratio ^b (95% C.I.) | 0.743 (0.436, 1.266) | | 0.877 (0.509, 1.511) | |
| | P-value ^c | 0.26590 | | 0.62827 | |
| | Interaction Test P-value ^d | 0.67105 | | | |
| | Median Time to Onset of the First Event (Days) (95% C.I.) ^e | - (8.9, -) | 5.6 (4.2, -) | - (4.3, -) | 5.8 (3.5, -) |
| | 25 th , 75 th Percentile | 3.6797, - | 2.9897, - | 2.7598, - | 2.4641, - |
| | Observed Min, Max ^f | 0.0329+, 16.0986+ | 0.0329+, 12.8131+ | 0.0329+, 12.9117+ | 0.0329+, 11.8275+ |

| Event | North America | | Rest of World | |
|-------|------------------------|-----------------------|-----------------------|-----------------------|
| | Tuc+Cap+Tra (N=124) | Pbo+Cap+Tra (N=65) | Tuc+Cap+Tra (N=93) | Pbo+Cap+Tra (N=47) |

Only subjects with baseline health scores are included.

- Event is defined as the first worsening ≥ 7 in EQ-5D-5L health score. Subjects without worsening ≥ 7 are censored to the last EQ5D assessment date with non-missing health score.
- Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the unstratified Cox proportional hazards model. A hazard ratio < 1.0 favors the Tuc+Cap+Tra arm.
- Two-sided p-value calculated from unstratified log-rank test.
- Interaction test p-value calculated from unstratified Cox proportional hazards model for the interaction term of treatment and geographic region.
- Calculated using the complementary log-log transformation method (Collett, 1994).
- '+' means the observed time is from censored subjects.
- Event is defined as the first worsening ≥ 10 in EQ-5D-5L health score. Subjects without worsening ≥ 10 are censored to the last EQ5D assessment date with non-missing health score.

Data Snapshot: 14OCT2019, Data Cutoff Date: 04SEP2019

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_1753\v01\outputs\tlfs\pgms\t-pro-ttw.sas Output: t-pro-ttw-gr-itts.rtf (14MAY20:14:35) Data: adsl, adcm, adttepro

Seattle Genetics Protocol ONT-380-206**Time to Worsening in EQ-5D-5L Health Score by Treatment Arm and Geographic Region
ITT - OS Population**

| Event | | North America | | Rest of World | |
|-----------------------------|--|------------------------|-----------------------|-----------------------|-----------------------|
| | | Tuc+Cap+Tra (N=124) | Pbo+Cap+Tra (N=65) | Tuc+Cap+Tra (N=93) | Pbo+Cap+Tra (N=47) |
| Time to Worsening \geq 10 | Number of Events ^g , n (%) | 35 (28.2) | 20 (30.8) | 36 (38.7) | 20 (42.6) |
| | Number of Censored ^g , n (%) | 89 (71.8) | 45 (69.2) | 57 (61.3) | 27 (57.4) |
| | Hazard Ratio ^b (95% C.I.) | 0.793 (0.457, 1.378) | | 0.849 (0.491, 1.466) | |
| | P-value ^c | 0.40311 | | 0.54623 | |
| | Interaction Test P-value ^d | 0.86675 | | | |
| | Median Time to Onset of the First Event (Days) (95% C.I.) ^e | - (8.9, -) | 6.7 (4.2, -) | - (4.3, -) | 5.8 (3.5, -) |
| | 25 th , 75 th Percentile | 4.1725, - | 3.9097, - | 2.7598, - | 2.4641, - |
| | Observed Min, Max ^f | 0.0329+, 16.0986+ | 0.0329+, 12.8131+ | 0.0329+, 12.9117+ | 0.0329+, 11.8275+ |

| Event | North America | | Rest of World | |
|-------|------------------------|-----------------------|-----------------------|-----------------------|
| | Tuc+Cap+Tra (N=124) | Pbo+Cap+Tra (N=65) | Tuc+Cap+Tra (N=93) | Pbo+Cap+Tra (N=47) |

Only subjects with baseline health scores are included.

- a. Event is defined as the first worsening ≥ 7 in EQ-5D-5L health score. Subjects without worsening ≥ 7 are censored to the last EQ5D assessment date with non-missing health score.
- b. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the unstratified Cox proportional hazards model. A hazard ratio < 1.0 favors the Tuc+Cap+Tra arm.
- c. Two-sided p-value calculated from unstratified log-rank test.
- d. Interaction test p-value calculated from unstratified Cox proportional hazards model for the interaction term of treatment and geographic region.
- e. Calculated using the complementary log-log transformation method (Collett, 1994).
- f. '+' means the observed time is from censored subjects.
- g. Event is defined as the first worsening ≥ 10 in EQ-5D-5L health score. Subjects without worsening ≥ 10 are censored to the last EQ5D assessment date with non-missing health score.

Data Snapshot: 14OCT2019, Data Cutoff Date: 04SEP2019

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_1753\v01\outputs\tlfs\pgms\t-pro-ttw.sas Output: t-pro-ttw-gr-itts.rtf (14MAY20:14:35) Data: adsl, adcm, adttepro

Seattle Genetics Protocol ONT-380-206**Time to Worsening in EQ-5D-5L Health Score by Treatment Arm and Age
ITT - OS Population**

| Event | | <65yr | | ≥65yr | |
|---------------------------------|--|------------------------|-----------------------|-----------------------|-----------------------|
| | | Tuc+Cap+Tra (N=171) | Pbo+Cap+Tra (N=96) | Tuc+Cap+Tra (N=46) | Pbo+Cap+Tra (N=16) |
| Time to Worsening _{≥7} | Number of Events ^a , n (%) | 61 (35.7) | 38 (39.6) | 12 (26.1) | 4 (25.0) |
| | Number of Censored ^a , n (%) | 110 (64.3) | 58 (60.4) | 34 (73.9) | 12 (75.0) |
| | Hazard Ratio ^b (95% C.I.) | 0.814 (0.542, 1.221) | | 0.918 (0.295, 2.853) | |
| | P-value ^c | 0.30933 | | 0.88044 | |
| | Interaction Test P-value ^d | 0.84300 | | | |
| | Median Time to Onset of the First Event (Days) (95% C.I.) ^e | - (7.6, -) | 5.6 (4.2, -) | - (5.6, -) | 5.8 (2.8, -) |
| | 25 th , 75 th Percentile | 2.7598, - | 2.7926, - | 4.3039, - | 4.5996, - |
| | Observed Min, Max ^f | 0.0329+, 16.0986+ | 0.0329+, 12.8131+ | 0.0329+, 15.9014+ | 0.0329+, 9.7248+ |

| Event | <65yr | | ≥65yr | |
|-------|------------------------|-----------------------|-----------------------|-----------------------|
| | Tuc+Cap+Tra (N=171) | Pbo+Cap+Tra (N=96) | Tuc+Cap+Tra (N=46) | Pbo+Cap+Tra (N=16) |

Only subjects with baseline health scores are included.

a. Event is defined as the first worsening ≥ 7 in EQ-5D-5L health score. Subjects without worsening ≥ 7 are censored to the last EQ5D assessment date with non-missing health score.

b. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the unstratified Cox proportional hazards model. A hazard ratio < 1.0 favors the Tuc+Cap+Tra arm.

c. Two-sided p-value calculated from unstratified log-rank test.

d. Interaction test p-value calculated from unstratified Cox proportional hazards model for the interaction term of treatment and age.

e. Calculated using the complementary log-log transformation method (Collett, 1994).

f. '+' means the observed time is from censored subjects.

g. Event is defined as the first worsening ≥ 10 in EQ-5D-5L health score. Subjects without worsening ≥ 10 are censored to the last EQ5D assessment date with non-missing health score.

Data Snapshot: 14OCT2019, Data Cutoff Date: 04SEP2019

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_1753\v01\outputs\tlfs\pgms\t-pro-ttw.sas Output: t-pro-ttw-age-itss.rtf (14MAY20:14:35) Data: adsl, adcm, adttepro

Seattle Genetics Protocol ONT-380-206**Time to Worsening in EQ-5D-5L Health Score by Treatment Arm and Age
ITT - OS Population**

| Event | | <65yr | | ≥65yr | |
|-----------------------|--|------------------------|-----------------------|-----------------------|-----------------------|
| | | Tuc+Cap+Tra (N=171) | Pbo+Cap+Tra (N=96) | Tuc+Cap+Tra (N=46) | Pbo+Cap+Tra (N=16) |
| Time to Worsening ≥10 | Number of Events ^g , n (%) | 60 (35.1) | 36 (37.5) | 11 (23.9) | 4 (25.0) |
| | Number of Censored ^g , n (%) | 111 (64.9) | 60 (62.5) | 35 (76.1) | 12 (75.0) |
| | Hazard Ratio ^b (95% C.I.) | 0.841 (0.556, 1.272) | | 0.843 (0.267, 2.654) | |
| | P-value ^c | 0.40344 | | 0.76636 | |
| | Interaction Test P-value ^d | 0.99551 | | | |
| | Median Time to Onset of the First Event (Days) (95% C.I.) ^e | - (7.6, -) | 6.7 (4.2, -) | - (-, -) | 5.8 (2.8, -) |
| | 25 th , 75 th Percentile | 2.7598, - | 2.7926, - | 4.3039, - | 4.5996, - |
| | Observed Min, Max ^f | 0.0329+, 16.0986+ | 0.0329+, 12.8131+ | 0.0329+, 15.9014+ | 0.0329+, 9.7248+ |

| Event | <65yr | | ≥65yr | |
|-------|------------------------|-----------------------|-----------------------|-----------------------|
| | Tuc+Cap+Tra (N=171) | Pbo+Cap+Tra (N=96) | Tuc+Cap+Tra (N=46) | Pbo+Cap+Tra (N=16) |

Only subjects with baseline health scores are included.

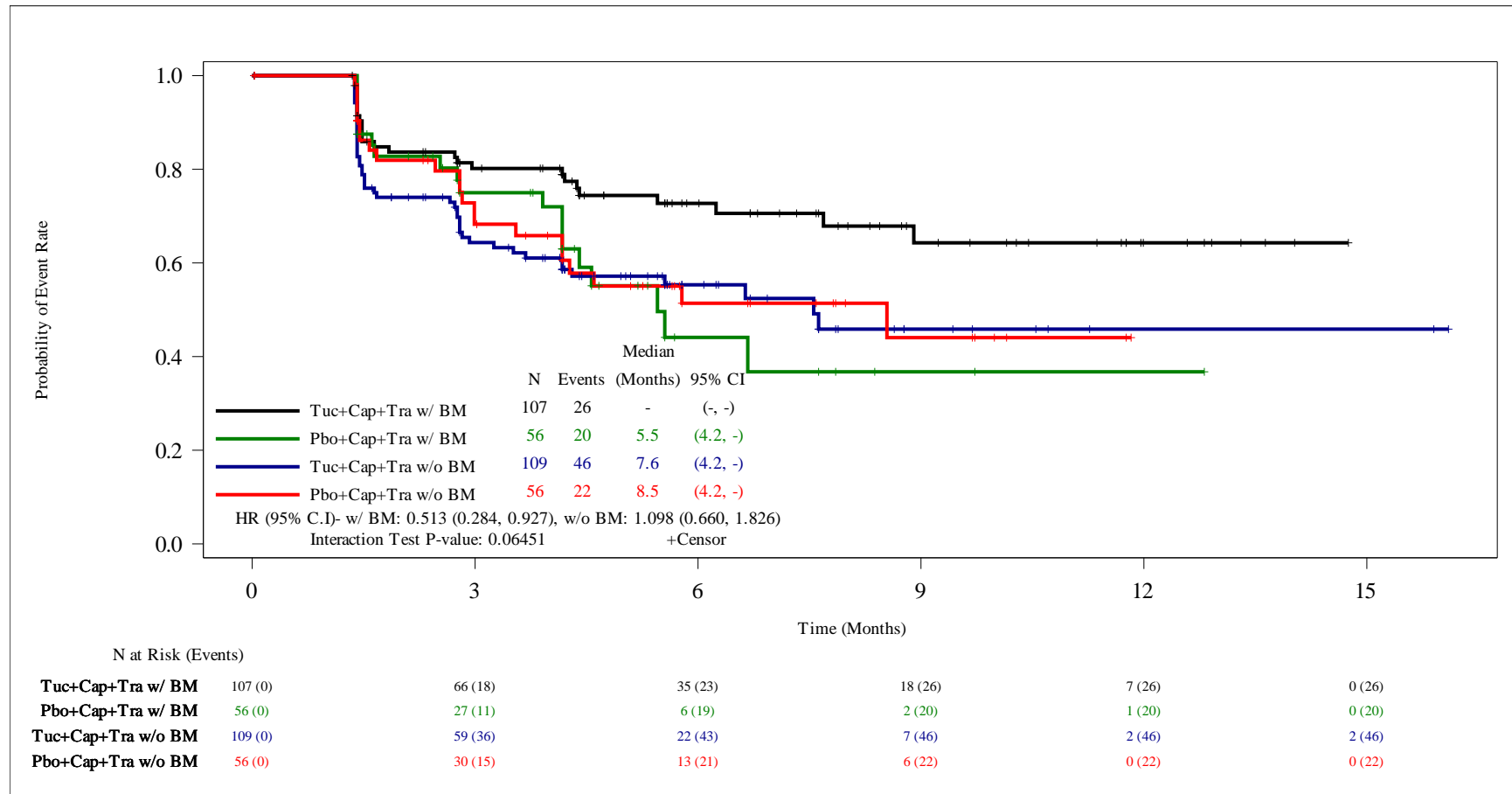
- Event is defined as the first worsening ≥ 7 in EQ-5D-5L health score. Subjects without worsening ≥ 7 are censored to the last EQ5D assessment date with non-missing health score.
- Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the unstratified Cox proportional hazards model. A hazard ratio < 1.0 favors the Tuc+Cap+Tra arm.
- Two-sided p-value calculated from unstratified log-rank test.
- Interaction test p-value calculated from unstratified Cox proportional hazards model for the interaction term of treatment and age.
- Calculated using the complementary log-log transformation method (Collett, 1994).
- '+' means the observed time is from censored subjects.
- Event is defined as the first worsening ≥ 10 in EQ-5D-5L health score. Subjects without worsening ≥ 10 are censored to the last EQ5D assessment date with non-missing health score.

Data Snapshot: 14OCT2019, Data Cutoff Date: 04SEP2019

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_1753\v01\outputs\tlfs\pgms\t-pro-ttw.sas Output: t-pro-ttw-age-itrs.rtf (14MAY20:14:35) Data: adsl, adcm, adttepro

Seattle Genetics Protocol ONT-380-206

**Figure <Insert Table Num> Time to Worsening ≥ 7 in EQ-5D-5L Health Score by Treatment Arm and Brain Metastases Status
ITT - OS Population**



Time to first worsening ≥ 7 in EQ-5D-5L Health Score.

Subjects without worsening ≥ 7 are censored to the last EQ-5D-5L assessment date with non-missing health score.

HR is computed from the unstratified Cox proportional hazards model.

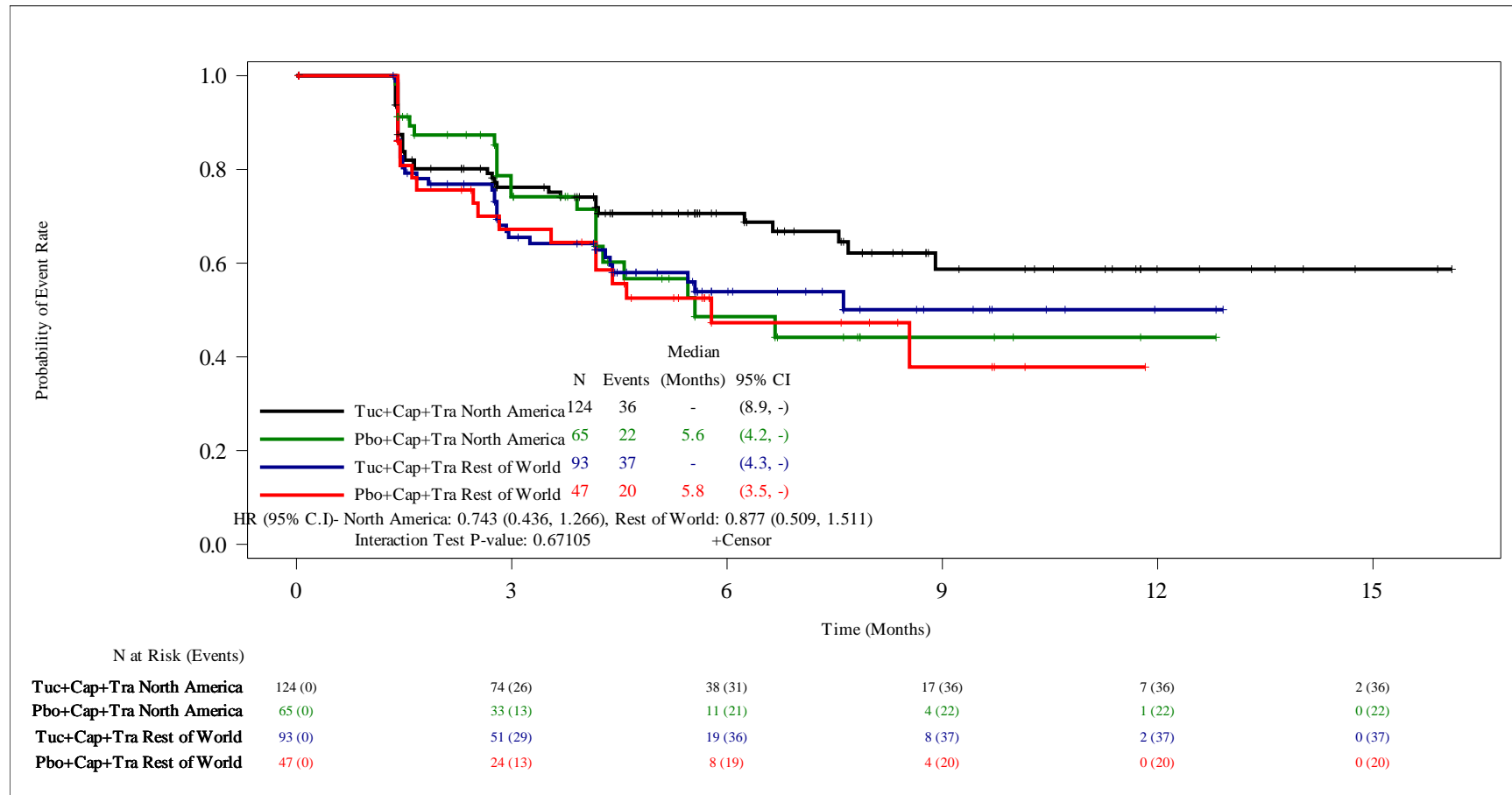
Interaction test p-value calculated from unstratified Cox proportional hazards model for the interaction term of treatment and brain metastases status.

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_1753\v01\outputs\tlfs\pgms\f-pro-km-ttw-tx.sas Output: f-pro-km-ttw7-txbm-itts.rtf(11MAY20:15:36)

Data: adsl,adcm,adttepro

Seattle Genetics Protocol ONT-380-206

**Figure <Insert Table Num> Time to Worsening ≥ 7 in EQ-5D-5L Health Score by Treatment Arm and Geographic Region
ITT - OS Population**



Time to first worsening ≥ 7 in EQ-5D-5L Health Score.

Subjects without worsening ≥ 7 are censored to the last EQ-5D-5L assessment date with non-missing health score.

HR is computed from the unstratified Cox proportional hazards model.

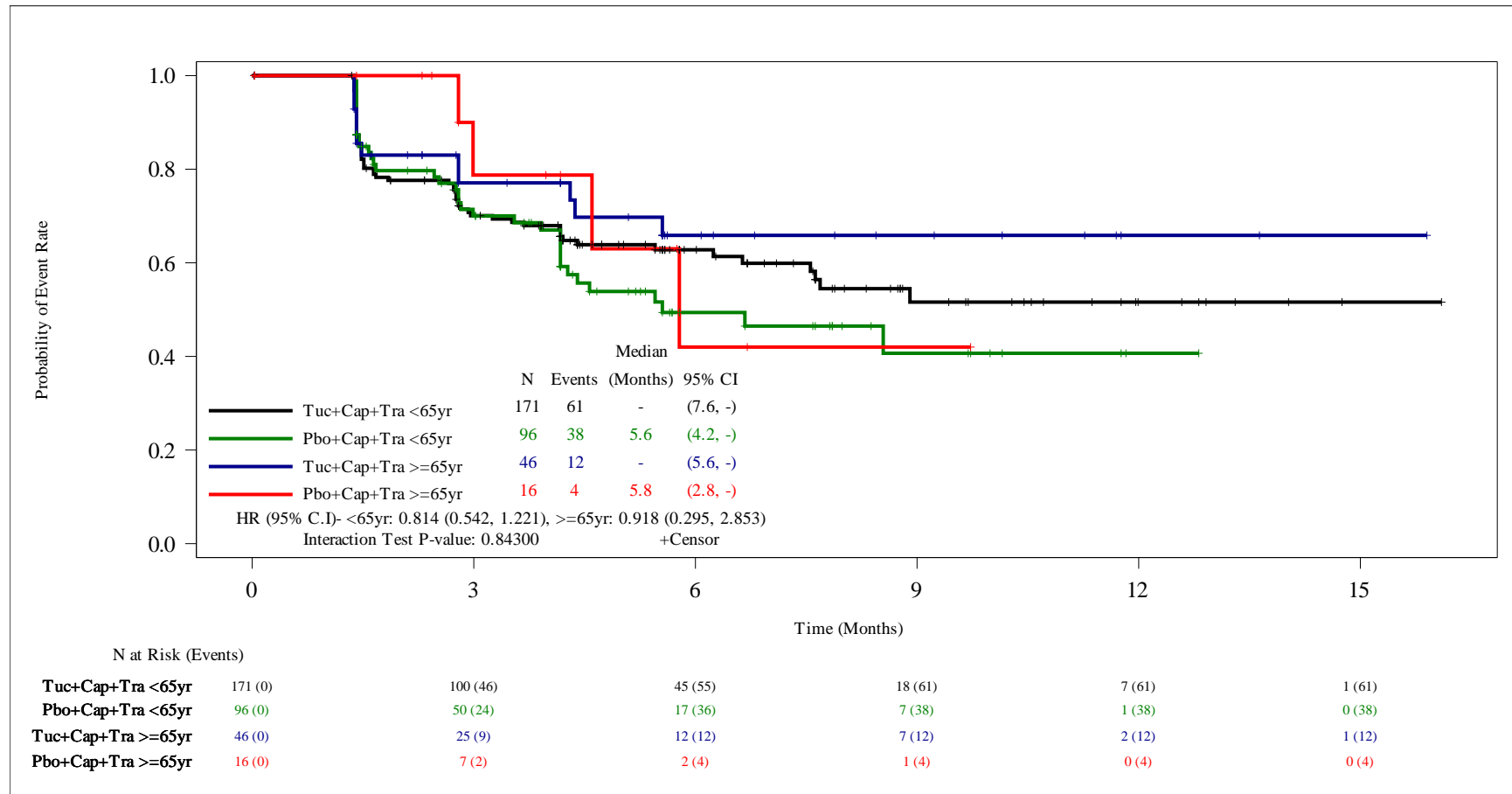
Interaction test p-value calculated from unstratified Cox proportional hazards model for the interaction term of treatment and geographic region.

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_1753\v01\outputs\tlfs\pgms\f-pro-km-ttw-tx.sas Output: f-pro-km-ttw7-txgr-itts.rtf(11MAY20:15:36)

Data: adsl,adcm,adttepro

Seattle Genetics Protocol ONT-380-206

**Figure <Insert Table Num> Time to Worsening ≥ 7 in EQ-5D-5L Health Score by Treatment Arm and Age
ITT - OS Population**



Time to first worsening ≥ 7 in EQ-5D-5L Health Score.

Subjects without worsening ≥ 7 are censored to the last EQ-5D-5L assessment date with non-missing health score.

HR is computed from the unstratified Cox proportional hazards model.

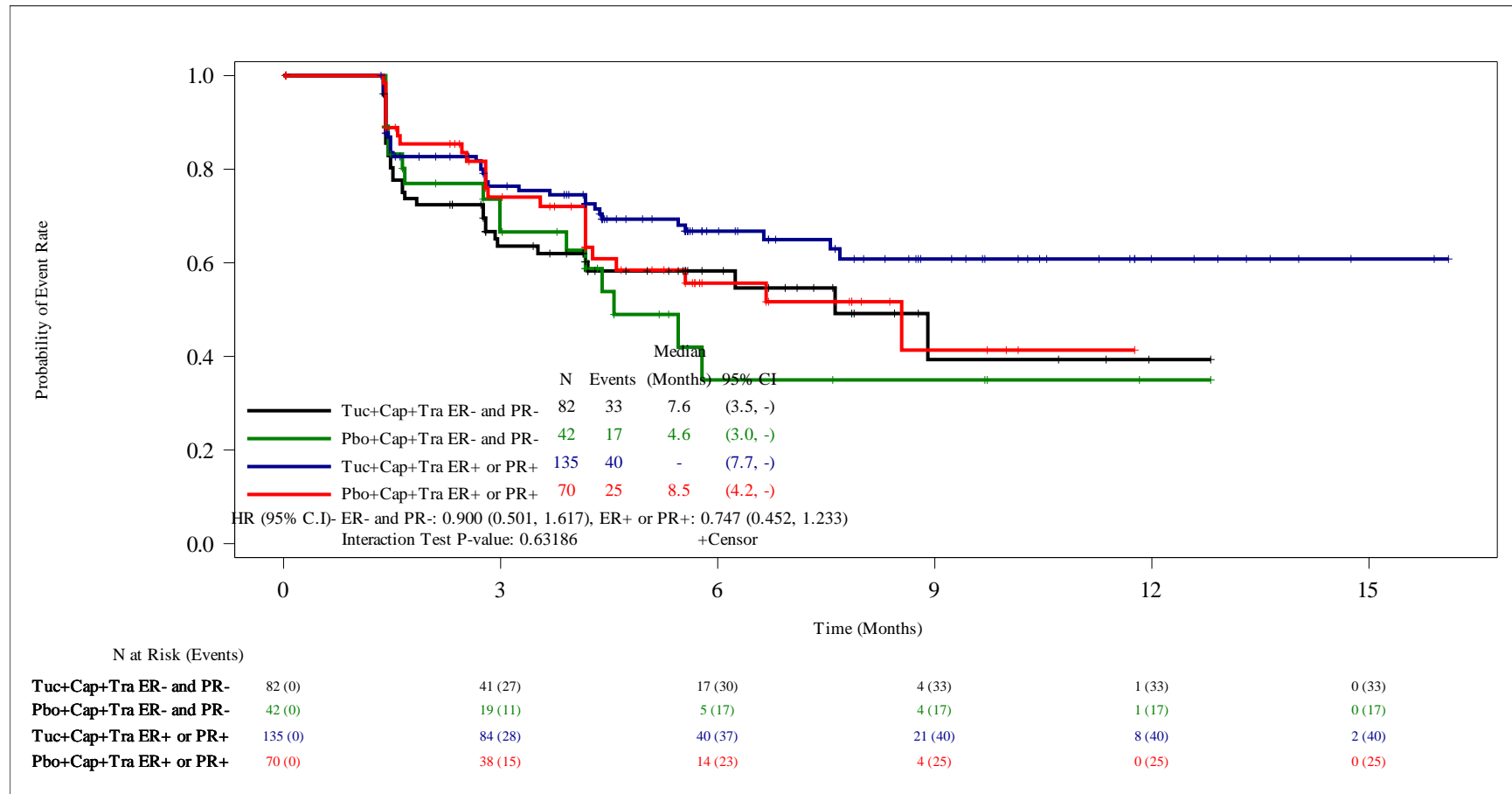
Interaction test p-value calculated from unstratified Cox proportional hazards model for the interaction term of treatment and age.

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_1753\v01\outputs\tlfs\pgms\f-pro-km-ttw-tx.sas Output: f-pro-km-ttw7-txage-itts.rtf(11MAY20:15:36)

Data: adsl,adcm,adttepro

Seattle Genetics Protocol ONT-380-206

**Figure <Insert Table Num> Time to Worsening ≥ 7 in EQ-5D-5L Health Score by Treatment Arm and Hormone Receptor Status
ITT - OS Population**



Time to first worsening ≥ 7 in EQ-5D-5L Health Score.

Subjects without worsening ≥ 7 are censored to the last EQ-5D-5L assessment date with non-missing health score.

HR is computed from the unstratified Cox proportional hazards model.

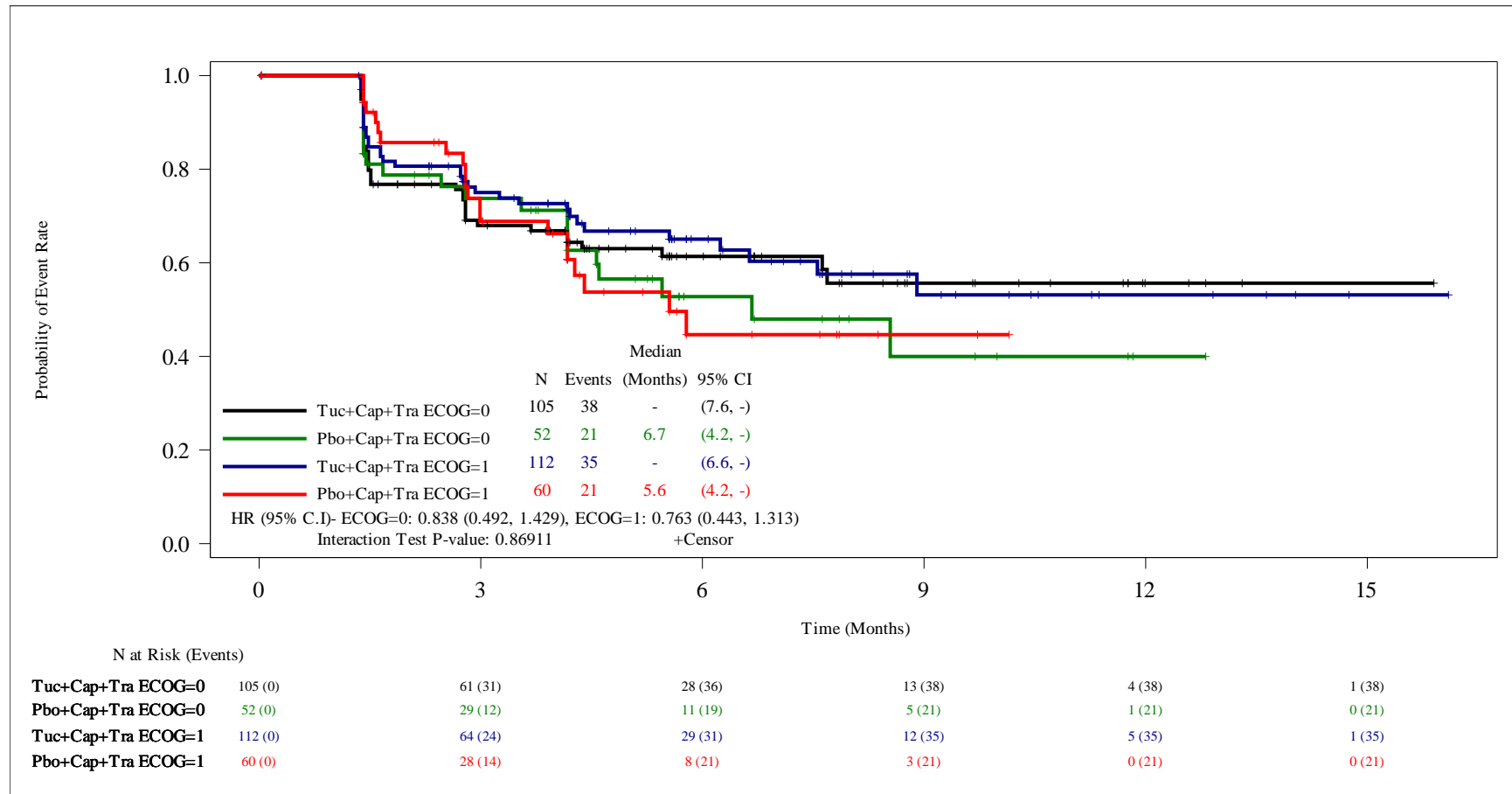
Interaction test p-value calculated from unstratified Cox proportional hazards model for the interaction term of treatment and hormone receptor status.

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_1753\v01\outputs\tlfs\pgms\f-pro-km-ttw-tx.sas Output: f-pro-km-ttw7-tx-hr-itts.rtf(11MAY20:15:36)

Data: adsl,adcm,adttepro

Seattle Genetics Protocol ONT-380-206

**Figure <Insert Table Num> Time to Worsening ≥ 7 in EQ-5D-5L Health Score by Treatment Arm and Baseline ECOG Statue
ITT - OS Population**



Time to first worsening ≥ 7 in EQ-5D-5L Health Score.

Subjects without worsening ≥ 7 are censored to the last EQ-5D-5L assessment date with non-missing health score.

HR is computed from the unstratified Cox proportional hazards model.

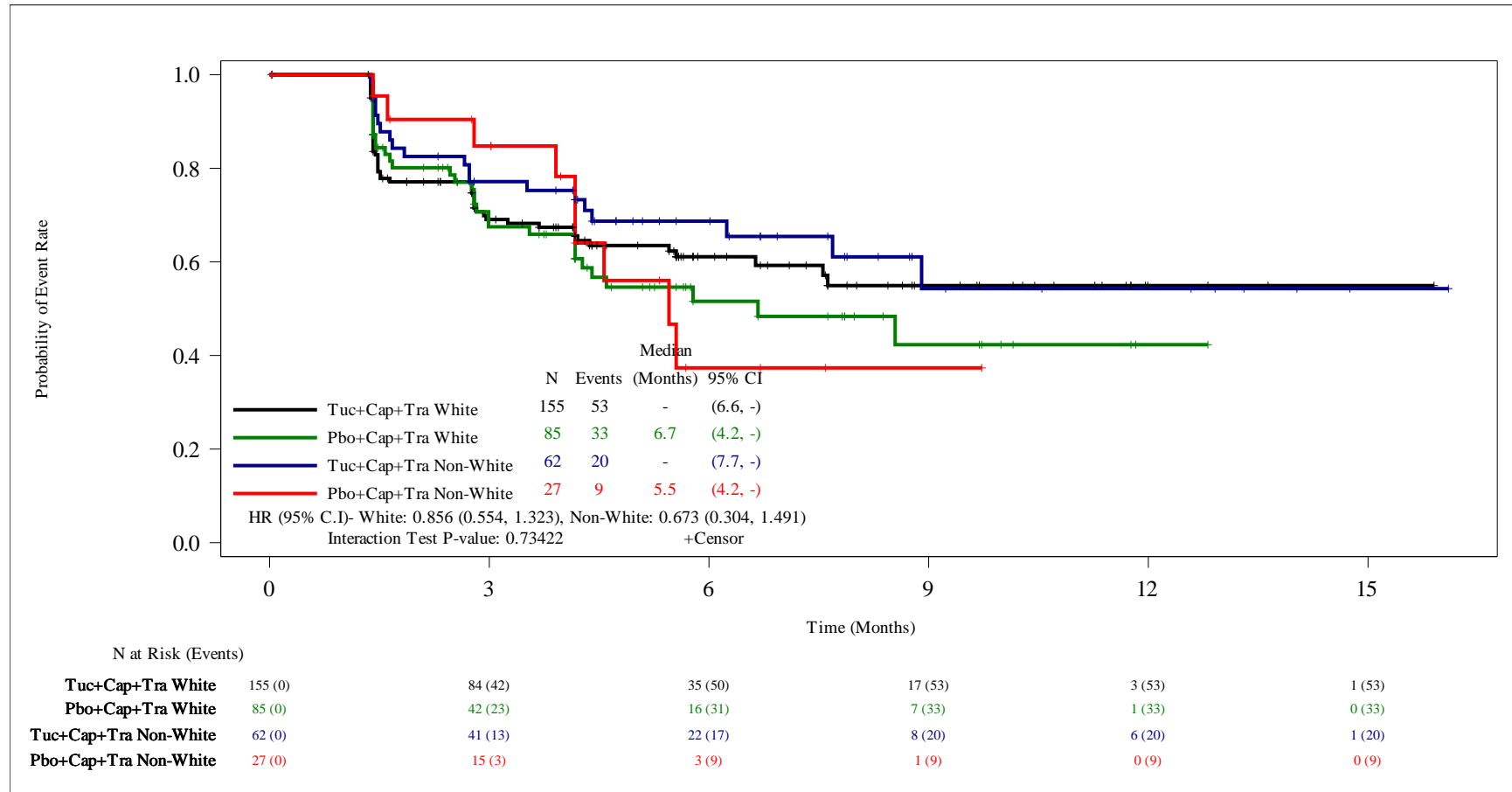
Interaction test p-value calculated from unstratified Cox proportional hazards model for the interaction term of treatment and baseline ECOG status.

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_1753\v01\outputs\tlfs\pgms\f-pro-km-ttw-tx.sas Output: f-pro-km-ttw7-txecog-itts.rtf(11MAY20:15:36)

Data: adsl,adcm,adttepro

Seattle Genetics Protocol ONT-380-206

**Figure <Insert Table Num> Time to Worsening ≥ 7 in EQ-5D-5L Health Score by Treatment Arm and Race
ITT - OS Population**



Time to first worsening ≥ 7 in EQ-5D-5L Health Score.

Subjects without worsening ≥ 7 are censored to the last EQ-5D-5L assessment date with non-missing health score.

HR is computed from the unstratified Cox proportional hazards model.

Interaction test p-value calculated from unstratified Cox proportional hazards model for the interaction term of treatment and race.

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_1753\v01\outputs\tlfs\pgms\f-pro-km-ttw-tx.sas Output: f-pro-km-ttw7-txrace-itts.rtf(11MAY20:15:36)

Data: adsl,adcm,adttepro

Seattle Genetics Protocol ONT-380-206**Table 2.4.3 Summary of Treatment-Emergent Adverse Events by History of Brain Metastases at Baseline - Time-to-Event Analysis Safety Analysis Set**

| Parameters | With Brain Metastases | | Without Brain Metastases | |
|--|------------------------|-----------------------|--------------------------|------------------------|
| | Tuc+Cap+Tra (N=194) | Pbo+Cap+Tra (N=91) | Tuc+Cap+Tra (N=209) | Pbo+Cap+Tra (N=105) |
| TEAE | | | | |
| Number of Subjects With at Least One Event, n (%) | 192 (99.0) | 86 (94.5) | 208 (99.5) | 104 (99.0) |
| Number of Censored Subjects, n (%) | 2 (1.0) | 5 (5.5) | 1 (0.5) | 1 (1.0) |
| Stratified Hazard Ratio ^{a, b} (95% C.I.) | | 1.717 (1.308, 2.255) | | 1.364 (1.066, 1.746) |
| P-value ^{b, c} | | 0.00010 | | 0.01367 |
| Interaction Test P-value ^d | | | 0.25841 | |
| Median Time to Onset of the First Event (Days) (95% C.I.) ^e | 4.0 (3.0, 5.0) | 8.0 (6.0, 11.0) | 4.0 (4.0, 6.0) | 7.0 (4.0, 11.0) |
| 25 th , 75 th Percentile | 1.0, 9.0 | 2.0, 15.0 | 2.0, 11.0 | 2.0, 14.0 |
| Observed Min, Max ^f | 1, 85 | 1, 262+ | 1, 436+ | 1, 158+ |

Page 1 of 4

a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.

c. Two-sided p-value calculated from Cox proportional hazards model.

d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and history of brain metastases at baseline.

e. Calculated using the complementary log-log transformation method (Collett, 1994).

f. '+' means the observed time is from censored subjects.

Data Snapshot: 14OCT2019, Data Cutoff Date: 04SEP2019

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_1753\v01\outputs\tlfs\pgms\t-ae-km-overall-subgrp.sas Output: t-ae-km-oval-sub-1-bm-safs.rtf (17JUL20:17:18)

Data: adsl, adae, adttesaf

Seattle Genetics Protocol ONT-380-206**Table 2.4.3 Summary of Treatment-Emergent Adverse Events by History of Brain Metastases at Baseline - Time-to-Event Analysis Safety Analysis Set**

| Parameters | With Brain Metastases | | Without Brain Metastases | |
|--|------------------------|-----------------------|--------------------------|------------------------|
| | Tuc+Cap+Tra (N=194) | Pbo+Cap+Tra (N=91) | Tuc+Cap+Tra (N=209) | Pbo+Cap+Tra (N=105) |
| Severe TEAE | | | | |
| Number of Subjects With at Least One Event, n (%) | 111 (57.2) | 48 (52.7) | 112 (53.6) | 48 (45.7) |
| Number of Censored Subjects, n (%) | 83 (42.8) | 43 (47.3) | 97 (46.4) | 57 (54.3) |
| Stratified Hazard Ratio ^{a, b} (95% C.I.) | | 1.021 (0.724, 1.439) | | 1.159 (0.823, 1.631) |
| P-value ^{b, c} | | 0.90516 | | 0.39837 |
| Interaction Test P-value ^d | | | | 0.61971 |
| Median Time to Onset of the First Event (Days) (95% C.I.) ^e | 127.0 (106.0, 255.0) | 138.0 (89.0, 304.0) | 192.0 (99.0, 316.0) | 307.0 (123.0, -) |
| 25 th , 75 th Percentile | 35.0, 529.0 | 43.0, 336.0 | 37.0, - | 42.0, - |
| Observed Min, Max ^f | 1, 891+ | 4, 405+ | 2, 863+ | 2, 762+ |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.

c. Two-sided p-value calculated from Cox proportional hazards model.

d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and history of brain metastases at baseline.

e. Calculated using the complementary log-log transformation method (Collett, 1994).

f. '+' means the observed time is from censored subjects.

Data Snapshot: 14OCT2019, Data Cutoff Date: 04SEP2019

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_1753\v01\outputs\tlfs\pgms\t-ae-km-overall-subgrp.sas Output: t-ae-km-oval-sub-1-bm-safs.rtf (17JUL20:17:18)

Data: adsl, adae, adttesaf

Seattle Genetics Protocol ONT-380-206**Table 2.4.3 Summary of Treatment-Emergent Adverse Events by History of Brain Metastases at Baseline - Time-to-Event Analysis Safety Analysis Set**

| Parameters | With Brain Metastases | | Without Brain Metastases | |
|--|------------------------|-----------------------|--------------------------|------------------------|
| | Tuc+Cap+Tra (N=194) | Pbo+Cap+Tra (N=91) | Tuc+Cap+Tra (N=209) | Pbo+Cap+Tra (N=105) |
| Serious TEAE | | | | |
| Number of Subjects With at Least One Event, n (%) | 55 (28.4) | 27 (29.7) | 49 (23.4) | 26 (24.8) |
| Number of Censored Subjects, n (%) | 139 (71.6) | 64 (70.3) | 160 (76.6) | 79 (75.2) |
| Stratified Hazard Ratio ^{a, b} (95% C.I.) | | 0.788 (0.492, 1.261) | | 0.833 (0.515, 1.348) |
| P-value ^{b, c} | | 0.32046 | | 0.45723 |
| Interaction Test P-value ^d | | | 0.91330 | |
| Median Time to Onset of the First Event (Days) (95% C.I.) ^e | 651.0 (500.0, -) | 336.0 (275.0, -) | 942.0 (698.0, -) | - (-, -) |
| 25 th , 75 th Percentile | 199.0, - | 143.0, - | 311.0, - | 190.0, - |
| Observed Min, Max ^f | 1, 944+ | 4, 583+ | 2, 1059+ | 2, 762+ |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.

c. Two-sided p-value calculated from Cox proportional hazards model.

d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and history of brain metastases at baseline.

e. Calculated using the complementary log-log transformation method (Collett, 1994).

f. '+' means the observed time is from censored subjects.

Data Snapshot: 14OCT2019, Data Cutoff Date: 04SEP2019

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_1753\v01\outputs\tlfs\pgms\t-ae-km-overall-subgrp.sas Output: t-ae-km-oval-sub-1-bm-safs.rtf (17JUL20:17:18)

Data: adsl, adae, adttesaf

Seattle Genetics Protocol ONT-380-206**Table 2.4.3 Summary of Treatment-Emergent Adverse Events by History of Brain Metastases at Baseline - Time-to-Event Analysis Safety Analysis Set**

| Parameters | | With Brian Metastases | | Without Brain Metastases | |
|--|--|------------------------|-----------------------|--------------------------|------------------------|
| | | Tuc+Cap+Tra (N=194) | Pbo+Cap+Tra (N=91) | Tuc+Cap+Tra (N=209) | Pbo+Cap+Tra (N=105) |
| Discontinuation of Any Study Treatment Due to TEAE | Number of Subjects With at Least One Event, n (%) | 21 (10.8) | 6 (6.6) | 24 (11.5) | 13 (12.4) |
| | Number of Censored Subjects, n (%) | 173 (89.2) | 85 (93.4) | 185 (88.5) | 92 (87.6) |
| | Stratified Hazard Ratio ^{a, b} (95% C.I.) | | 1.317 (0.522, 3.322) | | 0.764 (0.385, 1.517) |
| | P-value ^{b, c} | | 0.55947 | | 0.44190 |
| | Interaction Test P-value ^d | | | 0.33689 | |
| | Median Time to Onset of the First Event (Days) (95% C.I.) ^e | - (-, -) | 554.0 (554.0, -) | - (-, -) | - (495.0, -) |
| | 25 th , 75 th Percentile | -, - | 554.0, - | -, - | 495.0, - |
| Observed Min, Max ^f | 1, 1070+ | 26+, 580+ | 5, 1059+ | 4, 762+ | |

Page 4 of 4

a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.

c. Two-sided p-value calculated from Cox proportional hazards model.

d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and history of brain metastases at baseline.

e. Calculated using the complementary log-log transformation method (Collett, 1994).

f. '+' means the observed time is from censored subjects.

Data Snapshot: 14OCT2019, Data Cutoff Date: 04SEP2019

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_1753\v01\outputs\lfs\pgms\t-ae-km-overall-subgrp.sas Output: t-ae-km-oval-sub-1-bm-safs.rtf (17JUL20:17:18)

Data: adsl, adae, adttesaf

Seattle Genetics Protocol ONT-380-206**Table 2.4.4 Summary of Treatment-Emergent Adverse Events by Geographic Region - Time-to-Event Analysis
Safety Analysis Set**

| Parameters | North America | | Rest of World | |
|--|------------------------|------------------------|------------------------|-----------------------|
| | Tuc+Cap+Tra (N=241) | Pbo+Cap+Tra (N=119) | Tuc+Cap+Tra (N=163) | Pbo+Cap+Tra (N=78) |
| TEAE | | | | |
| Number of Subjects With at Least One Event, n (%) | 238 (98.8) | 117 (98.3) | 163 (100) | 74 (94.9) |
| Number of Censored Subjects, n (%) | 3 (1.2) | 2 (1.7) | 0 | 4 (5.1) |
| Stratified Hazard Ratio ^{a, b} (95% C.I.) | 1.548 (1.225, 1.957) | | 1.548 (1.157, 2.070) | |
| P-value ^{b, c} | 0.00025 | | 0.00326 | |
| Interaction Test P-value ^d | 0.57300 | | | |
| Median Time to Onset of the First Event (Days) (95% C.I.) ^e | 4.0 (4.0, 5.0) | 8.0 (6.0, 11.0) | 4.0 (2.0, 5.0) | 6.0 (3.0, 11.0) |
| 25 th , 75 th Percentile | 2.0, 10.0 | 2.0, 15.0 | 1.0, 9.0 | 1.0, 14.0 |
| Observed Min, Max ^f | 1, 436+ | 1, 83 | 1, 85 | 1, 262+ |

Page 1 of 5

a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (Presence or history of brain metastases: Yes/No and ECOG performance status: 0/1) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.

c. Two-sided p-value calculated from Cox proportional hazards model.

d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and geographic region.

e. Calculated using the complementary log-log transformation method (Collett, 1994).

f. '+' means the observed time is from censored subjects.

Data Snapshot: 14OCT2019, Data Cutoff Date: 04SEP2019

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_1753\v01\outputs\tlfs\pgms\t-ae-km-overall-subgrp.sas Output: t-ae-km-oval-sub-2-reg-safs.rtf (17JUL20:17:18)

Data: adsl, adae, adttesaf

Seattle Genetics Protocol ONT-380-206**Table 2.4.4 Summary of Treatment-Emergent Adverse Events by Geographic Region - Time-to-Event Analysis
Safety Analysis Set**

| Parameters | North America | | Rest of World | |
|--|------------------------|------------------------|------------------------|-----------------------|
| | Tuc+Cap+Tra (N=241) | Pbo+Cap+Tra (N=119) | Tuc+Cap+Tra (N=163) | Pbo+Cap+Tra (N=78) |
| Severe TEAE | | | | |
| Number of Subjects With at Least One Event, n (%) | 133 (55.2) | 61 (51.3) | 90 (55.2) | 35 (44.9) |
| Number of Censored Subjects, n (%) | 108 (44.8) | 58 (48.7) | 73 (44.8) | 43 (55.1) |
| Stratified Hazard Ratio ^{a, b} (95% C.I.) | | 1.029 (0.757, 1.397) | | 1.228 (0.828, 1.823) |
| P-value ^{b, c} | | 0.85688 | | 0.30739 |
| Interaction Test P-value ^d | | | | 0.60257 |
| Median Time to Onset of the First Event (Days) (95% C.I.) ^e | 176.0 (105.0, 302.0) | 192.0 (95.0, 318.0) | 127.0 (105.0, 255.0) | 275.0 (135.0, 337.0) |
| 25 th , 75 th Percentile | 35.0, 545.0 | 42.0, - | 37.0, - | 79.0, - |
| Observed Min, Max ^f | 1, 891+ | 4, 762+ | 3, 720+ | 2, 478+ |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (Presence or history of brain metastases: Yes/No and ECOG performance status: 0/1) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.

c. Two-sided p-value calculated from Cox proportional hazards model.

d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and geographic region.

e. Calculated using the complementary log-log transformation method (Collett, 1994).

f. '+' means the observed time is from censored subjects.

Data Snapshot: 14OCT2019, Data Cutoff Date: 04SEP2019

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_1753\v01\outputs\tlfs\pgms\t-ae-km-overall-subgrp.sas Output: t-ae-km-oval-sub-2-reg-safs.rtf (17JUL20:17:18)

Data: adsl, adae, adttesaf

Seattle Genetics Protocol ONT-380-206**Table 2.4.4 Summary of Treatment-Emergent Adverse Events by Geographic Region - Time-to-Event Analysis
Safety Analysis Set**

| Parameters | North America | | Rest of World | |
|--|------------------------|------------------------|------------------------|-----------------------|
| | Tuc+Cap+Tra (N=241) | Pbo+Cap+Tra (N=119) | Tuc+Cap+Tra (N=163) | Pbo+Cap+Tra (N=78) |
| Serious TEAE | | | | |
| Number of Subjects With at Least One Event, n (%) | 65 (27.0) | 31 (26.1) | 39 (23.9) | 22 (28.2) |
| Number of Censored Subjects, n (%) | 176 (73.0) | 88 (73.9) | 124 (76.1) | 56 (71.8) |
| Stratified Hazard Ratio ^{a, b} (95% C.I.) | | 0.907 (0.587, 1.402) | | 0.686 (0.404, 1.166) |
| P-value ^{b, c} | | 0.66025 | | 0.16351 |
| Interaction Test P-value ^d | | | 0.54339 | |
| Median Time to Onset of the First Event (Days) (95% C.I.) ^e | 698.0 (547.0, -) | - (-, -) | - (500.0, -) | - (275.0, -) |
| 25 th , 75 th Percentile | 272.0, - | 146.0, - | 243.0, - | 176.0, - |
| Observed Min, Max ^f | 1, 1059+ | 13, 762+ | 1, 720+ | 2, 588+ |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (Presence or history of brain metastases: Yes/No and ECOG performance status: 0/1) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.

c. Two-sided p-value calculated from Cox proportional hazards model.

d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and geographic region.

e. Calculated using the complementary log-log transformation method (Collett, 1994).

f. '+' means the observed time is from censored subjects.

Data Snapshot: 14OCT2019, Data Cutoff Date: 04SEP2019

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_1753\v01\outputs\tlfs\pgms\t-ae-km-overall-subgrp.sas Output: t-ae-km-oval-sub-2-reg-safs.rtf (17JUL20:17:18)

Data: adsl, adae, adttesaf

Seattle Genetics Protocol ONT-380-206**Table 2.4.4 Summary of Treatment-Emergent Adverse Events by Geographic Region - Time-to-Event Analysis
Safety Analysis Set**

| Parameters | North America | | Rest of World | |
|--|------------------------|------------------------|------------------------|-----------------------|
| | Tuc+Cap+Tra (N=241) | Pbo+Cap+Tra (N=119) | Tuc+Cap+Tra (N=163) | Pbo+Cap+Tra (N=78) |
| Discontinuation of Any Study Treatment Due to TEAE | | | | |
| Number of Subjects With at Least One Event, n (%) | 30 (12.4) | 17 (14.3) | 15 (9.2) | 2 (2.6) |
| Number of Censored Subjects, n (%) | 211 (87.6) | 102 (85.7) | 148 (90.8) | 76 (97.4) |
| Stratified Hazard Ratio ^{a, b} (95% C.I.) | | 0.655 (0.355, 1.207) | | 3.528 (0.804, 15.475) |
| P-value ^{b, c} | | 0.17482 | | 0.09473 |
| Interaction Test P-value ^d | | | 0.05524 | |
| Median Time to Onset of the First Event (Days) (95% C.I.) ^e | - (-, -) | 554.0 (495.0, -) | - (-, -) | - (-, -) |
| 25 th , 75 th Percentile | -, - | 495.0, - | -, - | -, - |
| Observed Min, Max ^f | 4+, 1070+ | 26+, 762+ | 1, 720+ | 4, 588+ |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (Presence or history of brain metastases: Yes/No and ECOG performance status: 0/1) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.

c. Two-sided p-value calculated from Cox proportional hazards model.

d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and geographic region.

e. Calculated using the complementary log-log transformation method (Collett, 1994).

f. '+' means the observed time is from censored subjects.

Data Snapshot: 14OCT2019, Data Cutoff Date: 04SEP2019

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_1753\v01\outputs\lfs\pgms\t-ae-km-overall-subgrp.sas Output: t-ae-km-oval-sub-2-reg-safs.rtf (17JUL20:17:18)

Data: adsl, adae, adttesaf

Seattle Genetics Protocol ONT-380-206**Table 2.4.5 Summary of Treatment-Emergent Adverse Events by Baseline ECOG Score - Time-to-Event Analysis
Safety Analysis Set**

| Parameters | ECOG=0 | | ECOG=1 | |
|--|------------------------|-----------------------|------------------------|------------------------|
| | Tuc+Cap+Tra (N=203) | Pbo+Cap+Tra (N=91) | Tuc+Cap+Tra (N=201) | Pbo+Cap+Tra (N=106) |
| TEAE | | | | |
| Number of Subjects With at Least One Event, n (%) | 200 (98.5) | 90 (98.9) | 201 (100) | 101 (95.3) |
| Number of Censored Subjects, n (%) | 3 (1.5) | 1 (1.1) | 0 | 5 (4.7) |
| Stratified Hazard Ratio ^{a, b} (95% C.I.) | | 1.337 (1.033, 1.731) | | 1.743 (1.352, 2.246) |
| P-value ^{b, c} | | 0.02750 | | 0.00002 |
| Interaction Test P-value ^d | | | 0.10968 | |
| Median Time to Onset of the First Event (Days) (95% C.I.) ^e | 4.0 (3.0, 6.0) | 7.0 (3.0, 10.0) | 4.0 (3.0, 4.0) | 8.0 (6.0, 12.0) |
| 25 th , 75 th Percentile | 1.0, 11.0 | 2.0, 13.0 | 2.0, 9.0 | 3.0, 15.0 |
| Observed Min, Max ^f | 1, 436+ | 1, 224+ | 1, 85 | 1, 262+ |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (Presence or history of brain metastases: Yes/No and Region of world: North America /Rest of World) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.

c. Two-sided p-value calculated from Cox proportional hazards model.

d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and baseline ECOG score.

e. Calculated using the complementary log-log transformation method (Collett, 1994).

f. '+' means the observed time is from censored subjects.

Data Snapshot: 14OCT2019, Data Cutoff Date: 04SEP2019

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_1753\v01\outputs\tlfs\pgms\t-ae-km-overall-subgrp.sas Output: t-ae-km-oval-sub-3-ecog-safs.rtf (17JUL20:17:18) Data: adsl, adae, adttesaf

Seattle Genetics Protocol ONT-380-206**Table 2.4.5 Summary of Treatment-Emergent Adverse Events by Baseline ECOG Score - Time-to-Event Analysis
Safety Analysis Set**

| Parameters | ECOG=0 | | ECOG=1 | |
|--|------------------------|-----------------------|------------------------|------------------------|
| | Tuc+Cap+Tra (N=203) | Pbo+Cap+Tra (N=91) | Tuc+Cap+Tra (N=201) | Pbo+Cap+Tra (N=106) |
| Severe TEAE | | | | |
| Number of Subjects With at Least One Event, n (%) | 106 (52.2) | 42 (46.2) | 117 (58.2) | 54 (50.9) |
| Number of Censored Subjects, n (%) | 97 (47.8) | 49 (53.8) | 84 (41.8) | 52 (49.1) |
| Stratified Hazard Ratio ^{a, b} (95% C.I.) | | 1.159 (0.808, 1.661) | | 1.057 (0.762, 1.466) |
| P-value ^{b, c} | | 0.42224 | | 0.74015 |
| Interaction Test P-value ^d | | | 0.67079 | |
| Median Time to Onset of the First Event (Days) (95% C.I.) ^e | 213.0 (114.0, 323.0) | 286.0 (127.0, -) | 123.0 (84.0, 215.0) | 163.0 (84.0, 336.0) |
| 25 th , 75 th Percentile | 37.0, - | 81.0, - | 35.0, 478.0 | 35.0, - |
| Observed Min, Max ^f | 1, 863+ | 2, 478+ | 2, 891+ | 4, 762+ |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (Presence or history of brain metastases: Yes/No and Region of world: North America /Rest of World) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.

c. Two-sided p-value calculated from Cox proportional hazards model.

d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and baseline ECOG score.

e. Calculated using the complementary log-log transformation method (Collett, 1994).

f. '+' means the observed time is from censored subjects.

Data Snapshot: 14OCT2019, Data Cutoff Date: 04SEP2019

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_1753\v01\outputs\tlfs\pgms\t-ae-km-overall-subgrp.sas Output: t-ae-km-oval-sub-3-ecog-safs.rtf (17JUL20:17:18) Data: adsl, adae, adttesaf

Seattle Genetics Protocol ONT-380-206**Table 2.4.5 Summary of Treatment-Emergent Adverse Events by Baseline ECOG Score - Time-to-Event Analysis
Safety Analysis Set**

| Parameters | ECOG=0 | | ECOG=1 | |
|--|------------------------|-----------------------|------------------------|------------------------|
| | Tuc+Cap+Tra (N=203) | Pbo+Cap+Tra (N=91) | Tuc+Cap+Tra (N=201) | Pbo+Cap+Tra (N=106) |
| Serious TEAE | | | | |
| Number of Subjects With at Least One Event, n (%) | 43 (21.2) | 23 (25.3) | 61 (30.3) | 30 (28.3) |
| Number of Censored Subjects, n (%) | 160 (78.8) | 68 (74.7) | 140 (69.7) | 76 (71.7) |
| Stratified Hazard Ratio ^{a, b} (95% C.I.) | | 0.697 (0.417, 1.166) | | 0.929 (0.595, 1.449) |
| P-value ^{b, c} | | 0.16920 | | 0.74521 |
| Interaction Test P-value ^d | | | | 0.51496 |
| Median Time to Onset of the First Event (Days) (95% C.I.) ^e | - (547.0, -) | - (-, -) | 942.0 (500.0, 942.0) | - (275.0, -) |
| 25 th , 75 th Percentile | 319.0, - | 169.0, - | 102.0, 942.0 | 152.0, - |
| Observed Min, Max ^f | 1, 1059+ | 13, 588+ | 1, 942 | 2, 762+ |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (Presence or history of brain metastases: Yes/No and Region of world: North America /Rest of World) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.

c. Two-sided p-value calculated from Cox proportional hazards model.

d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and baseline ECOG score.

e. Calculated using the complementary log-log transformation method (Collett, 1994).

f. '+' means the observed time is from censored subjects.

Data Snapshot: 14OCT2019, Data Cutoff Date: 04SEP2019

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_1753\v01\outputs\tlfs\pgms\t-ae-km-overall-subgrp.sas Output: t-ae-km-oval-sub-3-ecog-safs.rtf (17JUL20:17:18) Data: adsl, adae, adttesaf

Seattle Genetics Protocol ONT-380-206

**Table 2.4.5 Summary of Treatment-Emergent Adverse Events by Baseline ECOG Score - Time-to-Event Analysis
Safety Analysis Set**

| Parameters | ECOG=0 | | ECOG=1 | | |
|--|--|-----------------------|------------------------|------------------------|--------------|
| | Tuc+Cap+Tra (N=203) | Pbo+Cap+Tra (N=91) | Tuc+Cap+Tra (N=201) | Pbo+Cap+Tra (N=106) | |
| Discontinuation of Any Study Treatment Due to TEAE | Number of Subjects With at Least One Event, n (%) | 19 (9.4) | 8 (8.8) | 26 (12.9) | 11 (10.4) |
| | Number of Censored Subjects, n (%) | 184 (90.6) | 83 (91.2) | 175 (87.1) | 95 (89.6) |
| | Stratified Hazard Ratio ^{a, b} (95% C.I.) | 1.033 (0.451, 2.364) | | 1.068 (0.523, 2.181) | |
| | P-value ^{b, c} | 0.93960 | | 0.85602 | |
| | Interaction Test P-value ^d | 0.86388 | | | |
| | Median Time to Onset of the First Event (Days) (95% C.I.) ^e | - (-, -) | 554.0 (554.0, -) | - (-, -) | - (495.0, -) |
| | 25 th , 75 th Percentile | -, - | 554.0, - | 476.0, - | 495.0, - |
| | Observed Min, Max ^f | 4+, 1059+ | 50+, 588+ | 1, 1070+ | 4, 762+ |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (Presence or history of brain metastases: Yes/No and Region of world: North America /Rest of World) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.

c. Two-sided p-value calculated from Cox proportional hazards model.

d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and baseline ECOG score.

e. Calculated using the complementary log-log transformation method (Collett, 1994).

f. '+' means the observed time is from censored subjects.

Data Snapshot: 14OCT2019, Data Cutoff Date: 04SEP2019

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_1753\v01\outputs\lfs\pgms\t-ae-km-overall-subgrp.sas Output: t-ae-km-oval-sub-3-ecog-safs.rtf (17JUL20:17:18) Data: adsl, adae, adttesaf

Seattle Genetics Protocol ONT-380-206**Table 2.4.6 Summary of Treatment-Emergent Adverse Events by Age - Time-to-Event Analysis
Safety Analysis Set**

| Parameters | Age < 65 Years | | Age ≥ 65 Years | |
|--|------------------------|------------------------|-----------------------|-----------------------|
| | Tuc+Cap+Tra (N=322) | Pbo+Cap+Tra (N=164) | Tuc+Cap+Tra (N=82) | Pbo+Cap+Tra (N=33) |
| TEAE | | | | |
| Number of Subjects With at Least One Event, n (%) | 320 (99.4) | 159 (97.0) | 81 (98.8) | 32 (97.0) |
| Number of Censored Subjects, n (%) | 2 (0.6) | 5 (3.0) | 1 (1.2) | 1 (3.0) |
| Stratified Hazard Ratio ^{a, b} (95% C.I.) | | 1.486 (1.216, 1.815) | | 1.879 (1.154, 3.060) |
| P-value ^{b, c} | | 0.00011 | | 0.01127 |
| Interaction Test P-value ^d | | | 0.36318 | |
| Median Time to Onset of the First Event (Days) (95% C.I.) ^e | 4.0 (4.0, 5.0) | 7.0 (5.0, 10.0) | 4.0 (2.0, 6.0) | 11.0 (5.0, 13.0) |
| 25 th , 75 th Percentile | 2.0, 9.0 | 2.0, 15.0 | 1.0, 11.0 | 3.0, 13.0 |
| Observed Min, Max ^f | 1, 436+ | 1, 262+ | 1, 34 | 1, 107 |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (Presence or history of brain metastases: Yes/No, ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.

c. Two-sided p-value calculated from Cox proportional hazards model.

d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and age.

e. Calculated using the complementary log-log transformation method (Collett, 1994).

f. '+' means the observed time is from censored subjects.

Data Snapshot: 14OCT2019, Data Cutoff Date: 04SEP2019

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_1753\v01\outputs\tlfs\pgms\t-ae-km-overall-subgrp.sas Output: t-ae-km-oval-sub-4-age-safs.rtf (17JUL20:17:18)

Data: adsl, adae, adttesaf

Seattle Genetics Protocol ONT-380-206

**Table 2.4.6 Summary of Treatment-Emergent Adverse Events by Age - Time-to-Event Analysis
Safety Analysis Set**

| Parameters | Age < 65 Years | | Age ≥ 65 Years | |
|--|------------------------|------------------------|-----------------------|-----------------------|
| | Tuc+Cap+Tra (N=322) | Pbo+Cap+Tra (N=164) | Tuc+Cap+Tra (N=82) | Pbo+Cap+Tra (N=33) |
| Severe TEAE | | | | |
| Number of Subjects With at Least One Event, n (%) | 176 (54.7) | 73 (44.5) | 47 (57.3) | 23 (69.7) |
| Number of Censored Subjects, n (%) | 146 (45.3) | 91 (55.5) | 35 (42.7) | 10 (30.3) |
| Stratified Hazard Ratio ^{a, b} (95% C.I.) | | 1.194 (0.906, 1.574) | | 0.706 (0.409, 1.217) |
| P-value ^{b, c} | | 0.20881 | | 0.21032 |
| Interaction Test P-value ^d | | | | 0.10743 |
| Median Time to Onset of the First Event (Days) (95% C.I.) ^e | 183.0 (121.0, 300.0) | 307.0 (135.0, -) | 106.0 (50.0, 323.0) | 85.0 (42.0, 192.0) |
| 25 th , 75 th Percentile | 37.0, - | 57.0, - | 34.0, - | 33.0, 304.0 |
| Observed Min, Max ^f | 2, 891+ | 2, 762+ | 1, 458+ | 9, 318 |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (Presence or history of brain metastases: Yes/No, ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.

c. Two-sided p-value calculated from Cox proportional hazards model.

d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and age.

e. Calculated using the complementary log-log transformation method (Collett, 1994).

f. '+' means the observed time is from censored subjects.

Data Snapshot: 14OCT2019, Data Cutoff Date: 04SEP2019

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_1753\v01\outputs\tlfs\pgms\t-ae-km-overall-subgrp.sas Output: t-ae-km-oval-sub-4-age-safs.rtf (17JUL20:17:18)

Data: adsl, adae, adttesaf

Seattle Genetics Protocol ONT-380-206**Table 2.4.6 Summary of Treatment-Emergent Adverse Events by Age - Time-to-Event Analysis
Safety Analysis Set**

| Parameters | Age < 65 Years | | Age ≥ 65 Years | |
|--|------------------------|------------------------|-----------------------|-----------------------|
| | Tuc+Cap+Tra (N=322) | Pbo+Cap+Tra (N=164) | Tuc+Cap+Tra (N=82) | Pbo+Cap+Tra (N=33) |
| Serious TEAE | | | | |
| Number of Subjects With at Least One Event, n (%) | 76 (23.6) | 41 (25.0) | 28 (34.1) | 12 (36.4) |
| Number of Censored Subjects, n (%) | 246 (76.4) | 123 (75.0) | 54 (65.9) | 21 (63.6) |
| Stratified Hazard Ratio ^{a, b} (95% C.I.) | | 0.757 (0.513, 1.116) | | 0.886 (0.428, 1.833) |
| P-value ^{b, c} | | 0.15995 | | 0.74472 |
| Interaction Test P-value ^d | | | | 0.63476 |
| Median Time to Onset of the First Event (Days) (95% C.I.) ^e | 698.0 (547.0, -) | - (336.0, -) | 942.0 (309.0, 942.0) | 304.0 (116.0, -) |
| 25 th , 75 th Percentile | 292.0, - | 184.0, - | 84.0, 942.0 | 112.0, - |
| Observed Min, Max ^f | 1, 1059+ | 2, 762+ | 1, 942 | 13, 409+ |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (Presence or history of brain metastases: Yes/No, ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.

c. Two-sided p-value calculated from Cox proportional hazards model.

d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and age.

e. Calculated using the complementary log-log transformation method (Collett, 1994).

f. '+' means the observed time is from censored subjects.

Data Snapshot: 14OCT2019, Data Cutoff Date: 04SEP2019

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_1753\v01\outputs\tlfs\pgms\t-ae-km-overall-subgrp.sas Output: t-ae-km-oval-sub-4-age-safs.rtf (17JUL20:17:18)

Data: adsl, adae, adttesaf

Seattle Genetics Protocol ONT-380-206

**Table 2.4.6 Summary of Treatment-Emergent Adverse Events by Age - Time-to-Event Analysis
Safety Analysis Set**

| Parameters | Age < 65 Years | | Age ≥ 65 Years | |
|--|------------------------|------------------------|-----------------------|-----------------------|
| | Tuc+Cap+Tra (N=322) | Pbo+Cap+Tra (N=164) | Tuc+Cap+Tra (N=82) | Pbo+Cap+Tra (N=33) |
| Discontinuation of Any Study Treatment Due to TEAE | | | | |
| Number of Subjects With at Least One Event, n (%) | 30 (9.3) | 12 (7.3) | 15 (18.3) | 7 (21.2) |
| Number of Censored Subjects, n (%) | 292 (90.7) | 152 (92.7) | 67 (81.7) | 26 (78.8) |
| Stratified Hazard Ratio ^{a, b} (95% C.I.) | | 1.074 (0.545, 2.120) | | 0.631 (0.230, 1.730) |
| P-value ^{b, c} | | 0.83583 | | 0.37054 |
| Interaction Test P-value ^d | | | | 0.42680 |
| Median Time to Onset of the First Event (Days) (95% C.I.) ^e | - (-, -) | - (495.0, -) | 476.0 (476.0, -) | - (337.0, -) |
| 25 th , 75 th Percentile | -, - | 495.0, - | 302.0, - | 337.0, - |
| Observed Min, Max ^f | 1, 1070+ | 4, 762+ | 4+, 547+ | 31+, 387+ |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (Presence or history of brain metastases: Yes/No, ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.

c. Two-sided p-value calculated from Cox proportional hazards model.

d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and age.

e. Calculated using the complementary log-log transformation method (Collett, 1994).

f. '+' means the observed time is from censored subjects.

Data Snapshot: 14OCT2019, Data Cutoff Date: 04SEP2019

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_1753\v01\outputs\lfs\pgms\t-ae-km-overall-subgrp.sas Output: t-ae-km-oval-sub-4-age-safs.rtf (17JUL20:17:18)

Data: adsl, adae, adttesaf

Seattle Genetics Protocol ONT-380-206

**Table 2.4.7 Summary of Treatment-Emergent Adverse Events by Race - Time-to-Event Analysis
Safety Analysis Set**

| Parameters | White | | Non-White | |
|--|------------------------|------------------------|------------------------|-----------------------|
| | Tuc+Cap+Tra (N=283) | Pbo+Cap+Tra (N=153) | Tuc+Cap+Tra (N=121) | Pbo+Cap+Tra (N=44) |
| TEAE | | | | |
| Number of Subjects With at Least One Event, n (%) | 283 (100) | 149 (97.4) | 118 (97.5) | 42 (95.5) |
| Number of Censored Subjects, n (%) | 0 | 4 (2.6) | 3 (2.5) | 2 (4.5) |
| Stratified Hazard Ratio ^{a, b} (95% C.I.) | | 1.482 (1.202, 1.826) | | 1.568 (1.046, 2.349) |
| P-value ^{b, c} | | 0.00023 | | 0.02928 |
| Interaction Test P-value ^d | | | 0.47510 | |
| Median Time to Onset of the First Event (Days) (95% C.I.) ^e | 4.0 (4.0, 5.0) | 8.0 (5.0, 11.0) | 4.0 (3.0, 5.0) | 7.0 (3.0, 12.0) |
| 25 th , 75 th Percentile | 2.0, 11.0 | 2.0, 14.0 | 2.0, 9.0 | 2.0, 14.5 |
| Observed Min, Max ^f | 1, 85 | 1, 262+ | 1, 436+ | 1, 71+ |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (Presence or history of brain metastases: Yes/No, ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.

c. Two-sided p-value calculated from Cox proportional hazards model.

d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and race.

e. Calculated using the complementary log-log transformation method (Collett, 1994).

f. '+' means the observed time is from censored subjects.

Data Snapshot: 14OCT2019, Data Cutoff Date: 04SEP2019

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_1753\v01\outputs\tlfs\pgms\t-ae-km-overall-subgrp.sas Output: t-ae-km-oval-sub-5-race-safs.rtf (17JUL20:17:18) Data: adsl, adae, adttesaf

Seattle Genetics Protocol ONT-380-206

**Table 2.4.7 Summary of Treatment-Emergent Adverse Events by Race - Time-to-Event Analysis
Safety Analysis Set**

| Parameters | White | | Non-White | |
|--|------------------------|------------------------|------------------------|-----------------------|
| | Tuc+Cap+Tra (N=283) | Pbo+Cap+Tra (N=153) | Tuc+Cap+Tra (N=121) | Pbo+Cap+Tra (N=44) |
| Severe TEAE | | | | |
| Number of Subjects With at Least One Event, n (%) | 153 (54.1) | 77 (50.3) | 70 (57.9) | 19 (43.2) |
| Number of Censored Subjects, n (%) | 130 (45.9) | 76 (49.7) | 51 (42.1) | 25 (56.8) |
| Stratified Hazard Ratio ^{a, b} (95% C.I.) | | 1.049 (0.795, 1.385) | | 1.322 (0.787, 2.220) |
| P-value ^{b, c} | | 0.73339 | | 0.29201 |
| Interaction Test P-value ^d | | | 0.38737 | |
| Median Time to Onset of the First Event (Days) (95% C.I.) ^e | 146.0 (107.0, 300.0) | 275.0 (102.0, 308.0) | 190.0 (85.0, 302.0) | 197.0 (123.0, -) |
| 25 th , 75 th Percentile | 35.0, - | 44.0, - | 42.0, 529.0 | 40.0, - |
| Observed Min, Max ^f | 1, 891+ | 2, 762+ | 2, 538+ | 4, 449+ |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (Presence or history of brain metastases: Yes/No, ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.

c. Two-sided p-value calculated from Cox proportional hazards model .

d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and race.

e. Calculated using the complementary log-log transformation method (Collett, 1994).

f. '+' means the observed time is from censored subjects.

Data Snapshot: 14OCT2019, Data Cutoff Date: 04SEP2019

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_1753\v01\outputs\tlfs\pgms\t-ae-km-overall-subgrp.sas Output: t-ae-km-oval-sub-5-race-safs.rtf (17JUL20:17:18) Data: adsl, adae, adttesaf

Seattle Genetics Protocol ONT-380-206

Table 2.4.7 Summary of Treatment-Emergent Adverse Events by Race - Time-to-Event Analysis
Safety Analysis Set

| Parameters | White | | Non-White | |
|--|------------------------|------------------------|------------------------|-----------------------|
| | Tuc+Cap+Tra (N=283) | Pbo+Cap+Tra (N=153) | Tuc+Cap+Tra (N=121) | Pbo+Cap+Tra (N=44) |
| Serious TEAE | | | | |
| Number of Subjects With at Least One Event, n (%) | 75 (26.5) | 42 (27.5) | 29 (24.0) | 11 (25.0) |
| Number of Censored Subjects, n (%) | 208 (73.5) | 111 (72.5) | 92 (76.0) | 33 (75.0) |
| Stratified Hazard Ratio ^{a, b} (95% C.I.) | | 0.816 (0.555, 1.201) | | 0.859 (0.420, 1.756) |
| P-value ^{b, c} | | 0.30274 | | 0.67707 |
| Interaction Test P-value ^d | | | 0.70399 | |
| Median Time to Onset of the First Event (Days) (95% C.I.) ^e | 942.0 (651.0, -) | - (-, -) | 547.0 (500.0, -) | - (275.0, -) |
| 25 th , 75 th Percentile | 272.0, - | 146.0, - | 311.0, - | 275.0, - |
| Observed Min, Max ^f | 1, 1059+ | 2, 762+ | 2, 637+ | 13, 583+ |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (Presence or history of brain metastases: Yes/No, ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.

c. Two-sided p-value calculated from Cox proportional hazards model.

d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and race.

e. Calculated using the complementary log-log transformation method (Collett, 1994).

f. '+' means the observed time is from censored subjects.

Data Snapshot: 14OCT2019, Data Cutoff Date: 04SEP2019

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_1753\v01\outputs\tlfs\pgms\t-ae-km-overall-subgrp.sas Output: t-ae-km-oval-sub-5-race-safs.rtf (17JUL20:17:18) Data: adsl, adae, adttesaf

Seattle Genetics Protocol ONT-380-206

**Table 2.4.7 Summary of Treatment-Emergent Adverse Events by Race - Time-to-Event Analysis
Safety Analysis Set**

| Parameters | White | | Non-White | |
|--|------------------------|------------------------|------------------------|-----------------------|
| | Tuc+Cap+Tra (N=283) | Pbo+Cap+Tra (N=153) | Tuc+Cap+Tra (N=121) | Pbo+Cap+Tra (N=44) |
| Discontinuation of Any Study Treatment Due to TEAE | | | | |
| Number of Subjects With at Least One Event, n (%) | 33 (11.7) | 16 (10.5) | 12 (9.9) | 3 (6.8) |
| Number of Censored Subjects, n (%) | 250 (88.3) | 137 (89.5) | 109 (90.1) | 41 (93.2) |
| Stratified Hazard Ratio ^{a, b} (95% C.I.) | | 0.961 (0.525, 1.760) | | 1.000 (0.268, 3.739) |
| P-value ^{b, c} | | 0.89694 | | 0.99944 |
| Interaction Test P-value ^d | | | 0.81758 | |
| Median Time to Onset of the First Event (Days) (95% C.I.) ^e | - (-, -) | - (495.0, -) | - (-, -) | 554.0 (554.0, -) |
| 25 th , 75 th Percentile | -, - | 495.0, - | -, - | 554.0, - |
| Observed Min, Max ^f | 1, 1059+ | 4, 762+ | 4+, 1070+ | 40+, 580+ |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.
 b. Computed using stratification factors (Presence or history of brain metastases: Yes/No, ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.
 c. Two-sided p-value calculated from Cox proportional hazards model.
 d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and race.
 e. Calculated using the complementary log-log transformation method (Collett, 1994).
 f. '+' means the observed time is from censored subjects.
 Data Snapshot: 14OCT2019, Data Cutoff Date: 04SEP2019
 Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_1753\v01\outputs\lfs\pgms\t-ae-km-overall-subgrp.sas Output: t-ae-km-oval-sub-5-race-safs.rtf (17JUL20:17:18) Data: adsl, adae, adttesaf

Seattle Genetics Protocol ONT-380-206

**Table 2.4.8 Summary of Treatment-Emergent Adverse Events by Hormone Receptor Status - Time-to-Event Analysis
Safety Analysis Set**

| Parameters | Negative for Both | | Positive for ER or PR or Both | |
|--|------------------------|-----------------------|-------------------------------|------------------------|
| | Tuc+Cap+Tra (N=163) | Pbo+Cap+Tra (N=74) | Tuc+Cap+Tra (N=241) | Pbo+Cap+Tra (N=123) |
| TEAE | | | | |
| Number of Subjects With at Least One Event, n (%) | 162 (99.4) | 71 (95.9) | 239 (99.2) | 120 (97.6) |
| Number of Censored Subjects, n (%) | 1 (0.6) | 3 (4.1) | 2 (0.8) | 3 (2.4) |
| Stratified Hazard Ratio ^{a, b} (95% C.I.) | | 1.437 (1.064, 1.942) | | 1.599 (1.262, 2.026) |
| P-value ^{b, c} | | 0.01823 | | 0.00010 |
| Interaction Test P-value ^d | | | | 0.37817 |
| Median Time to Onset of the First Event (Days) (95% C.I.) ^e | 4.0 (3.0, 5.0) | 7.0 (5.0, 11.0) | 4.0 (3.0, 5.0) | 8.0 (6.0, 11.0) |
| 25 th , 75 th Percentile | 2.0, 9.0 | 2.0, 15.0 | 2.0, 10.0 | 2.0, 14.0 |
| Observed Min, Max ^f | 1, 85 | 1, 71+ | 1, 436+ | 1, 262+ |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (Presence or history of brain metastases: Yes/No, ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.

c. Two-sided p-value calculated from Cox proportional hazards model.

d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and hormone receptor status.

e. Calculated using the complementary log-log transformation method (Collett, 1994).

f. '+' means the observed time is from censored subjects.

Data Snapshot: 14OCT2019, Data Cutoff Date: 04SEP2019

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_1753\v01\outputs\tlfs\pgms\t-ae-km-overall-subgrp.sas Output: t-ae-km-oval-sub-6-hr-safs.rtf (17JUL20:17:18)

Data: adsl, adae, adttesaf

Seattle Genetics Protocol ONT-380-206

**Table 2.4.8 Summary of Treatment-Emergent Adverse Events by Hormone Receptor Status - Time-to-Event Analysis
Safety Analysis Set**

| Parameters | Negative for Both | | Positive for ER or PR or Both | |
|--|------------------------|-----------------------|-------------------------------|------------------------|
| | Tuc+Cap+Tra (N=163) | Pbo+Cap+Tra (N=74) | Tuc+Cap+Tra (N=241) | Pbo+Cap+Tra (N=123) |
| Severe TEAE | | | | |
| Number of Subjects With at Least One Event, n (%) | 92 (56.4) | 38 (51.4) | 131 (54.4) | 58 (47.2) |
| Number of Censored Subjects, n (%) | 71 (43.6) | 36 (48.6) | 110 (45.6) | 65 (52.8) |
| Stratified Hazard Ratio ^{a, b} (95% C.I.) | | 0.956 (0.647, 1.411) | | 1.185 (0.867, 1.620) |
| P-value ^{b, c} | | 0.81887 | | 0.28631 |
| Interaction Test P-value ^d | | | | 0.49353 |
| Median Time to Onset of the First Event (Days) (95% C.I.) ^e | 127.0 (99.0, 300.0) | 163.0 (89.0, 336.0) | 161.0 (105.0, 302.0) | 304.0 (105.0, -) |
| 25 th , 75 th Percentile | 37.0, - | 42.0, 337.0 | 36.0, - | 57.0, - |
| Observed Min, Max ^f | 2, 849+ | 2, 453+ | 1, 891+ | 4, 762+ |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (Presence or history of brain metastases: Yes/No, ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.

c. Two-sided p-value calculated from Cox proportional hazards model.

d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and hormone receptor status.

e. Calculated using the complementary log-log transformation method (Collett, 1994).

f. '+' means the observed time is from censored subjects.

Data Snapshot: 14OCT2019, Data Cutoff Date: 04SEP2019

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_1753\v01\outputs\tlfs\pgms\t-ae-km-overall-subgrp.sas Output: t-ae-km-oval-sub-6-hr-safs.rtf (17JUL20:17:18)

Data: adsl, adae, adttesaf

Seattle Genetics Protocol ONT-380-206

Table 2.4.8 Summary of Treatment-Emergent Adverse Events by Hormone Receptor Status - Time-to-Event Analysis
Safety Analysis Set

| Parameters | Negative for Both | | Positive for ER or PR or Both | |
|--|------------------------|-----------------------|-------------------------------|------------------------|
| | Tuc+Cap+Tra (N=163) | Pbo+Cap+Tra (N=74) | Tuc+Cap+Tra (N=241) | Pbo+Cap+Tra (N=123) |
| Serious TEAE | | | | |
| Number of Subjects With at Least One Event, n (%) | 50 (30.7) | 19 (25.7) | 54 (22.4) | 34 (27.6) |
| Number of Censored Subjects, n (%) | 113 (69.3) | 55 (74.3) | 187 (77.6) | 89 (72.4) |
| Stratified Hazard Ratio ^{a, b} (95% C.I.) | | 0.871 (0.499, 1.521) | | 0.763 (0.495, 1.177) |
| P-value ^{b, c} | | 0.62826 | | 0.22191 |
| Interaction Test P-value ^d | | | | 0.48454 |
| Median Time to Onset of the First Event (Days) (95% C.I.) ^e | 651.0 (500.0, -) | - (336.0, -) | - (698.0, -) | - (307.0, -) |
| 25 th , 75 th Percentile | 199.0, - | 152.0, - | 319.0, - | 169.0, - |
| Observed Min, Max ^f | 2, 1059+ | 14, 453+ | 1, 891+ | 2, 762+ |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (Presence or history of brain metastases: Yes/No, ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.

c. Two-sided p-value calculated from Cox proportional hazards model.

d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and hormone receptor status.

e. Calculated using the complementary log-log transformation method (Collett, 1994).

f. '+' means the observed time is from censored subjects.

Data Snapshot: 14OCT2019, Data Cutoff Date: 04SEP2019

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_1753\v01\outputs\tlfs\pgms\t-ae-km-overall-subgrp.sas Output: t-ae-km-oval-sub-6-hr-safs.rtf (17JUL20:17:18)

Data: adsl, adae, adttesaf

Seattle Genetics Protocol ONT-380-206

**Table 2.4.8 Summary of Treatment-Emergent Adverse Events by Hormone Receptor Status - Time-to-Event Analysis
Safety Analysis Set**

| Parameters | Negative for Both | | Positive for ER or PR or Both | |
|--|------------------------|-----------------------|-------------------------------|------------------------|
| | Tuc+Cap+Tra (N=163) | Pbo+Cap+Tra (N=74) | Tuc+Cap+Tra (N=241) | Pbo+Cap+Tra (N=123) |
| Discontinuation of Any Study Treatment Due to TEAE | | | | |
| Number of Subjects With at Least One Event, n (%) | 23 (14.1) | 4 (5.4) | 22 (9.1) | 15 (12.2) |
| Number of Censored Subjects, n (%) | 140 (85.9) | 70 (94.6) | 219 (90.9) | 108 (87.8) |
| Stratified Hazard Ratio ^{a, b} (95% C.I.) | | 2.490 (0.852, 7.279) | | 0.570 (0.288, 1.127) |
| P-value ^{b, c} | | 0.09563 | | 0.10610 |
| Interaction Test P-value ^d | | | | 0.03639 |
| Median Time to Onset of the First Event (Days) (95% C.I.) ^e | - (-, -) | - (-, -) | - (-, -) | 554.0 (495.0, -) |
| 25 th , 75 th Percentile | -, - | -, - | -, - | 495.0, - |
| Observed Min, Max ^f | 4+, 1070+ | 29+, 580+ | 1, 891+ | 4, 762+ |

Page 4 of 4

a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (Presence or history of brain metastases: Yes/No, ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.

c. Two-sided p-value calculated from Cox proportional hazards model.

d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and hormone receptor status.

e. Calculated using the complementary log-log transformation method (Collett, 1994).

f. '+' means the observed time is from censored subjects.

Data Snapshot: 14OCT2019, Data Cutoff Date: 04SEP2019

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_1753\v01\outputs\lfs\pgms\t-ae-km-overall-subgrp.sas Output: t-ae-km-oval-sub-6-hr-safs.rtf (17JUL20:17:18)

Data: adsl, adae, adttesaf

Seagen Protocol ONT-380-206**Table 2.4.3 Summary of Treatment-Emergent Adverse Events by History of Brain Metastases at Baseline - Time-to-Event Analysis Safety Analysis Set**

| Parameters | With Brain Metastases | | Without Brain Metastases | |
|--|------------------------|-----------------------|--------------------------|------------------------|
| | Tuc+Cap+Tra (N=194) | Pbo+Cap+Tra (N=91) | Tuc+Cap+Tra (N=209) | Pbo+Cap+Tra (N=105) |
| TEAE | | | | |
| Number of Subjects With at Least One Event, n (%) | 192 (99.0) | 86 (94.5) | 208 (99.5) | 104 (99.0) |
| Number of Censored Subjects, n (%) | 2 (1.0) | 5 (5.5) | 1 (0.5) | 1 (1.0) |
| Stratified Hazard Ratio ^{a, b} (95% C.I.) | | 1.719 (1.309, 2.257) | | 1.369 (1.070, 1.752) |
| P-value ^{b, c} | | 0.00010 | | 0.01253 |
| Interaction Test P-value ^d | | | 0.26782 | |
| Median Time to Onset of the First Event (Days) (95% C.I.) ^e | 4.0 (3.0, 5.0) | 8.0 (6.0, 11.0) | 4.0 (3.0, 6.0) | 7.0 (4.0, 11.0) |
| 25 th , 75 th Percentile | 1.0, 9.0 | 2.0, 15.0 | 2.0, 11.0 | 2.0, 14.0 |
| Observed Min, Max ^f | 1, 85 | 1, 265+ | 1, 436+ | 1, 158+ |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.

c. Two-sided p-value calculated from Cox proportional hazards model.

d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and history of brain metastases at baseline.

e. Calculated using the complementary log-log transformation method (Collett, 1994).

f. '+' means the observed time is from censored subjects.

Snapshot date: 10SEP2020, data cutoff date: 29MAY2020.

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_may2020_dco_1943\v01\outputs\tlfs\pgms\t-ae-km-overall-subgrp.sas Output: t02-04-03-ae-km-oval-sub-1-bm-safs.rtf (14DEC20:17:13) Data: adsl, adae, adttesaf

Seagen Protocol ONT-380-206**Table 2.4.3 Summary of Treatment-Emergent Adverse Events by History of Brain Metastases at Baseline - Time-to-Event Analysis Safety Analysis Set**

| Parameters | With Brian Metastases | | Without Brain Metastases | |
|--|------------------------|-----------------------|--------------------------|------------------------|
| | Tuc+Cap+Tra (N=194) | Pbo+Cap+Tra (N=91) | Tuc+Cap+Tra (N=209) | Pbo+Cap+Tra (N=105) |
| Severe TEAE | | | | |
| Number of Subjects With at Least One Event, n (%) | 119 (61.3) | 49 (53.8) | 120 (57.4) | 52 (49.5) |
| Number of Censored Subjects, n (%) | 75 (38.7) | 42 (46.2) | 89 (42.6) | 53 (50.5) |
| Stratified Hazard Ratio ^{a, b} (95% C.I.) | | 1.064 (0.760, 1.491) | | 1.125 (0.810, 1.564) |
| P-value ^{b, c} | | 0.71621 | | 0.48167 |
| Interaction Test P-value ^d | | | 0.79315 | |
| Median Time to Onset of the First Event (Days) (95% C.I.) ^e | 127.0 (106.0, 213.0) | 138.0 (89.0, 318.0) | 173.0 (98.0, 309.0) | 271.0 (106.0, 439.0) |
| 25 th , 75 th Percentile | 35.0, 529.0 | 43.0, 576.0 | 37.0, - | 42.0, - |
| Observed Min, Max ^f | 1, 899+ | 4, 598+ | 2, 1131+ | 2, 762+ |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.

c. Two-sided p-value calculated from Cox proportional hazards model.

d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and history of brain metastases at baseline.

e. Calculated using the complementary log-log transformation method (Collett, 1994).

f. '+' means the observed time is from censored subjects.

Snapshot date: 10SEP2020, data cutoff date: 29MAY2020.

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_may2020_dco_1943\v01\outputs\tlfs\pgms\t-ae-km-overall-subgrp.sas Output: t02-04-03-ae-km-oval-sub-1-bm-safs.rtf (14DEC20:17:13) Data: adsl, adae, adttesaf

Seagen Protocol ONT-380-206**Table 2.4.3 Summary of Treatment-Emergent Adverse Events by History of Brain Metastases at Baseline - Time-to-Event Analysis Safety Analysis Set**

| Parameters | With Brain Metastases | | Without Brain Metastases | |
|--|------------------------|-----------------------|--------------------------|------------------------|
| | Tuc+Cap+Tra (N=194) | Pbo+Cap+Tra (N=91) | Tuc+Cap+Tra (N=209) | Pbo+Cap+Tra (N=105) |
| Serious TEAE | | | | |
| Number of Subjects With at Least One Event, n (%) | 64 (33.0) | 27 (29.7) | 54 (25.8) | 31 (29.5) |
| Number of Censored Subjects, n (%) | 130 (67.0) | 64 (70.3) | 155 (74.2) | 74 (70.5) |
| Stratified Hazard Ratio ^{a, b} (95% C.I.) | | 0.848 (0.534, 1.345) | | 0.717 (0.458, 1.123) |
| P-value ^{b, c} | | 0.48382 | | 0.14593 |
| Interaction Test P-value ^d | | | 0.62891 | |
| Median Time to Onset of the First Event (Days) (95% C.I.) ^e | 651.0 (547.0, 1036.0) | - (275.0, -) | 942.0 (698.0, -) | - (358.0, -) |
| 25 th , 75 th Percentile | 199.0, 1036.0 | 143.0, - | 311.0, - | 190.0, - |
| Observed Min, Max ^f | 1, 1036 | 4, 583+ | 2, 1327+ | 2, 839+ |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.

c. Two-sided p-value calculated from Cox proportional hazards model.

d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and history of brain metastases at baseline.

e. Calculated using the complementary log-log transformation method (Collett, 1994).

f. '+' means the observed time is from censored subjects.

Snapshot date: 10SEP2020, data cutoff date: 29MAY2020.

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_may2020_dco_1943\v01\outputs\tlfs\pgms\t-ae-km-overall-subgrp.sas Output: t02-04-03-ae-km-oval-sub-1-bm-safs.rtf (14DEC20:17:13) Data: adsl, adae, adttesaf

Seagen Protocol ONT-380-206**Table 2.4.3 Summary of Treatment-Emergent Adverse Events by History of Brain Metastases at Baseline - Time-to-Event Analysis Safety Analysis Set**

| Parameters | | With Brian Metastases | | Without Brain Metastases | |
|--|--|------------------------|-----------------------|--------------------------|------------------------|
| | | Tuc+Cap+Tra (N=194) | Pbo+Cap+Tra (N=91) | Tuc+Cap+Tra (N=209) | Pbo+Cap+Tra (N=105) |
| Discontinuation of Any Study Treatment Due to TEAE | Number of Subjects With at Least One Event, n (%) | 24 (12.4) | 7 (7.7) | 24 (11.5) | 13 (12.4) |
| | Number of Censored Subjects, n (%) | 170 (87.6) | 84 (92.3) | 185 (88.5) | 92 (87.6) |
| | Stratified Hazard Ratio ^{a, b} (95% C.I.) | | 1.249 (0.529, 2.949) | 0.742 (0.374, 1.474) | |
| | P-value ^{b, c} | | 0.61115 | 0.39461 | |
| | Interaction Test P-value ^d | | | 0.37152 | |
| | Median Time to Onset of the First Event (Days) (95% C.I.) ^e | - (925.0, -) | 576.0 (554.0, -) | - (-, -) | - (495.0, -) |
| | 25 th , 75 th Percentile | 925.0, - | 554.0, - | -, - | 495.0, - |
| Observed Min, Max ^f | 1, 1154+ | 26+, 598+ | 5, 1327+ | 4, 839+ | |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.

c. Two-sided p-value calculated from Cox proportional hazards model.

d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and history of brain metastases at baseline.

e. Calculated using the complementary log-log transformation method (Collett, 1994).

f. '+' means the observed time is from censored subjects.

Snapshot date: 10SEP2020, data cutoff date: 29MAY2020.

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_may2020_dco_1943\v01\outputs\tlfs\pgms\t-ae-km-overall-subgrp.sas Output: t02-04-03-ae-km-oval-sub-1-bm-safs.rtf (14DEC20:17:13) Data: adsl, adae, adttesaf

Seagen Protocol ONT-380-206**Table 2.4.4 Summary of Treatment-Emergent Adverse Events by Geographic Region - Time-to-Event Analysis
Safety Analysis Set**

| Parameters | North America | | Rest of World | |
|--|------------------------|------------------------|------------------------|-----------------------|
| | Tuc+Cap+Tra (N=241) | Pbo+Cap+Tra (N=119) | Tuc+Cap+Tra (N=163) | Pbo+Cap+Tra (N=78) |
| TEAE | | | | |
| Number of Subjects With at Least One Event, n (%) | 238 (98.8) | 117 (98.3) | 163 (100) | 74 (94.9) |
| Number of Censored Subjects, n (%) | 3 (1.2) | 2 (1.7) | 0 | 4 (5.1) |
| Stratified Hazard Ratio ^{a, b} (95% C.I.) | | 1.554 (1.230, 1.964) | | 1.548 (1.157, 2.070) |
| P-value ^{b, c} | | 0.00022 | | 0.00326 |
| Interaction Test P-value ^d | | | 0.59529 | |
| Median Time to Onset of the First Event (Days) (95% C.I.) ^e | 4.0 (4.0, 5.0) | 8.0 (6.0, 11.0) | 4.0 (2.0, 5.0) | 6.0 (3.0, 11.0) |
| 25 th , 75 th Percentile | 2.0, 10.0 | 2.0, 15.0 | 1.0, 9.0 | 1.0, 14.0 |
| Observed Min, Max ^f | 1, 436+ | 1, 83 | 1, 85 | 1, 265+ |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (Presence or history of brain metastases: Yes/No and ECOG performance status: 0/1) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.

c. Two-sided p-value calculated from Cox proportional hazards model.

d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and geographic region.

e. Calculated using the complementary log-log transformation method (Collett, 1994).

f. '+' means the observed time is from censored subjects.

Snapshot date: 10SEP2020, data cutoff date: 29MAY2020.

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_may2020_dco_1943\v01\outputs\tlfs\pgms\t-ae-km-overall-subgrp.sas Output: t02-04-04-ae-km-oval-sub-2-reg-safs.rtf (14DEC20:17:13) Data: adsl, adae, adttesaf

Seagen Protocol ONT-380-206**Table 2.4.4 Summary of Treatment-Emergent Adverse Events by Geographic Region - Time-to-Event Analysis
Safety Analysis Set**

| Parameters | North America | | Rest of World | |
|--|------------------------|------------------------|------------------------|-----------------------|
| | Tuc+Cap+Tra (N=241) | Pbo+Cap+Tra (N=119) | Tuc+Cap+Tra (N=163) | Pbo+Cap+Tra (N=78) |
| Severe TEAE | | | | |
| Number of Subjects With at Least One Event, n (%) | 142 (58.9) | 61 (51.3) | 97 (59.5) | 40 (51.3) |
| Number of Censored Subjects, n (%) | 99 (41.1) | 58 (48.7) | 66 (40.5) | 38 (48.7) |
| Stratified Hazard Ratio ^{a, b} (95% C.I.) | | 1.084 (0.801, 1.467) | | 1.151 (0.793, 1.671) |
| P-value ^{b, c} | | 0.60225 | | 0.45987 |
| Interaction Test P-value ^d | | | | 0.88231 |
| Median Time to Onset of the First Event (Days) (95% C.I.) ^e | 169.0 (99.0, 284.0) | 192.0 (95.0, 318.0) | 127.0 (105.0, 243.0) | 243.0 (123.0, 423.0) |
| 25 th , 75 th Percentile | 35.0, 697.0 | 42.0, - | 37.0, - | 79.0, 576.0 |
| Observed Min, Max ^f | 1, 1131+ | 4, 762+ | 3, 873+ | 2, 598+ |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (Presence or history of brain metastases: Yes/No and ECOG performance status: 0/1) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.

c. Two-sided p-value calculated from Cox proportional hazards model.

d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and geographic region.

e. Calculated using the complementary log-log transformation method (Collett, 1994).

f. '+' means the observed time is from censored subjects.

Snapshot date: 10SEP2020, data cutoff date: 29MAY2020.

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_may2020_dco_1943\v01\outputs\tlfs\pgms\t-ae-km-overall-subgrp.sas Output: t02-04-04-ae-km-oval-sub-2-reg-safs.rtf (14DEC20:17:13) Data: adsl, adae, adttesaf

Seagen Protocol ONT-380-206**Table 2.4.4 Summary of Treatment-Emergent Adverse Events by Geographic Region - Time-to-Event Analysis
Safety Analysis Set**

| Parameters | North America | | Rest of World | |
|--|------------------------|------------------------|------------------------|-----------------------|
| | Tuc+Cap+Tra (N=241) | Pbo+Cap+Tra (N=119) | Tuc+Cap+Tra (N=163) | Pbo+Cap+Tra (N=78) |
| Serious TEAE | | | | |
| Number of Subjects With at Least One Event, n (%) | 73 (30.3) | 32 (26.9) | 45 (27.6) | 26 (33.3) |
| Number of Censored Subjects, n (%) | 168 (69.7) | 87 (73.1) | 118 (72.4) | 52 (66.7) |
| Stratified Hazard Ratio ^{a, b} (95% C.I.) | | 0.923 (0.604, 1.411) | | 0.615 (0.375, 1.009) |
| P-value ^{b, c} | | 0.71205 | | 0.05442 |
| Interaction Test P-value ^d | | | 0.28818 | |
| Median Time to Onset of the First Event (Days) (95% C.I.) ^e | 698.0 (547.0, 1036.0) | - (377.0, -) | - (-, -) | 358.0 (271.0, -) |
| 25 th , 75 th Percentile | 273.0, - | 146.0, - | 199.0, - | 176.0, - |
| Observed Min, Max ^f | 1, 1327+ | 13, 762+ | 1, 873+ | 2, 839+ |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (Presence or history of brain metastases: Yes/No and ECOG performance status: 0/1) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.

c. Two-sided p-value calculated from Cox proportional hazards model.

d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and geographic region.

e. Calculated using the complementary log-log transformation method (Collett, 1994).

f. '+' means the observed time is from censored subjects.

Snapshot date: 10SEP2020, data cutoff date: 29MAY2020.

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_may2020_dco_1943\v01\outputs\tlfs\pgms\t-ae-km-overall-subgrp.sas Output: t02-04-04-ae-km-oval-sub-2-reg-safs.rtf (14DEC20:17:13) Data: adsl, adae, adttesaf

Seagen Protocol ONT-380-206**Table 2.4.4 Summary of Treatment-Emergent Adverse Events by Geographic Region - Time-to-Event Analysis
Safety Analysis Set**

| Parameters | North America | | Rest of World | |
|--|------------------------|------------------------|------------------------|-----------------------|
| | Tuc+Cap+Tra (N=241) | Pbo+Cap+Tra (N=119) | Tuc+Cap+Tra (N=163) | Pbo+Cap+Tra (N=78) |
| Discontinuation of Any Study Treatment Due to TEAE | | | | |
| Number of Subjects With at Least One Event, n (%) | 32 (13.3) | 17 (14.3) | 16 (9.8) | 3 (3.8) |
| Number of Censored Subjects, n (%) | 209 (86.7) | 102 (85.7) | 147 (90.2) | 75 (96.2) |
| Stratified Hazard Ratio ^{a, b} (95% C.I.) | | 0.678 (0.370, 1.241) | | 2.411 (0.700, 8.305) |
| P-value ^{b, c} | | 0.20765 | | 0.16308 |
| Interaction Test P-value ^d | | | 0.10773 | |
| Median Time to Onset of the First Event (Days) (95% C.I.) ^e | - (925.0, -) | 554.0 (495.0, -) | - (-, -) | - (576.0, -) |
| 25 th , 75 th Percentile | 925.0, - | 495.0, - | -, - | 576.0, - |
| Observed Min, Max ^f | 4+, 1327+ | 26+, 762+ | 1, 954+ | 4, 839+ |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (Presence or history of brain metastases: Yes/No and ECOG performance status: 0/1) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.

c. Two-sided p-value calculated from Cox proportional hazards model.

d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and geographic region.

e. Calculated using the complementary log-log transformation method (Collett, 1994).

f. '+' means the observed time is from censored subjects.

Snapshot date: 10SEP2020, data cutoff date: 29MAY2020.

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_may2020_dco_1943\v01\outputs\tlfs\pgms\t-ae-km-overall-subgrp.sas Output: t02-04-04-ae-km-oval-sub-2-reg-safs.rtf (14DEC20:17:13) Data: adsl, adae, adttesaf

Seagen Protocol ONT-380-206**Table 2.4.5 Summary of Treatment-Emergent Adverse Events by Baseline ECOG Score - Time-to-Event Analysis
Safety Analysis Set**

| Parameters | ECOG=0 | | ECOG=1 | |
|--|------------------------|-----------------------|------------------------|------------------------|
| | Tuc+Cap+Tra (N=203) | Pbo+Cap+Tra (N=91) | Tuc+Cap+Tra (N=201) | Pbo+Cap+Tra (N=106) |
| TEAE | | | | |
| Number of Subjects With at Least One Event, n (%) | 200 (98.5) | 90 (98.9) | 201 (100) | 101 (95.3) |
| Number of Censored Subjects, n (%) | 3 (1.5) | 1 (1.1) | 0 | 5 (4.7) |
| Stratified Hazard Ratio ^{a, b} (95% C.I.) | | 1.337 (1.033, 1.731) | | 1.750 (1.358, 2.256) |
| P-value ^{b, c} | | 0.02750 | | 0.00002 |
| Interaction Test P-value ^d | | | 0.10082 | |
| Median Time to Onset of the First Event (Days) (95% C.I.) ^e | 4.0 (3.0, 6.0) | 7.0 (3.0, 10.0) | 4.0 (3.0, 4.0) | 8.0 (6.0, 12.0) |
| 25 th , 75 th Percentile | 1.0, 11.0 | 2.0, 13.0 | 2.0, 9.0 | 3.0, 15.0 |
| Observed Min, Max ^f | 1, 436+ | 1, 265+ | 1, 85 | 1, 262+ |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (Presence or history of brain metastases: Yes/No and Region of world: North America /Rest of World) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.

c. Two-sided p-value calculated from Cox proportional hazards model.

d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and baseline ECOG score.

e. Calculated using the complementary log-log transformation method (Collett, 1994).

f. '+' means the observed time is from censored subjects.

Snapshot date: 10SEP2020, data cutoff date: 29MAY2020.

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_may2020_dco_1943\v01\outputs\tlfs\pgms\t-ae-km-overall-subgrp.sas Output: t02-04-05-ae-km-oval-sub-3-ecog-safs.rtf (14DEC20:17:13) Data: adsl, adae, adttesaf

Seagen Protocol ONT-380-206**Table 2.4.5 Summary of Treatment-Emergent Adverse Events by Baseline ECOG Score - Time-to-Event Analysis
Safety Analysis Set**

| Parameters | ECOG=0 | | ECOG=1 | |
|--|------------------------|-----------------------|------------------------|------------------------|
| | Tuc+Cap+Tra (N=203) | Pbo+Cap+Tra (N=91) | Tuc+Cap+Tra (N=201) | Pbo+Cap+Tra (N=106) |
| Severe TEAE | | | | |
| Number of Subjects With at Least One Event, n (%) | 114 (56.2) | 46 (50.5) | 125 (62.2) | 55 (51.9) |
| Number of Censored Subjects, n (%) | 89 (43.8) | 45 (49.5) | 76 (37.8) | 51 (48.1) |
| Stratified Hazard Ratio ^{a, b} (95% C.I.) | | 1.133 (0.803, 1.599) | | 1.087 (0.788, 1.499) |
| P-value ^{b, c} | | 0.47816 | | 0.61290 |
| Interaction Test P-value ^d | | | 0.90444 | |
| Median Time to Onset of the First Event (Days) (95% C.I.) ^e | 192.0 (114.0, 311.0) | 271.0 (112.0, 423.0) | 121.0 (83.0, 173.0) | 163.0 (84.0, 336.0) |
| 25 th , 75 th Percentile | 37.0, - | 81.0, - | 35.0, 493.0 | 35.0, 576.0 |
| Observed Min, Max ^f | 1, 1131+ | 2, 598+ | 2, 899+ | 4, 762+ |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (Presence or history of brain metastases: Yes/No and Region of world: North America /Rest of World) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.

c. Two-sided p-value calculated from Cox proportional hazards model.

d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and baseline ECOG score.

e. Calculated using the complementary log-log transformation method (Collett, 1994).

f. '+' means the observed time is from censored subjects.

Snapshot date: 10SEP2020, data cutoff date: 29MAY2020.

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_may2020_dco_1943\v01\outputs\tlfs\pgms\t-ae-km-overall-subgrp.sas Output: t02-04-05-ae-km-oval-sub-3-ecog-safs.rtf (14DEC20:17:13) Data: adsl, adae, adttesaf

Seagen Protocol ONT-380-206**Table 2.4.5 Summary of Treatment-Emergent Adverse Events by Baseline ECOG Score - Time-to-Event Analysis
Safety Analysis Set**

| Parameters | ECOG=0 | | ECOG=1 | |
|--|------------------------|-----------------------|------------------------|------------------------|
| | Tuc+Cap+Tra (N=203) | Pbo+Cap+Tra (N=91) | Tuc+Cap+Tra (N=201) | Pbo+Cap+Tra (N=106) |
| Serious TEAE | | | | |
| Number of Subjects With at Least One Event, n (%) | 51 (25.1) | 27 (29.7) | 67 (33.3) | 31 (29.2) |
| Number of Censored Subjects, n (%) | 152 (74.9) | 64 (70.3) | 134 (66.7) | 75 (70.8) |
| Stratified Hazard Ratio ^{a, b} (95% C.I.) | | 0.651 (0.405, 1.048) | | 0.931 (0.603, 1.440) |
| P-value ^{b, c} | | 0.07706 | | 0.74901 |
| Interaction Test P-value ^d | | | 0.30540 | |
| Median Time to Onset of the First Event (Days) (95% C.I.) ^e | 1036.0 (577.0, -) | - (307.0, -) | 651.0 (493.0, 942.0) | 377.0 (304.0, -) |
| 25 th , 75 th Percentile | 319.0, - | 169.0, - | 102.0, 942.0 | 152.0, - |
| Observed Min, Max ^f | 1, 1327+ | 13, 839+ | 1, 942 | 2, 762+ |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (Presence or history of brain metastases: Yes/No and Region of world: North America /Rest of World) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.

c. Two-sided p-value calculated from Cox proportional hazards model.

d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and baseline ECOG score.

e. Calculated using the complementary log-log transformation method (Collett, 1994).

f. '+' means the observed time is from censored subjects.

Snapshot date: 10SEP2020, data cutoff date: 29MAY2020.

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_may2020_dco_1943\v01\outputs\tlfs\pgms\t-ae-km-overall-subgrp.sas Output: t02-04-05-ae-km-oval-sub-3-ecog-safs.rtf (14DEC20:17:13) Data: adsl, adae, adttesaf

Seagen Protocol ONT-380-206**Table 2.4.5 Summary of Treatment-Emergent Adverse Events by Baseline ECOG Score - Time-to-Event Analysis
Safety Analysis Set**

| Parameters | ECOG=0 | | ECOG=1 | |
|--|------------------------|-----------------------|------------------------|------------------------|
| | Tuc+Cap+Tra (N=203) | Pbo+Cap+Tra (N=91) | Tuc+Cap+Tra (N=201) | Pbo+Cap+Tra (N=106) |
| Discontinuation of Any Study Treatment Due to TEAE | | | | |
| Number of Subjects With at Least One Event, n (%) | 21 (10.3) | 8 (8.8) | 27 (13.4) | 12 (11.3) |
| Number of Censored Subjects, n (%) | 182 (89.7) | 83 (91.2) | 174 (86.6) | 94 (88.7) |
| Stratified Hazard Ratio ^{a, b} (95% C.I.) | | 1.017 (0.445, 2.322) | | 0.989 (0.497, 1.966) |
| P-value ^{b, c} | | 0.96829 | | 0.97417 |
| Interaction Test P-value ^d | | | 0.93907 | |
| Median Time to Onset of the First Event (Days) (95% C.I.) ^e | - (-, -) | - (554.0, -) | - (-, -) | 576.0 (495.0, -) |
| 25 th , 75 th Percentile | -, - | 554.0, - | -, - | 495.0, - |
| Observed Min, Max ^f | 4+, 1327+ | 50+, 839+ | 1, 1154+ | 4, 762+ |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (Presence or history of brain metastases: Yes/No and Region of world: North America /Rest of World) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.

c. Two-sided p-value calculated from Cox proportional hazards model.

d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and baseline ECOG score.

e. Calculated using the complementary log-log transformation method (Collett, 1994).

f. '+' means the observed time is from censored subjects.

Snapshot date: 10SEP2020, data cutoff date: 29MAY2020.

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_may2020_dco_1943\v01\outputs\tlfs\pgms\t-ae-km-overall-subgrp.sas Output:
t02-04-05-ae-km-oval-sub-3-ecog-safs.rtf (14DEC20:17:13) Data: adsl, adae, adttesaf

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**Table 2.4.6 Summary of Treatment-Emergent Adverse Events by Age - Time-to-Event Analysis
Safety Analysis Set**

| Parameters | Age < 65 Years | | Age ≥ 65 Years | |
|--|------------------------|------------------------|-----------------------|-----------------------|
| | Tuc+Cap+Tra (N=322) | Pbo+Cap+Tra (N=164) | Tuc+Cap+Tra (N=82) | Pbo+Cap+Tra (N=33) |
| TEAE | | | | |
| Number of Subjects With at Least One Event, n (%) | 320 (99.4) | 159 (97.0) | 81 (98.8) | 32 (97.0) |
| Number of Censored Subjects, n (%) | 2 (0.6) | 5 (3.0) | 1 (1.2) | 1 (3.0) |
| Stratified Hazard Ratio ^{a, b} (95% C.I.) | | 1.491 (1.221, 1.822) | | 1.879 (1.154, 3.060) |
| P-value ^{b, c} | | 0.00009 | | 0.01127 |
| Interaction Test P-value ^d | | | 0.38225 | |
| Median Time to Onset of the First Event (Days) (95% C.I.) ^e | 4.0 (3.0, 5.0) | 7.0 (5.0, 10.0) | 4.0 (2.0, 6.0) | 11.0 (5.0, 13.0) |
| 25 th , 75 th Percentile | 2.0, 9.0 | 2.0, 15.0 | 1.0, 11.0 | 3.0, 13.0 |
| Observed Min, Max ^f | 1, 436+ | 1, 265+ | 1, 34 | 1, 107 |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (Presence or history of brain metastases: Yes/No, ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.

c. Two-sided p-value calculated from Cox proportional hazards model.

d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and age.

e. Calculated using the complementary log-log transformation method (Collett, 1994).

f. '+' means the observed time is from censored subjects.

Snapshot date: 10SEP2020, data cutoff date: 29MAY2020.

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_may2020_dco_1943\v01\outputs\tlfs\pgms\t-ae-km-overall-subgrp.sas Output: t02-04-06-ae-km-oval-sub-4-age-safs.rtf (14DEC20:17:13) Data: adsl, adae, adtesaf

Seagen Protocol ONT-380-206

**Table 2.4.6 Summary of Treatment-Emergent Adverse Events by Age - Time-to-Event Analysis
Safety Analysis Set**

| Parameters | Age < 65 Years | | Age ≥ 65 Years | |
|--|------------------------|------------------------|-----------------------|-----------------------|
| | Tuc+Cap+Tra (N=322) | Pbo+Cap+Tra (N=164) | Tuc+Cap+Tra (N=82) | Pbo+Cap+Tra (N=33) |
| Severe TEAE | | | | |
| Number of Subjects With at Least One Event, n (%) | 190 (59.0) | 78 (47.6) | 49 (59.8) | 23 (69.7) |
| Number of Censored Subjects, n (%) | 132 (41.0) | 86 (52.4) | 33 (40.2) | 10 (30.3) |
| Stratified Hazard Ratio ^{a, b} (95% C.I.) | 1.189 (0.910, 1.553) | | 0.734 (0.428, 1.260) | |
| P-value ^{b, c} | 0.20397 | | 0.26273 | |
| Interaction Test P-value ^d | 0.13344 | | | |
| Median Time to Onset of the First Event (Days) (95% C.I.) ^e | 176.0 (118.0, 277.0) | 275.0 (127.0, 439.0) | 106.0 (50.0, 173.0) | 85.0 (42.0, 192.0) |
| 25 th , 75 th Percentile | 37.0, 697.0 | 57.0, 576.0 | 34.0, - | 33.0, 304.0 |
| Observed Min, Max ^f | 2, 1131+ | 2, 762+ | 1, 597+ | 9, 324+ |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (Presence or history of brain metastases: Yes/No, ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.

c. Two-sided p-value calculated from Cox proportional hazards model.

d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and age.

e. Calculated using the complementary log-log transformation method (Collett, 1994).

f. '+' means the observed time is from censored subjects.

Snapshot date: 10SEP2020, data cutoff date: 29MAY2020.

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_may2020_dco_1943\v01\outputs\tlfs\pgms\t-ae-km-overall-subgrp.sas Output: t02-04-06-ae-km-oval-sub-4-age-safs.rtf (14DEC20:17:13) Data: adsl, adae, adtesaf

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**Table 2.4.6 Summary of Treatment-Emergent Adverse Events by Age - Time-to-Event Analysis
Safety Analysis Set**

| Parameters | Age < 65 Years | | Age ≥ 65 Years | |
|--|------------------------|------------------------|-----------------------|-----------------------|
| | Tuc+Cap+Tra (N=322) | Pbo+Cap+Tra (N=164) | Tuc+Cap+Tra (N=82) | Pbo+Cap+Tra (N=33) |
| Serious TEAE | | | | |
| Number of Subjects With at Least One Event, n (%) | 89 (27.6) | 45 (27.4) | 29 (35.4) | 13 (39.4) |
| Number of Censored Subjects, n (%) | 233 (72.4) | 119 (72.6) | 53 (64.6) | 20 (60.6) |
| Stratified Hazard Ratio ^{a, b} (95% C.I.) | | 0.742 (0.513, 1.073) | | 0.829 (0.412, 1.669) |
| P-value ^{b, c} | | 0.11293 | | 0.59979 |
| Interaction Test P-value ^d | | | 0.77351 | |
| Median Time to Onset of the First Event (Days) (95% C.I.) ^e | 1036.0 (651.0, -) | - (358.0, -) | 565.0 (309.0, 942.0) | 377.0 (116.0, -) |
| 25 th , 75 th Percentile | 284.0, - | 184.0, - | 84.0, 942.0 | 112.0, - |
| Observed Min, Max ^f | 1, 1327+ | 2, 839+ | 1, 942 | 13, 409+ |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (Presence or history of brain metastases: Yes/No, ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.

c. Two-sided p-value calculated from Cox proportional hazards model.

d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and age.

e. Calculated using the complementary log-log transformation method (Collett, 1994).

f. '+' means the observed time is from censored subjects.

Snapshot date: 10SEP2020, data cutoff date: 29MAY2020.

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_may2020_dco_1943\v01\outputs\tlfs\pgms\t-ae-km-overall-subgrp.sas Output: t02-04-06-ae-km-oval-sub-4-age-safs.rtf (14DEC20:17:13) Data: adsl, adae, adtesaf

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**Table 2.4.6 Summary of Treatment-Emergent Adverse Events by Age - Time-to-Event Analysis
Safety Analysis Set**

| Parameters | Age < 65 Years | | Age ≥ 65 Years | |
|--|------------------------|------------------------|-----------------------|-----------------------|
| | Tuc+Cap+Tra (N=322) | Pbo+Cap+Tra (N=164) | Tuc+Cap+Tra (N=82) | Pbo+Cap+Tra (N=33) |
| Discontinuation of Any Study Treatment Due to TEAE | | | | |
| Number of Subjects With at Least One Event, n (%) | 33 (10.2) | 13 (7.9) | 15 (18.3) | 7 (21.2) |
| Number of Censored Subjects, n (%) | 289 (89.8) | 151 (92.1) | 67 (81.7) | 26 (78.8) |
| Stratified Hazard Ratio ^{a, b} (95% C.I.) | | 1.035 (0.539, 1.989) | | 0.577 (0.226, 1.475) |
| P-value ^{b, c} | | 0.91752 | | 0.25080 |
| Interaction Test P-value ^d | | | | 0.34012 |
| Median Time to Onset of the First Event (Days) (95% C.I.) ^e | - (-, -) | - (554.0, -) | - (476.0, -) | - (337.0, -) |
| 25 th , 75 th Percentile | -, - | 554.0, - | 476.0, - | 337.0, - |
| Observed Min, Max ^f | 1, 1327+ | 4, 839+ | 4+, 736+ | 31+, 428+ |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (Presence or history of brain metastases: Yes/No, ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.

c. Two-sided p-value calculated from Cox proportional hazards model.

d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and age.

e. Calculated using the complementary log-log transformation method (Collett, 1994).

f. '+' means the observed time is from censored subjects.

Snapshot date: 10SEP2020, data cutoff date: 29MAY2020.

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_may2020_dco_1943\v01\outputs\tlfs\pgms\t-ae-km-overall-subgrp.sas Output: t02-04-06-ae-km-oval-sub-4-age-safs.rtf (14DEC20:17:13) Data: adsl, adae, adttesaf

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**Table 2.4.7 Summary of Treatment-Emergent Adverse Events by Race - Time-to-Event Analysis
Safety Analysis Set**

| Parameters | White | | Non-White | |
|--|------------------------|------------------------|------------------------|-----------------------|
| | Tuc+Cap+Tra (N=283) | Pbo+Cap+Tra (N=153) | Tuc+Cap+Tra (N=121) | Pbo+Cap+Tra (N=44) |
| TEAE | | | | |
| Number of Subjects With at Least One Event, n (%) | 283 (100) | 149 (97.4) | 118 (97.5) | 42 (95.5) |
| Number of Censored Subjects, n (%) | 0 | 4 (2.6) | 3 (2.5) | 2 (4.5) |
| Stratified Hazard Ratio ^{a, b} (95% C.I.) | | 1.482 (1.202, 1.826) | | 1.587 (1.060, 2.376) |
| P-value ^{b, c} | | 0.00023 | | 0.02499 |
| Interaction Test P-value ^d | | | 0.43699 | |
| Median Time to Onset of the First Event (Days) (95% C.I.) ^e | 4.0 (4.0, 5.0) | 8.0 (5.0, 11.0) | 4.0 (2.0, 5.0) | 7.0 (3.0, 12.0) |
| 25 th , 75 th Percentile | 2.0, 11.0 | 2.0, 14.0 | 2.0, 9.0 | 2.0, 14.5 |
| Observed Min, Max ^f | 1, 85 | 1, 265+ | 1, 436+ | 1, 71+ |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.
 b. Computed using stratification factors (Presence or history of brain metastases: Yes/No, ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.
 c. Two-sided p-value calculated from Cox proportional hazards model .
 d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and race.
 e. Calculated using the complementary log-log transformation method (Collett, 1994).
 f. '+' means the observed time is from censored subjects.
 Snapshot date: 10SEP2020, data cutoff date: 29MAY2020.
 Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_may2020_dco_1943\v01\outputs\tlfs\pgms\t-ae-km-overall-subgrp.sas Output: t02-04-07-ae-km-oval-sub-5-race-safs.rtf (14DEC20:17:13) Data: adsl, adae, adttesaf

Seagen Protocol ONT-380-206**Table 2.4.7 Summary of Treatment-Emergent Adverse Events by Race - Time-to-Event Analysis
Safety Analysis Set**

| Parameters | White | | Non-White | |
|--|------------------------|------------------------|------------------------|-----------------------|
| | Tuc+Cap+Tra (N=283) | Pbo+Cap+Tra (N=153) | Tuc+Cap+Tra (N=121) | Pbo+Cap+Tra (N=44) |
| Severe TEAE | | | | |
| Number of Subjects With at Least One Event, n (%) | 164 (58.0) | 80 (52.3) | 75 (62.0) | 21 (47.7) |
| Number of Censored Subjects, n (%) | 119 (42.0) | 73 (47.7) | 46 (38.0) | 23 (52.3) |
| Stratified Hazard Ratio ^{a, b} (95% C.I.) | | 1.053 (0.803, 1.380) | | 1.415 (0.853, 2.345) |
| P-value ^{b, c} | | 0.70941 | | 0.17850 |
| Interaction Test P-value ^d | | | 0.38834 | |
| Median Time to Onset of the First Event (Days) (95% C.I.) ^e | 134.0 (107.0, 284.0) | 163.0 (102.0, 307.0) | 173.0 (85.0, 255.0) | 336.0 (123.0, 576.0) |
| 25 th , 75 th Percentile | 35.0, - | 44.0, - | 42.0, 456.0 | 40.0, 576.0 |
| Observed Min, Max ^f | 1, 1131+ | 2, 762+ | 2, 624+ | 4, 576 |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (Presence or history of brain metastases: Yes/No, ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.

c. Two-sided p-value calculated from Cox proportional hazards model.

d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and race.

e. Calculated using the complementary log-log transformation method (Collett, 1994).

f. '+' means the observed time is from censored subjects.

Snapshot date: 10SEP2020, data cutoff date: 29MAY2020.

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_may2020_dco_1943\v01\outputs\tlfs\pgms\t-ae-km-overall-subgrp.sas Output: t02-04-07-ae-km-oval-sub-5-race-safs.rtf (14DEC20:17:13) Data: adsl, adae, adttesaf

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**Table 2.4.7 Summary of Treatment-Emergent Adverse Events by Race - Time-to-Event Analysis
Safety Analysis Set**

| Parameters | White | | Non-White | |
|--|------------------------|------------------------|------------------------|-----------------------|
| | Tuc+Cap+Tra (N=283) | Pbo+Cap+Tra (N=153) | Tuc+Cap+Tra (N=121) | Pbo+Cap+Tra (N=44) |
| Serious TEAE | | | | |
| Number of Subjects With at Least One Event, n (%) | 87 (30.7) | 47 (30.7) | 31 (25.6) | 11 (25.0) |
| Number of Censored Subjects, n (%) | 196 (69.3) | 106 (69.3) | 90 (74.4) | 33 (75.0) |
| Stratified Hazard Ratio ^{a, b} (95% C.I.) | | 0.763 (0.529, 1.099) | | 0.896 (0.443, 1.811) |
| P-value ^{b, c} | | 0.14638 | | 0.76039 |
| Interaction Test P-value ^d | | | 0.54757 | |
| Median Time to Onset of the First Event (Days) (95% C.I.) ^e | 942.0 (565.0, -) | - (307.0, -) | 577.0 (547.0, -) | - (275.0, -) |
| 25 th , 75 th Percentile | 243.0, - | 146.0, - | 311.0, - | 275.0, - |
| Observed Min, Max ^f | 1, 1327+ | 2, 839+ | 2, 666+ | 13, 583+ |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.
 b. Computed using stratification factors (Presence or history of brain metastases: Yes/No, ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.
 c. Two-sided p-value calculated from Cox proportional hazards model .
 d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and race.
 e. Calculated using the complementary log-log transformation method (Collett, 1994).
 f. '+' means the observed time is from censored subjects.
 Snapshot date: 10SEP2020, data cutoff date: 29MAY2020.
 Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_may2020_dco_1943\v01\outputs\tlfs\pgms\t-ae-km-overall-subgrp.sas Output: t02-04-07-ae-km-oval-sub-5-race-safs.rtf (14DEC20:17:13) Data: adsl, adae, adttesaf

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**Table 2.4.7 Summary of Treatment-Emergent Adverse Events by Race - Time-to-Event Analysis
Safety Analysis Set**

| Parameters | White | | Non-White | |
|--|------------------------|------------------------|------------------------|-----------------------|
| | Tuc+Cap+Tra (N=283) | Pbo+Cap+Tra (N=153) | Tuc+Cap+Tra (N=121) | Pbo+Cap+Tra (N=44) |
| Discontinuation of Any Study Treatment Due to TEAE | | | | |
| Number of Subjects With at Least One Event, n (%) | 34 (12.0) | 16 (10.5) | 14 (11.6) | 4 (9.1) |
| Number of Censored Subjects, n (%) | 249 (88.0) | 137 (89.5) | 107 (88.4) | 40 (90.9) |
| Stratified Hazard Ratio ^{a, b} (95% C.I.) | | 0.956 (0.522, 1.749) | | 0.963 (0.303, 3.067) |
| P-value ^{b, c} | | 0.88312 | | 0.94965 |
| Interaction Test P-value ^d | | | 0.96995 | |
| Median Time to Onset of the First Event (Days) (95% C.I.) ^e | - (925.0, -) | - (495.0, -) | - (-, -) | 576.0 (554.0, -) |
| 25 th , 75 th Percentile | 925.0, - | 495.0, - | -, - | 554.0, - |
| Observed Min, Max ^f | 1, 1327+ | 4, 839+ | 4+, 1154+ | 40+, 580+ |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.
 b. Computed using stratification factors (Presence or history of brain metastases: Yes/No, ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.
 c. Two-sided p-value calculated from Cox proportional hazards model.
 d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and race.
 e. Calculated using the complementary log-log transformation method (Collett, 1994).
 f. '+' means the observed time is from censored subjects.
 Snapshot date: 10SEP2020, data cutoff date: 29MAY2020.
 Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_may2020_dco_1943\v01\outputs\tlfs\pgms\t-ae-km-overall-subgrp.sas Output:
 t02-04-07-ae-km-oval-sub-5-race-safs.rtf (14DEC20:17:13) Data: adsl, adae, adttesaf

Seagen Protocol ONT-380-206**Table 2.4.8 Summary of Treatment-Emergent Adverse Events by Hormone Receptor Status - Time-to-Event Analysis
Safety Analysis Set**

| Parameters | Negative for Both | | Positive for ER or PR or Both | |
|--|------------------------|-----------------------|-------------------------------|------------------------|
| | Tuc+Cap+Tra (N=163) | Pbo+Cap+Tra (N=74) | Tuc+Cap+Tra (N=241) | Pbo+Cap+Tra (N=123) |
| TEAE | | | | |
| Number of Subjects With at Least One Event, n (%) | 162 (99.4) | 71 (95.9) | 239 (99.2) | 120 (97.6) |
| Number of Censored Subjects, n (%) | 1 (0.6) | 3 (4.1) | 2 (0.8) | 3 (2.4) |
| Stratified Hazard Ratio ^{a, b} (95% C.I.) | | 1.438 (1.064, 1.943) | | 1.604 (1.266, 2.032) |
| P-value ^{b, c} | | 0.01798 | | 0.00009 |
| Interaction Test P-value ^d | | | | 0.37594 |
| Median Time to Onset of the First Event (Days) (95% C.I.) ^e | 4.0 (3.0, 5.0) | 7.0 (5.0, 11.0) | 4.0 (3.0, 5.0) | 8.0 (6.0, 11.0) |
| 25 th , 75 th Percentile | 2.0, 9.0 | 2.0, 15.0 | 2.0, 9.0 | 2.0, 14.0 |
| Observed Min, Max ^f | 1, 85 | 1, 71+ | 1, 436+ | 1, 265+ |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (Presence or history of brain metastases: Yes/No, ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.

c. Two-sided p-value calculated from Cox proportional hazards model.

d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and hormone receptor status.

e. Calculated using the complementary log-log transformation method (Collett, 1994).

f. '+' means the observed time is from censored subjects.

Snapshot date: 10SEP2020, data cutoff date: 29MAY2020.

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_may2020_dco_1943\v01\outputs\tlfs\pgms\t-ae-km-overall-subgrp.sas Output: t02-04-08-ae-km-oval-sub-6-hr-safs.rtf (14DEC20:17:13) Data: adsl, adae, adttesaf

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**Table 2.4.8 Summary of Treatment-Emergent Adverse Events by Hormone Receptor Status - Time-to-Event Analysis
Safety Analysis Set**

| Parameters | Negative for Both | | Positive for ER or PR or Both | |
|--|------------------------|-----------------------|-------------------------------|------------------------|
| | Tuc+Cap+Tra (N=163) | Pbo+Cap+Tra (N=74) | Tuc+Cap+Tra (N=241) | Pbo+Cap+Tra (N=123) |
| Severe TEAE | | | | |
| Number of Subjects With at Least One Event, n (%) | 98 (60.1) | 41 (55.4) | 141 (58.5) | 60 (48.8) |
| Number of Censored Subjects, n (%) | 65 (39.9) | 33 (44.6) | 100 (41.5) | 63 (51.2) |
| Stratified Hazard Ratio ^{a, b} (95% C.I.) | | 0.916 (0.629, 1.335) | | 1.231 (0.908, 1.671) |
| P-value ^{b, c} | | 0.64802 | | 0.18136 |
| Interaction Test P-value ^d | | | | 0.25168 |
| Median Time to Onset of the First Event (Days) (95% C.I.) ^e | 127.0 (98.0, 284.0) | 163.0 (89.0, 275.0) | 146.0 (105.0, 243.0) | 304.0 (105.0, 576.0) |
| 25 th , 75 th Percentile | 37.0, 697.0 | 42.0, 336.0 | 36.0, - | 57.0, - |
| Observed Min, Max ^f | 2, 1117+ | 2, 562+ | 1, 1131+ | 4, 762+ |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.
 b. Computed using stratification factors (Presence or history of brain metastases: Yes/No, ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.
 c. Two-sided p-value calculated from Cox proportional hazards model .
 d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and hormone receptor status.
 e. Calculated using the complementary log-log transformation method (Collett, 1994).
 f. '+' means the observed time is from censored subjects.
 Snapshot date: 10SEP2020, data cutoff date: 29MAY2020.
 Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_may2020_dco_1943\v01\outputs\tlfs\pgms\t-ae-km-overall-subgrp.sas Output: t02-04-08-ae-km-oval-sub-6-hr-safs.rtf (14DEC20:17:13) Data: adsl, adae, adttesaf

Seagen Protocol ONT-380-206**Table 2.4.8 Summary of Treatment-Emergent Adverse Events by Hormone Receptor Status - Time-to-Event Analysis
Safety Analysis Set**

| Parameters | Negative for Both | | Positive for ER or PR or Both | |
|--|------------------------|-----------------------|-------------------------------|------------------------|
| | Tuc+Cap+Tra (N=163) | Pbo+Cap+Tra (N=74) | Tuc+Cap+Tra (N=241) | Pbo+Cap+Tra (N=123) |
| Serious TEAE | | | | |
| Number of Subjects With at Least One Event, n (%) | 55 (33.7) | 24 (32.4) | 63 (26.1) | 34 (27.6) |
| Number of Censored Subjects, n (%) | 108 (66.3) | 50 (67.6) | 178 (73.9) | 89 (72.4) |
| Stratified Hazard Ratio ^{a, b} (95% C.I.) | | 0.696 (0.418, 1.158) | | 0.834 (0.546, 1.273) |
| P-value ^{b, c} | | 0.16305 | | 0.40020 |
| Interaction Test P-value ^d | | | | 0.85350 |
| Median Time to Onset of the First Event (Days) (95% C.I.) ^e | 942.0 (361.0, -) | 358.0 (243.0, 399.0) | - (577.0, -) | - (-, -) |
| 25 th , 75 th Percentile | 199.0, - | 152.0, 399.0 | 311.0, - | 169.0, - |
| Observed Min, Max ^f | 2, 1327+ | 14, 562+ | 1, 1080+ | 2, 839+ |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (Presence or history of brain metastases: Yes/No, ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.

c. Two-sided p-value calculated from Cox proportional hazards model.

d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and hormone receptor status.

e. Calculated using the complementary log-log transformation method (Collett, 1994).

f. '+' means the observed time is from censored subjects.

Snapshot date: 10SEP2020, data cutoff date: 29MAY2020.

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_may2020_dco_1943\v01\outputs\tlfs\pgms\t-ae-km-overall-subgrp.sas Output: t02-04-08-ae-km-oval-sub-6-hr-safs.rtf (14DEC20:17:13) Data: adsl, adae, adttesaf

Seagen Protocol ONT-380-206

**Table 2.4.8 Summary of Treatment-Emergent Adverse Events by Hormone Receptor Status - Time-to-Event Analysis
Safety Analysis Set**

| Parameters | Negative for Both | | Positive for ER or PR or Both | |
|--|------------------------|-----------------------|-------------------------------|------------------------|
| | Tuc+Cap+Tra (N=163) | Pbo+Cap+Tra (N=74) | Tuc+Cap+Tra (N=241) | Pbo+Cap+Tra (N=123) |
| Discontinuation of Any Study Treatment Due to TEAE | | | | |
| Number of Subjects With at Least One Event, n (%) | 24 (14.7) | 4 (5.4) | 24 (10.0) | 16 (13.0) |
| Number of Censored Subjects, n (%) | 139 (85.3) | 70 (94.6) | 217 (90.0) | 107 (87.0) |
| Stratified Hazard Ratio ^{a, b} (95% C.I.) | | 2.458 (0.840, 7.189) | | 0.583 (0.304, 1.115) |
| P-value ^{b, c} | | 0.10051 | | 0.10285 |
| Interaction Test P-value ^d | | | 0.04350 | |
| Median Time to Onset of the First Event (Days) (95% C.I.) ^e | - (925.0, -) | - (-, -) | - (-, -) | 576.0 (495.0, -) |
| 25 th , 75 th Percentile | 925.0, - | -, - | -, - | 495.0, - |
| Observed Min, Max ^f | 4+, 1327+ | 29+, 580+ | 1, 1131+ | 4, 839+ |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.
 b. Computed using stratification factors (Presence or history of brain metastases: Yes/No, ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.
 c. Two-sided p-value calculated from Cox proportional hazards model.
 d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and hormone receptor status.
 e. Calculated using the complementary log-log transformation method (Collett, 1994).
 f. '+' means the observed time is from censored subjects.
 Snapshot date: 10SEP2020, data cutoff date: 29MAY2020.
 Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_may2020_dco_1943\v01\outputs\tlfs\pgms\t-ae-km-overall-subgrp.sas Output:
 t02-04-08-ae-km-oval-sub-6-hr-safs.rtf (14DEC20:17:13) Data: adsl, adae, adttesaf

Seattle Genetics Protocol ONT-380-206**Table 2.2.1 Summary of Gastrointestinal Adverse Events by System Organ Class, Preferred Term and History of Brain Metastases at Baseline
Safety Analysis Set**

| System Organ Class/ Preferred Term | Parameters | With Brain Metastases | | Without Brain Metastases | |
|---------------------------------------|--|------------------------|-----------------------|--------------------------|------------------------|
| | | Tuc+Cap+Tra (N=194) | Pbo+Cap+Tra (N=91) | Tuc+Cap+Tra (N=209) | Pbo+Cap+Tra (N=105) |
| Gastrointestinal Disorders | Number of Subjects With at Least One Event, n (%) | 183 (94.3) | 71 (78.0) | 198 (94.7) | 91 (86.7) |
| | Number of Censored Subjects, n (%) | 11 (5.7) | 20 (22.0) | 11 (5.3) | 14 (13.3) |
| | Stratified Hazard Ratio ^{a, b} (95% C.I.) | | 2.127 (1.601, 2.825) | | 1.703 (1.319, 2.198) |
| | P-value ^{b, c} | | <.00001 | | 0.00004 |
| | Interaction Test P-value ^d | | | 0.31807 | |
| | Median Time to Onset of the First Event (Days) (95% C.I.) ^e | 7.0 (5.0, 8.0) | 15.0 (11.0, 22.0) | 7.0 (5.0, 8.0) | 15.0 (12.0, 25.0) |
| | 25 th , 75 th Percentile | 2.0, 15.0 | 8.0, 125.0 | 3.0, 14.0 | 5.0, 60.0 |
| Observed Min, Max ^f | 1, 420 | 1, 275+ | 1, 436+ | 1, 409+ | |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was ran.

c. Two-sided p-value calculated from Cox proportional hazards model.

d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and history of brain metastases at baseline.

e. Calculated using the complementary log-log transformation method (Collett, 1994).

f. '+' means the observed time is from censored subjects.

Data Snapshot: 14OCT2019, Data Cutoff Date: 04SEP2019

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_1753\v01\outputs\lfs\pgms\t-ae-km-gisoc-subgrp.sas Output: t-ae-km-gisoc-sub-1-bm-safs.rtf (17APR20:16:56) Data: adsl, adae, adttesaf

Seattle Genetics Protocol ONT-380-206**Table 2.2.1 Summary of Gastrointestinal Adverse Events by System Organ Class, Preferred Term and History of Brain Metastases at Baseline
Safety Analysis Set**

| System Organ Class/ Preferred Term | Parameters | With Brian Metastases | | Without Brain Metastases | |
|---------------------------------------|--|------------------------|-----------------------|--------------------------|------------------------|
| | | Tuc+Cap+Tra (N=194) | Pbo+Cap+Tra (N=91) | Tuc+Cap+Tra (N=209) | Pbo+Cap+Tra (N=105) |
| Diarrhoea | Number of Subjects With at Least One Event, n (%) | 158 (81.4) | 46 (50.5) | 168 (80.4) | 59 (56.2) |
| | Number of Censored Subjects, n (%) | 36 (18.6) | 45 (49.5) | 41 (19.6) | 46 (43.8) |
| | Stratified Hazard Ratio ^{a, b} (95% C.I.) | | 2.567 (1.840, 3.582) | | 2.208 (1.635, 2.980) |
| | P-value ^{b, c} | | <.00001 | | <.00001 |
| | Interaction Test P-value ^d | | | 0.54280 | |
| | Median Time to Onset of the First Event (Days) (95% C.I.) ^e | 15.0 (13.0, 16.0) | 157.0 (56.0, -) | 14.0 (12.0, 18.0) | 96.0 (60.0, 169.0) |
| | 25 th , 75 th Percentile | 8.0, 60.0 | 19.0, - | 7.0, 68.0 | 22.0, - |
| Observed Min, Max ^f | 1, 426+ | 1, 344+ | 1, 436+ | 1, 588+ | |

Page 2 of 6

a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was ran.

c. Two-sided p-value calculated from Cox proportional hazards model.

d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and history of brain metastases at baseline.

e. Calculated using the complementary log-log transformation method (Collett, 1994).

f. '+' means the observed time is from censored subjects.

Data Snapshot: 14OCT2019, Data Cutoff Date: 04SEP2019

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_1753\v01\outputs\lfs\pgms\t-ae-km-gisoc-subgrp.sas Output: t-ae-km-gisoc-sub-1-bm-safs.rtf (17APR20:16:56) Data: adsl, adae, adttesaf

Seattle Genetics Protocol ONT-380-206**Table 2.2.1 Summary of Gastrointestinal Adverse Events by System Organ Class, Preferred Term and History of Brain Metastases at Baseline
Safety Analysis Set**

| System Organ Class/ Preferred Term | Parameters | With Brain Metastases | | Without Brain Metastases | |
|---------------------------------------|--|------------------------|-----------------------|--------------------------|------------------------|
| | | Tuc+Cap+Tra (N=194) | Pbo+Cap+Tra (N=91) | Tuc+Cap+Tra (N=209) | Pbo+Cap+Tra (N=105) |
| Nausea | Number of Subjects With at Least One Event, n (%) | 115 (59.3) | 36 (39.6) | 120 (57.4) | 50 (47.6) |
| | Number of Censored Subjects, n (%) | 79 (40.7) | 55 (60.4) | 89 (42.6) | 55 (52.4) |
| | Stratified Hazard Ratio ^{a, b} (95% C.I.) | | 1.746 (1.197, 2.546) | | 1.298 (0.932, 1.809) |
| | P-value ^{b, c} | | 0.00379 | | 0.12334 |
| | Interaction Test P-value ^d | | | 0.26165 | |
| | Median Time to Onset of the First Event (Days) (95% C.I.) ^e | 43.0 (22.0, 160.0) | - (146.0, -) | 43.0 (15.0, 171.0) | 197.0 (50.0, -) |
| | 25 th , 75 th Percentile | 7.0, 599.0 | 15.0, - | 6.0, - | 15.0, - |
| Observed Min, Max ^f | 1, 688+ | 1, 580+ | 1, 1059+ | 1, 762+ | |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was ran.

c. Two-sided p-value calculated from Cox proportional hazards model.

d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and history of brain metastases at baseline.

e. Calculated using the complementary log-log transformation method (Collett, 1994).

f. '+' means the observed time is from censored subjects.

Data Snapshot: 14OCT2019, Data Cutoff Date: 04SEP2019

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_1753\v01\outputs\lfs\pgms\t-ae-km-gisoc-subgrp.sas Output: t-ae-km-gisoc-sub-1-bm-safs.rtf (17APR20:16:56) Data: adsl, adae, adttesaf

Seattle Genetics Protocol ONT-380-206**Table 2.2.1 Summary of Gastrointestinal Adverse Events by System Organ Class, Preferred Term and History of Brain Metastases at Baseline
Safety Analysis Set**

| System Organ Class/ Preferred Term | Parameters | With Brian Metastases | | Without Brain Metastases | |
|---------------------------------------|--|------------------------|-----------------------|--------------------------|------------------------|
| | | Tuc+Cap+Tra (N=194) | Pbo+Cap+Tra (N=91) | Tuc+Cap+Tra (N=209) | Pbo+Cap+Tra (N=105) |
| Vomiting | Number of Subjects With at Least One Event, n (%) | 79 (40.7) | 22 (24.2) | 65 (31.1) | 28 (26.7) |
| | Number of Censored Subjects, n (%) | 115 (59.3) | 69 (75.8) | 144 (68.9) | 77 (73.3) |
| | Stratified Hazard Ratio ^{a, b} (95% C.I.) | | 1.751 (1.089, 2.815) | | 1.206 (0.774, 1.880) |
| | P-value ^{b, c} | | 0.02080 | | 0.40736 |
| | Interaction Test P-value ^d | | | 0.25713 | |
| | Median Time to Onset of the First Event (Days) (95% C.I.) ^e | 599.0 (270.0, -) | - (-, -) | - (-, -) | - (332.0, -) |
| | 25 th , 75 th Percentile | 40.0, - | 173.0, - | 52.0, - | 214.0, - |
| Observed Min, Max ^f | 1, 891+ | 1, 583+ | 1, 1059+ | 1, 762+ | |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was ran.

c. Two-sided p-value calculated from Cox proportional hazards model.

d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and history of brain metastases at baseline.

e. Calculated using the complementary log-log transformation method (Collett, 1994).

f. '+' means the observed time is from censored subjects.

Data Snapshot: 14OCT2019, Data Cutoff Date: 04SEP2019

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_1753\v01\outputs\lfs\pgms\t-ae-km-gisoc-subgrp.sas Output: t-ae-km-gisoc-sub-1-bm-safs.rtf (17APR20:16:56) Data: adsl, adae, adttesaf

Seattle Genetics Protocol ONT-380-206**Table 2.2.1 Summary of Gastrointestinal Adverse Events by System Organ Class, Preferred Term and History of Brain Metastases at Baseline
Safety Analysis Set**

| System Organ Class/ Preferred Term | Parameters | With Brain Metastases | | Without Brain Metastases | |
|---------------------------------------|--|------------------------|-----------------------|--------------------------|------------------------|
| | | Tuc+Cap+Tra (N=194) | Pbo+Cap+Tra (N=91) | Tuc+Cap+Tra (N=209) | Pbo+Cap+Tra (N=105) |
| Stomatitis | Number of Subjects With at Least One Event, n (%) | 50 (25.8) | 12 (13.2) | 52 (24.9) | 16 (15.2) |
| | Number of Censored Subjects, n (%) | 144 (74.2) | 79 (86.8) | 157 (75.1) | 89 (84.8) |
| | Stratified Hazard Ratio ^{a, b} (95% C.I.) | | 1.960 (1.039, 3.699) | | 1.674 (0.953, 2.939) |
| | P-value ^{b, c} | | 0.03779 | | 0.07293 |
| | Interaction Test P-value ^d | | | 0.62403 | |
| | Median Time to Onset of the First Event (Days) (95% C.I.) ^e | - (-, -) | - (-, -) | - (615.0, -) | - (-, -) |
| | 25 th , 75 th Percentile | 190.0, - | -, - | 271.0, - | -, - |
| Observed Min, Max ^f | 1, 743+ | 7, 583+ | 1, 1059+ | 7, 762+ | |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was ran.

c. Two-sided p-value calculated from Cox proportional hazards model.

d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and history of brain metastases at baseline.

e. Calculated using the complementary log-log transformation method (Collett, 1994).

f. '+' means the observed time is from censored subjects.

Data Snapshot: 14OCT2019, Data Cutoff Date: 04SEP2019

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_1753\v01\outputs\lfs\pgms\t-ae-km-gisoc-subgrp.sas Output: t-ae-km-gisoc-sub-1-bm-safs.rtf (17APR20:16:56) Data: adsl, adae, adttesaf

Seattle Genetics Protocol ONT-380-206**Table 2.2.1 Summary of Gastrointestinal Adverse Events by System Organ Class, Preferred Term and History of Brain Metastases at Baseline
Safety Analysis Set**

| System Organ Class/ Preferred Term | Parameters | With Brain Metastases | | Without Brain Metastases | |
|---------------------------------------|--|------------------------|-----------------------|--------------------------|------------------------|
| | | Tuc+Cap+Tra (N=194) | Pbo+Cap+Tra (N=91) | Tuc+Cap+Tra (N=209) | Pbo+Cap+Tra (N=105) |
| Constipation | Number of Subjects With at Least One Event, n (%) | 37 (19.1) | 18 (19.8) | 22 (10.5) | 21 (20.0) |
| | Number of Censored Subjects, n (%) | 157 (80.9) | 73 (80.2) | 187 (89.5) | 84 (80.0) |
| | Stratified Hazard Ratio ^{a, b} (95% C.I.) | | 0.830 (0.468, 1.472) | | 0.448 (0.244, 0.822) |
| | P-value ^{b, c} | | 0.52381 | | 0.00958 |
| | Interaction Test P-value ^d | | | 0.13947 | |
| | Median Time to Onset of the First Event (Days) (95% C.I.) ^e | 709.0 (643.0, -) | - (-, -) | - (660.0, -) | - (-, -) |
| | 25 th , 75 th Percentile | 643.0, - | -, - | 660.0, - | 313.0, - |
| Observed Min, Max ^f | 1, 743+ | 3, 583+ | 1, 1059+ | 1, 762+ | |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was ran.

c. Two-sided p-value calculated from Cox proportional hazards model.

d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and history of brain metastases at baseline.

e. Calculated using the complementary log-log transformation method (Collett, 1994).

f. '+' means the observed time is from censored subjects.

Data Snapshot: 14OCT2019, Data Cutoff Date: 04SEP2019

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_1753\v01\outputs\tfs\pgms\t-ae-km-gisoc-subgrp.sas Output: t-ae-km-gisoc-sub-1-bm-safs.rtf (17APR20:16:56) Data: adsl, adae, adttesaf

Seattle Genetics Protocol ONT-380-206

Table 2.2.2 Summary of Gastrointestinal Adverse Events by System Organ Class, Preferred Term and Geographic Region
Safety Analysis Set

| System Organ Class/ Preferred Term | Parameters | North America | | Rest of World | |
|---------------------------------------|--|------------------------|------------------------|------------------------|-----------------------|
| | | Tuc+Cap+Tra (N=241) | Pbo+Cap+Tra (N=119) | Tuc+Cap+Tra (N=163) | Pbo+Cap+Tra (N=78) |
| Gastrointestinal Disorders | Number of Subjects With at Least One Event, n (%) | 231 (95.9) | 101 (84.9) | 151 (92.6) | 61 (78.2) |
| | Number of Censored Subjects, n (%) | 10 (4.1) | 18 (15.1) | 12 (7.4) | 17 (21.8) |
| | Stratified Hazard Ratio ^{a, b} (95% C.I.) | | 1.876 (1.473, 2.390) | | 1.956 (1.438, 2.660) |
| | P-value ^{b, c} | | <.00001 | | 0.00002 |
| | Interaction Test P-value ^d | | | 0.40952 | |
| | Median Time to Onset of the First Event (Days) (95% C.I.) ^e | 8.0 (7.0, 9.0) | 15.0 (12.0, 22.0) | 5.0 (4.0, 7.0) | 15.0 (11.0, 35.0) |
| | 25 th , 75 th Percentile | 3.0, 14.0 | 7.0, 55.0 | 2.0, 13.0 | 3.0, 114.0 |
| Observed Min, Max ^f | 1, 436+ | 1, 307 | 1, 246+ | 1, 409+ | |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (Presence or history of brain metastases: Yes/No and ECOG performance status: 0/1) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was ran.

c. Two-sided p-value calculated from Cox proportional hazards model.

d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and geographic region.

e. Calculated using the complementary log-log transformation method (Collett, 1994).

f. '+' means the observed time is from censored subjects.

Data Snapshot: 14OCT2019, Data Cutoff Date: 04SEP2019

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_1753\v01\outputs\tlfs\pgms\t-ae-km-gisoc-subgrp.sas Output: t-ae-km-gisoc-sub-2-reg-safs.rtf (17APR20:16:56) Data: adsl, adae, adttesaf

Seattle Genetics Protocol ONT-380-206

Table 2.2.2 Summary of Gastrointestinal Adverse Events by System Organ Class, Preferred Term and Geographic Region
Safety Analysis Set

| System Organ Class/ Preferred Term | Parameters | North America | | Rest of World | |
|---------------------------------------|--|------------------------|------------------------|------------------------|-----------------------|
| | | Tuc+Cap+Tra (N=241) | Pbo+Cap+Tra (N=119) | Tuc+Cap+Tra (N=163) | Pbo+Cap+Tra (N=78) |
| Diarrhoea | Number of Subjects With at Least One Event, n (%) | 201 (83.4) | 68 (57.1) | 126 (77.3) | 37 (47.4) |
| | Number of Censored Subjects, n (%) | 40 (16.6) | 51 (42.9) | 37 (22.7) | 41 (52.6) |
| | Stratified Hazard Ratio ^{a, b} (95% C.I.) | | 2.356 (1.782, 3.113) | | 2.463 (1.700, 3.570) |
| | P-value ^{b, c} | | <.00001 | | <.00001 |
| | Interaction Test P-value ^d | | | 0.57691 | |
| | Median Time to Onset of the First Event (Days) (95% C.I.) ^e | 15.0 (13.0, 16.0) | 80.0 (43.0, 167.0) | 15.0 (12.0, 18.0) | 169.0 (62.0, -) |
| | 25 th , 75 th Percentile | 8.0, 49.0 | 22.0, - | 5.0, 118.0 | 21.0, - |
| Observed Min, Max ^f | 1, 436+ | 1, 407+ | 1, 343+ | 1, 588+ | |

Page 2 of 6

a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (Presence or history of brain metastases: Yes/No and ECOG performance status: 0/1) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was ran.

c. Two-sided p-value calculated from Cox proportional hazards model.

d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and geographic region.

e. Calculated using the complementary log-log transformation method (Collett, 1994).

f. '+' means the observed time is from censored subjects.

Data Snapshot: 14OCT2019, Data Cutoff Date: 04SEP2019

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_1753\v01\outputs\tlfs\pgms\t-ae-km-gisoc-subgrp.sas Output: t-ae-km-gisoc-sub-2-reg-safs.rtf (17APR20:16:56) Data: adsl, adae, adttesaf

Seattle Genetics Protocol ONT-380-206

Table 2.2.2 Summary of Gastrointestinal Adverse Events by System Organ Class, Preferred Term and Geographic Region
Safety Analysis Set

| System Organ Class/ Preferred Term | Parameters | North America | | Rest of World | |
|---------------------------------------|--|------------------------|------------------------|------------------------|-----------------------|
| | | Tuc+Cap+Tra (N=241) | Pbo+Cap+Tra (N=119) | Tuc+Cap+Tra (N=163) | Pbo+Cap+Tra (N=78) |
| Nausea | Number of Subjects With at Least One Event, n (%) | 145 (60.2) | 57 (47.9) | 91 (55.8) | 29 (37.2) |
| | Number of Censored Subjects, n (%) | 96 (39.8) | 62 (52.1) | 72 (44.2) | 49 (62.8) |
| | Stratified Hazard Ratio ^{a, b} (95% C.I.) | | 1.429 (1.050, 1.944) | | 1.644 (1.079, 2.505) |
| | P-value ^{b, c} | | 0.02305 | | 0.02068 |
| | Interaction Test P-value ^d | | | 0.57327 | |
| | Median Time to Onset of the First Event (Days) (95% C.I.) ^e | 31.0 (16.0, 66.0) | 197.0 (64.0, -) | 82.0 (36.0, 599.0) | - (342.0, -) |
| | 25 th , 75 th Percentile | 7.0, - | 15.0, - | 6.0, 599.0 | 14.0, - |
| Observed Min, Max ^f | 1, 1059+ | 1, 762+ | 1, 688+ | 1, 580+ | |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (Presence or history of brain metastases: Yes/No and ECOG performance status: 0/1) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was ran.

c. Two-sided p-value calculated from Cox proportional hazards model.

d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and geographic region.

e. Calculated using the complementary log-log transformation method (Collett, 1994).

f. '+' means the observed time is from censored subjects.

Data Snapshot: 14OCT2019, Data Cutoff Date: 04SEP2019

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_1753\v01\outputs\tlfs\pgms\t-ae-km-gisoc-subgrp.sas Output: t-ae-km-gisoc-sub-2-reg-safs.rtf (17APR20:16:56) Data: adsl, adae, adttesaf

Seattle Genetics Protocol ONT-380-206

Table 2.2.2 Summary of Gastrointestinal Adverse Events by System Organ Class, Preferred Term and Geographic Region
Safety Analysis Set

| System Organ Class/ Preferred Term | Parameters | North America | | Rest of World | |
|---------------------------------------|--|------------------------|------------------------|------------------------|-----------------------|
| | | Tuc+Cap+Tra (N=241) | Pbo+Cap+Tra (N=119) | Tuc+Cap+Tra (N=163) | Pbo+Cap+Tra (N=78) |
| Vomiting | Number of Subjects With at Least One Event, n (%) | 93 (38.6) | 29 (24.4) | 52 (31.9) | 21 (26.9) |
| | Number of Censored Subjects, n (%) | 148 (61.4) | 90 (75.6) | 111 (68.1) | 57 (73.1) |
| | Stratified Hazard Ratio ^{a, b} (95% C.I.) | | 1.734 (1.142, 2.635) | | 1.163 (0.699, 1.937) |
| | P-value ^{b, c} | | 0.00983 | | 0.56055 |
| | Interaction Test P-value ^d | | | 0.23021 | |
| | Median Time to Onset of the First Event (Days) (95% C.I.) ^e | - (359.0, -) | - (-, -) | 599.0 (599.0, -) | - (266.0, -) |
| | 25 th , 75 th Percentile | 34.0, - | 146.0, - | 52.0, - | 240.0, - |
| Observed Min, Max ^f | 1, 1059+ | 1, 762+ | 1, 720+ | 1, 588+ | |

Page 4 of 6

a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (Presence or history of brain metastases: Yes/No and ECOG performance status: 0/1) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was ran.

c. Two-sided p-value calculated from Cox proportional hazards model.

d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and geographic region.

e. Calculated using the complementary log-log transformation method (Collett, 1994).

f. '+' means the observed time is from censored subjects.

Data Snapshot: 14OCT2019, Data Cutoff Date: 04SEP2019

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_1753\v01\outputs\tlfs\pgms\t-ae-km-gisoc-subgrp.sas Output: t-ae-km-gisoc-sub-2-reg-safs.rtf (17APR20:16:56) Data: adsl, adae, adttesaf

Seattle Genetics Protocol ONT-380-206

Table 2.2.2 Summary of Gastrointestinal Adverse Events by System Organ Class, Preferred Term and Geographic Region
Safety Analysis Set

| System Organ Class/ Preferred Term | Parameters | North America | | Rest of World | |
|---------------------------------------|--|------------------------|------------------------|------------------------|-----------------------|
| | | Tuc+Cap+Tra (N=241) | Pbo+Cap+Tra (N=119) | Tuc+Cap+Tra (N=163) | Pbo+Cap+Tra (N=78) |
| Stomatitis | Number of Subjects With at Least One Event, n (%) | 66 (27.4) | 23 (19.3) | 37 (22.7) | 5 (6.4) |
| | Number of Censored Subjects, n (%) | 175 (72.6) | 96 (80.7) | 126 (77.3) | 73 (93.6) |
| | Stratified Hazard Ratio ^{a, b} (95% C.I.) | | 1.395 (0.865, 2.250) | | 4.088 (1.603, 10.425) |
| | P-value ^{b, c} | | 0.17253 | | 0.00320 |
| | Interaction Test P-value ^d | | | 0.05785 | |
| | Median Time to Onset of the First Event (Days) (95% C.I.) ^e | - (615.0, -) | - (-, -) | - (-, -) | - (-, -) |
| | 25 th , 75 th Percentile | 176.0, - | -, - | 255.0, - | -, - |
| Observed Min, Max ^f | 1, 1059+ | 7, 762+ | 2, 694+ | 8, 588+ | |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (Presence or history of brain metastases: Yes/No and ECOG performance status: 0/1) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was ran.

c. Two-sided p-value calculated from Cox proportional hazards model.

d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and geographic region.

e. Calculated using the complementary log-log transformation method (Collett, 1994).

f. '+' means the observed time is from censored subjects.

Data Snapshot: 14OCT2019, Data Cutoff Date: 04SEP2019

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_1753\v01\outputs\tlfs\pgms\t-ae-km-gisoc-subgrp.sas Output: t-ae-km-gisoc-sub-2-reg-safs.rtf (17APR20:16:56) Data: adsl, adae, adttesaf

Seattle Genetics Protocol ONT-380-206

Table 2.2.2 Summary of Gastrointestinal Adverse Events by System Organ Class, Preferred Term and Geographic Region
Safety Analysis Set

| System Organ Class/ Preferred Term | Parameters | North America | | Rest of World | |
|---------------------------------------|--|------------------------|------------------------|------------------------|-----------------------|
| | | Tuc+Cap+Tra (N=241) | Pbo+Cap+Tra (N=119) | Tuc+Cap+Tra (N=163) | Pbo+Cap+Tra (N=78) |
| Constipation | Number of Subjects With at Least One Event, n (%) | 39 (16.2) | 22 (18.5) | 20 (12.3) | 17 (21.8) |
| | Number of Censored Subjects, n (%) | 202 (83.8) | 97 (81.5) | 143 (87.7) | 61 (78.2) |
| | Stratified Hazard Ratio ^{a, b} (95% C.I.) | | 0.782 (0.460, 1.330) | | 0.462 (0.240, 0.889) |
| | P-value ^{b, c} | | 0.36435 | | 0.02075 |
| | Interaction Test P-value ^d | | | 0.29242 | |
| | Median Time to Onset of the First Event (Days) (95% C.I.) ^e | - (660.0, -) | - (-, -) | - (-, -) | - (342.0, -) |
| | 25 th , 75 th Percentile | 660.0, - | -, - | -, - | 313.0, - |
| Observed Min, Max ^f | 1, 1059+ | 3, 762+ | 1, 694+ | 1, 588+ | |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (Presence or history of brain metastases: Yes/No and ECOG performance status: 0/1) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was ran.

c. Two-sided p-value calculated from Cox proportional hazards model.

d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and geographic region.

e. Calculated using the complementary log-log transformation method (Collett, 1994).

f. '+' means the observed time is from censored subjects.

Data Snapshot: 14OCT2019, Data Cutoff Date: 04SEP2019

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_1753\v01\outputs\tlfs\pgms\t-ae-km-gisoc-subgrp.sas Output: t-ae-km-gisoc-sub-2-reg-safs.rtf (17APR20:16:56) Data: adsl, adae, adttesaf

Seattle Genetics Protocol ONT-380-206**Table 2.2.3 Summary of Gastrointestinal Adverse Events by System Organ Class, Preferred Term and Baseline ECOG Score
Safety Analysis Set**

| System Organ Class/ Preferred Term | Parameters | ECOG=0 | | ECOG=1 | |
|---------------------------------------|--|------------------------|-----------------------|------------------------|------------------------|
| | | Tuc+Cap+Tra (N=203) | Pbo+Cap+Tra (N=91) | Tuc+Cap+Tra (N=201) | Pbo+Cap+Tra (N=106) |
| Gastrointestinal Disorders | Number of Subjects With at Least One Event, n (%) | 190 (93.6) | 76 (83.5) | 192 (95.5) | 86 (81.1) |
| | Number of Censored Subjects, n (%) | 13 (6.4) | 15 (16.5) | 9 (4.5) | 20 (18.9) |
| | Stratified Hazard Ratio ^{a, b} (95% C.I.) | | 1.747 (1.323, 2.305) | | 2.167 (1.662, 2.827) |
| | P-value ^{b, c} | | 0.00008 | | <.00001 |
| | Interaction Test P-value ^d | | | 0.38716 | |
| | Median Time to Onset of the First Event (Days) (95% C.I.) ^e | 7.0 (5.0, 8.0) | 14.0 (9.0, 21.0) | 7.0 (5.0, 9.0) | 21.0 (14.0, 35.0) |
| | 25 th , 75 th Percentile | 2.0, 14.0 | 4.0, 61.0 | 3.0, 14.0 | 8.0, 77.0 |
| Observed Min, Max ^f | 1, 436+ | 1, 409+ | 1, 433+ | 1, 318+ | |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (Presence or history of brain metastases: Yes/No and Region of world: North America /Rest of World) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was ran.

c. Two-sided p-value calculated from Cox proportional hazards model.

d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and baseline ECOG score.

e. Calculated using the complementary log-log transformation method (Collett, 1994).

f. '+' means the observed time is from censored subjects.

Data Snapshot: 14OCT2019, Data Cutoff Date: 04SEP2019

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_1753\v01\outputs\tlfs\pgms\t-ae-km-gisoc-subgrp.sas Output: t-ae-km-gisoc-sub-3-ecog-safs.rtf (17APR20:16:56) Data: adsl, adae, adttesaf

Seattle Genetics Protocol ONT-380-206**Table 2.2.3 Summary of Gastrointestinal Adverse Events by System Organ Class, Preferred Term and Baseline ECOG Score
Safety Analysis Set**

| System Organ Class/ Preferred Term | Parameters | ECOG=0 | | ECOG=1 | |
|---------------------------------------|--|------------------------|-----------------------|------------------------|------------------------|
| | | Tuc+Cap+Tra (N=203) | Pbo+Cap+Tra (N=91) | Tuc+Cap+Tra (N=201) | Pbo+Cap+Tra (N=106) |
| Diarrhoea | Number of Subjects With at Least One Event, n (%) | 165 (81.3) | 52 (57.1) | 162 (80.6) | 53 (50.0) |
| | Number of Censored Subjects, n (%) | 38 (18.7) | 39 (42.9) | 39 (19.4) | 53 (50.0) |
| | Stratified Hazard Ratio ^{a, b} (95% C.I.) | | 2.344 (1.704, 3.225) | | 2.456 (1.795, 3.362) |
| | P-value ^{b, c} | | <.00001 | | <.00001 |
| | Interaction Test P-value ^d | | | 0.81798 | |
| | Median Time to Onset of the First Event (Days) (95% C.I.) ^e | 15.0 (13.0, 17.0) | 114.0 (43.0, 194.0) | 15.0 (13.0, 19.0) | 98.0 (61.0, -) |
| | 25 th , 75 th Percentile | 7.0, 59.0 | 16.0, - | 7.0, 86.0 | 25.0, - |
| Observed Min, Max ^f | 1, 436+ | 1, 588+ | 1, 433+ | 1, 407+ | |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (Presence or history of brain metastases: Yes/No and Region of world: North America /Rest of World) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was ran.

c. Two-sided p-value calculated from Cox proportional hazards model.

d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and baseline ECOG score.

e. Calculated using the complementary log-log transformation method (Collett, 1994).

f. '+' means the observed time is from censored subjects.

Data Snapshot: 14OCT2019, Data Cutoff Date: 04SEP2019

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_1753\v01\outputs\tlfs\pgms\t-ae-km-gisoc-subgrp.sas Output: t-ae-km-gisoc-sub-3-ecog-safs.rtf (17APR20:16:56) Data: adsl, adae, adttesaf

Seattle Genetics Protocol ONT-380-206**Table 2.2.3 Summary of Gastrointestinal Adverse Events by System Organ Class, Preferred Term and Baseline ECOG Score
Safety Analysis Set**

| System Organ Class/ Preferred Term | Parameters | ECOG=0 | | ECOG=1 | |
|---------------------------------------|--|------------------------|-----------------------|------------------------|------------------------|
| | | Tuc+Cap+Tra (N=203) | Pbo+Cap+Tra (N=91) | Tuc+Cap+Tra (N=201) | Pbo+Cap+Tra (N=106) |
| Nausea | Number of Subjects With at Least One Event, n (%) | 119 (58.6) | 41 (45.1) | 117 (58.2) | 45 (42.5) |
| | Number of Censored Subjects, n (%) | 84 (41.4) | 50 (54.9) | 84 (41.8) | 61 (57.5) |
| | Stratified Hazard Ratio ^{a, b} (95% C.I.) | | 1.441 (1.009, 2.059) | | 1.552 (1.098, 2.194) |
| | P-value ^{b, c} | | 0.04470 | | 0.01283 |
| | Interaction Test P-value ^d | | | 0.79281 | |
| | Median Time to Onset of the First Event (Days) (95% C.I.) ^e | 43.0 (17.0, 171.0) | 342.0 (75.0, -) | 49.0 (22.0, 160.0) | -(104.0, -) |
| | 25 th , 75 th Percentile | 6.0, - | 12.0, - | 7.0, - | 21.0, - |
| Observed Min, Max ^f | 1, 1059+ | 1, 409+ | 1, 945+ | 1, 762+ | |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (Presence or history of brain metastases: Yes/No and Region of world: North America /Rest of World) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was ran.

c. Two-sided p-value calculated from Cox proportional hazards model.

d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and baseline ECOG score.

e. Calculated using the complementary log-log transformation method (Collett, 1994).

f. '+' means the observed time is from censored subjects.

Data Snapshot: 14OCT2019, Data Cutoff Date: 04SEP2019

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_1753\v01\outputs\tlfs\pgms\t-ae-km-gisoc-subgrp.sas Output: t-ae-km-gisoc-sub-3-ecog-safs.rtf (17APR20:16:56) Data: adsl, adae, adttesaf

Seattle Genetics Protocol ONT-380-206**Table 2.2.3 Summary of Gastrointestinal Adverse Events by System Organ Class, Preferred Term and Baseline ECOG Score
Safety Analysis Set**

| System Organ Class/ Preferred Term | Parameters | ECOG=0 | | ECOG=1 | |
|---------------------------------------|--|------------------------|-----------------------|------------------------|------------------------|
| | | Tuc+Cap+Tra (N=203) | Pbo+Cap+Tra (N=91) | Tuc+Cap+Tra (N=201) | Pbo+Cap+Tra (N=106) |
| Vomiting | Number of Subjects With at Least One Event, n (%) | 70 (34.5) | 25 (27.5) | 75 (37.3) | 25 (23.6) |
| | Number of Censored Subjects, n (%) | 133 (65.5) | 66 (72.5) | 126 (62.7) | 81 (76.4) |
| | Stratified Hazard Ratio ^{a, b} (95% C.I.) | | 1.332 (0.842, 2.106) | | 1.641 (1.041, 2.586) |
| | P-value ^{b, c} | | 0.22030 | | 0.03275 |
| | Interaction Test P-value ^d | | | 0.49673 | |
| | Median Time to Onset of the First Event (Days) (95% C.I.) ^e | - (-, -) | - (332.0, -) | 599.0 (599.0, -) | - (-, -) |
| | 25 th , 75 th Percentile | 45.0, - | 173.0, - | 42.0, - | 214.0, - |
| Observed Min, Max ^f | 1, 1059+ | 1, 588+ | 1, 891+ | 3, 762+ | |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (Presence or history of brain metastases: Yes/No and Region of world: North America /Rest of World) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was ran.

c. Two-sided p-value calculated from Cox proportional hazards model.

d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and baseline ECOG score.

e. Calculated using the complementary log-log transformation method (Collett, 1994).

f. '+' means the observed time is from censored subjects.

Data Snapshot: 14OCT2019, Data Cutoff Date: 04SEP2019

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_1753\v01\outputs\tlfs\pgms\t-ae-km-gisoc-subgrp.sas Output: t-ae-km-gisoc-sub-3-ecog-safs.rtf (17APR20:16:56) Data: adsl, adae, adttesaf

Seattle Genetics Protocol ONT-380-206**Table 2.2.3 Summary of Gastrointestinal Adverse Events by System Organ Class, Preferred Term and Baseline ECOG Score
Safety Analysis Set**

| System Organ Class/ Preferred Term | Parameters | ECOG=0 | | ECOG=1 | |
|---------------------------------------|--|------------------------|-----------------------|------------------------|------------------------|
| | | Tuc+Cap+Tra (N=203) | Pbo+Cap+Tra (N=91) | Tuc+Cap+Tra (N=201) | Pbo+Cap+Tra (N=106) |
| Stomatitis | Number of Subjects With at Least One Event, n (%) | 50 (24.6) | 15 (16.5) | 53 (26.4) | 13 (12.3) |
| | Number of Censored Subjects, n (%) | 153 (75.4) | 76 (83.5) | 148 (73.6) | 93 (87.7) |
| | Stratified Hazard Ratio ^{a, b} (95% C.I.) | | 1.612 (0.904, 2.875) | | 2.207 (1.200, 4.060) |
| | P-value ^{b, c} | | 0.10572 | | 0.01093 |
| | Interaction Test P-value ^d | | | | 0.37713 |
| | Median Time to Onset of the First Event (Days) (95% C.I.) ^e | - (-, -) | - (-, -) | - (615.0, -) | - (-, -) |
| | 25 th , 75 th Percentile | 206.0, - | -, - | 176.0, - | -, - |
| Observed Min, Max ^f | 1, 1059+ | 7, 588+ | 1, 945+ | 8, 762+ | |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (Presence or history of brain metastases: Yes/No and Region of world: North America /Rest of World) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was ran.

c. Two-sided p-value calculated from Cox proportional hazards model.

d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and baseline ECOG score.

e. Calculated using the complementary log-log transformation method (Collett, 1994).

f. '+' means the observed time is from censored subjects.

Data Snapshot: 14OCT2019, Data Cutoff Date: 04SEP2019

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_1753\v01\outputs\tlfs\pgms\t-ae-km-gisoc-subgrp.sas Output: t-ae-km-gisoc-sub-3-ecog-safs.rtf (17APR20:16:56) Data: adsl, adae, adttesaf

Seattle Genetics Protocol ONT-380-206

Table 2.2.3 Summary of Gastrointestinal Adverse Events by System Organ Class, Preferred Term and Baseline ECOG Score
Safety Analysis Set

| System Organ Class/ Preferred Term | Parameters | ECOG=0 | | ECOG=1 | |
|---------------------------------------|--|------------------------|-----------------------|------------------------|------------------------|
| | | Tuc+Cap+Tra (N=203) | Pbo+Cap+Tra (N=91) | Tuc+Cap+Tra (N=201) | Pbo+Cap+Tra (N=106) |
| Constipation | Number of Subjects With at Least One Event, n (%) | 21 (10.3) | 19 (20.9) | 38 (18.9) | 20 (18.9) |
| | Number of Censored Subjects, n (%) | 182 (89.7) | 72 (79.1) | 163 (81.1) | 86 (81.1) |
| | Stratified Hazard Ratio ^{a, b} (95% C.I.) | | 0.419 (0.221, 0.793) | | 0.882 (0.510, 1.525) |
| | P-value ^{b, c} | | 0.00759 | | 0.65267 |
| | Interaction Test P-value ^d | | | 0.06082 | |
| | Median Time to Onset of the First Event (Days) (95% C.I.) ^e | - (660.0, -) | - (342.0, -) | - (643.0, -) | - (-, -) |
| | 25 th , 75 th Percentile | 709.0, - | 313.0, - | 643.0, - | -, - |
| Observed Min, Max ^f | 1, 1059+ | 1, 588+ | 1, 945+ | 1, 762+ | |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (Presence or history of brain metastases: Yes/No and Region of world: North America /Rest of World) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was ran.

c. Two-sided p-value calculated from Cox proportional hazards model.

d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and baseline ECOG score.

e. Calculated using the complementary log-log transformation method (Collett, 1994).

f. '+' means the observed time is from censored subjects.

Data Snapshot: 14OCT2019, Data Cutoff Date: 04SEP2019

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_1753\v01\outputs\tlfs\pgms\t-ae-km-gisoc-subgrp.sas Output: t-ae-km-gisoc-sub-3-ecog-safs.rtf (17APR20:16:56) Data: adsl, adae, adttesaf

Seattle Genetics Protocol ONT-380-206**Table 2.2.4 Summary of Gastrointestinal Adverse Events by System Organ Class, Preferred Term and Age Safety Analysis Set**

| System Organ Class/ Preferred Term | Parameters | Age < 65 Years | | Age ≥ 65 Years | |
|---------------------------------------|--|------------------------|------------------------|-----------------------|-----------------------|
| | | Tuc+Cap+Tra (N=322) | Pbo+Cap+Tra (N=164) | Tuc+Cap+Tra (N=82) | Pbo+Cap+Tra (N=33) |
| Gastrointestinal Disorders | Number of Subjects With at Least One Event, n (%) | 303 (94.1) | 137 (83.5) | 79 (96.3) | 25 (75.8) |
| | Number of Censored Subjects, n (%) | 19 (5.9) | 27 (16.5) | 3 (3.7) | 8 (24.2) |
| | Stratified Hazard Ratio ^{a, b} (95% C.I.) | | 1.685 (1.369, 2.073) | | 3.951 (2.210, 7.062) |
| | P-value ^{b, c} | | <.00001 | | <.00001 |
| | Interaction Test P-value ^d | | | 0.01999 | |
| | Median Time to Onset of the First Event (Days) (95% C.I.) ^e | 7.0 (5.0, 8.0) | 14.5 (11.0, 21.0) | 7.0 (5.0, 9.0) | 41.0 (14.0, 77.0) |
| | 25 th , 75 th Percentile | 2.0, 15.0 | 5.0, 55.0 | 3.0, 13.0 | 13.0, 125.0 |
| Observed Min, Max ^f | 1, 436+ | 1, 307 | 1, 177+ | 1, 409+ | |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (Presence or history of brain metastases: Yes/No, ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was ran.

c. Two-sided p-value calculated from Cox proportional hazards model.

d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and age.

e. Calculated using the complementary log-log transformation method (Collett, 1994).

f. '+' means the observed time is from censored subjects.

Data Snapshot: 14OCT2019, Data Cutoff Date: 04SEP2019

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Table 2.2.4 Summary of Gastrointestinal Adverse Events by System Organ Class, Preferred Term and Age Safety Analysis Set

| System Organ Class/ Preferred Term | Parameters | Age < 65 Years | | Age ≥ 65 Years | |
|---------------------------------------|--|------------------------|------------------------|-----------------------|-----------------------|
| | | Tuc+Cap+Tra (N=322) | Pbo+Cap+Tra (N=164) | Tuc+Cap+Tra (N=82) | Pbo+Cap+Tra (N=33) |
| Diarrhoea | Number of Subjects With at Least One Event, n (%) | 256 (79.5) | 90 (54.9) | 71 (86.6) | 15 (45.5) |
| | Number of Censored Subjects, n (%) | 66 (20.5) | 74 (45.1) | 11 (13.4) | 18 (54.5) |
| | Stratified Hazard Ratio ^{a, b} (95% C.I.) | | 2.127 (1.668, 2.713) | | 4.410 (2.386, 8.152) |
| | P-value ^{b, c} | | <.00001 | | <.00001 |
| | Interaction Test P-value ^d | | | 0.03483 | |
| | Median Time to Onset of the First Event (Days) (95% C.I.) ^e | 16.0 (14.0, 19.0) | 96.0 (59.0, 183.0) | 12.0 (10.0, 14.0) | 129.0 (64.0, -) |
| | 25 th , 75 th Percentile | 7.0, 94.0 | 20.0, - | 6.0, 21.0 | 41.0, - |
| Observed Min, Max ^f | 1, 436+ | 1, 588+ | 1, 343+ | 2, 409+ | |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (Presence or history of brain metastases: Yes/No, ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was ran.

c. Two-sided p-value calculated from Cox proportional hazards model.

d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and age.

e. Calculated using the complementary log-log transformation method (Collett, 1994).

f. '+' means the observed time is from censored subjects.

Data Snapshot: 14OCT2019, Data Cutoff Date: 04SEP2019

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_1753\v01\outputs\tlfs\pgms\t-ae-km-gisoc-subgrp.sas Output: t-ae-km-gisoc-sub-4-age-safs.rtf (17APR20:16:56) Data: adsl, adae, adttesaf

Seattle Genetics Protocol ONT-380-206

Table 2.2.4 Summary of Gastrointestinal Adverse Events by System Organ Class, Preferred Term and Age Safety Analysis Set

| System Organ Class/ Preferred Term | Parameters | Age < 65 Years | | Age >= 65 Years | |
|---------------------------------------|--|------------------------|------------------------|-----------------------|-----------------------|
| | | Tuc+Cap+Tra (N=322) | Pbo+Cap+Tra (N=164) | Tuc+Cap+Tra (N=82) | Pbo+Cap+Tra (N=33) |
| Nausea | Number of Subjects With at Least One Event, n (%) | 185 (57.5) | 76 (46.3) | 51 (62.2) | 10 (30.3) |
| | Number of Censored Subjects, n (%) | 137 (42.5) | 88 (53.7) | 31 (37.8) | 23 (69.7) |
| | Stratified Hazard Ratio ^{a, b} (95% C.I.) | | 1.346 (1.029, 1.762) | | 2.739 (1.361, 5.512) |
| | P-value ^{b, c} | | 0.03039 | | 0.00475 |
| | Interaction Test P-value ^d | | | 0.07659 | |
| | Median Time to Onset of the First Event (Days) (95% C.I.) ^e | 43.0 (21.0, 160.0) | 342.0 (75.0, -) | 53.0 (22.0, 136.0) | -(119.0, -) |
| | 25 th , 75 th Percentile | 6.0, - | 12.0, - | 9.0, - | 104.0, - |
| Observed Min, Max ^f | 1, 1059+ | 1, 762+ | 1, 945+ | 7, 409+ | |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (Presence or history of brain metastases: Yes/No, ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was ran.

c. Two-sided p-value calculated from Cox proportional hazards model.

d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and age.

e. Calculated using the complementary log-log transformation method (Collett, 1994).

f. '+' means the observed time is from censored subjects.

Data Snapshot: 14OCT2019, Data Cutoff Date: 04SEP2019

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_1753\v01\outputs\tlfs\pgms\t-ae-km-gisoc-subgrp.sas Output: t-ae-km-gisoc-sub-4-age-safs.rtf (17APR20:16:56) Data: adsl, adae, adttesaf

Seattle Genetics Protocol ONT-380-206**Table 2.2.4 Summary of Gastrointestinal Adverse Events by System Organ Class, Preferred Term and Age Safety Analysis Set**

| System Organ Class/ Preferred Term | Parameters | Age < 65 Years | | Age ≥ 65 Years | |
|---------------------------------------|--|------------------------|------------------------|-----------------------|-----------------------|
| | | Tuc+Cap+Tra (N=322) | Pbo+Cap+Tra (N=164) | Tuc+Cap+Tra (N=82) | Pbo+Cap+Tra (N=33) |
| Vomiting | Number of Subjects With at Least One Event, n (%) | 111 (34.5) | 42 (25.6) | 34 (41.5) | 8 (24.2) |
| | Number of Censored Subjects, n (%) | 211 (65.5) | 122 (74.4) | 48 (58.5) | 25 (75.8) |
| | Stratified Hazard Ratio ^{a, b} (95% C.I.) | | 1.356 (0.948, 1.938) | | 2.165 (0.988, 4.746) |
| | P-value ^{b, c} | | 0.09527 | | 0.05377 |
| | Interaction Test P-value ^d | | | 0.34384 | |
| | Median Time to Onset of the First Event (Days) (95% C.I.) ^e | - (599.0, -) | - (-, -) | - (73.0, -) | - (214.0, -) |
| | 25 th , 75 th Percentile | 48.0, - | 173.0, - | 34.0, - | 214.0, - |
| Observed Min, Max ^f | 1, 1059+ | 1, 762+ | 1, 458+ | 5, 409+ | |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (Presence or history of brain metastases: Yes/No, ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was ran.

c. Two-sided p-value calculated from Cox proportional hazards model.

d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and age.

e. Calculated using the complementary log-log transformation method (Collett, 1994).

f. '+' means the observed time is from censored subjects.

Data Snapshot: 14OCT2019, Data Cutoff Date: 04SEP2019

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_1753\v01\outputs\tlfs\pgms\t-ae-km-gisoc-subgrp.sas Output: t-ae-km-gisoc-sub-4-age-safs.rtf (17APR20:16:56) Data: adsl, adae, adttesaf

Seattle Genetics Protocol ONT-380-206**Table 2.2.4 Summary of Gastrointestinal Adverse Events by System Organ Class, Preferred Term and Age Safety Analysis Set**

| System Organ Class/ Preferred Term | Parameters | Age < 65 Years | | Age ≥ 65 Years | |
|---------------------------------------|--|------------------------|------------------------|-----------------------|-----------------------|
| | | Tuc+Cap+Tra (N=322) | Pbo+Cap+Tra (N=164) | Tuc+Cap+Tra (N=82) | Pbo+Cap+Tra (N=33) |
| Stomatitis | Number of Subjects With at Least One Event, n (%) | 80 (24.8) | 21 (12.8) | 23 (28.0) | 7 (21.2) |
| | Number of Censored Subjects, n (%) | 242 (75.2) | 143 (87.2) | 59 (72.0) | 26 (78.8) |
| | Stratified Hazard Ratio ^{a, b} (95% C.I.) | | 1.982 (1.222, 3.216) | | 1.446 (0.607, 3.448) |
| | P-value ^{b, c} | | 0.00559 | | 0.40518 |
| | Interaction Test P-value ^d | | | 0.43151 | |
| | Median Time to Onset of the First Event (Days) (95% C.I.) ^e | - (615.0, -) | - (-, -) | - (-, -) | - (-, -) |
| | 25 th , 75 th Percentile | 198.0, - | -, - | 72.0, - | 186.0, - |
| Observed Min, Max ^f | 2, 1059+ | 7, 762+ | 1, 945+ | 7, 409+ | |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (Presence or history of brain metastases: Yes/No, ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was ran.

c. Two-sided p-value calculated from Cox proportional hazards model.

d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and age.

e. Calculated using the complementary log-log transformation method (Collett, 1994).

f. '+' means the observed time is from censored subjects.

Data Snapshot: 14OCT2019, Data Cutoff Date: 04SEP2019

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_1753\v01\outputs\tlfs\pgms\t-ae-km-gisoc-subgrp.sas Output: t-ae-km-gisoc-sub-4-age-safs.rtf (17APR20:16:56) Data: adsl, adae, adttesaf

Seattle Genetics Protocol ONT-380-206**Table 2.2.4 Summary of Gastrointestinal Adverse Events by System Organ Class, Preferred Term and Age Safety Analysis Set**

| System Organ Class/ Preferred Term | Parameters | Age < 65 Years | | Age ≥ 65 Years | |
|---------------------------------------|--|------------------------|------------------------|-----------------------|-----------------------|
| | | Tuc+Cap+Tra (N=322) | Pbo+Cap+Tra (N=164) | Tuc+Cap+Tra (N=82) | Pbo+Cap+Tra (N=33) |
| Constipation | Number of Subjects With at Least One Event, n (%) | 46 (14.3) | 34 (20.7) | 13 (15.9) | 5 (15.2) |
| | Number of Censored Subjects, n (%) | 276 (85.7) | 130 (79.3) | 69 (84.1) | 28 (84.8) |
| | Stratified Hazard Ratio ^{a, b} (95% C.I.) | | 0.581 (0.368, 0.916) | | 1.221 (0.420, 3.547) |
| | P-value ^{b, c} | | 0.01946 | | 0.71360 |
| | Interaction Test P-value ^d | | | 0.35527 | |
| | Median Time to Onset of the First Event (Days) (95% C.I.) ^e | - (660.0, -) | - (-, -) | - (-, -) | - (-, -) |
| | 25 th , 75 th Percentile | 643.0, - | 313.0, - | -, - | -, - |
| Observed Min, Max ^f | 1, 1059+ | 1, 762+ | 4+, 945+ | 9, 409+ | |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (Presence or history of brain metastases: Yes/No, ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was ran.

c. Two-sided p-value calculated from Cox proportional hazards model.

d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and age.

e. Calculated using the complementary log-log transformation method (Collett, 1994).

f. '+' means the observed time is from censored subjects.

Data Snapshot: 14OCT2019, Data Cutoff Date: 04SEP2019

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_1753\v01\outputs\tlfs\pgms\t-ae-km-gisoc-subgrp.sas Output: t-ae-km-gisoc-sub-4-age-safs.rtf (17APR20:16:56) Data: adsl, adae, adttesaf

Seattle Genetics Protocol ONT-380-206

Table 2.2.5 Summary of Gastrointestinal Adverse Events by System Organ Class, Preferred Term and Race Safety Analysis Set

| System Organ Class/ Preferred Term | Parameters | White | | Non-White | |
|---------------------------------------|--|------------------------|------------------------|------------------------|-----------------------|
| | | Tuc+Cap+Tra (N=283) | Pbo+Cap+Tra (N=153) | Tuc+Cap+Tra (N=121) | Pbo+Cap+Tra (N=44) |
| Gastrointestinal Disorders | Number of Subjects With at Least One Event, n (%) | 267 (94.3) | 126 (82.4) | 115 (95.0) | 36 (81.8) |
| | Number of Censored Subjects, n (%) | 16 (5.7) | 27 (17.6) | 6 (5.0) | 8 (18.2) |
| | Stratified Hazard Ratio ^{a, b} (95% C.I.) | | 1.818 (1.459, 2.266) | | 2.570 (1.675, 3.942) |
| | P-value ^{b, c} | | <.00001 | | 0.00002 |
| | Interaction Test P-value ^d | | | 0.36820 | |
| | Median Time to Onset of the First Event (Days) (95% C.I.) ^e | 7.0 (6.0, 8.0) | 15.0 (12.0, 21.0) | 7.0 (5.0, 8.0) | 22.0 (9.0, 49.0) |
| | 25 th , 75 th Percentile | 3.0, 14.0 | 5.0, 68.0 | 2.0, 14.0 | 8.0, 64.0 |
| Observed Min, Max ^f | 1, 433+ | 1, 409+ | 1, 436+ | 1, 205+ | |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (Presence or history of brain metastases: Yes/No, ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was ran.

c. Two-sided p-value calculated from Cox proportional hazards model.

d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and race.

e. Calculated using the complementary log-log transformation method (Collett, 1994).

f. '+' means the observed time is from censored subjects.

Data Snapshot: 14OCT2019, Data Cutoff Date: 04SEP2019

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_1753\v01\outputs\tlfs\pgms\t-ae-km-gisoc-subgrp.sas Output: t-ae-km-gisoc-sub-5-race-safs.rtf (17APR20:16:56) Data: adsl, adae, adttesaf

Seattle Genetics Protocol ONT-380-206

Table 2.2.5 Summary of Gastrointestinal Adverse Events by System Organ Class, Preferred Term and Race Safety Analysis Set

| System Organ Class/ Preferred Term | Parameters | White | | Non-White | |
|---------------------------------------|--|------------------------|------------------------|------------------------|-----------------------|
| | | Tuc+Cap+Tra (N=283) | Pbo+Cap+Tra (N=153) | Tuc+Cap+Tra (N=121) | Pbo+Cap+Tra (N=44) |
| Diarrhoea | Number of Subjects With at Least One Event, n (%) | 228 (80.6) | 86 (56.2) | 99 (81.8) | 19 (43.2) |
| | Number of Censored Subjects, n (%) | 55 (19.4) | 67 (43.8) | 22 (18.2) | 25 (56.8) |
| | Stratified Hazard Ratio ^{a, b} (95% C.I.) | | 2.226 (1.732, 2.861) | | 3.427 (2.041, 5.755) |
| | P-value ^{b, c} | | <.00001 | | <.00001 |
| | Interaction Test P-value ^d | | | 0.17687 | |
| | Median Time to Onset of the First Event (Days) (95% C.I.) ^e | 15.0 (13.0, 16.0) | 89.0 (57.0, 167.0) | 15.0 (11.0, 21.0) | 205.0 (64.0, -) |
| | 25 th , 75 th Percentile | 7.0, 71.0 | 18.0, - | 7.0, 60.0 | 35.0, - |
| Observed Min, Max ^f | 1, 433+ | 1, 588+ | 1, 436+ | 1, 344+ | |

a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (Presence or history of brain metastases: Yes/No, ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was ran.

c. Two-sided p-value calculated from Cox proportional hazards model.

d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and race.

e. Calculated using the complementary log-log transformation method (Collett, 1994).

f. '+' means the observed time is from censored subjects.

Data Snapshot: 14OCT2019, Data Cutoff Date: 04SEP2019

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_1753\v01\outputs\tlfs\pgms\t-ae-km-gisoc-subgrp.sas Output: t-ae-km-gisoc-sub-5-race-safs.rtf (17APR20:16:56) Data: adsl, adae, adttesaf

Seattle Genetics Protocol ONT-380-206**Table 2.2.5 Summary of Gastrointestinal Adverse Events by System Organ Class, Preferred Term and Race Safety Analysis Set**

| System Organ Class/ Preferred Term | Parameters | White | | Non-White | |
|---------------------------------------|--|------------------------|------------------------|------------------------|-----------------------|
| | | Tuc+Cap+Tra (N=283) | Pbo+Cap+Tra (N=153) | Tuc+Cap+Tra (N=121) | Pbo+Cap+Tra (N=44) |
| Nausea | Number of Subjects With at Least One Event, n (%) | 166 (58.7) | 72 (47.1) | 70 (57.9) | 14 (31.8) |
| | Number of Censored Subjects, n (%) | 117 (41.3) | 81 (52.9) | 51 (42.1) | 30 (68.2) |
| | Stratified Hazard Ratio ^{a, b} (95% C.I.) | | 1.373 (1.039, 1.813) | | 2.235 (1.247, 4.008) |
| | P-value ^{b, c} | | 0.02576 | | 0.00693 |
| | Interaction Test P-value ^d | | | 0.14582 | |
| | Median Time to Onset of the First Event (Days) (95% C.I.) ^e | 43.0 (21.0, 148.0) | 342.0 (64.0, -) | 49.0 (21.0, 228.0) | -(172.0, -) |
| | 25 th , 75 th Percentile | 5.0, - | 13.0, - | 7.0, 599.0 | 65.0, - |
| Observed Min, Max ^f | 1, 1059+ | 1, 762+ | 1, 599 | 1, 580+ | |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (Presence or history of brain metastases: Yes/No, ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was ran.

c. Two-sided p-value calculated from Cox proportional hazards model.

d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and race.

e. Calculated using the complementary log-log transformation method (Collett, 1994).

f. '+' means the observed time is from censored subjects.

Data Snapshot: 14OCT2019, Data Cutoff Date: 04SEP2019

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Table 2.2.5 Summary of Gastrointestinal Adverse Events by System Organ Class, Preferred Term and Race Safety Analysis Set

| System Organ Class/ Preferred Term | Parameters | White | | Non-White | |
|---------------------------------------|--|------------------------|------------------------|------------------------|-----------------------|
| | | Tuc+Cap+Tra (N=283) | Pbo+Cap+Tra (N=153) | Tuc+Cap+Tra (N=121) | Pbo+Cap+Tra (N=44) |
| Vomiting | Number of Subjects With at Least One Event, n (%) | 103 (36.4) | 40 (26.1) | 42 (34.7) | 10 (22.7) |
| | Number of Censored Subjects, n (%) | 180 (63.6) | 113 (73.9) | 79 (65.3) | 34 (77.3) |
| | Stratified Hazard Ratio ^{a, b} (95% C.I.) | | 1.491 (1.032, 2.154) | | 1.432 (0.712, 2.882) |
| | P-value ^{b, c} | | 0.03314 | | 0.31436 |
| | Interaction Test P-value ^d | | | 0.85241 | |
| | Median Time to Onset of the First Event (Days) (95% C.I.) ^e | - (428.0, -) | - (332.0, -) | 599.0 (599.0, -) | - (-, -) |
| | 25 th , 75 th Percentile | 40.0, - | 214.0, - | 62.0, - | 173.0, - |
| Observed Min, Max ^f | 1, 1059+ | 1, 762+ | 1, 875+ | 1, 583+ | |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (Presence or history of brain metastases: Yes/No, ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was ran.

c. Two-sided p-value calculated from Cox proportional hazards model.

d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and race.

e. Calculated using the complementary log-log transformation method (Collett, 1994).

f. '+' means the observed time is from censored subjects.

Data Snapshot: 14OCT2019, Data Cutoff Date: 04SEP2019

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Seattle Genetics Protocol ONT-380-206**Table 2.2.5 Summary of Gastrointestinal Adverse Events by System Organ Class, Preferred Term and Race Safety Analysis Set**

| System Organ Class/ Preferred Term | Parameters | White | | Non-White | |
|---------------------------------------|--|------------------------|------------------------|------------------------|-----------------------|
| | | Tuc+Cap+Tra (N=283) | Pbo+Cap+Tra (N=153) | Tuc+Cap+Tra (N=121) | Pbo+Cap+Tra (N=44) |
| Stomatitis | Number of Subjects With at Least One Event, n (%) | 65 (23.0) | 24 (15.7) | 38 (31.4) | 4 (9.1) |
| | Number of Censored Subjects, n (%) | 218 (77.0) | 129 (84.3) | 83 (68.6) | 40 (90.9) |
| | Stratified Hazard Ratio ^{a, b} (95% C.I.) | | 1.499 (0.936, 2.401) | | 4.225 (1.466, 12.180) |
| | P-value ^{b, c} | | 0.09195 | | 0.00763 |
| | Interaction Test P-value ^d | | | 0.09667 | |
| | Median Time to Onset of the First Event (Days) (95% C.I.) ^e | - (-, -) | - (-, -) | - (271.0, -) | - (-, -) |
| | 25 th , 75 th Percentile | 360.0, - | -, - | 120.0, - | -, - |
| Observed Min, Max ^f | 1, 1059+ | 7, 762+ | 2, 637+ | 11, 583+ | |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (Presence or history of brain metastases: Yes/No, ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was ran.

c. Two-sided p-value calculated from Cox proportional hazards model.

d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and race.

e. Calculated using the complementary log-log transformation method (Collett, 1994).

f. '+' means the observed time is from censored subjects.

Data Snapshot: 14OCT2019, Data Cutoff Date: 04SEP2019

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Seattle Genetics Protocol ONT-380-206**Table 2.2.5 Summary of Gastrointestinal Adverse Events by System Organ Class, Preferred Term and Race Safety Analysis Set**

| System Organ Class/ Preferred Term | Parameters | White | | Non-White | |
|---------------------------------------|--|------------------------|------------------------|------------------------|-----------------------|
| | | Tuc+Cap+Tra (N=283) | Pbo+Cap+Tra (N=153) | Tuc+Cap+Tra (N=121) | Pbo+Cap+Tra (N=44) |
| Constipation | Number of Subjects With at Least One Event, n (%) | 41 (14.5) | 31 (20.3) | 18 (14.9) | 8 (18.2) |
| | Number of Censored Subjects, n (%) | 242 (85.5) | 122 (79.7) | 103 (85.1) | 36 (81.8) |
| | Stratified Hazard Ratio ^{a, b} (95% C.I.) | | 0.613 (0.381, 0.986) | | 0.880 (0.360, 2.154) |
| | P-value ^{b, c} | | 0.04338 | | 0.78014 |
| | Interaction Test P-value ^d | | | 0.76921 | |
| | Median Time to Onset of the First Event (Days) (95% C.I.) ^e | - (660.0, -) | - (-, -) | 709.0 (709.0, -) | - (313.0, -) |
| | 25 th , 75 th Percentile | 643.0, - | 342.0, - | 709.0, - | 313.0, - |
| Observed Min, Max ^f | 1, 1059+ | 1, 762+ | 1, 875+ | 1, 583+ | |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (Presence or history of brain metastases: Yes/No, ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was ran.

c. Two-sided p-value calculated from Cox proportional hazards model.

d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and race.

e. Calculated using the complementary log-log transformation method (Collett, 1994).

f. '+' means the observed time is from censored subjects.

Data Snapshot: 14OCT2019, Data Cutoff Date: 04SEP2019

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Seattle Genetics Protocol ONT-380-206**Table 2.2.6 Summary of Gastrointestinal Adverse Events by System Organ Class, Preferred Term and Hormone Receptor Status Safety Analysis Set**

| System Organ Class/ Preferred Term | Parameters | Negative for Both | | Positive for ER or PR or Both | |
|---------------------------------------|--|------------------------|-----------------------|-------------------------------|------------------------|
| | | Tuc+Cap+Tra (N=163) | Pbo+Cap+Tra (N=74) | Tuc+Cap+Tra (N=241) | Pbo+Cap+Tra (N=123) |
| Gastrointestinal Disorders | Number of Subjects With at Least One Event, n (%) | 152 (93.3) | 59 (79.7) | 230 (95.4) | 103 (83.7) |
| | Number of Censored Subjects, n (%) | 11 (6.7) | 15 (20.3) | 11 (4.6) | 20 (16.3) |
| | Stratified Hazard Ratio ^{a, b} (95% C.I.) | | 1.753 (1.283, 2.394) | | 2.037 (1.594, 2.604) |
| | P-value ^{b, c} | | 0.00042 | | <.00001 |
| | Interaction Test P-value ^d | | | 0.68939 | |
| | Median Time to Onset of the First Event (Days) (95% C.I.) ^e | 7.0 (5.0, 8.0) | 15.5 (11.0, 22.0) | 7.0 (6.0, 8.0) | 15.0 (12.0, 25.0) |
| | 25 th , 75 th Percentile | 2.0, 15.0 | 7.0, 66.0 | 3.0, 14.0 | 6.0, 77.0 |
| Observed Min, Max ^f | 1, 433+ | 1, 205+ | 1, 436+ | 1, 409+ | |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (Presence or history of brain metastases: Yes/No, ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was ran.

c. Two-sided p-value calculated from Cox proportional hazards model.

d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and hormone receptor status.

e. Calculated using the complementary log-log transformation method (Collett, 1994).

f. '+' means the observed time is from censored subjects.

Data Snapshot: 14OCT2019, Data Cutoff Date: 04SEP2019

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_1753\v01\outputs\tlfs\pgms\t-ae-km-gisoc-subgrp.sas Output: t-ae-km-gisoc-sub-6-hr-safs.rtf (17APR20:16:56) Data: adsl, adae, adttesaf

Seattle Genetics Protocol ONT-380-206

Table 2.2.6 Summary of Gastrointestinal Adverse Events by System Organ Class, Preferred Term and Hormone Receptor Status Safety Analysis Set

| System Organ Class/ Preferred Term | Parameters | Negative for Both | | Positive for ER or PR or Both | |
|---------------------------------------|--|------------------------|-----------------------|-------------------------------|------------------------|
| | | Tuc+Cap+Tra (N=163) | Pbo+Cap+Tra (N=74) | Tuc+Cap+Tra (N=241) | Pbo+Cap+Tra (N=123) |
| Diarrhoea | Number of Subjects With at Least One Event, n (%) | 137 (84.0) | 36 (48.6) | 190 (78.8) | 69 (56.1) |
| | Number of Censored Subjects, n (%) | 26 (16.0) | 38 (51.4) | 51 (21.2) | 54 (43.9) |
| | Stratified Hazard Ratio ^{a, b} (95% C.I.) | | 2.613 (1.796, 3.800) | | 2.236 (1.689, 2.961) |
| | P-value ^{b, c} | | <.00001 | | <.00001 |
| | Interaction Test P-value ^d | | | 0.59668 | |
| | Median Time to Onset of the First Event (Days) (95% C.I.) ^e | 15.0 (13.0, 20.0) | 129.0 (43.0, -) | 14.0 (13.0, 16.0) | 89.0 (57.0, 183.0) |
| | 25 th , 75 th Percentile | 7.0, 87.0 | 22.0, - | 7.0, 60.0 | 19.0, - |
| Observed Min, Max ^f | 1, 433+ | 2, 386+ | 1, 436+ | 1, 588+ | |

a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (Presence or history of brain metastases: Yes/No, ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was ran.

c. Two-sided p-value calculated from Cox proportional hazards model.

d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and hormone receptor status.

e. Calculated using the complementary log-log transformation method (Collett, 1994).

f. '+' means the observed time is from censored subjects.

Data Snapshot: 14OCT2019, Data Cutoff Date: 04SEP2019

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_1753\v01\outputs\tlfs\pgms\t-ae-km-gisoc-subgrp.sas Output: t-ae-km-gisoc-sub-6-hr-safs.rtf (17APR20:16:56) Data: adsl, adae, adttesaf

Seattle Genetics Protocol ONT-380-206**Table 2.2.6 Summary of Gastrointestinal Adverse Events by System Organ Class, Preferred Term and Hormone Receptor Status Safety Analysis Set**

| System Organ Class/ Preferred Term | Parameters | Negative for Both | | Positive for ER or PR or Both | |
|---------------------------------------|--|------------------------|-----------------------|-------------------------------|------------------------|
| | | Tuc+Cap+Tra (N=163) | Pbo+Cap+Tra (N=74) | Tuc+Cap+Tra (N=241) | Pbo+Cap+Tra (N=123) |
| Nausea | Number of Subjects With at Least One Event, n (%) | 89 (54.6) | 29 (39.2) | 147 (61.0) | 57 (46.3) |
| | Number of Censored Subjects, n (%) | 74 (45.4) | 45 (60.8) | 94 (39.0) | 66 (53.7) |
| | Stratified Hazard Ratio ^{a, b} (95% C.I.) | | 1.598 (1.042, 2.451) | | 1.488 (1.094, 2.025) |
| | P-value ^{b, c} | | 0.03169 | | 0.01144 |
| | Interaction Test P-value ^d | | | 0.86297 | |
| | Median Time to Onset of the First Event (Days) (95% C.I.) ^e | 148.0 (36.0, 560.0) | 342.0 (110.0, -) | 30.0 (15.0, 63.0) | 205.0 (63.0, -) |
| | 25 th , 75 th Percentile | 7.0, - | 21.0, - | 6.0, - | 13.0, - |
| Observed Min, Max ^f | 1, 1059+ | 1, 580+ | 1, 688+ | 1, 762+ | |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (Presence or history of brain metastases: Yes/No, ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was ran.

c. Two-sided p-value calculated from Cox proportional hazards model.

d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and hormone receptor status.

e. Calculated using the complementary log-log transformation method (Collett, 1994).

f. '+' means the observed time is from censored subjects.

Data Snapshot: 14OCT2019, Data Cutoff Date: 04SEP2019

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_1753\v01\outputs\tlfs\pgms\t-ae-km-gisoc-subgrp.sas Output: t-ae-km-gisoc-sub-6-hr-safs.rtf (17APR20:16:56) Data: adsl, adae, adttesaf

Seattle Genetics Protocol ONT-380-206**Table 2.2.6 Summary of Gastrointestinal Adverse Events by System Organ Class, Preferred Term and Hormone Receptor Status Safety Analysis Set**

| System Organ Class/ Preferred Term | Parameters | Negative for Both | | Positive for ER or PR or Both | |
|---------------------------------------|--|------------------------|-----------------------|-------------------------------|------------------------|
| | | Tuc+Cap+Tra (N=163) | Pbo+Cap+Tra (N=74) | Tuc+Cap+Tra (N=241) | Pbo+Cap+Tra (N=123) |
| Vomiting | Number of Subjects With at Least One Event, n (%) | 63 (38.7) | 19 (25.7) | 82 (34.0) | 31 (25.2) |
| | Number of Censored Subjects, n (%) | 100 (61.3) | 55 (74.3) | 159 (66.0) | 92 (74.8) |
| | Stratified Hazard Ratio ^{a, b} (95% C.I.) | | 1.544 (0.916, 2.603) | | 1.445 (0.954, 2.189) |
| | P-value ^{b, c} | | 0.10318 | | 0.08206 |
| | Interaction Test P-value ^d | | | 0.87320 | |
| | Median Time to Onset of the First Event (Days) (95% C.I.) ^e | - (599.0, -) | - (214.0, -) | - (428.0, -) | - (-, -) |
| | 25 th , 75 th Percentile | 43.0, - | 173.0, - | 42.0, - | 240.0, - |
| Observed Min, Max ^f | 1, 1059+ | 1, 580+ | 1, 891+ | 1, 762+ | |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (Presence or history of brain metastases: Yes/No, ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was ran.

c. Two-sided p-value calculated from Cox proportional hazards model.

d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and hormone receptor status.

e. Calculated using the complementary log-log transformation method (Collett, 1994).

f. '+' means the observed time is from censored subjects.

Data Snapshot: 14OCT2019, Data Cutoff Date: 04SEP2019

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_1753\v01\outputs\tlfs\pgms\t-ae-km-gisoc-subgrp.sas Output: t-ae-km-gisoc-sub-6-hr-safs.rtf (17APR20:16:56) Data: adsl, adae, adttesaf

Seattle Genetics Protocol ONT-380-206**Table 2.2.6 Summary of Gastrointestinal Adverse Events by System Organ Class, Preferred Term and Hormone Receptor Status Safety Analysis Set**

| System Organ Class/ Preferred Term | Parameters | Negative for Both | | Positive for ER or PR or Both | |
|---------------------------------------|--|------------------------|-----------------------|-------------------------------|------------------------|
| | | Tuc+Cap+Tra (N=163) | Pbo+Cap+Tra (N=74) | Tuc+Cap+Tra (N=241) | Pbo+Cap+Tra (N=123) |
| Stomatitis | Number of Subjects With at Least One Event, n (%) | 35 (21.5) | 10 (13.5) | 68 (28.2) | 18 (14.6) |
| | Number of Censored Subjects, n (%) | 128 (78.5) | 64 (86.5) | 173 (71.8) | 105 (85.4) |
| | Stratified Hazard Ratio ^{a, b} (95% C.I.) | | 1.569 (0.767, 3.211) | | 1.990 (1.179, 3.359) |
| | P-value ^{b, c} | | 0.21752 | | 0.00994 |
| | Interaction Test P-value ^d | | | 0.68778 | |
| | Median Time to Onset of the First Event (Days) (95% C.I.) ^e | - (-, -) | - (-, -) | - (615.0, -) | - (-, -) |
| | 25 th , 75 th Percentile | 347.0, - | -, - | 148.0, - | -, - |
| Observed Min, Max ^f | 1, 1059+ | 7, 580+ | 1, 863+ | 7, 762+ | |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (Presence or history of brain metastases: Yes/No, ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was ran.

c. Two-sided p-value calculated from Cox proportional hazards model.

d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and hormone receptor status.

e. Calculated using the complementary log-log transformation method (Collett, 1994).

f. '+' means the observed time is from censored subjects.

Data Snapshot: 14OCT2019, Data Cutoff Date: 04SEP2019

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_1753\v01\outputs\tlfs\pgms\t-ae-km-gisoc-subgrp.sas Output: t-ae-km-gisoc-sub-6-hr-safs.rtf (17APR20:16:56) Data: adsl, adae, adttesaf

Seattle Genetics Protocol ONT-380-206**Table 2.2.6 Summary of Gastrointestinal Adverse Events by System Organ Class, Preferred Term and Hormone Receptor Status Safety Analysis Set**

| System Organ Class/ Preferred Term | Parameters | Negative for Both | | Positive for ER or PR or Both | |
|---------------------------------------|--|------------------------|-----------------------|-------------------------------|------------------------|
| | | Tuc+Cap+Tra (N=163) | Pbo+Cap+Tra (N=74) | Tuc+Cap+Tra (N=241) | Pbo+Cap+Tra (N=123) |
| Constipation | Number of Subjects With at Least One Event, n (%) | 28 (17.2) | 17 (23.0) | 31 (12.9) | 22 (17.9) |
| | Number of Censored Subjects, n (%) | 135 (82.8) | 57 (77.0) | 210 (87.1) | 101 (82.1) |
| | Stratified Hazard Ratio ^{a, b} (95% C.I.) | | 0.657 (0.350, 1.233) | | 0.645 (0.370, 1.123) |
| | P-value ^{b, c} | | 0.19135 | | 0.12135 |
| | Interaction Test P-value ^d | | | 0.82917 | |
| | Median Time to Onset of the First Event (Days) (95% C.I.) ^e | - (643.0, -) | - (342.0, -) | - (660.0, -) | - (-, -) |
| | 25 th , 75 th Percentile | 487.0, - | 342.0, - | 660.0, - | -, - |
| Observed Min, Max ^f | 1, 1059+ | 1, 580+ | 1, 875+ | 3, 762+ | |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (Presence or history of brain metastases: Yes/No, ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was ran.

c. Two-sided p-value calculated from Cox proportional hazards model.

d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and hormone receptor status.

e. Calculated using the complementary log-log transformation method (Collett, 1994).

f. '+' means the observed time is from censored subjects.

Data Snapshot: 14OCT2019, Data Cutoff Date: 04SEP2019

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_1753\v01\outputs\tlfs\pgms\t-ae-km-gisoc-subgrp.sas Output: t-ae-km-gisoc-sub-6-hr-safs.rtf (17APR20:16:56) Data: adsl, adae, adttesaf

Seattle Genetics Protocol ONT-380-206**Table 2.6.2 Summary of Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and History of Brain Metastases at Baseline - Time-to-Event Analysis Safety Analysis Set**

| System Organ Class/ Preferred Term | Parameters | With Brian Metastases | | Without Brain Metastases | |
|---------------------------------------|--|------------------------|-----------------------|--------------------------|------------------------|
| | | Tuc+Cap+Tra (N=194) | Pbo+Cap+Tra (N=91) | Tuc+Cap+Tra (N=209) | Pbo+Cap+Tra (N=105) |
| Anaemia (PT) | Number of Subjects With at Least One Event, n (%) | 35 (18.0) | 11 (12.1) | 44 (21.1) | 12 (11.4) |
| | Number of Censored Subjects, n (%) | 159 (82.0) | 80 (87.9) | 165 (78.9) | 93 (88.6) |
| | Stratified Hazard Ratio ^{a, b} (95% C.I.) | 1.419 (0.717, 2.811) | | 1.759 (0.926, 3.338) | |
| | P-value ^{b, c} | 0.31507 | | 0.08438 | |
| | Interaction Test P-value ^d | 0.62462 | | | |
| | Median Time to Onset of the First Event (Days) (95% C.I.) ^e | - (924.0, -) | - (-, -) | - (-, -) | - (-, -) |
| | 25 th , 75 th Percentile | 924.0, - | -, - | 356.0, - | -, - |
| | Observed Min, Max ^f | 4+, 1070+ | 12, 583+ | 1, 1059+ | 12, 762+ |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.

c. Two-sided p-value calculated from Cox proportional hazards model.

d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and history of brain metastases at baseline.

e. Calculated using the complementary log-log transformation method (Collett, 1994). f. '+' means the observed time is from censored subjects.

Data Snapshot: 14OCT2019, Data Cutoff Date: 04SEP2019

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_1753\v01\outputs\tlfs\pgms\t-ae-km-socpt-subgrp.sas Output: t-ae-km-socpt-sub-1-bm-safs.rtf (17JUL20:17:19)

Data: adsl, adae, adttesaf

Seattle Genetics Protocol ONT-380-206**Table 2.6.2 Summary of Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and History of Brain Metastases at Baseline - Time-to-Event Analysis Safety Analysis Set**

| System Organ Class/ Preferred Term | Parameters | With Brian Metastases | | Without Brain Metastases | |
|---------------------------------------|--|------------------------|-----------------------|--------------------------|------------------------|
| | | Tuc+Cap+Tra (N=194) | Pbo+Cap+Tra (N=91) | Tuc+Cap+Tra (N=209) | Pbo+Cap+Tra (N=105) |
| Investigations (SOC) | Number of Subjects With at Least One Event, n (%) | 121 (62.4) | 28 (30.8) | 120 (57.4) | 43 (41.0) |
| | Number of Censored Subjects, n (%) | 73 (37.6) | 63 (69.2) | 89 (42.6) | 62 (59.0) |
| | Stratified Hazard Ratio ^{a, b} (95% C.I.) | | 2.323 (1.537, 3.513) | | 1.575 (1.110, 2.234) |
| | P-value ^{b, c} | | 0.00006 | | 0.01095 |
| | Interaction Test P-value ^d | | | 0.19569 | |
| | Median Time to Onset of the First Event (Days) (95% C.I.) ^e | 64.0 (43.0, 112.0) | - (283.0, -) | 126.0 (50.0, 197.0) | 317.0 (200.0, -) |
| | 25 th , 75 th Percentile | 22.0, - | 64.0, - | 23.0, - | 63.0, - |
| Observed Min, Max ^f | 1, 891+ | 1, 387+ | 1, 555+ | 6, 478+ | |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.

c. Two-sided p-value calculated from Cox proportional hazards model.

d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and history of brain metastases at baseline.

e. Calculated using the complementary log-log transformation method (Collett, 1994). f. '+' means the observed time is from censored subjects.

Data Snapshot: 14OCT2019, Data Cutoff Date: 04SEP2019

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Data: adsl, adae, adttesaf

Seattle Genetics Protocol ONT-380-206**Table 2.6.2 Summary of Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and History of Brain Metastases at Baseline - Time-to-Event Analysis Safety Analysis Set**

| System Organ Class/ Preferred Term | Parameters | With Brian Metastases | | Without Brain Metastases | |
|---|---|-------------------------|-----------------------|--------------------------|------------------------|
| | | Tuc+Cap+Tra (N=194) | Pbo+Cap+Tra (N=91) | Tuc+Cap+Tra (N=209) | Pbo+Cap+Tra (N=105) |
| Aspartate Aminotransferase Increased (PT) | Number of Subjects With at Least One Event, n (%) | 38 (19.6) | 9 (9.9) | 48 (23.0) | 13 (12.4) |
| | Number of Censored Subjects, n (%) | 156 (80.4) | 82 (90.1) | 161 (77.0) | 92 (87.6) |
| | Stratified Hazard Ratio ^{a, b} (95% C.I.) | 2.024 (0.977, 4.191) | | 1.868 (1.010, 3.453) | |
| | P-value ^{b, c} | 0.05772 | | 0.04635 | |
| | Interaction Test P-value ^d | 0.92168 | | | |
| | Median Time to Onset of the First Event (Days) (95% C.I.) ^e | - (-, -) | -(335.0, -) | - (-, -) | - (-, -) |
| | 25 th , 75 th Percentile | -, - | 335.0, - | 335.0, - | -, - |
| Observed Min, Max ^f | 4+, 1070+ | 1, 405+ | 11, 849+ | 11, 762+ | |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.

c. Two-sided p-value calculated from Cox proportional hazards model.

d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and history of brain metastases at baseline.

e. Calculated using the complementary log-log transformation method (Collett, 1994). f. '+' means the observed time is from censored subjects.

Data Snapshot: 14OCT2019, Data Cutoff Date: 04SEP2019

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Data: adsl, adae, adttesaf

Seattle Genetics Protocol ONT-380-206**Table 2.6.2 Summary of Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and History of Brain Metastases at Baseline - Time-to-Event Analysis Safety Analysis Set**

| System Organ Class/ Preferred Term | Parameters | With Brian Metastases | | Without Brain Metastases | |
|---|---|-------------------------|-----------------------|--------------------------|------------------------|
| | | Tuc+Cap+Tra (N=194) | Pbo+Cap+Tra (N=91) | Tuc+Cap+Tra (N=209) | Pbo+Cap+Tra (N=105) |
| Alanine Aminotransferase Increased (PT) | Number of Subjects With at Least One Event, n (%) | 35 (18.0) | 8 (8.8) | 46 (22.0) | 5 (4.8) |
| | Number of Censored Subjects, n (%) | 159 (82.0) | 83 (91.2) | 163 (78.0) | 100 (95.2) |
| | Stratified Hazard Ratio ^{a, b} (95% C.I.) | 1.999 (0.924, 4.323) | | 5.015 (1.991, 12.631) | |
| | P-value ^{b, c} | 0.07834 | | 0.00062 | |
| | Interaction Test P-value ^d | 0.12344 | | | |
| | Median Time to Onset of the First Event (Days) (95% C.I.) ^e | - (-, -) | - (357.0, -) | - (-, -) | - (-, -) |
| | 25 th , 75 th Percentile | -, - | 357.0, - | 407.0, - | -, - |
| Observed Min, Max ^f | 4+, 1070+ | 21, 396+ | 11, 863+ | 14, 762+ | |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.

c. Two-sided p-value calculated from Cox proportional hazards model.

d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and history of brain metastases at baseline.

e. Calculated using the complementary log-log transformation method (Collett, 1994). f. '+' means the observed time is from censored subjects.

Data Snapshot: 14OCT2019, Data Cutoff Date: 04SEP2019

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Data: adsl, adae, adtesaf

Seattle Genetics Protocol ONT-380-206**Table 2.6.2 Summary of Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and History of Brain Metastases at Baseline - Time-to-Event Analysis Safety Analysis Set**

| System Organ Class/ Preferred Term | Parameters | With Brian Metastases | | Without Brain Metastases | |
|---------------------------------------|--|------------------------|-----------------------|--------------------------|------------------------|
| | | Tuc+Cap+Tra (N=194) | Pbo+Cap+Tra (N=91) | Tuc+Cap+Tra (N=209) | Pbo+Cap+Tra (N=105) |
| Blood Bilirubin Increased (PT) | Number of Subjects With at Least One Event, n (%) | 36 (18.6) | 8 (8.8) | 39 (18.7) | 12 (11.4) |
| | Number of Censored Subjects, n (%) | 158 (81.4) | 83 (91.2) | 170 (81.3) | 93 (88.6) |
| | Stratified Hazard Ratio ^{a, b} (95% C.I.) | | 2.080 (0.964, 4.486) | | 1.690 (0.883, 3.235) |
| | P-value ^{b, c} | | 0.06184 | | 0.11328 |
| | Interaction Test P-value ^d | | | 0.67189 | |
| | Median Time to Onset of the First Event (Days) (95% C.I.) ^e | - (-, -) | - (-, -) | - (-, -) | - (-, -) |
| | 25 th , 75 th Percentile | -, - | -, - | 358.0, - | -, - |
| | Observed Min, Max ^f | 4+, 1070+ | 7, 583+ | 11, 945+ | 6, 762+ |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.

c. Two-sided p-value calculated from Cox proportional hazards model.

d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and history of brain metastases at baseline.

e. Calculated using the complementary log-log transformation method (Collett, 1994). f. '+' means the observed time is from censored subjects.

Data Snapshot: 14OCT2019, Data Cutoff Date: 04SEP2019

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Data: adsl, adae, adttesaf

Seattle Genetics Protocol ONT-380-206**Table 2.6.2 Summary of Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and History of Brain Metastases at Baseline - Time-to-Event Analysis
Safety Analysis Set**

| System Organ Class/ Preferred Term | Parameters | With Brian Metastases | | Without Brain Metastases | |
|---------------------------------------|---|--------------------------|-----------------------|-------------------------------|------------------------|
| | | Tuc+Cap+Tra (N=194) | Pbo+Cap+Tra (N=91) | Tuc+Cap+Tra (N=209) | Pbo+Cap+Tra (N=105) |
| Blood Creatinine Increased (PT) | Number of Subjects With at Least One Event, n (%) | 24 (12.4) | 2 (2.2) | 32 (15.3) | 1 (1.0) |
| | Number of Censored Subjects, n (%) | 170 (87.6) | 89 (97.8) | 177 (84.7) | 104 (99.0) |
| | Stratified Hazard Ratio ^{a, b} (95% C.I.) | 5.386 (1.268, 22.876) | | 16.205 (2.213, 118.693) | |
| | P-value ^{b, c} | 0.02251 | | 0.00611 | |
| | Interaction Test P-value ^d | | | 0.34600 | |
| | Median Time to Onset of the First Event (Days) (95% C.I.) ^e | -(747.0, -) | - (-, -) | - (-, -) | - (-, -) |
| | 25 th , 75 th Percentile | 747.0, - | -, - | 610.0, - | -, - |
| Observed Min, Max ^f | 4+, 1070+ | 13, 583+ | 5, 945+ | 29+, 762+ | |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.

c. Two-sided p-value calculated from Cox proportional hazards model.

d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and history of brain metastases at baseline.

e. Calculated using the complementary log-log transformation method (Collett, 1994). f. '+' means the observed time is from censored subjects.

Data Snapshot: 14OCT2019, Data Cutoff Date: 04SEP2019

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_1753\v01\outputs\tlfs\pgms\t-ae-km-socpt-subgrp.sas Output: t-ae-km-socpt-sub-1-bm-safs.rtf (17JUL20:17:19)

Data: adsl, adae, adttesaf

Seattle Genetics Protocol ONT-380-206**Table 2.6.2 Summary of Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and History of Brain Metastases at Baseline - Time-to-Event Analysis
Safety Analysis Set**

| System Organ Class/ Preferred Term | Parameters | With Brian Metastases | | Without Brain Metastases | |
|---------------------------------------|--|------------------------|-----------------------|--------------------------|------------------------|
| | | Tuc+Cap+Tra (N=194) | Pbo+Cap+Tra (N=91) | Tuc+Cap+Tra (N=209) | Pbo+Cap+Tra (N=105) |
| Weight Decreased (PT) | Number of Subjects With at Least One Event, n (%) | 35 (18.0) | 6 (6.6) | 19 (9.1) | 5 (4.8) |
| | Number of Censored Subjects, n (%) | 159 (82.0) | 85 (93.4) | 190 (90.9) | 100 (95.2) |
| | Stratified Hazard Ratio ^{a, b} (95% C.I.) | 2.658 (1.115, 6.340) | | 1.737 (0.647, 4.665) | |
| | P-value ^{b, c} | 0.02747 | | 0.27294 | |
| | Interaction Test P-value ^d | 0.58960 | | | |
| | Median Time to Onset of the First Event (Days) (95% C.I.) ^e | - (-, -) | - (-, -) | - (-, -) | - (-, -) |
| | 25 th , 75 th Percentile | -, - | -, - | -, - | -, - |
| | Observed Min, Max ^f | 4+, 891+ | 9, 580+ | 6, 1059+ | 25, 762+ |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.

c. Two-sided p-value calculated from Cox proportional hazards model.

d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and history of brain metastases at baseline.

e. Calculated using the complementary log-log transformation method (Collett, 1994). f. '+' means the observed time is from censored subjects.

Data Snapshot: 14OCT2019, Data Cutoff Date: 04SEP2019

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_1753\v01\outputs\tlfs\pgms\t-ae-km-socpt-subgrp.sas Output: t-ae-km-socpt-sub-1-bm-safs.rtf (17JUL20:17:19)

Data: adsl, adae, adttesaf

Seattle Genetics Protocol ONT-380-206**Table 2.6.2 Summary of Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and History of Brain Metastases at Baseline - Time-to-Event Analysis
Safety Analysis Set**

| System Organ Class/ Preferred Term | Parameters | With Brian Metastases | | Without Brain Metastases | |
|--|---|------------------------|-------------------------|--------------------------|-------------------------|
| | | Tuc+Cap+Tra (N=194) | Pbo+Cap+Tra (N=91) | Tuc+Cap+Tra (N=209) | Pbo+Cap+Tra (N=105) |
| Metabolism And Nutrition Disorders (SOC) | Number of Subjects With at Least One Event, n (%) | 102 (52.6) | 32 (35.2) | 101 (48.3) | 39 (37.1) |
| | Number of Censored Subjects, n (%) | 92 (47.4) | 59 (64.8) | 108 (51.7) | 66 (62.9) |
| | Stratified Hazard Ratio ^{a, b} (95% C.I.) | | 1.658 (1.111, 2.474) | | 1.362 (0.941, 1.974) |
| | P-value ^{b, c} | | 0.01336 | | 0.10192 |
| | Interaction Test P-value ^d | | | 0.49337 | |
| | Median Time to Onset of the First Event (Days) (95% C.I.) ^e | 127.0 (79.0, 422.0) | 335.0 (216.0, -) | 211.0 (120.0, -) | - (201.0, -) |
| | 25 th , 75 th Percentile | 22.0, - | 45.0, - | 23.0, - | 43.0, - |
| Observed Min, Max ^f | 1, 694+ | 7, 396+ | 1, 863+ | 1, 762+ | |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.

c. Two-sided p-value calculated from Cox proportional hazards model.

d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and history of brain metastases at baseline.

e. Calculated using the complementary log-log transformation method (Collett, 1994). f. '+' means the observed time is from censored subjects.

Data Snapshot: 14OCT2019, Data Cutoff Date: 04SEP2019

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_1753\v01\outputs\tlfs\pgms\t-ae-km-socpt-subgrp.sas Output: t-ae-km-socpt-sub-1-bm-safs.rtf (17JUL20:17:19)

Data: adsl, adae, adtesaf

Seattle Genetics Protocol ONT-380-206

Table 2.6.2 Summary of Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and History of Brain Metastases at Baseline - Time-to-Event Analysis Safety Analysis Set

| System Organ Class/ Preferred Term | Parameters | With Brian Metastases | | Without Brain Metastases | |
|---------------------------------------|--|-----------------------------|-----------------------|--------------------------|------------------------|
| | | Tuc+Cap+Tra (N=194) | Pbo+Cap+Tra (N=91) | Tuc+Cap+Tra (N=209) | Pbo+Cap+Tra (N=105) |
| Hyperglycaemia (PT) | Number of Subjects With at Least One Event, n (%) | 10 (5.2) | 0 | 13 (6.2) | 3 (2.9) |
| | Number of Censored Subjects, n (%) | 184 (94.8) | 91 (100) | 196 (93.8) | 102 (97.1) |
| | Stratified Hazard Ratio ^{a, b} (95% C.I.) | 16534523.88 8 (0.000, -) | | 1.853 (0.526, 6.522) | |
| | P-value ^{b, c} | 0.99305 | | 0.33687 | |
| | Interaction Test P-value ^d | | | 0.98790 | |
| | Median Time to Onset of the First Event (Days) (95% C.I.) ^e | - (-, -) | - (-, -) | - (-, -) | - (-, -) |
| | 25 th , 75 th Percentile | -, - | -, - | -, - | -, - |
| Observed Min, Max ^f | 2, 1070+ | 26+, 583+ | 10, 1059+ | 12, 762+ | |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.

c. Two-sided p-value calculated from Cox proportional hazards model.

d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and history of brain metastases at baseline.

e. Calculated using the complementary log-log transformation method (Collett, 1994). f. '+' means the observed time is from censored subjects.

Data Snapshot: 14OCT2019, Data Cutoff Date: 04SEP2019

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Data: adsl, adae, adttesaf

Seattle Genetics Protocol ONT-380-206**Table 2.6.2 Summary of Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and History of Brain Metastases at Baseline - Time-to-Event Analysis Safety Analysis Set**

| System Organ Class/ Preferred Term | Parameters | With Brian Metastases | | Without Brain Metastases | |
|--|---|-------------------------|-----------------------|--------------------------|------------------------|
| | | Tuc+Cap+Tra (N=194) | Pbo+Cap+Tra (N=91) | Tuc+Cap+Tra (N=209) | Pbo+Cap+Tra (N=105) |
| Musculoskeletal And Connective Tissue Disorders (SOC) | Number of Subjects With at Least One Event, n (%) | 91 (46.9) | 30 (33.0) | 92 (44.0) | 37 (35.2) |
| | Number of Censored Subjects, n (%) | 103 (53.1) | 61 (67.0) | 117 (56.0) | 68 (64.8) |
| | Stratified Hazard Ratio ^{a, b} (95% C.I.) | 1.322 (0.869, 2.012) | | 1.287 (0.877, 1.889) | |
| | P-value ^{b, c} | 0.19213 | | 0.19800 | |
| | Interaction Test P-value ^d | 0.80211 | | | |
| | Median Time to Onset of the First Event (Days) (95% C.I.) ^e | 255.0 (169.0, 319.0) | 286.0 (253.0, -) | 253.0 (156.0, -) | 399.0 (148.0, -) |
| | 25 th , 75 th Percentile | 64.0, 721.0 | 92.0, - | 61.0, - | 102.0, - |
| | Observed Min, Max ^f | 1, 743+ | 2, 405+ | 1, 849+ | 1, 760+ |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.

c. Two-sided p-value calculated from Cox proportional hazards model.

d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and history of brain metastases at baseline.

e. Calculated using the complementary log-log transformation method (Collett, 1994). f. '+' means the observed time is from censored subjects.

Data Snapshot: 14OCT2019, Data Cutoff Date: 04SEP2019

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Data: adsl, adae, adttesaf

Seattle Genetics Protocol ONT-380-206**Table 2.6.2 Summary of Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and History of Brain Metastases at Baseline - Time-to-Event Analysis Safety Analysis Set**

| System Organ Class/ Preferred Term | Parameters | With Brian Metastases | | Without Brain Metastases | |
|---------------------------------------|--|------------------------|-----------------------|--------------------------|------------------------|
| | | Tuc+Cap+Tra (N=194) | Pbo+Cap+Tra (N=91) | Tuc+Cap+Tra (N=209) | Pbo+Cap+Tra (N=105) |
| Arthralgia (PT) | Number of Subjects With at Least One Event, n (%) | 28 (14.4) | 6 (6.6) | 31 (14.8) | 3 (2.9) |
| | Number of Censored Subjects, n (%) | 166 (85.6) | 85 (93.4) | 178 (85.2) | 102 (97.1) |
| | Stratified Hazard Ratio ^{a, b} (95% C.I.) | 1.928 (0.792, 4.694) | | 4.610 (1.403, 15.153) | |
| | P-value ^{b, c} | 0.14841 | | 0.01182 | |
| | Interaction Test P-value ^d | 0.18849 | | | |
| | Median Time to Onset of the First Event (Days) (95% C.I.) ^e | - (-, -) | - (-, -) | - (602.0, -) | - (-, -) |
| | 25 th , 75 th Percentile | -, - | -, - | 449.0, - | -, - |
| | Observed Min, Max ^f | 1, 1070+ | 7, 583+ | 2, 875+ | 4, 762+ |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.

c. Two-sided p-value calculated from Cox proportional hazards model.

d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and history of brain metastases at baseline.

e. Calculated using the complementary log-log transformation method (Collett, 1994). f. '+' means the observed time is from censored subjects.

Data Snapshot: 14OCT2019, Data Cutoff Date: 04SEP2019

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Data: adsl, adae, adttesaf

Seattle Genetics Protocol ONT-380-206**Table 2.6.2 Summary of Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and History of Brain Metastases at Baseline - Time-to-Event Analysis Safety Analysis Set**

| System Organ Class/ Preferred Term | Parameters | With Brian Metastases | | Without Brain Metastases | |
|---------------------------------------|--|------------------------|-----------------------|--------------------------|------------------------|
| | | Tuc+Cap+Tra (N=194) | Pbo+Cap+Tra (N=91) | Tuc+Cap+Tra (N=209) | Pbo+Cap+Tra (N=105) |
| Muscle Spasms (PT) | Number of Subjects With at Least One Event, n (%) | 22 (11.3) | 2 (2.2) | 16 (7.7) | 3 (2.9) |
| | Number of Censored Subjects, n (%) | 172 (88.7) | 89 (97.8) | 193 (92.3) | 102 (97.1) |
| | Stratified Hazard Ratio ^{a, b} (95% C.I.) | 4.379 (1.020, 18.803) | | 2.377 (0.685, 8.245) | |
| | P-value ^{b, c} | 0.04700 | | 0.17232 | |
| | Interaction Test P-value ^d | 0.53426 | | | |
| | Median Time to Onset of the First Event (Days) (95% C.I.) ^e | 966.0 (-, -) | - (-, -) | - (787.0, -) | - (-, -) |
| | 25 th , 75 th Percentile | 966.0, 966.0 | -, - | 787.0, - | -, - |
| | Observed Min, Max ^f | 1, 966 | 21, 583+ | 8, 1059+ | 29+, 762+ |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.

c. Two-sided p-value calculated from Cox proportional hazards model.

d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and history of brain metastases at baseline.

e. Calculated using the complementary log-log transformation method (Collett, 1994). f. '+' means the observed time is from censored subjects.

Data Snapshot: 14OCT2019, Data Cutoff Date: 04SEP2019

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Data: adsl, adae, adttesaf

Seattle Genetics Protocol ONT-380-206**Table 2.6.2 Summary of Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and History of Brain Metastases at Baseline - Time-to-Event Analysis
Safety Analysis Set**

| System Organ Class/ Preferred Term | Parameters | With Brian Metastases | | Without Brain Metastases | |
|---------------------------------------|--|------------------------|-----------------------|-----------------------------|------------------------|
| | | Tuc+Cap+Tra (N=194) | Pbo+Cap+Tra (N=91) | Tuc+Cap+Tra (N=209) | Pbo+Cap+Tra (N=105) |
| Dysgeusia (PT) | Number of Subjects With at Least One Event, n (%) | 14 (7.2) | 5 (5.5) | 16 (7.7) | 0 |
| | Number of Censored Subjects, n (%) | 180 (92.8) | 86 (94.5) | 193 (92.3) | 105 (100) |
| | Stratified Hazard Ratio ^{a, b} (95% C.I.) | 1.054 (0.367, 3.029) | | 17785233.31 7 (0.000, -) | |
| | P-value ^{b, c} | 0.92213 | | 0.99091 | |
| | Interaction Test P-value ^d | | | 0.98993 | |
| | Median Time to Onset of the First Event (Days) (95% C.I.) ^e | - (-, -) | - (-, -) | - (-, -) | - (-, -) |
| | 25 th , 75 th Percentile | -, - | -, - | -, - | -, - |
| | Observed Min, Max ^f | 1, 891+ | 11, 580+ | 2, 1059+ | 29+, 762+ |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.

c. Two-sided p-value calculated from Cox proportional hazards model.

d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and history of brain metastases at baseline.

e. Calculated using the complementary log-log transformation method (Collett, 1994). f. '+' means the observed time is from censored subjects.

Data Snapshot: 14OCT2019, Data Cutoff Date: 04SEP2019

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Data: adsl, adae, adttesaf

Seattle Genetics Protocol ONT-380-206**Table 2.6.2 Summary of Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and History of Brain Metastases at Baseline - Time-to-Event Analysis
Safety Analysis Set**

| System Organ Class/ Preferred Term | Parameters | With Brian Metastases | | Without Brain Metastases | |
|---------------------------------------|--|------------------------|-----------------------|--------------------------|------------------------|
| | | Tuc+Cap+Tra (N=194) | Pbo+Cap+Tra (N=91) | Tuc+Cap+Tra (N=209) | Pbo+Cap+Tra (N=105) |
| Renal And Urinary Disorders (SOC) | Number of Subjects With at Least One Event, n (%) | 21 (10.8) | 5 (5.5) | 19 (9.1) | 4 (3.8) |
| | Number of Censored Subjects, n (%) | 173 (89.2) | 86 (94.5) | 190 (90.9) | 101 (96.2) |
| | Stratified Hazard Ratio ^{a, b} (95% C.I.) | | 1.900 (0.713, 5.058) | | 2.325 (0.789, 6.852) |
| | P-value ^{b, c} | | 0.19909 | | 0.12588 |
| | Interaction Test P-value ^d | | | 0.76731 | |
| | Median Time to Onset of the First Event (Days) (95% C.I.) ^e | - (-, -) | - (-, -) | - (-, -) | - (529.0, -) |
| | 25 th , 75 th Percentile | -, - | -, - | -, - | 529.0, - |
| Observed Min, Max ^f | 2, 1070+ | 18, 583+ | 4, 945+ | 1, 762+ | |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.

c. Two-sided p-value calculated from Cox proportional hazards model.

d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and history of brain metastases at baseline.

e. Calculated using the complementary log-log transformation method (Collett, 1994). f. '+' means the observed time is from censored subjects.

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Data: adsl, adae, adtesaf

Seattle Genetics Protocol ONT-380-206**Table 2.6.2 Summary of Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and History of Brain Metastases at Baseline - Time-to-Event Analysis Safety Analysis Set**

| System Organ Class/ Preferred Term | Parameters | With Brian Metastases | | Without Brain Metastases | |
|---------------------------------------|--|------------------------|-----------------------|--------------------------|------------------------|
| | | Tuc+Cap+Tra (N=194) | Pbo+Cap+Tra (N=91) | Tuc+Cap+Tra (N=209) | Pbo+Cap+Tra (N=105) |
| Epistaxis (PT) | Number of Subjects With at Least One Event, n (%) | 20 (10.3) | 2 (2.2) | 27 (12.9) | 8 (7.6) |
| | Number of Censored Subjects, n (%) | 174 (89.7) | 89 (97.8) | 182 (87.1) | 97 (92.4) |
| | Stratified Hazard Ratio ^{a, b} (95% C.I.) | 4.731 (1.103, 20.285) | | 1.622 (0.734, 3.582) | |
| | P-value ^{b, c} | 0.03640 | | 0.23180 | |
| | Interaction Test P-value ^d | | | 0.22582 | |
| | Median Time to Onset of the First Event (Days) (95% C.I.) ^e | - (-, -) | - (-, -) | - (-, -) | - (-, -) |
| | 25 th , 75 th Percentile | -, - | -, - | -, - | -, - |
| | Observed Min, Max ^f | 2, 988+ | 19, 583+ | 1, 1059+ | 3, 762+ |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.

c. Two-sided p-value calculated from Cox proportional hazards model.

d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and history of brain metastases at baseline.

e. Calculated using the complementary log-log transformation method (Collett, 1994). f. '+' means the observed time is from censored subjects.

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Data: adsl, adae, adttesaf

Seattle Genetics Protocol ONT-380-206

Table 2.6.2 Summary of Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and History of Brain Metastases at Baseline - Time-to-Event Analysis Safety Analysis Set

| System Organ Class/ Preferred Term | Parameters | With Brain Metastases | | Without Brain Metastases | |
|--|--|------------------------|-----------------------|--------------------------|------------------------|
| | | Tuc+Cap+Tra (N=194) | Pbo+Cap+Tra (N=91) | Tuc+Cap+Tra (N=209) | Pbo+Cap+Tra (N=105) |
| Pleural Effusion (PT) | Number of Subjects With at Least One Event, n (%) | 7 (3.6) | 4 (4.4) | 3 (1.4) | 7 (6.7) |
| | Number of Censored Subjects, n (%) | 187 (96.4) | 87 (95.6) | 206 (98.6) | 98 (93.3) |
| | Stratified Hazard Ratio ^{a, b} (95% C.I.) | 0.690 (0.197, 2.417) | | 0.140 (0.029, 0.673) | |
| | P-value ^{b, c} | 0.56187 | | 0.01417 | |
| | Interaction Test P-value ^d | 0.19209 | | | |
| | Median Time to Onset of the First Event (Days) (95% C.I.) ^e | - (-, -) | - (-, -) | 942.0 (942.0, -) | - (-, -) |
| 25 th , 75 th Percentile | -, - | -, - | 942.0, - | -, - | |
| Observed Min, Max ^f | 4+, 1070+ | 21, 583+ | 24+, 1059+ | 6, 762+ | |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.

c. Two-sided p-value calculated from Cox proportional hazards model.

d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and history of brain metastases at baseline.

e. Calculated using the complementary log-log transformation method (Collett, 1994). f. '+' means the observed time is from censored subjects.

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Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_1753\v01\outputs\tlfs\pgms\t-ae-km-socpt-subgrp.sas Output: t-ae-km-socpt-sub-1-bm-safs.rtf (17JUL20:17:19)

Data: adsl, adae, adttesaf

Seattle Genetics Protocol ONT-380-206**Table 2.6.2 Summary of Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and History of Brain Metastases at Baseline - Time-to-Event Analysis Safety Analysis Set**

| System Organ Class/ Preferred Term | Parameters | With Brian Metastases | | Without Brain Metastases | |
|---|--|------------------------|-----------------------|--------------------------|------------------------|
| | | Tuc+Cap+Tra (N=194) | Pbo+Cap+Tra (N=91) | Tuc+Cap+Tra (N=209) | Pbo+Cap+Tra (N=105) |
| Palmar-Plantar Erythrodyssaesthesia Syndrome (PT) | Number of Subjects With at Least One Event, n (%) | 125 (64.4) | 43 (47.3) | 130 (62.2) | 61 (58.1) |
| | Number of Censored Subjects, n (%) | 69 (35.6) | 48 (52.7) | 79 (37.8) | 44 (41.9) |
| | Stratified Hazard Ratio ^{a, b} (95% C.I.) | 1.449 (1.019, 2.060) | | 1.125 (0.828, 1.528) | |
| | P-value ^{b, c} | 0.03908 | | 0.45081 | |
| | Interaction Test P-value ^d | 0.27760 | | | |
| | Median Time to Onset of the First Event (Days) (95% C.I.) ^e | 61.0 (45.0, 85.0) | 141.0 (71.0, -) | 64.0 (43.0, 85.0) | 72.0 (63.0, 127.0) |
| | 25 th , 75 th Percentile | 31.0, 267.0 | 35.0, - | 25.0, 648.0 | 33.0, - |
| Observed Min, Max ^f | 1, 602+ | 1, 405+ | 1, 648 | 1, 409+ | |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.

c. Two-sided p-value calculated from Cox proportional hazards model.

d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and history of brain metastases at baseline.

e. Calculated using the complementary log-log transformation method (Collett, 1994). f. '+' means the observed time is from censored subjects.

Data Snapshot: 14OCT2019, Data Cutoff Date: 04SEP2019

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_1753\v01\outputs\tlfs\pgms\t-ae-km-socpt-subgrp.sas Output: t-ae-km-socpt-sub-1-bm-safs.rtf (17JUL20:17:19)

Data: adsl, adae, adttesaf

Seattle Genetics Protocol ONT-380-206**Table 2.6.3 Summary of Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Geographic Region - Time-to-Event Analysis Safety Analysis Set**

| System Organ Class/ Preferred Term | Parameters | North America | | Rest of World | |
|---------------------------------------|--|------------------------|------------------------|------------------------|-----------------------|
| | | Tuc+Cap+Tra (N=241) | Pbo+Cap+Tra (N=119) | Tuc+Cap+Tra (N=163) | Pbo+Cap+Tra (N=78) |
| Anaemia (PT) | Number of Subjects With at Least One Event, n (%) | 49 (20.3) | 14 (11.8) | 31 (19.0) | 9 (11.5) |
| | Number of Censored Subjects, n (%) | 192 (79.7) | 105 (88.2) | 132 (81.0) | 69 (88.5) |
| | Stratified Hazard Ratio ^{a, b} (95% C.I.) | 1.595 (0.877, 2.903) | | 1.684 (0.801, 3.544) | |
| | P-value ^{b, c} | 0.12612 | | 0.16938 | |
| | Interaction Test P-value ^d | 0.99242 | | | |
| | Median Time to Onset of the First Event (Days) (95% C.I.) ^e | - (924.0, -) | - (-, -) | - (-, -) | - (-, -) |
| | 25 th , 75 th Percentile | 390.0, - | -, - | -, - | -, - |
| | Observed Min, Max ^f | 1, 1070+ | 12, 762+ | 1, 694+ | 12, 588+ |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (Presence or history of brain metastases: Yes/No and ECOG performance status: 0/1) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.

c. Two-sided p-value calculated from Cox proportional hazards model.

d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and geographic region.

e. Calculated using the complementary log-log transformation method (Collett, 1994). f. '+' means the observed time is from censored subjects.

Data Snapshot: 14OCT2019, Data Cutoff Date: 04SEP2019

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_1753\v01\outputs\tlfs\pgms\t-ae-km-socpt-subgrp.sas Output: t-ae-km-socpt-sub-2-reg-safs.rtf (17JUL20:17:19)

Data: adsl, adae, adttesaf

Seattle Genetics Protocol ONT-380-206**Table 2.6.3 Summary of Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Geographic Region - Time-to-Event Analysis Safety Analysis Set**

| System Organ Class/ Preferred Term | Parameters | North America | | Rest of World | |
|---------------------------------------|--|------------------------|------------------------|------------------------|-----------------------|
| | | Tuc+Cap+Tra (N=241) | Pbo+Cap+Tra (N=119) | Tuc+Cap+Tra (N=163) | Pbo+Cap+Tra (N=78) |
| Investigations (SOC) | Number of Subjects With at Least One Event, n (%) | 143 (59.3) | 48 (40.3) | 98 (60.1) | 23 (29.5) |
| | Number of Censored Subjects, n (%) | 98 (40.7) | 71 (59.7) | 65 (39.9) | 55 (70.5) |
| | Stratified Hazard Ratio ^{a, b} (95% C.I.) | 1.626 (1.171, 2.257) | | 2.415 (1.530, 3.811) | |
| | P-value ^{b, c} | 0.00367 | | 0.00015 | |
| | Interaction Test P-value ^d | 0.14499 | | | |
| | Median Time to Onset of the First Event (Days) (95% C.I.) ^e | 64.0 (44.0, 148.0) | 356.0 (133.0, -) | 105.0 (63.0, 181.0) | - (231.0, -) |
| | 25 th , 75 th Percentile | 22.0, - | 43.0, - | 30.0, - | 147.0, - |
| Observed Min, Max ^f | 1, 891+ | 1, 453+ | 2, 533+ | 6, 478+ | |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (Presence or history of brain metastases: Yes/No and ECOG performance status: 0/1) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.

c. Two-sided p-value calculated from Cox proportional hazards model.

d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and geographic region.

e. Calculated using the complementary log-log transformation method (Collett, 1994). f. '+' means the observed time is from censored subjects.

Data Snapshot: 14OCT2019, Data Cutoff Date: 04SEP2019

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_1753\v01\outputs\tlfs\pgms\t-ae-km-socpt-subgrp.sas Output: t-ae-km-socpt-sub-2-reg-safs.rtf (17JUL20:17:19)

Data: adsl, adae, adttesaf

Seattle Genetics Protocol ONT-380-206

Table 2.6.3 Summary of Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Geographic Region - Time-to-Event Analysis Safety Analysis Set

| | | North America | | Rest of World | | |
|---|--|------------------------|------------------------|------------------------|-----------------------|----------|
| System Organ Class/ Preferred Term | Parameters | Tuc+Cap+Tra (N=241) | Pbo+Cap+Tra (N=119) | Tuc+Cap+Tra (N=163) | Pbo+Cap+Tra (N=78) | |
| Aspartate Aminotransferase Increased (PT) | Number of Subjects With at Least One Event, n (%) | 52 (21.6) | 17 (14.3) | 34 (20.9) | 5 (6.4) | |
| | Number of Censored Subjects, n (%) | 189 (78.4) | 102 (85.7) | 129 (79.1) | 73 (93.6) | |
| | Stratified Hazard Ratio ^{a, b} (95% C.I.) | | 1.504 (0.869, 2.602) | | 3.350 (1.308, 8.579) | |
| | P-value ^{b, c} | | 0.14463 | | 0.01172 | |
| | Interaction Test P-value ^d | | | 0.13539 | | |
| | Median Time to Onset of the First Event (Days) (95% C.I.) ^e | | - (-, -) | - (-, -) | - (-, -) | - (-, -) |
| | 25 th , 75 th Percentile | | 407.0, - | -, - | 358.0, - | -, - |
| Observed Min, Max ^f | | 4+, 1070+ | 1, 762+ | 6+, 720+ | 14, 588+ | |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.
 b. Computed using stratification factors (Presence or history of brain metastases: Yes/No and ECOG performance status: 0/1) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.
 c. Two-sided p-value calculated from Cox proportional hazards model.
 d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and geographic region.
 e. Calculated using the complementary log-log transformation method (Collett, 1994). f. '+' means the observed time is from censored subjects.
 Data Snapshot: 14OCT2019, Data Cutoff Date: 04SEP2019
 Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_1753\v01\outputs\tlfs\pgms\t-ae-km-socpt-subgrp.sas Output: t-ae-km-socpt-sub-2-reg-safs.rtf (17JUL20:17:19)
 Data: adsl, adae, adttesaf

Seattle Genetics Protocol ONT-380-206**Table 2.6.3 Summary of Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Geographic Region - Time-to-Event Analysis Safety Analysis Set**

| System Organ Class/ Preferred Term | Parameters | North America | | Rest of World | |
|---|--|------------------------|------------------------|------------------------|-----------------------|
| | | Tuc+Cap+Tra (N=241) | Pbo+Cap+Tra (N=119) | Tuc+Cap+Tra (N=163) | Pbo+Cap+Tra (N=78) |
| Alanine Aminotransferase Increased (PT) | Number of Subjects With at Least One Event, n (%) | 44 (18.3) | 9 (7.6) | 37 (22.7) | 4 (5.1) |
| | Number of Censored Subjects, n (%) | 197 (81.7) | 110 (92.4) | 126 (77.3) | 74 (94.9) |
| | Stratified Hazard Ratio ^{a, b} (95% C.I.) | 2.496 (1.218, 5.114) | | 4.557 (1.620, 12.821) | |
| | P-value ^{b, c} | 0.01248 | | 0.00406 | |
| | Interaction Test P-value ^d | | | 0.29194 | |
| | Median Time to Onset of the First Event (Days) (95% C.I.) ^e | - (-, -) | - (-, -) | - (-, -) | - (357.0, -) |
| | 25 th , 75 th Percentile | -, - | -, - | 254.0, - | -, - |
| Observed Min, Max ^f | 4+, 1070+ | 14, 762+ | 6+, 720+ | 22, 588+ | |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (Presence or history of brain metastases: Yes/No and ECOG performance status: 0/1) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.

c. Two-sided p-value calculated from Cox proportional hazards model.

d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and geographic region.

e. Calculated using the complementary log-log transformation method (Collett, 1994). f. '+' means the observed time is from censored subjects.

Data Snapshot: 14OCT2019, Data Cutoff Date: 04SEP2019

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_1753\v01\outputs\tlfs\pgms\t-ae-km-socpt-subgrp.sas Output: t-ae-km-socpt-sub-2-reg-safs.rtf (17JUL20:17:19)

Data: adsl, adae, adttesaf

Seattle Genetics Protocol ONT-380-206**Table 2.6.3 Summary of Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Geographic Region - Time-to-Event Analysis Safety Analysis Set**

| System Organ Class/ Preferred Term | Parameters | North America | | Rest of World | |
|---------------------------------------|--|------------------------|------------------------|------------------------|-----------------------|
| | | Tuc+Cap+Tra (N=241) | Pbo+Cap+Tra (N=119) | Tuc+Cap+Tra (N=163) | Pbo+Cap+Tra (N=78) |
| Blood Bilirubin Increased (PT) | Number of Subjects With at Least One Event, n (%) | 44 (18.3) | 14 (11.8) | 31 (19.0) | 6 (7.7) |
| | Number of Censored Subjects, n (%) | 197 (81.7) | 105 (88.2) | 132 (81.0) | 72 (92.3) |
| | Stratified Hazard Ratio ^{a, b} (95% C.I.) | 1.545 (0.846, 2.821) | | 2.534 (1.053, 6.094) | |
| | P-value ^{b, c} | 0.15696 | | 0.03789 | |
| | Interaction Test P-value ^d | 0.34776 | | | |
| | Median Time to Onset of the First Event (Days) (95% C.I.) ^e | - (-, -) | - (-, -) | - (-, -) | - (-, -) |
| | 25 th , 75 th Percentile | -, - | -, - | 358.0, - | -, - |
| Observed Min, Max ^f | 4+, 1070+ | 7, 762+ | 6+, 720+ | 6, 588+ | |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (Presence or history of brain metastases: Yes/No and ECOG performance status: 0/1) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.

c. Two-sided p-value calculated from Cox proportional hazards model.

d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and geographic region.

e. Calculated using the complementary log-log transformation method (Collett, 1994). f. '+' means the observed time is from censored subjects.

Data Snapshot: 14OCT2019, Data Cutoff Date: 04SEP2019

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_1753\v01\outputs\tlfs\pgms\t-ae-km-socpt-subgrp.sas Output: t-ae-km-socpt-sub-2-reg-safs.rtf (17JUL20:17:19)

Data: adsl, adae, adttesaf

Seattle Genetics Protocol ONT-380-206**Table 2.6.3 Summary of Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Geographic Region - Time-to-Event Analysis Safety Analysis Set**

| System Organ Class/ Preferred Term | Parameters | North America | | Rest of World | |
|---------------------------------------|--|------------------------|------------------------|------------------------|-----------------------|
| | | Tuc+Cap+Tra (N=241) | Pbo+Cap+Tra (N=119) | Tuc+Cap+Tra (N=163) | Pbo+Cap+Tra (N=78) |
| Blood Creatinine Increased (PT) | Number of Subjects With at Least One Event, n (%) | 33 (13.7) | 2 (1.7) | 23 (14.1) | 1 (1.3) |
| | Number of Censored Subjects, n (%) | 208 (86.3) | 117 (98.3) | 140 (85.9) | 77 (98.7) |
| | Stratified Hazard Ratio ^{a, b} (95% C.I.) | 7.842 (1.878, 32.744) | | 11.527 (1.555, 85.466) | |
| | P-value ^{b, c} | 0.00474 | | 0.01677 | |
| | Interaction Test P-value ^d | 0.76615 | | | |
| | Median Time to Onset of the First Event (Days) (95% C.I.) ^e | - (-, -) | - (-, -) | - (-, -) | - (-, -) |
| | 25 th , 75 th Percentile | 747.0, - | -, - | -, - | -, - |
| Observed Min, Max ^f | 4+, 1070+ | 13, 762+ | 5, 720+ | 34+, 588+ | |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (Presence or history of brain metastases: Yes/No and ECOG performance status: 0/1) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.

c. Two-sided p-value calculated from Cox proportional hazards model.

d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and geographic region.

e. Calculated using the complementary log-log transformation method (Collett, 1994). f. '+' means the observed time is from censored subjects.

Data Snapshot: 14OCT2019, Data Cutoff Date: 04SEP2019

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_1753\v01\outputs\tlfs\pgms\t-ae-km-socpt-subgrp.sas Output: t-ae-km-socpt-sub-2-reg-safs.rtf (17JUL20:17:19)

Data: adsl, adae, adtesaf

Seattle Genetics Protocol ONT-380-206**Table 2.6.3 Summary of Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Geographic Region - Time-to-Event Analysis Safety Analysis Set**

| System Organ Class/ Preferred Term | Parameters | North America | | Rest of World | |
|---------------------------------------|--|------------------------|------------------------|-----------------------------|-----------------------|
| | | Tuc+Cap+Tra (N=241) | Pbo+Cap+Tra (N=119) | Tuc+Cap+Tra (N=163) | Pbo+Cap+Tra (N=78) |
| Weight Decreased (PT) | Number of Subjects With at Least One Event, n (%) | 37 (15.4) | 11 (9.2) | 17 (10.4) | 0 |
| | Number of Censored Subjects, n (%) | 204 (84.6) | 108 (90.8) | 146 (89.6) | 78 (100) |
| | Stratified Hazard Ratio ^{a, b} (95% C.I.) | 1.595 (0.811, 3.137) | | 16954589.23 1 (0.000, -) | |
| | P-value ^{b, c} | 0.17620 | | 0.99083 | |
| | Interaction Test P-value ^d | | | 0.98263 | |
| | Median Time to Onset of the First Event (Days) (95% C.I.) ^e | - (-, -) | - (-, -) | - (-, -) | - (-, -) |
| | 25 th , 75 th Percentile | -, - | -, - | -, - | -, - |
| | Observed Min, Max ^f | 4+, 1059+ | 9, 762+ | 6+, 720+ | 34+, 588+ |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (Presence or history of brain metastases: Yes/No and ECOG performance status: 0/1) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.

c. Two-sided p-value calculated from Cox proportional hazards model.

d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and geographic region.

e. Calculated using the complementary log-log transformation method (Collett, 1994). f. '+' means the observed time is from censored subjects.

Data Snapshot: 14OCT2019, Data Cutoff Date: 04SEP2019

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_1753\v01\outputs\tlfs\pgms\t-ae-km-socpt-subgrp.sas Output: t-ae-km-socpt-sub-2-reg-safs.rtf (17JUL20:17:19)

Data: adsl, adae, adttesaf

Seattle Genetics Protocol ONT-380-206**Table 2.6.3 Summary of Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Geographic Region - Time-to-Event Analysis Safety Analysis Set**

| System Organ Class/ Preferred Term | Parameters | North America | | Rest of World | |
|--|--|------------------------|------------------------|------------------------|-----------------------|
| | | Tuc+Cap+Tra (N=241) | Pbo+Cap+Tra (N=119) | Tuc+Cap+Tra (N=163) | Pbo+Cap+Tra (N=78) |
| Metabolism And Nutrition Disorders (SOC) | Number of Subjects With at Least One Event, n (%) | 139 (57.7) | 49 (41.2) | 65 (39.9) | 22 (28.2) |
| | Number of Censored Subjects, n (%) | 102 (42.3) | 70 (58.8) | 98 (60.1) | 56 (71.8) |
| | Stratified Hazard Ratio ^{a, b} (95% C.I.) | 1.557 (1.122, 2.159) | | 1.428 (0.879, 2.322) | |
| | P-value ^{b, c} | 0.00800 | | 0.15048 | |
| | Interaction Test P-value ^d | 0.81274 | | | |
| | Median Time to Onset of the First Event (Days) (95% C.I.) ^e | 94.0 (64.0, 147.0) | -(147.0, -) | -(245.0, -) | -(335.0, -) |
| | 25 th , 75 th Percentile | 22.0, 630.0 | 36.0, - | 41.0, - | 127.0, - |
| Observed Min, Max ^f | 1, 863+ | 4, 762+ | 1, 694+ | 1, 588+ | |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (Presence or history of brain metastases: Yes/No and ECOG performance status: 0/1) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.

c. Two-sided p-value calculated from Cox proportional hazards model.

d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and geographic region.

e. Calculated using the complementary log-log transformation method (Collett, 1994). f. '+' means the observed time is from censored subjects.

Data Snapshot: 14OCT2019, Data Cutoff Date: 04SEP2019

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_1753\v01\outputs\tlfs\pgms\t-ae-km-socpt-subgrp.sas Output: t-ae-km-socpt-sub-2-reg-safs.rtf (17JUL20:17:19)

Data: adsl, adae, adttesaf

Seattle Genetics Protocol ONT-380-206**Table 2.6.3 Summary of Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Geographic Region - Time-to-Event Analysis
Safety Analysis Set**

| System Organ Class/ Preferred Term | Parameters | North America | | Rest of World | |
|---------------------------------------|--|------------------------|------------------------|------------------------|-----------------------|
| | | Tuc+Cap+Tra (N=241) | Pbo+Cap+Tra (N=119) | Tuc+Cap+Tra (N=163) | Pbo+Cap+Tra (N=78) |
| Hyperglycaemia (PT) | Number of Subjects With at Least One Event, n (%) | 20 (8.3) | 2 (1.7) | 3 (1.8) | 1 (1.3) |
| | Number of Censored Subjects, n (%) | 221 (91.7) | 117 (98.3) | 160 (98.2) | 77 (98.7) |
| | Stratified Hazard Ratio ^{a, b} (95% C.I.) | 4.490 (1.048, 19.241) | | 1.317 (0.136, 12.702) | |
| | P-value ^{b, c} | 0.04308 | | 0.81205 | |
| | Interaction Test P-value ^d | 0.37195 | | | |
| | Median Time to Onset of the First Event (Days) (95% C.I.) ^e | - (-, -) | - (-, -) | - (-, -) | - (-, -) |
| | 25 th , 75 th Percentile | -, - | -, - | -, - | -, - |
| Observed Min, Max ^f | 4+, 1070+ | 13, 762+ | 2, 720+ | 12, 588+ | |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (Presence or history of brain metastases: Yes/No and ECOG performance status: 0/1) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.

c. Two-sided p-value calculated from Cox proportional hazards model.

d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and geographic region.

e. Calculated using the complementary log-log transformation method (Collett, 1994). f. '+' means the observed time is from censored subjects.

Data Snapshot: 14OCT2019, Data Cutoff Date: 04SEP2019

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_1753\v01\outputs\tlfs\pgms\t-ae-km-socpt-subgrp.sas Output: t-ae-km-socpt-sub-2-reg-safs.rtf (17JUL20:17:19)

Data: adsl, adae, adttesaf

Seattle Genetics Protocol ONT-380-206**Table 2.6.3 Summary of Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Geographic Region - Time-to-Event Analysis Safety Analysis Set**

| System Organ Class/ Preferred Term | Parameters | North America | | Rest of World | |
|--|---|-------------------------|-------------------------|------------------------|-------------------------|
| | | Tuc+Cap+Tra (N=241) | Pbo+Cap+Tra (N=119) | Tuc+Cap+Tra (N=163) | Pbo+Cap+Tra (N=78) |
| Musculoskeletal And Connective Tissue Disorders (SOC) | Number of Subjects With at Least One Event, n (%) | 127 (52.7) | 39 (32.8) | 56 (34.4) | 28 (35.9) |
| | Number of Censored Subjects, n (%) | 114 (47.3) | 80 (67.2) | 107 (65.6) | 50 (64.1) |
| | Stratified Hazard Ratio ^{a, b} (95% C.I.) | | 1.613 (1.123, 2.317) | | 0.938 (0.592, 1.484) |
| | P-value ^{b, c} | | 0.00966 | | 0.78304 |
| | Interaction Test P-value ^d | | | 0.04134 | |
| | Median Time to Onset of the First Event (Days) (95% C.I.) ^e | 183.0 (128.0, 257.0) | 399.0 (215.0, -) | - (253.0, -) | 304.0 (138.0, -) |
| | 25 th , 75 th Percentile | 49.0, 609.0 | 92.0, - | 85.0, - | 111.0, - |
| Observed Min, Max ^f | 1, 849+ | 1, 760+ | 1, 694+ | 1, 588+ | |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (Presence or history of brain metastases: Yes/No and ECOG performance status: 0/1) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.

c. Two-sided p-value calculated from Cox proportional hazards model.

d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and geographic region.

e. Calculated using the complementary log-log transformation method (Collett, 1994). f. '+' means the observed time is from censored subjects.

Data Snapshot: 14OCT2019, Data Cutoff Date: 04SEP2019

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_1753\v01\outputs\tlfs\pgms\t-ae-km-socpt-subgrp.sas Output: t-ae-km-socpt-sub-2-reg-safs.rtf (17JUL20:17:19)

Data: adsl, adae, adttesaf

Seattle Genetics Protocol ONT-380-206**Table 2.6.3 Summary of Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Geographic Region - Time-to-Event Analysis Safety Analysis Set**

| System Organ Class/ Preferred Term | Parameters | North America | | Rest of World | |
|---------------------------------------|--|------------------------|------------------------|------------------------|-----------------------|
| | | Tuc+Cap+Tra (N=241) | Pbo+Cap+Tra (N=119) | Tuc+Cap+Tra (N=163) | Pbo+Cap+Tra (N=78) |
| Arthralgia (PT) | Number of Subjects With at Least One Event, n (%) | 40 (16.6) | 6 (5.0) | 19 (11.7) | 3 (3.8) |
| | Number of Censored Subjects, n (%) | 201 (83.4) | 113 (95.0) | 144 (88.3) | 75 (96.2) |
| | Stratified Hazard Ratio ^{a, b} (95% C.I.) | 2.995 (1.262, 7.111) | | 2.610 (0.769, 8.857) | |
| | P-value ^{b, c} | 0.01289 | | 0.12395 | |
| | Interaction Test P-value ^d | 0.90185 | | | |
| | Median Time to Onset of the First Event (Days) (95% C.I.) ^e | - (707.0, -) | - (-, -) | - (-, -) | - (-, -) |
| | 25 th , 75 th Percentile | 449.0, - | -, - | -, - | -, - |
| | Observed Min, Max ^f | 1, 1070+ | 4, 762+ | 1, 720+ | 7, 588+ |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (Presence or history of brain metastases: Yes/No and ECOG performance status: 0/1) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.

c. Two-sided p-value calculated from Cox proportional hazards model.

d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and geographic region.

e. Calculated using the complementary log-log transformation method (Collett, 1994). f. '+' means the observed time is from censored subjects.

Data Snapshot: 14OCT2019, Data Cutoff Date: 04SEP2019

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_1753\v01\outputs\tlfs\pgms\t-ae-km-socpt-subgrp.sas Output: t-ae-km-socpt-sub-2-reg-safs.rtf (17JUL20:17:19)

Data: adsl, adae, adttesaf

Seattle Genetics Protocol ONT-380-206**Table 2.6.3 Summary of Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Geographic Region - Time-to-Event Analysis Safety Analysis Set**

| System Organ Class/ Preferred Term | Parameters | North America | | Rest of World | |
|---------------------------------------|--|------------------------|------------------------|------------------------|-----------------------|
| | | Tuc+Cap+Tra (N=241) | Pbo+Cap+Tra (N=119) | Tuc+Cap+Tra (N=163) | Pbo+Cap+Tra (N=78) |
| Muscle Spasms (PT) | Number of Subjects With at Least One Event, n (%) | 26 (10.8) | 3 (2.5) | 12 (7.4) | 2 (2.6) |
| | Number of Censored Subjects, n (%) | 215 (89.2) | 116 (97.5) | 151 (92.6) | 76 (97.4) |
| | Stratified Hazard Ratio ^{a, b} (95% C.I.) | 3.566 (1.067, 11.917) | | 2.920 (0.651, 13.104) | |
| | P-value ^{b, c} | 0.03889 | | 0.16174 | |
| | Interaction Test P-value ^d | 0.75516 | | | |
| | Median Time to Onset of the First Event (Days) (95% C.I.) ^e | 966.0 (787.0, -) | -(399.0, -) | - (-, -) | - (-, -) |
| | 25 th , 75 th Percentile | 787.0, - | -, - | -, - | -, - |
| Observed Min, Max ^f | 2, 1059+ | 21, 762+ | 1, 720+ | 34+, 588+ | |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (Presence or history of brain metastases: Yes/No and ECOG performance status: 0/1) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.

c. Two-sided p-value calculated from Cox proportional hazards model.

d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and geographic region.

e. Calculated using the complementary log-log transformation method (Collett, 1994). f. '+' means the observed time is from censored subjects.

Data Snapshot: 14OCT2019, Data Cutoff Date: 04SEP2019

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_1753\v01\outputs\tlfs\pgms\t-ae-km-socpt-subgrp.sas Output: t-ae-km-socpt-sub-2-reg-safs.rtf (17JUL20:17:19)

Data: adsl, adae, adttesaf

Seattle Genetics Protocol ONT-380-206**Table 2.6.3 Summary of Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Geographic Region - Time-to-Event Analysis
Safety Analysis Set**

| System Organ Class/ Preferred Term | Parameters | North America | | Rest of World | |
|---------------------------------------|--|------------------------|------------------------|------------------------|-----------------------|
| | | Tuc+Cap+Tra (N=241) | Pbo+Cap+Tra (N=119) | Tuc+Cap+Tra (N=163) | Pbo+Cap+Tra (N=78) |
| Dysgeusia (PT) | Number of Subjects With at Least One Event, n (%) | 22 (9.1) | 4 (3.4) | 8 (4.9) | 1 (1.3) |
| | Number of Censored Subjects, n (%) | 219 (90.9) | 115 (96.6) | 155 (95.1) | 77 (98.7) |
| | Stratified Hazard Ratio ^{a, b} (95% C.I.) | 2.417 (0.825, 7.082) | | 3.832 (0.475, 30.883) | |
| | P-value ^{b, c} | 0.10751 | | 0.20708 | |
| | Interaction Test P-value ^d | 0.74685 | | | |
| | Median Time to Onset of the First Event (Days) (95% C.I.) ^e | - (-, -) | - (-, -) | - (-, -) | - (-, -) |
| | 25 th , 75 th Percentile | -, - | -, - | -, - | -, - |
| Observed Min, Max ^f | 1, 1059+ | 12, 762+ | 3, 720+ | 11, 588+ | |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (Presence or history of brain metastases: Yes/No and ECOG performance status: 0/1) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.

c. Two-sided p-value calculated from Cox proportional hazards model.

d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and geographic region.

e. Calculated using the complementary log-log transformation method (Collett, 1994). f. '+' means the observed time is from censored subjects.

Data Snapshot: 14OCT2019, Data Cutoff Date: 04SEP2019

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_1753\v01\outputs\tlfs\pgms\t-ae-km-socpt-subgrp.sas Output: t-ae-km-socpt-sub-2-reg-safs.rtf (17JUL20:17:19)

Data: adsl, adae, adttesaf

Seattle Genetics Protocol ONT-380-206

Table 2.6.3 Summary of Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Geographic Region - Time-to-Event Analysis Safety Analysis Set

| | | North America | | Rest of World | |
|---------------------------------------|--|------------------------|------------------------|------------------------|-----------------------|
| System Organ Class/ Preferred Term | Parameters | Tuc+Cap+Tra (N=241) | Pbo+Cap+Tra (N=119) | Tuc+Cap+Tra (N=163) | Pbo+Cap+Tra (N=78) |
| Renal And Urinary Disorders (SOC) | Number of Subjects With at Least One Event, n (%) | 25 (10.4) | 6 (5.0) | 15 (9.2) | 3 (3.8) |
| | Number of Censored Subjects, n (%) | 216 (89.6) | 113 (95.0) | 148 (90.8) | 75 (96.2) |
| | Stratified Hazard Ratio ^{a, b} (95% C.I.) | | 2.040 (0.835, 4.983) | | 2.266 (0.653, 7.859) |
| | P-value ^{b, c} | | 0.11781 | | 0.19728 |
| | Interaction Test P-value ^d | | | 0.89554 | |
| | Median Time to Onset of the First Event (Days) (95% C.I.) ^e | - (-, -) | - (529.0, -) | - (-, -) | - (-, -) |
| | 25 th , 75 th Percentile | -, - | 529.0, - | -, - | -, - |
| Observed Min, Max ^f | 2, 1070+ | 18, 762+ | 4, 720+ | 1, 588+ | |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.
 b. Computed using stratification factors (Presence or history of brain metastases: Yes/No and ECOG performance status: 0/1) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.
 c. Two-sided p-value calculated from Cox proportional hazards model.
 d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and geographic region.
 e. Calculated using the complementary log-log transformation method (Collett, 1994). f. '+' means the observed time is from censored subjects.
 Data Snapshot: 14OCT2019, Data Cutoff Date: 04SEP2019
 Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_1753\v01\outputs\tlfs\pgms\t-ae-km-socpt-subgrp.sas Output: t-ae-km-socpt-sub-2-reg-safs.rtf (17JUL20:17:19)
 Data: adsl, adae, adttesaf

Seattle Genetics Protocol ONT-380-206

Table 2.6.3 Summary of Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Geographic Region - Time-to-Event Analysis Safety Analysis Set

| System Organ Class/ Preferred Term | Parameters | North America | | Rest of World | |
|---------------------------------------|--|------------------------|------------------------|------------------------|-----------------------|
| | | Tuc+Cap+Tra (N=241) | Pbo+Cap+Tra (N=119) | Tuc+Cap+Tra (N=163) | Pbo+Cap+Tra (N=78) |
| Epistaxis (PT) | Number of Subjects With at Least One Event, n (%) | 29 (12.0) | 6 (5.0) | 18 (11.0) | 4 (5.1) |
| | Number of Censored Subjects, n (%) | 212 (88.0) | 113 (95.0) | 145 (89.0) | 74 (94.9) |
| | Stratified Hazard Ratio ^{a, b} (95% C.I.) | 2.249 (0.931, 5.435) | | 2.282 (0.769, 6.767) | |
| | P-value ^{b, c} | 0.07173 | | 0.13692 | |
| | Interaction Test P-value ^d | 0.98715 | | | |
| | Median Time to Onset of the First Event (Days) (95% C.I.) ^e | - (-, -) | - (-, -) | - (-, -) | - (-, -) |
| | 25 th , 75 th Percentile | -, - | -, - | -, - | -, - |
| | Observed Min, Max ^f | 2, 1059+ | 5, 762+ | 1, 720+ | 3, 588+ |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (Presence or history of brain metastases: Yes/No and ECOG performance status: 0/1) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.

c. Two-sided p-value calculated from Cox proportional hazards model.

d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and geographic region.

e. Calculated using the complementary log-log transformation method (Collett, 1994). f. '+' means the observed time is from censored subjects.

Data Snapshot: 14OCT2019, Data Cutoff Date: 04SEP2019

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_1753\v01\outputs\tlfs\pgms\t-ae-km-socpt-subgrp.sas Output: t-ae-km-socpt-sub-2-reg-safs.rtf (17JUL20:17:19)

Data: adsl, adae, adttesaf

Seattle Genetics Protocol ONT-380-206

Table 2.6.3 Summary of Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Geographic Region - Time-to-Event Analysis Safety Analysis Set

| System Organ Class/ Preferred Term | Parameters | North America | | Rest of World | |
|---------------------------------------|--|------------------------|------------------------|------------------------|-----------------------|
| | | Tuc+Cap+Tra (N=241) | Pbo+Cap+Tra (N=119) | Tuc+Cap+Tra (N=163) | Pbo+Cap+Tra (N=78) |
| Pleural Effusion (PT) | Number of Subjects With at Least One Event, n (%) | 10 (4.1) | 7 (5.9) | 0 | 4 (5.1) |
| | Number of Censored Subjects, n (%) | 231 (95.9) | 112 (94.1) | 163 (100) | 74 (94.9) |
| | Stratified Hazard Ratio ^{a, b} (95% C.I.) | 0.553 (0.202, 1.511) | | 0.000 (0.000, -) | |
| | P-value ^{b, c} | 0.24776 | | 0.99524 | |
| | Interaction Test P-value ^d | 0.99104 | | | |
| | Median Time to Onset of the First Event (Days) (95% C.I.) ^e | - (942.0, -) | - (-, -) | - (-, -) | - (-, -) |
| | 25 th , 75 th Percentile | 942.0, - | -, - | -, - | -, - |
| Observed Min, Max ^f | 4+, 1070+ | 13, 762+ | 6+, 720+ | 6, 588+ | |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (Presence or history of brain metastases: Yes/No and ECOG performance status: 0/1) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.

c. Two-sided p-value calculated from Cox proportional hazards model.

d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and geographic region.

e. Calculated using the complementary log-log transformation method (Collett, 1994). f. '+' means the observed time is from censored subjects.

Data Snapshot: 14OCT2019, Data Cutoff Date: 04SEP2019

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Data: adsl, adae, adttesaf

Seattle Genetics Protocol ONT-380-206**Table 2.6.3 Summary of Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Geographic Region - Time-to-Event Analysis Safety Analysis Set**

| System Organ Class/ Preferred Term | Parameters | North America | | Rest of World | |
|--|---|-------------------------|------------------------|-------------------------|-----------------------|
| | | Tuc+Cap+Tra (N=241) | Pbo+Cap+Tra (N=119) | Tuc+Cap+Tra (N=163) | Pbo+Cap+Tra (N=78) |
| Palmar-Plantar Erythrodysesthesia Syndrome (PT) | Number of Subjects With at Least One Event, n (%) | 161 (66.8) | 65 (54.6) | 95 (58.3) | 39 (50.0) |
| | Number of Censored Subjects, n (%) | 80 (33.2) | 54 (45.4) | 68 (41.7) | 39 (50.0) |
| | Stratified Hazard Ratio ^{a, b} (95% C.I.) | 1.329 (0.995, 1.777) | | 1.205 (0.825, 1.759) | |
| | P-value ^{b, c} | 0.05427 | | 0.33572 | |
| | Interaction Test P-value ^d | 0.81633 | | | |
| | Median Time to Onset of the First Event (Days) (95% C.I.) ^e | 56.0 (43.0, 66.0) | 84.0 (63.0, 141.0) | 85.0 (56.0, 148.0) | 127.0 (65.0, -) |
| | 25 th , 75 th Percentile | 29.0, 324.0 | 33.0, - | 26.0, - | 34.0, - |
| Observed Min, Max ^f | 3, 648 | 1, 407+ | 1, 605+ | 1, 409+ | |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (Presence or history of brain metastases: Yes/No and ECOG performance status: 0/1) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.

c. Two-sided p-value calculated from Cox proportional hazards model.

d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and geographic region.

e. Calculated using the complementary log-log transformation method (Collett, 1994). f. '+' means the observed time is from censored subjects.

Data Snapshot: 14OCT2019, Data Cutoff Date: 04SEP2019

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_1753\v01\outputs\tlfs\pgms\t-ae-km-socpt-subgrp.sas Output: t-ae-km-socpt-sub-2-reg-safs.rtf (17JUL20:17:19)

Data: adsl, adae, adttesaf

Seattle Genetics Protocol ONT-380-206**Table 2.6.4 Summary of Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Baseline ECOG Score - Time-to-Event Analysis
Safety Analysis Set**

| System Organ Class/ Preferred Term | Parameters | ECOG=0 | | ECOG=1 | |
|---------------------------------------|--|------------------------|-----------------------|------------------------|------------------------|
| | | Tuc+Cap+Tra (N=203) | Pbo+Cap+Tra (N=91) | Tuc+Cap+Tra (N=201) | Pbo+Cap+Tra (N=106) |
| Anaemia (PT) | Number of Subjects With at Least One Event, n (%) | 36 (17.7) | 7 (7.7) | 44 (21.9) | 16 (15.1) |
| | Number of Censored Subjects, n (%) | 167 (82.3) | 84 (92.3) | 157 (78.1) | 90 (84.9) |
| | Stratified Hazard Ratio ^{a, b} (95% C.I.) | 2.126 (0.941, 4.802) | | 1.460 (0.823, 2.591) | |
| | P-value ^{b, c} | 0.06960 | | 0.19604 | |
| | Interaction Test P-value ^d | | | 0.34895 | |
| | Median Time to Onset of the First Event (Days) (95% C.I.) ^e | 924.0 (924.0, -) | - (-, -) | - (-, -) | - (-, -) |
| | 25 th , 75 th Percentile | 472.0, - | -, - | -, - | -, - |
| | Observed Min, Max ^f | 1, 1059+ | 12, 588+ | 1, 1070+ | 12, 762+ |

Page 1 of 17

a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (Presence or history of brain metastases: Yes/No and Region of world: North America /Rest of World) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.

c. Two-sided p-value calculated from Cox proportional hazards model.

d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and baseline ECOG score.

e. Calculated using the complementary log-log transformation method (Collett, 1994). f. '+' means the observed time is from censored subjects.

Data Snapshot: 14OCT2019, Data Cutoff Date: 04SEP2019

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_1753\v01\outputs\tlfs\pgms\t-ae-km-socpt-subgrp.sas Output: t-ae-km-socpt-sub-3-ecog-safs.rtf (17JUL20:17:19)

Data: adsl, adae, adttesaf

Seattle Genetics Protocol ONT-380-206**Table 2.6.4 Summary of Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Baseline ECOG Score - Time-to-Event Analysis Safety Analysis Set**

| System Organ Class/ Preferred Term | Parameters | ECOG=0 | | ECOG=1 | |
|---------------------------------------|--|------------------------|-----------------------|------------------------|------------------------|
| | | Tuc+Cap+Tra (N=203) | Pbo+Cap+Tra (N=91) | Tuc+Cap+Tra (N=201) | Pbo+Cap+Tra (N=106) |
| Investigations (SOC) | Number of Subjects With at Least One Event, n (%) | 120 (59.1) | 35 (38.5) | 121 (60.2) | 36 (34.0) |
| | Number of Censored Subjects, n (%) | 83 (40.9) | 56 (61.5) | 80 (39.8) | 70 (66.0) |
| | Stratified Hazard Ratio ^{a, b} (95% C.I.) | 1.729 (1.185, 2.523) | | 2.013 (1.384, 2.926) | |
| | P-value ^{b, c} | 0.00448 | | 0.00025 | |
| | Interaction Test P-value ^d | 0.56882 | | | |
| | Median Time to Onset of the First Event (Days) (95% C.I.) ^e | 88.0 (45.0, 168.0) | - (200.0, -) | 84.0 (44.0, 152.0) | 283.0 (231.0, -) |
| | 25 th , 75 th Percentile | 28.0, - | 51.0, - | 22.0, - | 85.0, - |
| Observed Min, Max ^f | 4+, 637+ | 1, 478+ | 1, 891+ | 6, 393+ | |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (Presence or history of brain metastases: Yes/No and Region of world: North America /Rest of World) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.

c. Two-sided p-value calculated from Cox proportional hazards model.

d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and baseline ECOG score.

e. Calculated using the complementary log-log transformation method (Collett, 1994). f. '+' means the observed time is from censored subjects.

Data Snapshot: 14OCT2019, Data Cutoff Date: 04SEP2019

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_1753\v01\outputs\tlfs\pgms\t-ae-km-socpt-subgrp.sas Output: t-ae-km-socpt-sub-3-ecog-safs.rtf (17JUL20:17:19)

Data: adsl, adae, adttesaf

Seattle Genetics Protocol ONT-380-206**Table 2.6.4 Summary of Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Baseline ECOG Score - Time-to-Event Analysis Safety Analysis Set**

| System Organ Class/ Preferred Term | Parameters | ECOG=0 | | ECOG=1 | |
|---|--|------------------------|-----------------------|------------------------|------------------------|
| | | Tuc+Cap+Tra (N=203) | Pbo+Cap+Tra (N=91) | Tuc+Cap+Tra (N=201) | Pbo+Cap+Tra (N=106) |
| Aspartate Aminotransferase Increased (PT) | Number of Subjects With at Least One Event, n (%) | 46 (22.7) | 8 (8.8) | 40 (19.9) | 14 (13.2) |
| | Number of Censored Subjects, n (%) | 157 (77.3) | 83 (91.2) | 161 (80.1) | 92 (86.8) |
| | Stratified Hazard Ratio ^{a, b} (95% C.I.) | 2.670 (1.259, 5.660) | | 1.478 (0.803, 2.719) | |
| | P-value ^{b, c} | 0.01044 | | 0.20978 | |
| | Interaction Test P-value ^d | 0.22802 | | | |
| | Median Time to Onset of the First Event (Days) (95% C.I.) ^e | - (-, -) | - (-, -) | - (-, -) | - (335.0, -) |
| | 25 th , 75 th Percentile | 358.0, - | -, - | -, - | 335.0, - |
| | Observed Min, Max ^f | 4+, 988+ | 1, 588+ | 6+, 1070+ | 11, 762+ |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (Presence or history of brain metastases: Yes/No and Region of world: North America /Rest of World) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.

c. Two-sided p-value calculated from Cox proportional hazards model.

d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and baseline ECOG score.

e. Calculated using the complementary log-log transformation method (Collett, 1994). f. '+' means the observed time is from censored subjects.

Data Snapshot: 14OCT2019, Data Cutoff Date: 04SEP2019

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_1753\v01\outputs\tlfs\pgms\t-ae-km-socpt-subgrp.sas Output: t-ae-km-socpt-sub-3-ecog-safs.rtf (17JUL20:17:19)

Data: adsl, adae, adttesaf

Seattle Genetics Protocol ONT-380-206**Table 2.6.4 Summary of Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Baseline ECOG Score - Time-to-Event Analysis Safety Analysis Set**

| System Organ Class/ Preferred Term | Parameters | ECOG=0 | | ECOG=1 | |
|---|--|------------------------|-----------------------|------------------------|------------------------|
| | | Tuc+Cap+Tra (N=203) | Pbo+Cap+Tra (N=91) | Tuc+Cap+Tra (N=201) | Pbo+Cap+Tra (N=106) |
| Alanine Aminotransferase Increased (PT) | Number of Subjects With at Least One Event, n (%) | 47 (23.2) | 9 (9.9) | 34 (16.9) | 4 (3.8) |
| | Number of Censored Subjects, n (%) | 156 (76.8) | 82 (90.1) | 167 (83.1) | 102 (96.2) |
| | Stratified Hazard Ratio ^{a, b} (95% C.I.) | 2.409 (1.178, 4.926) | | 4.537 (1.607, 12.811) | |
| | P-value ^{b, c} | 0.01596 | | 0.00430 | |
| | Interaction Test P-value ^d | 0.31986 | | | |
| | Median Time to Onset of the First Event (Days) (95% C.I.) ^e | - (-, -) | - (-, -) | - (-, -) | - (357.0, -) |
| | 25 th , 75 th Percentile | 356.0, - | -, - | -, - | -, - |
| Observed Min, Max ^f | 4+, 988+ | 21, 588+ | 6+, 1070+ | 14, 762+ | |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (Presence or history of brain metastases: Yes/No and Region of world: North America /Rest of World) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.

c. Two-sided p-value calculated from Cox proportional hazards model.

d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and baseline ECOG score.

e. Calculated using the complementary log-log transformation method (Collett, 1994). f. '+' means the observed time is from censored subjects.

Data Snapshot: 14OCT2019, Data Cutoff Date: 04SEP2019

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_1753\v01\outputs\tlfs\pgms\t-ae-km-socpt-subgrp.sas Output: t-ae-km-socpt-sub-3-ecog-safs.rtf (17JUL20:17:19)

Data: adsl, adae, adttesaf

Seattle Genetics Protocol ONT-380-206**Table 2.6.4 Summary of Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Baseline ECOG Score - Time-to-Event Analysis Safety Analysis Set**

| System Organ Class/ Preferred Term | Parameters | ECOG=0 | | ECOG=1 | |
|---------------------------------------|--|------------------------|-----------------------|------------------------|------------------------|
| | | Tuc+Cap+Tra (N=203) | Pbo+Cap+Tra (N=91) | Tuc+Cap+Tra (N=201) | Pbo+Cap+Tra (N=106) |
| Blood Bilirubin Increased (PT) | Number of Subjects With at Least One Event, n (%) | 40 (19.7) | 7 (7.7) | 35 (17.4) | 13 (12.3) |
| | Number of Censored Subjects, n (%) | 163 (80.3) | 84 (92.3) | 166 (82.6) | 93 (87.7) |
| | Stratified Hazard Ratio ^{a, b} (95% C.I.) | 2.633 (1.179, 5.881) | | 1.385 (0.731, 2.624) | |
| | P-value ^{b, c} | 0.01822 | | 0.31753 | |
| | Interaction Test P-value ^d | 0.18762 | | | |
| | Median Time to Onset of the First Event (Days) (95% C.I.) ^e | - (-, -) | - (-, -) | - (-, -) | - (-, -) |
| | 25 th , 75 th Percentile | 279.0, - | -, - | -, - | -, - |
| | Observed Min, Max ^f | 4+, 988+ | 7, 588+ | 6+, 1070+ | 6, 762+ |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (Presence or history of brain metastases: Yes/No and Region of world: North America /Rest of World) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.

c. Two-sided p-value calculated from Cox proportional hazards model.

d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and baseline ECOG score.

e. Calculated using the complementary log-log transformation method (Collett, 1994). f. '+' means the observed time is from censored subjects.

Data Snapshot: 14OCT2019, Data Cutoff Date: 04SEP2019

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_1753\v01\outputs\tlfs\pgms\t-ae-km-socpt-subgrp.sas Output: t-ae-km-socpt-sub-3-ecog-safs.rtf (17JUL20:17:19)

Data: adsl, adae, adttesaf

Seattle Genetics Protocol ONT-380-206

Table 2.6.4 Summary of Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Baseline ECOG Score - Time-to-Event Analysis Safety Analysis Set

| System Organ Class/ Preferred Term | Parameters | ECOG=0 | | ECOG=1 | |
|---------------------------------------|--|------------------------|-----------------------|------------------------|------------------------|
| | | Tuc+Cap+Tra (N=203) | Pbo+Cap+Tra (N=91) | Tuc+Cap+Tra (N=201) | Pbo+Cap+Tra (N=106) |
| Blood Creatinine Increased (PT) | Number of Subjects With at Least One Event, n (%) | 37 (18.2) | 2 (2.2) | 19 (9.5) | 1 (0.9) |
| | Number of Censored Subjects, n (%) | 166 (81.8) | 89 (97.8) | 182 (90.5) | 105 (99.1) |
| | Stratified Hazard Ratio ^{a, b} (95% C.I.) | 8.345 (2.007, 34.705) | | 9.941 (1.329, 74.348) | |
| | P-value ^{b, c} | 0.00353 | | 0.02528 | |
| | Interaction Test P-value ^d | 0.90521 | | | |
| | Median Time to Onset of the First Event (Days) (95% C.I.) ^e | - (747.0, -) | - (-, -) | - (-, -) | - (356.0, -) |
| | 25 th , 75 th Percentile | 610.0, - | -, - | -, - | -, - |
| Observed Min, Max ^f | 4+, 988+ | 13, 588+ | 6+, 1070+ | 26+, 762+ | |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (Presence or history of brain metastases: Yes/No and Region of world: North America /Rest of World) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.

c. Two-sided p-value calculated from Cox proportional hazards model.

d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and baseline ECOG score.

e. Calculated using the complementary log-log transformation method (Collett, 1994). f. '+' means the observed time is from censored subjects.

Data Snapshot: 14OCT2019, Data Cutoff Date: 04SEP2019

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_1753\v01\outputs\tlfs\pgms\t-ae-km-socpt-subgrp.sas Output: t-ae-km-socpt-sub-3-ecog-safs.rtf (17JUL20:17:19)

Data: adsl, adae, adttesaf

Seattle Genetics Protocol ONT-380-206**Table 2.6.4 Summary of Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Baseline ECOG Score - Time-to-Event Analysis
Safety Analysis Set**

| System Organ Class/ Preferred Term | Parameters | ECOG=0 | | ECOG=1 | |
|---------------------------------------|--|------------------------|-----------------------|------------------------|------------------------|
| | | Tuc+Cap+Tra (N=203) | Pbo+Cap+Tra (N=91) | Tuc+Cap+Tra (N=201) | Pbo+Cap+Tra (N=106) |
| Weight Decreased (PT) | Number of Subjects With at Least One Event, n (%) | 19 (9.4) | 3 (3.3) | 35 (17.4) | 8 (7.5) |
| | Number of Censored Subjects, n (%) | 184 (90.6) | 88 (96.7) | 166 (82.6) | 98 (92.5) |
| | Stratified Hazard Ratio ^{a, b} (95% C.I.) | 2.865 (0.845, 9.717) | | 2.195 (1.015, 4.745) | |
| | P-value ^{b, c} | 0.09120 | | 0.04567 | |
| | Interaction Test P-value ^d | 0.68386 | | | |
| | Median Time to Onset of the First Event (Days) (95% C.I.) ^e | - (-, -) | - (-, -) | - (-, -) | - (-, -) |
| | 25 th , 75 th Percentile | -, - | -, - | -, - | -, - |
| | Observed Min, Max ^f | 4+, 1059+ | 9, 588+ | 6, 945+ | 22, 762+ |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (Presence or history of brain metastases: Yes/No and Region of world: North America /Rest of World) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.

c. Two-sided p-value calculated from Cox proportional hazards model.

d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and baseline ECOG score.

e. Calculated using the complementary log-log transformation method (Collett, 1994). f. '+' means the observed time is from censored subjects.

Data Snapshot: 14OCT2019, Data Cutoff Date: 04SEP2019

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_1753\v01\outputs\tlfs\pgms\t-ae-km-socpt-subgrp.sas Output: t-ae-km-socpt-sub-3-ecog-safs.rtf (17JUL20:17:19)

Data: adsl, adae, adttesaf

Seattle Genetics Protocol ONT-380-206**Table 2.6.4 Summary of Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Baseline ECOG Score - Time-to-Event Analysis Safety Analysis Set**

| System Organ Class/ Preferred Term | Parameters | ECOG=0 | | ECOG=1 | |
|--|---|-------------------------|-----------------------|-------------------------|------------------------|
| | | Tuc+Cap+Tra (N=203) | Pbo+Cap+Tra (N=91) | Tuc+Cap+Tra (N=201) | Pbo+Cap+Tra (N=106) |
| Metabolism And Nutrition Disorders (SOC) | Number of Subjects With at Least One Event, n (%) | 96 (47.3) | 27 (29.7) | 108 (53.7) | 44 (41.5) |
| | Number of Censored Subjects, n (%) | 107 (52.7) | 64 (70.3) | 93 (46.3) | 62 (58.5) |
| | Stratified Hazard Ratio ^{a, b} (95% C.I.) | 1.753 (1.142, 2.691) | | 1.366 (0.959, 1.945) | |
| | P-value ^{b, c} | 0.01020 | | 0.08405 | |
| | Interaction Test P-value ^d | 0.42906 | | | |
| | Median Time to Onset of the First Event (Days) (95% C.I.) ^e | 365.0 (113.0, -) | - (-, -) | 127.0 (69.0, 401.0) | 281.0 (147.0, -) |
| | 25 th , 75 th Percentile | 35.0, - | 102.0, - | 22.0, 595.0 | 42.0, - |
| Observed Min, Max ^f | 1, 863+ | 4, 588+ | 1, 694+ | 1, 762+ | |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (Presence or history of brain metastases: Yes/No and Region of world: North America /Rest of World) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.

c. Two-sided p-value calculated from Cox proportional hazards model.

d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and baseline ECOG score.

e. Calculated using the complementary log-log transformation method (Collett, 1994). f. '+' means the observed time is from censored subjects.

Data Snapshot: 14OCT2019, Data Cutoff Date: 04SEP2019

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_1753\v01\outputs\tlfs\pgms\t-ae-km-socpt-subgrp.sas Output: t-ae-km-socpt-sub-3-ecog-safs.rtf (17JUL20:17:19)

Data: adsl, adae, adttesaf

Seattle Genetics Protocol ONT-380-206**Table 2.6.4 Summary of Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Baseline ECOG Score - Time-to-Event Analysis Safety Analysis Set**

| System Organ Class/ Preferred Term | Parameters | ECOG=0 | | ECOG=1 | |
|---------------------------------------|--|------------------------|-----------------------|------------------------|------------------------|
| | | Tuc+Cap+Tra (N=203) | Pbo+Cap+Tra (N=91) | Tuc+Cap+Tra (N=201) | Pbo+Cap+Tra (N=106) |
| Hyperglycaemia (PT) | Number of Subjects With at Least One Event, n (%) | 8 (3.9) | 1 (1.1) | 15 (7.5) | 2 (1.9) |
| | Number of Censored Subjects, n (%) | 195 (96.1) | 90 (98.9) | 186 (92.5) | 104 (98.1) |
| | Stratified Hazard Ratio ^{a, b} (95% C.I.) | 3.165 (0.389, 25.744) | | 3.686 (0.843, 16.127) | |
| | P-value ^{b, c} | 0.28129 | | 0.08320 | |
| | Interaction Test P-value ^d | 0.92200 | | | |
| | Median Time to Onset of the First Event (Days) (95% C.I.) ^e | - (-, -) | - (-, -) | - (-, -) | - (-, -) |
| | 25 th , 75 th Percentile | -, - | -, - | -, - | -, - |
| Observed Min, Max ^f | 4+, 1059+ | 12, 588+ | 2, 1070+ | 13, 762+ | |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (Presence or history of brain metastases: Yes/No and Region of world: North America /Rest of World) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.

c. Two-sided p-value calculated from Cox proportional hazards model.

d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and baseline ECOG score.

e. Calculated using the complementary log-log transformation method (Collett, 1994). f. '+' means the observed time is from censored subjects.

Data Snapshot: 14OCT2019, Data Cutoff Date: 04SEP2019

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Data: adsl, adae, adttesaf

Seattle Genetics Protocol ONT-380-206**Table 2.6.4 Summary of Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Baseline ECOG Score - Time-to-Event Analysis Safety Analysis Set**

| System Organ Class/ Preferred Term | Parameters | ECOG=0 | | ECOG=1 | |
|--|---|-------------------------|-------------------------|-------------------------|-------------------------|
| | | Tuc+Cap+Tra (N=203) | Pbo+Cap+Tra (N=91) | Tuc+Cap+Tra (N=201) | Pbo+Cap+Tra (N=106) |
| Musculoskeletal And Connective Tissue Disorders (SOC) | Number of Subjects With at Least One Event, n (%) | 93 (45.8) | 30 (33.0) | 90 (44.8) | 37 (34.9) |
| | Number of Censored Subjects, n (%) | 110 (54.2) | 61 (67.0) | 111 (55.2) | 69 (65.1) |
| | Stratified Hazard Ratio ^{a, b} (95% C.I.) | | 1.509 (0.997, 2.283) | | 1.201 (0.814, 1.773) |
| | P-value ^{b, c} | | 0.05169 | | 0.35543 |
| | Interaction Test P-value ^d | | | 0.59273 | |
| | Median Time to Onset of the First Event (Days) (95% C.I.) ^e | 257.0 (207.0, 721.0) | - (286.0, -) | 255.0 (155.0, 392.0) | 275.0 (145.0, -) |
| | 25 th , 75 th Percentile | 49.0, 787.0 | 102.0, - | 65.0, 609.0 | 106.0, - |
| Observed Min, Max ^f | 1, 849+ | 1, 588+ | 1, 830+ | 1, 760+ | |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (Presence or history of brain metastases: Yes/No and Region of world: North America /Rest of World) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.

c. Two-sided p-value calculated from Cox proportional hazards model.

d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and baseline ECOG score.

e. Calculated using the complementary log-log transformation method (Collett, 1994). f. '+' means the observed time is from censored subjects.

Data Snapshot: 14OCT2019, Data Cutoff Date: 04SEP2019

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Data: adsl, adae, adttesaf

Seattle Genetics Protocol ONT-380-206**Table 2.6.4 Summary of Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Baseline ECOG Score - Time-to-Event Analysis
Safety Analysis Set**

| System Organ Class/ Preferred Term | Parameters | ECOG=0 | | ECOG=1 | |
|---------------------------------------|--|------------------------|-----------------------|------------------------|------------------------|
| | | Tuc+Cap+Tra (N=203) | Pbo+Cap+Tra (N=91) | Tuc+Cap+Tra (N=201) | Pbo+Cap+Tra (N=106) |
| Arthralgia (PT) | Number of Subjects With at Least One Event, n (%) | 26 (12.8) | 4 (4.4) | 33 (16.4) | 5 (4.7) |
| | Number of Censored Subjects, n (%) | 177 (87.2) | 87 (95.6) | 168 (83.6) | 101 (95.3) |
| | Stratified Hazard Ratio ^{a, b} (95% C.I.) | 2.546 (0.881, 7.352) | | 3.201 (1.241, 8.256) | |
| | P-value ^{b, c} | 0.08422 | | 0.01611 | |
| | Interaction Test P-value ^d | 0.72803 | | | |
| | Median Time to Onset of the First Event (Days) (95% C.I.) ^e | - (707.0, -) | - (-, -) | - (-, -) | - (-, -) |
| | 25 th , 75 th Percentile | 707.0, - | -, - | 383.0, - | -, - |
| | Observed Min, Max ^f | 1, 988+ | 4, 588+ | 1, 1070+ | 7, 762+ |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (Presence or history of brain metastases: Yes/No and Region of world: North America /Rest of World) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.

c. Two-sided p-value calculated from Cox proportional hazards model.

d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and baseline ECOG score.

e. Calculated using the complementary log-log transformation method (Collett, 1994). f. '+' means the observed time is from censored subjects.

Data Snapshot: 14OCT2019, Data Cutoff Date: 04SEP2019

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Data: adsl, adae, adttesaf

Seattle Genetics Protocol ONT-380-206**Table 2.6.4 Summary of Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Baseline ECOG Score - Time-to-Event Analysis
Safety Analysis Set**

| System Organ Class/ Preferred Term | Parameters | ECOG=0 | | ECOG=1 | |
|---------------------------------------|--|------------------------|-----------------------|------------------------|------------------------|
| | | Tuc+Cap+Tra (N=203) | Pbo+Cap+Tra (N=91) | Tuc+Cap+Tra (N=201) | Pbo+Cap+Tra (N=106) |
| Muscle Spasms (PT) | Number of Subjects With at Least One Event, n (%) | 22 (10.8) | 2 (2.2) | 16 (8.0) | 3 (2.8) |
| | Number of Censored Subjects, n (%) | 181 (89.2) | 89 (97.8) | 185 (92.0) | 103 (97.2) |
| | Stratified Hazard Ratio ^{a, b} (95% C.I.) | 4.471 (1.043, 19.167) | | 2.490 (0.713, 8.703) | |
| | P-value ^{b, c} | 0.04375 | | 0.15293 | |
| | Interaction Test P-value ^d | 0.58527 | | | |
| | Median Time to Onset of the First Event (Days) (95% C.I.) ^e | 966.0 (787.0, -) | - (399.0, -) | - (538.0, -) | - (-, -) |
| | 25 th , 75 th Percentile | 787.0, - | -, - | 538.0, - | -, - |
| Observed Min, Max ^f | 1, 1059+ | 50+, 588+ | 6+, 830+ | 21, 762+ | |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (Presence or history of brain metastases: Yes/No and Region of world: North America /Rest of World) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.

c. Two-sided p-value calculated from Cox proportional hazards model.

d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and baseline ECOG score.

e. Calculated using the complementary log-log transformation method (Collett, 1994). f. '+' means the observed time is from censored subjects.

Data Snapshot: 14OCT2019, Data Cutoff Date: 04SEP2019

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Data: adsl, adae, adttesaf

Seattle Genetics Protocol ONT-380-206**Table 2.6.4 Summary of Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Baseline ECOG Score - Time-to-Event Analysis
Safety Analysis Set**

| System Organ Class/ Preferred Term | Parameters | ECOG=0 | | ECOG=1 | |
|---------------------------------------|--|------------------------|-----------------------|------------------------|------------------------|
| | | Tuc+Cap+Tra (N=203) | Pbo+Cap+Tra (N=91) | Tuc+Cap+Tra (N=201) | Pbo+Cap+Tra (N=106) |
| Dysgeusia (PT) | Number of Subjects With at Least One Event, n (%) | 14 (6.9) | 3 (3.3) | 16 (8.0) | 2 (1.9) |
| | Number of Censored Subjects, n (%) | 189 (93.1) | 88 (96.7) | 185 (92.0) | 104 (98.1) |
| | Stratified Hazard Ratio ^{a, b} (95% C.I.) | 2.033 (0.580, 7.122) | | 3.727 (0.849, 16.357) | |
| | P-value ^{b, c} | 0.26730 | | 0.08132 | |
| | Interaction Test P-value ^d | 0.48484 | | | |
| | Median Time to Onset of the First Event (Days) (95% C.I.) ^e | - (-, -) | - (-, -) | - (-, -) | - (-, -) |
| | 25 th , 75 th Percentile | -, - | -, - | -, - | -, - |
| Observed Min, Max ^f | 2, 1059+ | 12, 588+ | 1, 945+ | 11, 762+ | |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (Presence or history of brain metastases: Yes/No and Region of world: North America /Rest of World) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.

c. Two-sided p-value calculated from Cox proportional hazards model.

d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and baseline ECOG score.

e. Calculated using the complementary log-log transformation method (Collett, 1994). f. '+' means the observed time is from censored subjects.

Data Snapshot: 14OCT2019, Data Cutoff Date: 04SEP2019

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Data: adsl, adae, adttesaf

Seattle Genetics Protocol ONT-380-206**Table 2.6.4 Summary of Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Baseline ECOG Score - Time-to-Event Analysis Safety Analysis Set**

| | | ECOG=0 | | ECOG=1 | |
|---------------------------------------|--|------------------------|-----------------------|------------------------|------------------------|
| System Organ Class/ Preferred Term | Parameters | Tuc+Cap+Tra (N=203) | Pbo+Cap+Tra (N=91) | Tuc+Cap+Tra (N=201) | Pbo+Cap+Tra (N=106) |
| Renal And Urinary Disorders (SOC) | Number of Subjects With at Least One Event, n (%) | 21 (10.3) | 1 (1.1) | 19 (9.5) | 8 (7.5) |
| | Number of Censored Subjects, n (%) | 182 (89.7) | 90 (98.9) | 182 (90.5) | 98 (92.5) |
| | Stratified Hazard Ratio ^{a, b} (95% C.I.) | | 9.191 (1.235, 68.394) | | 1.179 (0.513, 2.710) |
| | P-value ^{b, c} | | 0.03029 | | 0.69773 |
| | Interaction Test P-value ^d | | | 0.06469 | |
| | Median Time to Onset of the First Event (Days) (95% C.I.) ^e | - (-, -) | - (-, -) | - (-, -) | - (529.0, -) |
| | 25 th , 75 th Percentile | -, - | -, - | -, - | 529.0, - |
| Observed Min, Max ^f | 4, 988+ | 20, 588+ | 2, 1070+ | 1, 762+ | |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (Presence or history of brain metastases: Yes/No and Region of world: North America /Rest of World) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.

c. Two-sided p-value calculated from Cox proportional hazards model.

d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and baseline ECOG score.

e. Calculated using the complementary log-log transformation method (Collett, 1994). f. '+' means the observed time is from censored subjects.

Data Snapshot: 14OCT2019, Data Cutoff Date: 04SEP2019

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_1753\v01\outputs\tlfs\pgms\t-ae-km-socpt-subgrp.sas Output: t-ae-km-socpt-sub-3-ecog-safs.rtf (17JUL20:17:19)

Data: adsl, adae, adttesaf

Seattle Genetics Protocol ONT-380-206**Table 2.6.4 Summary of Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Baseline ECOG Score - Time-to-Event Analysis Safety Analysis Set**

| System Organ Class/ Preferred Term | Parameters | ECOG=0 | | ECOG=1 | |
|---------------------------------------|--|------------------------|-----------------------|------------------------|------------------------|
| | | Tuc+Cap+Tra (N=203) | Pbo+Cap+Tra (N=91) | Tuc+Cap+Tra (N=201) | Pbo+Cap+Tra (N=106) |
| Epistaxis (PT) | Number of Subjects With at Least One Event, n (%) | 26 (12.8) | 3 (3.3) | 21 (10.4) | 7 (6.6) |
| | Number of Censored Subjects, n (%) | 177 (87.2) | 88 (96.7) | 180 (89.6) | 99 (93.4) |
| | Stratified Hazard Ratio ^{a, b} (95% C.I.) | 3.896 (1.175, 12.915) | | 1.557 (0.660, 3.673) | |
| | P-value ^{b, c} | 0.02616 | | 0.31180 | |
| | Interaction Test P-value ^d | 0.22054 | | | |
| | Median Time to Onset of the First Event (Days) (95% C.I.) ^e | - (-, -) | - (-, -) | - (-, -) | - (-, -) |
| | 25 th , 75 th Percentile | -, - | -, - | -, - | -, - |
| | Observed Min, Max ^f | 1, 1059+ | 3, 588+ | 1, 945+ | 5, 762+ |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (Presence or history of brain metastases: Yes/No and Region of world: North America /Rest of World) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.

c. Two-sided p-value calculated from Cox proportional hazards model.

d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and baseline ECOG score.

e. Calculated using the complementary log-log transformation method (Collett, 1994). f. '+' means the observed time is from censored subjects.

Data Snapshot: 14OCT2019, Data Cutoff Date: 04SEP2019

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_1753\v01\outputs\tlfs\pgms\t-ae-km-socpt-subgrp.sas Output: t-ae-km-socpt-sub-3-ecog-safs.rtf (17JUL20:17:19)

Data: adsl, adae, adttesaf

Seattle Genetics Protocol ONT-380-206**Table 2.6.4 Summary of Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Baseline ECOG Score - Time-to-Event Analysis Safety Analysis Set**

| System Organ Class/ Preferred Term | Parameters | ECOG=0 | | ECOG=1 | |
|---------------------------------------|--|------------------------|-----------------------|------------------------|------------------------|
| | | Tuc+Cap+Tra (N=203) | Pbo+Cap+Tra (N=91) | Tuc+Cap+Tra (N=201) | Pbo+Cap+Tra (N=106) |
| Pleural Effusion (PT) | Number of Subjects With at Least One Event, n (%) | 3 (1.5) | 6 (6.6) | 7 (3.5) | 5 (4.7) |
| | Number of Censored Subjects, n (%) | 200 (98.5) | 85 (93.4) | 194 (96.5) | 101 (95.3) |
| | Stratified Hazard Ratio ^{a, b} (95% C.I.) | 0.217 (0.054, 0.870) | | 0.509 (0.150, 1.727) | |
| | P-value ^{b, c} | 0.03099 | | 0.27879 | |
| | Interaction Test P-value ^d | 0.24660 | | | |
| | Median Time to Onset of the First Event (Days) (95% C.I.) ^e | - (-, -) | - (-, -) | 942.0 (942.0, -) | - (-, -) |
| | 25 th , 75 th Percentile | -, - | -, - | 942.0, - | -, - |
| Observed Min, Max ^f | 4+, 1059+ | 6, 588+ | 6+, 1070+ | 8, 762+ | |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (Presence or history of brain metastases: Yes/No and Region of world: North America /Rest of World) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.

c. Two-sided p-value calculated from Cox proportional hazards model.

d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and baseline ECOG score.

e. Calculated using the complementary log-log transformation method (Collett, 1994). f. '+' means the observed time is from censored subjects.

Data Snapshot: 14OCT2019, Data Cutoff Date: 04SEP2019

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_1753\v01\outputs\tlfs\pgms\t-ae-km-socpt-subgrp.sas Output: t-ae-km-socpt-sub-3-ecog-safs.rtf (17JUL20:17:19)

Data: adsl, adae, adttesaf

Seattle Genetics Protocol ONT-380-206**Table 2.6.4 Summary of Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Baseline ECOG Score - Time-to-Event Analysis Safety Analysis Set**

| System Organ Class/ Preferred Term | Parameters | ECOG=0 | | ECOG=1 | |
|---|--|------------------------|-----------------------|------------------------|------------------------|
| | | Tuc+Cap+Tra (N=203) | Pbo+Cap+Tra (N=91) | Tuc+Cap+Tra (N=201) | Pbo+Cap+Tra (N=106) |
| Palmar-Plantar Erythrodyssaesthesia Syndrome (PT) | Number of Subjects With at Least One Event, n (%) | 135 (66.5) | 53 (58.2) | 121 (60.2) | 51 (48.1) |
| | Number of Censored Subjects, n (%) | 68 (33.5) | 38 (41.8) | 80 (39.8) | 55 (51.9) |
| | Stratified Hazard Ratio ^{a, b} (95% C.I.) | | 1.249 (0.908, 1.719) | | 1.329 (0.954, 1.852) |
| | P-value ^{b, c} | | 0.17205 | | 0.09315 |
| | Interaction Test P-value ^d | | | 0.75345 | |
| | Median Time to Onset of the First Event (Days) (95% C.I.) ^e | 46.0 (36.0, 64.0) | 65.0 (44.0, 149.0) | 84.0 (61.0, 106.0) | 127.0 (72.0, -) |
| | 25 th , 75 th Percentile | 25.0, 648.0 | 32.0, - | 31.0, 337.0 | 35.0, - |
| Observed Min, Max ^f | 1, 648 | 1, 409+ | 3, 602+ | 1, 407+ | |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (Presence or history of brain metastases: Yes/No and Region of world: North America /Rest of World) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.

c. Two-sided p-value calculated from Cox proportional hazards model.

d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and baseline ECOG score.

e. Calculated using the complementary log-log transformation method (Collett, 1994). f. '+' means the observed time is from censored subjects.

Data Snapshot: 14OCT2019, Data Cutoff Date: 04SEP2019

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_1753\v01\outputs\tlfs\pgms\t-ae-km-socpt-subgrp.sas Output: t-ae-km-socpt-sub-3-ecog-safs.rtf (17JUL20:17:19)

Data: adsl, adae, adttesaf

Seattle Genetics Protocol ONT-380-206**Table 2.6.5 Summary of Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Age - Time-to-Event Analysis Safety Analysis Set**

| System Organ Class/ Preferred Term | Parameters | Age < 65 Years | | Age >= 65 Years | |
|---------------------------------------|--|------------------------|------------------------|-----------------------|-----------------------|
| | | Tuc+Cap+Tra (N=322) | Pbo+Cap+Tra (N=164) | Tuc+Cap+Tra (N=82) | Pbo+Cap+Tra (N=33) |
| Anaemia (PT) | Number of Subjects With at Least One Event, n (%) | 59 (18.3) | 19 (11.6) | 21 (25.6) | 4 (12.1) |
| | Number of Censored Subjects, n (%) | 263 (81.7) | 145 (88.4) | 61 (74.4) | 29 (87.9) |
| | Stratified Hazard Ratio ^{a, b} (95% C.I.) | 1.494 (0.888, 2.515) | | 2.206 (0.747, 6.518) | |
| | P-value ^{b, c} | 0.13045 | | 0.15231 | |
| | Interaction Test P-value ^d | 0.51573 | | | |
| | Median Time to Onset of the First Event (Days) (95% C.I.) ^e | - (924.0, -) | - (-, -) | - (472.0, -) | - (-, -) |
| | 25 th , 75 th Percentile | 924.0, - | -, - | 197.0, - | -, - |
| | Observed Min, Max ^f | 1, 1070+ | 12, 762+ | 4+, 945+ | 12, 387+ |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (Presence or history of brain metastases: Yes/No, ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.

c. Two-sided p-value calculated from Cox proportional hazards model.

d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and age.

e. Calculated using the complementary log-log transformation method (Collett, 1994). f. '+' means the observed time is from censored subjects.

Data Snapshot: 14OCT2019, Data Cutoff Date: 04SEP2019

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_1753\v01\outputs\tlfs\pgms\t-ae-km-socpt-subgrp.sas Output: t-ae-km-socpt-sub-4-age-safs.rtf (17JUL20:17:19)

Data: adsl, adae, adttesaf

Seattle Genetics Protocol ONT-380-206**Table 2.6.5 Summary of Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Age - Time-to-Event Analysis Safety Analysis Set**

| System Organ Class/ Preferred Term | Parameters | Age < 65 Years | | Age >= 65 Years | |
|---------------------------------------|--|------------------------|------------------------|-----------------------|-----------------------|
| | | Tuc+Cap+Tra (N=322) | Pbo+Cap+Tra (N=164) | Tuc+Cap+Tra (N=82) | Pbo+Cap+Tra (N=33) |
| Investigations (SOC) | Number of Subjects With at Least One Event, n (%) | 189 (58.7) | 61 (37.2) | 52 (63.4) | 10 (30.3) |
| | Number of Censored Subjects, n (%) | 133 (41.3) | 103 (62.8) | 30 (36.6) | 23 (69.7) |
| | Stratified Hazard Ratio ^{a, b} (95% C.I.) | 1.720 (1.287, 2.300) | | 2.776 (1.351, 5.702) | |
| | P-value ^{b, c} | 0.00025 | | 0.00543 | |
| | Interaction Test P-value ^d | 0.21475 | | | |
| | Median Time to Onset of the First Event (Days) (95% C.I.) ^e | 106.0 (64.0, 152.0) | 317.0 (231.0, -) | 64.0 (42.0, 106.0) | 356.0 (356.0, -) |
| | 25 th , 75 th Percentile | 22.0, - | 62.0, - | 30.0, - | 127.0, - |
| Observed Min, Max ^f | 1, 891+ | 1, 478+ | 4+, 547+ | 9, 409+ | |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (Presence or history of brain metastases: Yes/No, ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.

c. Two-sided p-value calculated from Cox proportional hazards model.

d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and age.

e. Calculated using the complementary log-log transformation method (Collett, 1994). f. '+' means the observed time is from censored subjects.

Data Snapshot: 14OCT2019, Data Cutoff Date: 04SEP2019

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Data: adsl, adae, adttesaf

Seattle Genetics Protocol ONT-380-206**Table 2.6.5 Summary of Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Age - Time-to-Event Analysis Safety Analysis Set**

| System Organ Class/ Preferred Term | Parameters | Age < 65 Years | | Age ≥ 65 Years | |
|---|--|------------------------|------------------------|-----------------------|-----------------------|
| | | Tuc+Cap+Tra (N=322) | Pbo+Cap+Tra (N=164) | Tuc+Cap+Tra (N=82) | Pbo+Cap+Tra (N=33) |
| Aspartate Aminotransferase Increased (PT) | Number of Subjects With at Least One Event, n (%) | 62 (19.3) | 21 (12.8) | 24 (29.3) | 1 (3.0) |
| | Number of Censored Subjects, n (%) | 260 (80.7) | 143 (87.2) | 58 (70.7) | 32 (97.0) |
| | Stratified Hazard Ratio ^{a, b} (95% C.I.) | 1.503 (0.915, 2.467) | | 9.808 (1.317, 73.050) | |
| | P-value ^{b, c} | 0.10753 | | 0.02584 | |
| | Interaction Test P-value ^d | 0.07079 | | | |
| | Median Time to Onset of the First Event (Days) (95% C.I.) ^e | - (-, -) | - (-, -) | - (-, -) | - (-, -) |
| | 25 th , 75 th Percentile | -, - | -, - | 64.0, - | -, - |
| | Observed Min, Max ^f | 6+, 1070+ | 1, 762+ | 4+, 830+ | 14, 409+ |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (Presence or history of brain metastases: Yes/No, ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.

c. Two-sided p-value calculated from Cox proportional hazards model.

d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and age.

e. Calculated using the complementary log-log transformation method (Collett, 1994). f. '+' means the observed time is from censored subjects.

Data Snapshot: 14OCT2019, Data Cutoff Date: 04SEP2019

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Data: adsl, адае, адттеsaf

Seattle Genetics Protocol ONT-380-206**Table 2.6.5 Summary of Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Age - Time-to-Event Analysis Safety Analysis Set**

| System Organ Class/ Preferred Term | Parameters | Age < 65 Years | | Age ≥ 65 Years | |
|---|---|-------------------------|------------------------|-----------------------------|-----------------------|
| | | Tuc+Cap+Tra (N=322) | Pbo+Cap+Tra (N=164) | Tuc+Cap+Tra (N=82) | Pbo+Cap+Tra (N=33) |
| Alanine Aminotransferase Increased (PT) | Number of Subjects With at Least One Event, n (%) | 59 (18.3) | 13 (7.9) | 22 (26.8) | 0 |
| | Number of Censored Subjects, n (%) | 263 (81.7) | 151 (92.1) | 60 (73.2) | 33 (100) |
| | Stratified Hazard Ratio ^{a, b} (95% C.I.) | 2.328 (1.275, 4.252) | | 45715308.35 5 (0.000, -) | |
| | P-value ^{b, c} | 0.00597 | | 0.99357 | |
| | Interaction Test P-value ^d | | | 0.97939 | |
| | Median Time to Onset of the First Event (Days) (95% C.I.) ^e | - (-, -) | - (-, -) | - (-, -) | - (-, -) |
| | 25 th , 75 th Percentile | -, - | -, - | 92.0, - | -, - |
| Observed Min, Max ^f | 6+, 1070+ | 14, 762+ | 4+, 830+ | 31+, 409+ | |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (Presence or history of brain metastases: Yes/No, ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.

c. Two-sided p-value calculated from Cox proportional hazards model.

d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and age.

e. Calculated using the complementary log-log transformation method (Collett, 1994). f. '+' means the observed time is from censored subjects.

Data Snapshot: 14OCT2019, Data Cutoff Date: 04SEP2019

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Table 2.6.5 Summary of Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Age - Time-to-Event Analysis Safety Analysis Set

| System Organ Class/ Preferred Term | Parameters | Age < 65 Years | | Age >= 65 Years | |
|---------------------------------------|--|------------------------|------------------------|-----------------------|-----------------------|
| | | Tuc+Cap+Tra (N=322) | Pbo+Cap+Tra (N=164) | Tuc+Cap+Tra (N=82) | Pbo+Cap+Tra (N=33) |
| Blood Bilirubin Increased (PT) | Number of Subjects With at Least One Event, n (%) | 57 (17.7) | 17 (10.4) | 18 (22.0) | 3 (9.1) |
| | Number of Censored Subjects, n (%) | 265 (82.3) | 147 (89.6) | 64 (78.0) | 30 (90.9) |
| | Stratified Hazard Ratio ^{a, b} (95% C.I.) | 1.659 (0.962, 2.861) | | 2.753 (0.792, 9.570) | |
| | P-value ^{b, c} | 0.06847 | | 0.11114 | |
| | Interaction Test P-value ^d | 0.44457 | | | |
| | Median Time to Onset of the First Event (Days) (95% C.I.) ^e | - (-, -) | - (-, -) | - (-, -) | - (-, -) |
| | 25 th , 75 th Percentile | -, - | -, - | 232.0, - | -, - |
| Observed Min, Max ^f | 6+, 1070+ | 6, 762+ | 4+, 945+ | 14, 409+ | |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (Presence or history of brain metastases: Yes/No, ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.

c. Two-sided p-value calculated from Cox proportional hazards model .

d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and age.

e. Calculated using the complementary log-log transformation method (Collett, 1994). f. '+' means the observed time is from censored subjects.

Data Snapshot: 14OCT2019, Data Cutoff Date: 04SEP2019

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Data: adsl, adae, adttesaf

Seattle Genetics Protocol ONT-380-206**Table 2.6.5 Summary of Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Age - Time-to-Event Analysis Safety Analysis Set**

| System Organ Class/ Preferred Term | Parameters | Age < 65 Years | | Age ≥ 65 Years | |
|---------------------------------------|--|------------------------|-------------------------------|-----------------------|-------------------------|
| | | Tuc+Cap+Tra (N=322) | Pbo+Cap+Tra (N=164) | Tuc+Cap+Tra (N=82) | Pbo+Cap+Tra (N=33) |
| Blood Creatinine Increased (PT) | Number of Subjects With at Least One Event, n (%) | 48 (14.9) | 1 (0.6) | 8 (9.8) | 2 (6.1) |
| | Number of Censored Subjects, n (%) | 274 (85.1) | 163 (99.4) | 74 (90.2) | 31 (93.9) |
| | Stratified Hazard Ratio ^{a, b} (95% C.I.) | | 24.365 (3.360, 176.678) | | 1.531 (0.321, 7.294) |
| | P-value ^{b, c} | | 0.00158 | | 0.59305 |
| | Interaction Test P-value ^d | | | 0.03483 | |
| | Median Time to Onset of the First Event (Days) (95% C.I.) ^e | - (747.0, -) | - (-, -) | - (-, -) | - (356.0, -) |
| | 25 th , 75 th Percentile | 747.0, - | -, - | -, - | 356.0, - |
| Observed Min, Max ^f | 5, 1070+ | 26+, 762+ | 4+, 945+ | 13, 409+ | |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (Presence or history of brain metastases: Yes/No, ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.

c. Two-sided p-value calculated from Cox proportional hazards model.

d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and age.

e. Calculated using the complementary log-log transformation method (Collett, 1994). f. '+' means the observed time is from censored subjects.

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Data: adsl, adae, adttesaf

Seattle Genetics Protocol ONT-380-206**Table 2.6.5 Summary of Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Age - Time-to-Event Analysis Safety Analysis Set**

| System Organ Class/ Preferred Term | Parameters | Age < 65 Years | | Age ≥ 65 Years | |
|---------------------------------------|--|------------------------|------------------------|-----------------------|-----------------------|
| | | Tuc+Cap+Tra (N=322) | Pbo+Cap+Tra (N=164) | Tuc+Cap+Tra (N=82) | Pbo+Cap+Tra (N=33) |
| Weight Decreased (PT) | Number of Subjects With at Least One Event, n (%) | 40 (12.4) | 7 (4.3) | 14 (17.1) | 4 (12.1) |
| | Number of Censored Subjects, n (%) | 282 (87.6) | 157 (95.7) | 68 (82.9) | 29 (87.9) |
| | Stratified Hazard Ratio ^{a, b} (95% C.I.) | 2.835 (1.265, 6.355) | | 1.479 (0.478, 4.571) | |
| | P-value ^{b, c} | 0.01137 | | 0.49716 | |
| | Interaction Test P-value ^d | 0.29827 | | | |
| | Median Time to Onset of the First Event (Days) (95% C.I.) ^e | - (-, -) | - (-, -) | - (-, -) | - (-, -) |
| | 25 th , 75 th Percentile | -, - | -, - | -, - | -, - |
| | Observed Min, Max ^f | 6, 1059+ | 22, 762+ | 4+, 945+ | 9, 409+ |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (Presence or history of brain metastases: Yes/No, ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.

c. Two-sided p-value calculated from Cox proportional hazards model.

d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and age.

e. Calculated using the complementary log-log transformation method (Collett, 1994). f. '+' means the observed time is from censored subjects.

Data Snapshot: 14OCT2019, Data Cutoff Date: 04SEP2019

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Data: adsl, adae, adttesaf

Seattle Genetics Protocol ONT-380-206**Table 2.6.5 Summary of Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Age - Time-to-Event Analysis Safety Analysis Set**

| System Organ Class/ Preferred Term | Parameters | Age < 65 Years | | Age ≥ 65 Years | |
|--|---|-------------------------|-------------------------|-----------------------|-------------------------|
| | | Tuc+Cap+Tra (N=322) | Pbo+Cap+Tra (N=164) | Tuc+Cap+Tra (N=82) | Pbo+Cap+Tra (N=33) |
| Metabolism And Nutrition Disorders (SOC) | Number of Subjects With at Least One Event, n (%) | 155 (48.1) | 55 (33.5) | 49 (59.8) | 16 (48.5) |
| | Number of Censored Subjects, n (%) | 167 (51.9) | 109 (66.5) | 33 (40.2) | 17 (51.5) |
| | Stratified Hazard Ratio ^{a, b} (95% C.I.) | | 1.566 (1.146, 2.139) | | 1.381 (0.748, 2.548) |
| | P-value ^{b, c} | | 0.00484 | | 0.30229 |
| | Interaction Test P-value ^d | | | 0.66359 | |
| | Median Time to Onset of the First Event (Days) (95% C.I.) ^e | 245.0 (131.0, 595.0) | - (335.0, -) | 64.0 (43.0, 127.0) | 127.0 (51.0, -) |
| | 25 th , 75 th Percentile | 24.0, - | 56.0, - | 22.0, - | 33.0, - |
| Observed Min, Max ^f | 1, 863+ | 1, 762+ | 1, 408+ | 9, 387+ | |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (Presence or history of brain metastases: Yes/No, ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.

c. Two-sided p-value calculated from Cox proportional hazards model.

d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and age.

e. Calculated using the complementary log-log transformation method (Collett, 1994). f. '+' means the observed time is from censored subjects.

Data Snapshot: 14OCT2019, Data Cutoff Date: 04SEP2019

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_1753\v01\outputs\tlfs\pgms\t-ae-km-socpt-subgrp.sas Output: t-ae-km-socpt-sub-4-age-safs.rtf (17JUL20:17:19)

Data: adsl, adae, adttesaf

Seattle Genetics Protocol ONT-380-206**Table 2.6.5 Summary of Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Age - Time-to-Event Analysis Safety Analysis Set**

| System Organ Class/ Preferred Term | Parameters | Age < 65 Years | | Age >= 65 Years | |
|---------------------------------------|--|------------------------|------------------------|-----------------------|-----------------------|
| | | Tuc+Cap+Tra (N=322) | Pbo+Cap+Tra (N=164) | Tuc+Cap+Tra (N=82) | Pbo+Cap+Tra (N=33) |
| Hyperglycaemia (PT) | Number of Subjects With at Least One Event, n (%) | 21 (6.5) | 2 (1.2) | 2 (2.4) | 1 (3.0) |
| | Number of Censored Subjects, n (%) | 301 (93.5) | 162 (98.8) | 80 (97.6) | 32 (97.0) |
| | Stratified Hazard Ratio ^{a, b} (95% C.I.) | 5.251 (1.228, 22.450) | | 0.772 (0.069, 8.670) | |
| | P-value ^{b, c} | 0.02527 | | 0.83419 | |
| | Interaction Test P-value ^d | 0.12313 | | | |
| | Median Time to Onset of the First Event (Days) (95% C.I.) ^e | - (-, -) | - (-, -) | - (-, -) | - (-, -) |
| | 25 th , 75 th Percentile Observed Min, Max ^f | -, - 2, 1070+ | -, - 13, 762+ | -, - 4+, 945+ | -, - 12, 409+ |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (Presence or history of brain metastases: Yes/No, ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.

c. Two-sided p-value calculated from Cox proportional hazards model.

d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and age.

e. Calculated using the complementary log-log transformation method (Collett, 1994). f. '+' means the observed time is from censored subjects.

Data Snapshot: 14OCT2019, Data Cutoff Date: 04SEP2019

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_1753\v01\outputs\tlfs\pgms\t-ae-km-socpt-subgrp.sas Output: t-ae-km-socpt-sub-4-age-safs.rtf (17JUL20:17:19)

Data: adsl, adae, adttesaf

Seattle Genetics Protocol ONT-380-206**Table 2.6.5 Summary of Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Age - Time-to-Event Analysis Safety Analysis Set**

| System Organ Class/ Preferred Term | Parameters | Age < 65 Years | | Age ≥ 65 Years | |
|--|---|-------------------------|-------------------------|-----------------------|-------------------------|
| | | Tuc+Cap+Tra (N=322) | Pbo+Cap+Tra (N=164) | Tuc+Cap+Tra (N=82) | Pbo+Cap+Tra (N=33) |
| Musculoskeletal And Connective Tissue Disorders (SOC) | Number of Subjects With at Least One Event, n (%) | 154 (47.8) | 55 (33.5) | 29 (35.4) | 12 (36.4) |
| | Number of Censored Subjects, n (%) | 168 (52.2) | 109 (66.5) | 53 (64.6) | 21 (63.6) |
| | Stratified Hazard Ratio ^{a, b} (95% C.I.) | | 1.465 (1.073, 2.001) | | 0.794 (0.393, 1.605) |
| | P-value ^{b, c} | | 0.01625 | | 0.52034 |
| | Interaction Test P-value ^d | | | 0.17761 | |
| | Median Time to Onset of the First Event (Days) (95% C.I.) ^e | 218.0 (169.0, 354.0) | 399.0 (275.0, -) | 309.0 (165.0, -) | 215.0 (125.0, -) |
| | 25 th , 75 th Percentile | 48.0, 787.0 | 106.0, - | 113.0, - | 102.0, - |
| Observed Min, Max ^f | 1, 849+ | 1, 760+ | 1, 830+ | 4, 409+ | |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (Presence or history of brain metastases: Yes/No, ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.

c. Two-sided p-value calculated from Cox proportional hazards model.

d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and age.

e. Calculated using the complementary log-log transformation method (Collett, 1994). f. '+' means the observed time is from censored subjects.

Data Snapshot: 14OCT2019, Data Cutoff Date: 04SEP2019

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_1753\v01\outputs\tlfs\pgms\t-ae-km-socpt-subgrp.sas Output: t-ae-km-socpt-sub-4-age-safs.rtf (17JUL20:17:19)

Data: adsl, adae, adttesaf

Seattle Genetics Protocol ONT-380-206

Table 2.6.5 Summary of Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Age - Time-to-Event Analysis Safety Analysis Set

| System Organ Class/ Preferred Term | Parameters | Age < 65 Years | | Age >= 65 Years | |
|---------------------------------------|--|------------------------|------------------------|-------------------------|-----------------------|
| | | Tuc+Cap+Tra (N=322) | Pbo+Cap+Tra (N=164) | Tuc+Cap+Tra (N=82) | Pbo+Cap+Tra (N=33) |
| Arthralgia (PT) | Number of Subjects With at Least One Event, n (%) | 53 (16.5) | 9 (5.5) | 6 (7.3) | 0 |
| | Number of Censored Subjects, n (%) | 269 (83.5) | 155 (94.5) | 76 (92.7) | 33 (100) |
| | Stratified Hazard Ratio ^{a, b} (95% C.I.) | 2.752 (1.350, 5.607) | | 15778036.734 (0.000, -) | |
| | P-value ^{b, c} | 0.00532 | | 0.99540 | |
| | Interaction Test P-value ^d | 0.98438 | | | |
| | Median Time to Onset of the First Event (Days) (95% C.I.) ^e | - (707.0, -) | - (-, -) | - (449.0, -) | - (-, -) |
| | 25 th , 75 th Percentile | 602.0, - | -, - | -, - | -, - |
| Observed Min, Max ^f | 1, 1070+ | 4, 762+ | 2, 830+ | 31+, 409+ | |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.
 b. Computed using stratification factors (Presence or history of brain metastases: Yes/No, ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.
 c. Two-sided p-value calculated from Cox proportional hazards model.
 d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and age.
 e. Calculated using the complementary log-log transformation method (Collett, 1994). f. '+' means the observed time is from censored subjects.
 Data Snapshot: 14OCT2019, Data Cutoff Date: 04SEP2019
 Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_1753\v01\outputs\tlfs\pgms\t-ae-km-socpt-subgrp.sas Output: t-ae-km-socpt-sub-4-age-safs.rtf (17JUL20:17:19)
 Data: adsl, adae, adttesaf

Seattle Genetics Protocol ONT-380-206**Table 2.6.5 Summary of Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Age - Time-to-Event Analysis Safety Analysis Set**

| System Organ Class/ Preferred Term | Parameters | Age < 65 Years | | Age >= 65 Years | |
|---------------------------------------|--|------------------------|------------------------|-----------------------|-----------------------|
| | | Tuc+Cap+Tra (N=322) | Pbo+Cap+Tra (N=164) | Tuc+Cap+Tra (N=82) | Pbo+Cap+Tra (N=33) |
| Muscle Spasms (PT) | Number of Subjects With at Least One Event, n (%) | 31 (9.6) | 4 (2.4) | 7 (8.5) | 1 (3.0) |
| | Number of Censored Subjects, n (%) | 291 (90.4) | 160 (97.6) | 75 (91.5) | 32 (97.0) |
| | Stratified Hazard Ratio ^{a, b} (95% C.I.) | 3.376 (1.179, 9.664) | | 3.092 (0.378, 25.312) | |
| | P-value ^{b, c} | 0.02336 | | 0.29274 | |
| | Interaction Test P-value ^d | 0.85386 | | | |
| | Median Time to Onset of the First Event (Days) (95% C.I.) ^e | 966.0 (787.0, -) | - (-, -) | - (-, -) | - (-, -) |
| | 25 th , 75 th Percentile Observed Min, Max ^f | 787.0, - 1, 1059+ | -, - 21, 762+ | -, - 2, 830+ | -, - 31+, 409+ |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (Presence or history of brain metastases: Yes/No, ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.

c. Two-sided p-value calculated from Cox proportional hazards model.

d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and age.

e. Calculated using the complementary log-log transformation method (Collett, 1994). f. '+' means the observed time is from censored subjects.

Data Snapshot: 14OCT2019, Data Cutoff Date: 04SEP2019

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_1753\v01\outputs\tlfs\pgms\t-ae-km-socpt-subgrp.sas Output: t-ae-km-socpt-sub-4-age-safs.rtf (17JUL20:17:19)

Data: adsl, adae, adttesaf

Seattle Genetics Protocol ONT-380-206**Table 2.6.5 Summary of Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Age - Time-to-Event Analysis Safety Analysis Set**

| System Organ Class/ Preferred Term | Parameters | Age < 65 Years | | Age ≥ 65 Years | |
|---------------------------------------|--|------------------------|------------------------|-----------------------|-----------------------|
| | | Tuc+Cap+Tra (N=322) | Pbo+Cap+Tra (N=164) | Tuc+Cap+Tra (N=82) | Pbo+Cap+Tra (N=33) |
| Dysgeusia (PT) | Number of Subjects With at Least One Event, n (%) | 28 (8.7) | 4 (2.4) | 2 (2.4) | 1 (3.0) |
| | Number of Censored Subjects, n (%) | 294 (91.3) | 160 (97.6) | 80 (97.6) | 32 (97.0) |
| | Stratified Hazard Ratio ^{a, b} (95% C.I.) | 3.317 (1.155, 9.526) | | 0.913 (0.075, 11.167) | |
| | P-value ^{b, c} | 0.02590 | | 0.94327 | |
| | Interaction Test P-value ^d | 0.27210 | | | |
| | Median Time to Onset of the First Event (Days) (95% C.I.) ^e | - (-, -) | - (-, -) | - (-, -) | - (-, -) |
| | 25 th , 75 th Percentile Observed Min, Max ^f | - , - 1, 1059+ | - , - 12, 762+ | - , - 4+, 945+ | - , - 11, 409+ |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (Presence or history of brain metastases: Yes/No, ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.

c. Two-sided p-value calculated from Cox proportional hazards model.

d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and age.

e. Calculated using the complementary log-log transformation method (Collett, 1994). f. '+' means the observed time is from censored subjects.

Data Snapshot: 14OCT2019, Data Cutoff Date: 04SEP2019

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_1753\v01\outputs\tlfs\pgms\t-ae-km-socpt-subgrp.sas Output: t-ae-km-socpt-sub-4-age-safs.rtf (17JUL20:17:19)

Data: adsl, adae, adttesaf

Seattle Genetics Protocol ONT-380-206**Table 2.6.5 Summary of Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Age - Time-to-Event Analysis Safety Analysis Set**

| System Organ Class/ Preferred Term | Parameters | Age < 65 Years | | Age ≥ 65 Years | |
|---------------------------------------|--|------------------------|------------------------|-----------------------|-----------------------|
| | | Tuc+Cap+Tra (N=322) | Pbo+Cap+Tra (N=164) | Tuc+Cap+Tra (N=82) | Pbo+Cap+Tra (N=33) |
| Renal And Urinary Disorders (SOC) | Number of Subjects With at Least One Event, n (%) | 30 (9.3) | 8 (4.9) | 10 (12.2) | 1 (3.0) |
| | Number of Censored Subjects, n (%) | 292 (90.7) | 156 (95.1) | 72 (87.8) | 32 (97.0) |
| | Stratified Hazard Ratio ^{a, b} (95% C.I.) | 1.829 (0.836, 4.005) | | 2.909 (0.365, 23.165) | |
| | P-value ^{b, c} | 0.13082 | | 0.31318 | |
| | Interaction Test P-value ^d | 0.47837 | | | |
| | Median Time to Onset of the First Event (Days) (95% C.I.) ^e | - (-, -) | -(529.0, -) | - (-, -) | -(295.0, -) |
| | 25 th , 75 th Percentile | -, - | -, - | -, - | -, - |
| Observed Min, Max ^f | 2, 1070+ | 1, 762+ | 4+, 945+ | 31+, 409+ | |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (Presence or history of brain metastases: Yes/No, ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.

c. Two-sided p-value calculated from Cox proportional hazards model.

d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and age.

e. Calculated using the complementary log-log transformation method (Collett, 1994). f. '+' means the observed time is from censored subjects.

Data Snapshot: 14OCT2019, Data Cutoff Date: 04SEP2019

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_1753\v01\outputs\tlfs\pgms\t-ae-km-socpt-subgrp.sas Output: t-ae-km-socpt-sub-4-age-safs.rtf (17JUL20:17:19)

Data: adsl, adae, adttesaf

Seattle Genetics Protocol ONT-380-206**Table 2.6.5 Summary of Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Age - Time-to-Event Analysis Safety Analysis Set**

| System Organ Class/ Preferred Term | Parameters | Age < 65 Years | | Age ≥ 65 Years | |
|---------------------------------------|--|------------------------|------------------------|-----------------------|-----------------------|
| | | Tuc+Cap+Tra (N=322) | Pbo+Cap+Tra (N=164) | Tuc+Cap+Tra (N=82) | Pbo+Cap+Tra (N=33) |
| Epistaxis (PT) | Number of Subjects With at Least One Event, n (%) | 32 (9.9) | 7 (4.3) | 15 (18.3) | 3 (9.1) |
| | Number of Censored Subjects, n (%) | 290 (90.1) | 157 (95.7) | 67 (81.7) | 30 (90.9) |
| | Stratified Hazard Ratio ^{a, b} (95% C.I.) | 2.335 (1.027, 5.309) | | 1.886 (0.532, 6.695) | |
| | P-value ^{b, c} | 0.04300 | | 0.32608 | |
| | Interaction Test P-value ^d | 0.77248 | | | |
| | Median Time to Onset of the First Event (Days) (95% C.I.) ^e | - (-, -) | - (-, -) | - (-, -) | - (-, -) |
| | 25 th , 75 th Percentile | -, - | -, - | -, - | -, - |
| Observed Min, Max ^f | 1, 1059+ | 5, 762+ | 1, 945+ | 3, 409+ | |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (Presence or history of brain metastases: Yes/No, ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.

c. Two-sided p-value calculated from Cox proportional hazards model.

d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and age.

e. Calculated using the complementary log-log transformation method (Collett, 1994). f. '+' means the observed time is from censored subjects.

Data Snapshot: 14OCT2019, Data Cutoff Date: 04SEP2019

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Data: adsl, adae, adttesaf

Seattle Genetics Protocol ONT-380-206**Table 2.6.5 Summary of Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Age - Time-to-Event Analysis Safety Analysis Set**

| System Organ Class/ Preferred Term | Parameters | Age < 65 Years | | Age ≥ 65 Years | |
|---------------------------------------|--|------------------------|------------------------|-----------------------|-----------------------|
| | | Tuc+Cap+Tra (N=322) | Pbo+Cap+Tra (N=164) | Tuc+Cap+Tra (N=82) | Pbo+Cap+Tra (N=33) |
| Pleural Effusion (PT) | Number of Subjects With at Least One Event, n (%) | 5 (1.6) | 8 (4.9) | 5 (6.1) | 3 (9.1) |
| | Number of Censored Subjects, n (%) | 317 (98.4) | 156 (95.1) | 77 (93.9) | 30 (90.9) |
| | Stratified Hazard Ratio ^{a, b} (95% C.I.) | 0.297 (0.096, 0.920) | | 0.425 (0.085, 2.140) | |
| | P-value ^{b, c} | 0.03529 | | 0.29964 | |
| | Interaction Test P-value ^d | 0.66573 | | | |
| | Median Time to Onset of the First Event (Days) (95% C.I.) ^e | - (-, -) | - (-, -) | 942.0 (-, -) | - (-, -) |
| | 25 th , 75 th Percentile | -, - | -, - | 942.0, 942.0 | -, - |
| Observed Min, Max ^f | 6+, 1070+ | 6, 762+ | 4+, 942 | 14, 409+ | |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (Presence or history of brain metastases: Yes/No, ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.

c. Two-sided p-value calculated from Cox proportional hazards model.

d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and age.

e. Calculated using the complementary log-log transformation method (Collett, 1994). f. '+' means the observed time is from censored subjects.

Data Snapshot: 14OCT2019, Data Cutoff Date: 04SEP2019

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Data: adsl, adae, adttesaf

Seattle Genetics Protocol ONT-380-206**Table 2.6.5 Summary of Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Age - Time-to-Event Analysis Safety Analysis Set**

| System Organ Class/ Preferred Term | Parameters | Age < 65 Years | | Age ≥ 65 Years | |
|--|---|-------------------------|------------------------|-------------------------|-----------------------|
| | | Tuc+Cap+Tra (N=322) | Pbo+Cap+Tra (N=164) | Tuc+Cap+Tra (N=82) | Pbo+Cap+Tra (N=33) |
| Palmar-Plantar Erythrodysesthesia Syndrome (PT) | Number of Subjects With at Least One Event, n (%) | 204 (63.4) | 92 (56.1) | 52 (63.4) | 12 (36.4) |
| | Number of Censored Subjects, n (%) | 118 (36.6) | 72 (43.9) | 30 (36.6) | 21 (63.6) |
| | Stratified Hazard Ratio ^{a, b} (95% C.I.) | 1.194 (0.931, 1.531) | | 2.070 (1.060, 4.045) | |
| | P-value ^{b, c} | 0.16279 | | 0.03321 | |
| | Interaction Test P-value ^d | 0.10999 | | | |
| | Median Time to Onset of the First Event (Days) (95% C.I.) ^e | 64.0 (48.0, 80.0) | 75.0 (63.0, 127.0) | 70.0 (42.0, 106.0) | - (126.0, -) |
| | 25 th , 75 th Percentile | 28.0, 648.0 | 33.0, - | 29.0, 337.0 | 75.0, - |
| Observed Min, Max ^f | 1, 648 | 1, 407+ | 1, 337 | 3, 409+ | |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (Presence or history of brain metastases: Yes/No, ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.

c. Two-sided p-value calculated from Cox proportional hazards model.

d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and age.

e. Calculated using the complementary log-log transformation method (Collett, 1994). f. '+' means the observed time is from censored subjects.

Data Snapshot: 14OCT2019, Data Cutoff Date: 04SEP2019

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Data: adsl, adae, adttesaf

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**Table 2.6.6 Summary of Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Race - Time-to-Event Analysis
Safety Analysis Set**

| System Organ Class/ Preferred Term | Parameters | White | | Non-White | |
|---------------------------------------|--|------------------------|------------------------|------------------------|-----------------------|
| | | Tuc+Cap+Tra (N=283) | Pbo+Cap+Tra (N=153) | Tuc+Cap+Tra (N=121) | Pbo+Cap+Tra (N=44) |
| Anaemia (PT) | Number of Subjects With at Least One Event, n (%) | 58 (20.5) | 20 (13.1) | 22 (18.2) | 3 (6.8) |
| | Number of Censored Subjects, n (%) | 225 (79.5) | 133 (86.9) | 99 (81.8) | 41 (93.2) |
| | Stratified Hazard Ratio ^{a, b} (95% C.I.) | 1.556 (0.934, 2.594) | | 2.383 (0.706, 8.043) | |
| | P-value ^{b, c} | 0.08965 | | 0.16169 | |
| | Interaction Test P-value ^d | 0.52894 | | | |
| | Median Time to Onset of the First Event (Days) (95% C.I.) ^e | - (-, -) | - (-, -) | 924.0 (924.0, -) | - (-, -) |
| | 25 th , 75 th Percentile | 390.0, - | -, - | 924.0, - | -, - |
| | Observed Min, Max ^f | 1, 1059+ | 12, 762+ | 4+, 1070+ | 22, 583+ |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (Presence or history of brain metastases: Yes/No, ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.

c. Two-sided p-value calculated from Cox proportional hazards model.

d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and race.

e. Calculated using the complementary log-log transformation method (Collett, 1994). f. '+' means the observed time is from censored subjects.

Data Snapshot: 14OCT2019, Data Cutoff Date: 04SEP2019

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_1753\v01\outputs\tlfs\pgms\t-ae-km-socpt-subgrp.sas Output: t-ae-km-socpt-sub-5-race-safs.rtf (17JUL20:17:19)

Data: adsl, adae, adttesaf

Seattle Genetics Protocol ONT-380-206

Table 2.6.6 Summary of Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Race - Time-to-Event Analysis
Safety Analysis Set

| System Organ Class/ Preferred Term | Parameters | White | | Non-White | |
|---------------------------------------|--|------------------------|------------------------|------------------------|-----------------------|
| | | Tuc+Cap+Tra (N=283) | Pbo+Cap+Tra (N=153) | Tuc+Cap+Tra (N=121) | Pbo+Cap+Tra (N=44) |
| Investigations (SOC) | Number of Subjects With at Least One Event, n (%) | 178 (62.9) | 54 (35.3) | 63 (52.1) | 17 (38.6) |
| | Number of Censored Subjects, n (%) | 105 (37.1) | 99 (64.7) | 58 (47.9) | 27 (61.4) |
| | Stratified Hazard Ratio ^{a, b} (95% C.I.) | 2.144 (1.578, 2.913) | | 1.444 (0.836, 2.495) | |
| | P-value ^{b, c} | <.00001 | | 0.18807 | |
| | Interaction Test P-value ^d | | | 0.20237 | |
| | Median Time to Onset of the First Event (Days) (95% C.I.) ^e | 64.0 (43.0, 106.0) | 356.0 (255.0, -) | 210.0 (63.0, 315.0) | 283.0 (103.0, -) |
| | 25 th , 75 th Percentile | 28.0, - | 64.0, - | 22.0, - | 46.0, - |
| | Observed Min, Max ^f | 1, 891+ | 1, 478+ | 4+, 637+ | 13, 387+ |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (Presence or history of brain metastases: Yes/No, ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.

c. Two-sided p-value calculated from Cox proportional hazards model.

d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and race.

e. Calculated using the complementary log-log transformation method (Collett, 1994). f. '+' means the observed time is from censored subjects.

Data Snapshot: 14OCT2019, Data Cutoff Date: 04SEP2019

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_1753\v01\outputs\tlfs\pgms\t-ae-km-socpt-subgrp.sas Output: t-ae-km-socpt-sub-5-race-safs.rtf (17JUL20:17:19)

Data: adsl, adae, adttesaf

Seattle Genetics Protocol ONT-380-206

**Table 2.6.6 Summary of Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Race - Time-to-Event Analysis
Safety Analysis Set**

| System Organ Class/ Preferred Term | Parameters | White | | Non-White | |
|---|--|------------------------|------------------------|------------------------|-----------------------|
| | | Tuc+Cap+Tra (N=283) | Pbo+Cap+Tra (N=153) | Tuc+Cap+Tra (N=121) | Pbo+Cap+Tra (N=44) |
| Aspartate Aminotransferase Increased (PT) | Number of Subjects With at Least One Event, n (%) | 62 (21.9) | 16 (10.5) | 24 (19.8) | 6 (13.6) |
| | Number of Censored Subjects, n (%) | 221 (78.1) | 137 (89.5) | 97 (80.2) | 38 (86.4) |
| | Stratified Hazard Ratio ^{a, b} (95% C.I.) | 2.170 (1.252, 3.763) | | 1.543 (0.625, 3.809) | |
| | P-value ^{b, c} | 0.00580 | | 0.34704 | |
| | Interaction Test P-value ^d | 0.44114 | | | |
| | Median Time to Onset of the First Event (Days) (95% C.I.) ^e | - (-, -) | - (-, -) | - (-, -) | - (335.0, -) |
| | 25 th , 75 th Percentile | 358.0, - | -, - | -, - | 335.0, - |
| | Observed Min, Max ^f | 6+, 944+ | 1, 762+ | 4+, 1070+ | 22, 449+ |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (Presence or history of brain metastases: Yes/No, ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.

c. Two-sided p-value calculated from Cox proportional hazards model.

d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and race.

e. Calculated using the complementary log-log transformation method (Collett, 1994). f. '+' means the observed time is from censored subjects.

Data Snapshot: 14OCT2019, Data Cutoff Date: 04SEP2019

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_1753\v01\outputs\tlfs\pgms\t-ae-km-socpt-subgrp.sas Output: t-ae-km-socpt-sub-5-race-safs.rtf (17JUL20:17:19)

Data: adsl, adae, adttesaf

Seattle Genetics Protocol ONT-380-206

**Table 2.6.6 Summary of Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Race - Time-to-Event Analysis
Safety Analysis Set**

| System Organ Class/ Preferred Term | Parameters | White | | Non-White | |
|---|--|------------------------|------------------------|------------------------|-----------------------|
| | | Tuc+Cap+Tra (N=283) | Pbo+Cap+Tra (N=153) | Tuc+Cap+Tra (N=121) | Pbo+Cap+Tra (N=44) |
| Alanine Aminotransferase Increased (PT) | Number of Subjects With at Least One Event, n (%) | 61 (21.6) | 9 (5.9) | 20 (16.5) | 4 (9.1) |
| | Number of Censored Subjects, n (%) | 222 (78.4) | 144 (94.1) | 101 (83.5) | 40 (90.9) |
| | Stratified Hazard Ratio ^{a, b} (95% C.I.) | | 3.918 (1.942, 7.903) | | 1.867 (0.634, 5.496) |
| | P-value ^{b, c} | | 0.00014 | | 0.25742 |
| | Interaction Test P-value ^d | | | 0.23618 | |
| | Median Time to Onset of the First Event (Days) (95% C.I.) ^e | - (-, -) | - (-, -) | - (-, -) | - (357.0, -) |
| | 25 th , 75 th Percentile | 407.0, - | -, - | -, - | 357.0, - |
| Observed Min, Max ^f | 6+, 944+ | 21, 762+ | 4+, 1070+ | 14, 449+ | |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.
 b. Computed using stratification factors (Presence or history of brain metastases: Yes/No, ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.
 c. Two-sided p-value calculated from Cox proportional hazards model.
 d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and race.
 e. Calculated using the complementary log-log transformation method (Collett, 1994). f. '+' means the observed time is from censored subjects.
 Data Snapshot: 14OCT2019, Data Cutoff Date: 04SEP2019
 Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_1753\v01\outputs\tlfs\pgms\t-ae-km-socpt-subgrp.sas Output: t-ae-km-socpt-sub-5-race-safs.rtf (17JUL20:17:19)
 Data: adsl, adae, adttesaf

Seattle Genetics Protocol ONT-380-206

**Table 2.6.6 Summary of Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Race - Time-to-Event Analysis
Safety Analysis Set**

| System Organ Class/ Preferred Term | Parameters | White | | Non-White | |
|--|---|-------------------------|------------------------|-------------------------|-----------------------|
| | | Tuc+Cap+Tra (N=283) | Pbo+Cap+Tra (N=153) | Tuc+Cap+Tra (N=121) | Pbo+Cap+Tra (N=44) |
| Blood Bilirubin Increased (PT) | Number of Subjects With at Least One Event, n (%) | 55 (19.4) | 13 (8.5) | 20 (16.5) | 7 (15.9) |
| | Number of Censored Subjects, n (%) | 228 (80.6) | 140 (91.5) | 101 (83.5) | 37 (84.1) |
| | Stratified Hazard Ratio ^{a, b} (95% C.I.) | 2.368 (1.292, 4.339) | | 0.979 (0.410, 2.341) | |
| | P-value ^{b, c} | 0.00527 | | 0.96282 | |
| | Interaction Test P-value ^d | | | 0.10572 | |
| | Median Time to Onset of the First Event (Days) (95% C.I.) ^e | - (-, -) | - (-, -) | - (-, -) | - (-, -) |
| 25 th , 75 th Percentile | -, - | -, - | -, - | -, - | |
| Observed Min, Max ^f | 6+, 945+ | 6, 762+ | 4+, 1070+ | 15, 583+ | |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (Presence or history of brain metastases: Yes/No, ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.

c. Two-sided p-value calculated from Cox proportional hazards model.

d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and race.

e. Calculated using the complementary log-log transformation method (Collett, 1994). f. '+' means the observed time is from censored subjects.

Data Snapshot: 14OCT2019, Data Cutoff Date: 04SEP2019

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_1753\v01\outputs\tlfs\pgms\t-ae-km-socpt-subgrp.sas Output: t-ae-km-socpt-sub-5-race-safs.rtf (17JUL20:17:19)

Data: adsl, adae, adttesaf

Seattle Genetics Protocol ONT-380-206

**Table 2.6.6 Summary of Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Race - Time-to-Event Analysis
Safety Analysis Set**

| System Organ Class/ Preferred Term | Parameters | White | | Non-White | |
|---------------------------------------|--|------------------------|------------------------|------------------------|-----------------------|
| | | Tuc+Cap+Tra (N=283) | Pbo+Cap+Tra (N=153) | Tuc+Cap+Tra (N=121) | Pbo+Cap+Tra (N=44) |
| Blood Creatinine Increased (PT) | Number of Subjects With at Least One Event, n (%) | 35 (12.4) | 2 (1.3) | 21 (17.4) | 1 (2.3) |
| | Number of Censored Subjects, n (%) | 248 (87.6) | 151 (98.7) | 100 (82.6) | 43 (97.7) |
| | Stratified Hazard Ratio ^{a, b} (95% C.I.) | 9.789 (2.351, 40.760) | | 7.182 (0.960, 53.758) | |
| | P-value ^{b, c} | 0.00172 | | 0.05488 | |
| | Interaction Test P-value ^d | 0.77445 | | | |
| | Median Time to Onset of the First Event (Days) (95% C.I.) ^e | - (747.0, -) | - (-, -) | - (-, -) | - (-, -) |
| | 25 th , 75 th Percentile | 747.0, - | -, - | -, - | -, - |
| Observed Min, Max ^f | 5, 945+ | 26+, 762+ | 4+, 1070+ | 13, 583+ | |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.
 b. Computed using stratification factors (Presence or history of brain metastases: Yes/No, ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.
 c. Two-sided p-value calculated from Cox proportional hazards model.
 d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and race.
 e. Calculated using the complementary log-log transformation method (Collett, 1994). f. '+' means the observed time is from censored subjects.
 Data Snapshot: 14OCT2019, Data Cutoff Date: 04SEP2019
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 Data: adsl, adae, adttesaf

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Table 2.6.6 Summary of Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Race - Time-to-Event Analysis
Safety Analysis Set

| System Organ Class/ Preferred Term | Parameters | White | | Non-White | |
|---------------------------------------|--|------------------------|------------------------|------------------------|-----------------------|
| | | Tuc+Cap+Tra (N=283) | Pbo+Cap+Tra (N=153) | Tuc+Cap+Tra (N=121) | Pbo+Cap+Tra (N=44) |
| Weight Decreased (PT) | Number of Subjects With at Least One Event, n (%) | 37 (13.1) | 7 (4.6) | 17 (14.0) | 4 (9.1) |
| | Number of Censored Subjects, n (%) | 246 (86.9) | 146 (95.4) | 104 (86.0) | 40 (90.9) |
| | Stratified Hazard Ratio ^{a, b} (95% C.I.) | 2.924 (1.303, 6.564) | | 1.270 (0.418, 3.860) | |
| | P-value ^{b, c} | 0.00930 | | 0.67315 | |
| | Interaction Test P-value ^d | 0.32244 | | | |
| | Median Time to Onset of the First Event (Days) (95% C.I.) ^e | - (-, -) | - (-, -) | - (-, -) | - (-, -) |
| | 25 th , 75 th Percentile | -, - | -, - | -, - | -, - |
| | Observed Min, Max ^f | 6+, 1059+ | 9, 762+ | 4+, 875+ | 22, 580+ |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (Presence or history of brain metastases: Yes/No, ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.

c. Two-sided p-value calculated from Cox proportional hazards model.

d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and race.

e. Calculated using the complementary log-log transformation method (Collett, 1994). f. '+' means the observed time is from censored subjects.

Data Snapshot: 14OCT2019, Data Cutoff Date: 04SEP2019

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Data: adsl, adae, adttesaf

Seattle Genetics Protocol ONT-380-206

**Table 2.6.6 Summary of Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Race - Time-to-Event Analysis
Safety Analysis Set**

| System Organ Class/ Preferred Term | Parameters | White | | Non-White | |
|--|--|------------------------|------------------------|------------------------|-----------------------|
| | | Tuc+Cap+Tra (N=283) | Pbo+Cap+Tra (N=153) | Tuc+Cap+Tra (N=121) | Pbo+Cap+Tra (N=44) |
| Metabolism And Nutrition Disorders (SOC) | Number of Subjects With at Least One Event, n (%) | 144 (50.9) | 57 (37.3) | 60 (49.6) | 14 (31.8) |
| | Number of Censored Subjects, n (%) | 139 (49.1) | 96 (62.7) | 61 (50.4) | 30 (68.2) |
| | Stratified Hazard Ratio ^{a, b} (95% C.I.) | | 1.481 (1.088, 2.017) | | 1.792 (0.996, 3.224) |
| | P-value ^{b, c} | | 0.01252 | | 0.05146 |
| | Interaction Test P-value ^d | | | 0.63623 | |
| | Median Time to Onset of the First Event (Days) (95% C.I.) ^e | 167.0 (105.0, 401.0) | - (216.0, -) | 147.0 (83.0, -) | - (335.0, -) |
| | 25 th , 75 th Percentile | 24.0, - | 51.0, - | 22.0, - | 43.5, - |
| Observed Min, Max ^f | 1, 863+ | 3, 762+ | 2, 637+ | 1, 449+ | |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.
 b. Computed using stratification factors (Presence or history of brain metastases: Yes/No, ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.
 c. Two-sided p-value calculated from Cox proportional hazards model.
 d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and race.
 e. Calculated using the complementary log-log transformation method (Collett, 1994). f. '+' means the observed time is from censored subjects.
 Data Snapshot: 14OCT2019, Data Cutoff Date: 04SEP2019
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 Data: adsl, adae, adttesaf

Seattle Genetics Protocol ONT-380-206**Table 2.6.6 Summary of Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Race - Time-to-Event Analysis
Safety Analysis Set**

| System Organ Class/ Preferred Term | Parameters | White | | Non-White | |
|---------------------------------------|--|------------------------|------------------------|------------------------|-----------------------|
| | | Tuc+Cap+Tra (N=283) | Pbo+Cap+Tra (N=153) | Tuc+Cap+Tra (N=121) | Pbo+Cap+Tra (N=44) |
| Hyperglycaemia (PT) | Number of Subjects With at Least One Event, n (%) | 16 (5.7) | 2 (1.3) | 7 (5.8) | 1 (2.3) |
| | Number of Censored Subjects, n (%) | 267 (94.3) | 151 (98.7) | 114 (94.2) | 43 (97.7) |
| | Stratified Hazard Ratio ^{a, b} (95% C.I.) | 4.203 (0.964, 18.321) | | 2.087 (0.252, 17.289) | |
| | P-value ^{b, c} | 0.05596 | | 0.49535 | |
| | Interaction Test P-value ^d | 0.54502 | | | |
| | Median Time to Onset of the First Event (Days) (95% C.I.) ^e | - (-, -) | - (-, -) | - (-, -) | - (-, -) |
| | 25 th , 75 th Percentile | -, - | -, - | -, - | -, - |
| | Observed Min, Max ^f | 6+, 1059+ | 12, 762+ | 2, 1070+ | 13, 583+ |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (Presence or history of brain metastases: Yes/No, ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.

c. Two-sided p-value calculated from Cox proportional hazards model.

d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and race.

e. Calculated using the complementary log-log transformation method (Collett, 1994). f. '+' means the observed time is from censored subjects.

Data Snapshot: 14OCT2019, Data Cutoff Date: 04SEP2019

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Data: adsl, adae, adttesaf

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**Table 2.6.6 Summary of Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Race - Time-to-Event Analysis
Safety Analysis Set**

| System Organ Class/ Preferred Term | Parameters | White | | Non-White | |
|--|---|-------------------------|------------------------|-------------------------|-------------------------|
| | | Tuc+Cap+Tra (N=283) | Pbo+Cap+Tra (N=153) | Tuc+Cap+Tra (N=121) | Pbo+Cap+Tra (N=44) |
| Musculoskeletal And Connective Tissue Disorders (SOC) | Number of Subjects With at Least One Event, n (%) | 132 (46.6) | 53 (34.6) | 51 (42.1) | 14 (31.8) |
| | Number of Censored Subjects, n (%) | 151 (53.4) | 100 (65.4) | 70 (57.9) | 30 (68.2) |
| | Stratified Hazard Ratio ^{a, b} (95% C.I.) | 1.406 (1.019, 1.939) | | 1.183 (0.637, 2.197) | |
| | P-value ^{b, c} | 0.03802 | | 0.59408 | |
| | Interaction Test P-value ^d | 0.61469 | | | |
| | Median Time to Onset of the First Event (Days) (95% C.I.) ^e | 221.0 (147.0, 309.0) | - (215.0, -) | 319.0 (212.0, 721.0) | 275.0 (253.0, 399.0) |
| | 25 th , 75 th Percentile | 61.0, - | 102.0, - | 65.0, 721.0 | 123.0, 399.0 |
| Observed Min, Max ^f | 1, 849+ | 1, 760+ | 1, 721 | 1, 399 | |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (Presence or history of brain metastases: Yes/No, ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.

c. Two-sided p-value calculated from Cox proportional hazards model.

d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and race.

e. Calculated using the complementary log-log transformation method (Collett, 1994). f. '+' means the observed time is from censored subjects.

Data Snapshot: 14OCT2019, Data Cutoff Date: 04SEP2019

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Data: adsl, adae, adttesaf

Seattle Genetics Protocol ONT-380-206

Table 2.6.6 Summary of Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Race - Time-to-Event Analysis
Safety Analysis Set

| System Organ Class/ Preferred Term | Parameters | White | | Non-White | |
|---------------------------------------|--|------------------------|------------------------|------------------------|-----------------------|
| | | Tuc+Cap+Tra (N=283) | Pbo+Cap+Tra (N=153) | Tuc+Cap+Tra (N=121) | Pbo+Cap+Tra (N=44) |
| Arthralgia (PT) | Number of Subjects With at Least One Event, n (%) | 40 (14.1) | 8 (5.2) | 19 (15.7) | 1 (2.3) |
| | Number of Censored Subjects, n (%) | 243 (85.9) | 145 (94.8) | 102 (84.3) | 43 (97.7) |
| | Stratified Hazard Ratio ^{a, b} (95% C.I.) | 2.323 (1.077, 5.012) | | 6.484 (0.858, 49.028) | |
| | P-value ^{b, c} | 0.03159 | | 0.07012 | |
| | Interaction Test P-value ^d | 0.41951 | | | |
| | Median Time to Onset of the First Event (Days) (95% C.I.) ^e | - (707.0, -) | - (-, -) | - (-, -) | - (-, -) |
| | 25 th , 75 th Percentile | 602.0, - | -, - | -, - | -, - |
| Observed Min, Max ^f | 1, 944+ | 7, 762+ | 1, 1070+ | 4, 583+ | |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (Presence or history of brain metastases: Yes/No, ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.

c. Two-sided p-value calculated from Cox proportional hazards model.

d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and race.

e. Calculated using the complementary log-log transformation method (Collett, 1994). f. '+' means the observed time is from censored subjects.

Data Snapshot: 14OCT2019, Data Cutoff Date: 04SEP2019

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_1753\v01\outputs\tlfs\pgms\t-ae-km-socpt-subgrp.sas Output: t-ae-km-socpt-sub-5-race-safs.rtf (17JUL20:17:19)

Data: adsl, adae, adttesaf

Seattle Genetics Protocol ONT-380-206

Table 2.6.6 Summary of Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Race - Time-to-Event Analysis
Safety Analysis Set

| System Organ Class/ Preferred Term | Parameters | White | | Non-White | |
|---------------------------------------|--|------------------------|------------------------|------------------------|-----------------------|
| | | Tuc+Cap+Tra (N=283) | Pbo+Cap+Tra (N=153) | Tuc+Cap+Tra (N=121) | Pbo+Cap+Tra (N=44) |
| Muscle Spasms (PT) | Number of Subjects With at Least One Event, n (%) | 26 (9.2) | 2 (1.3) | 12 (9.9) | 3 (6.8) |
| | Number of Censored Subjects, n (%) | 257 (90.8) | 151 (98.7) | 109 (90.1) | 41 (93.2) |
| | Stratified Hazard Ratio ^{a, b} (95% C.I.) | 6.538 (1.543, 27.701) | | 1.027 (0.266, 3.958) | |
| | P-value ^{b, c} | 0.01080 | | 0.96945 | |
| | Interaction Test P-value ^d | | | 0.08875 | |
| | Median Time to Onset of the First Event (Days) (95% C.I.) ^e | - (787.0, -) | - (-, -) | 966.0 (538.0, 966.0) | - (399.0, -) |
| | 25 th , 75 th Percentile | 787.0, - | -, - | 538.0, 966.0 | 399.0, - |
| Observed Min, Max ^f | 2, 1059+ | 21, 762+ | 1, 966 | 40+, 583+ | |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (Presence or history of brain metastases: Yes/No, ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.

c. Two-sided p-value calculated from Cox proportional hazards model.

d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and race.

e. Calculated using the complementary log-log transformation method (Collett, 1994). f. '+' means the observed time is from censored subjects.

Data Snapshot: 14OCT2019, Data Cutoff Date: 04SEP2019

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_1753\v01\outputs\tlfs\pgms\t-ae-km-socpt-subgrp.sas Output: t-ae-km-socpt-sub-5-race-safs.rtf (17JUL20:17:19)

Data: adsl, adae, adttesaf

Seattle Genetics Protocol ONT-380-206

**Table 2.6.6 Summary of Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Race - Time-to-Event Analysis
Safety Analysis Set**

| System Organ Class/ Preferred Term | Parameters | White | | Non-White | |
|---------------------------------------|--|------------------------|------------------------|------------------------|-----------------------|
| | | Tuc+Cap+Tra (N=283) | Pbo+Cap+Tra (N=153) | Tuc+Cap+Tra (N=121) | Pbo+Cap+Tra (N=44) |
| Dysgeusia (PT) | Number of Subjects With at Least One Event, n (%) | 13 (4.6) | 4 (2.6) | 17 (14.0) | 1 (2.3) |
| | Number of Censored Subjects, n (%) | 270 (95.4) | 149 (97.4) | 104 (86.0) | 43 (97.7) |
| | Stratified Hazard Ratio ^{a, b} (95% C.I.) | 1.814 (0.591, 5.568) | | 4.863 (0.635, 37.240) | |
| | P-value ^{b, c} | 0.29795 | | 0.12779 | |
| | Interaction Test P-value ^d | 0.28640 | | | |
| | Median Time to Onset of the First Event (Days) (95% C.I.) ^e | - (-, -) | - (-, -) | - (-, -) | - (-, -) |
| | 25 th , 75 th Percentile | -, - | -, - | -, - | -, - |
| Observed Min, Max ^f | 2, 1059+ | 11, 762+ | 1, 875+ | 40+, 580+ | |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (Presence or history of brain metastases: Yes/No, ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.

c. Two-sided p-value calculated from Cox proportional hazards model.

d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and race.

e. Calculated using the complementary log-log transformation method (Collett, 1994). f. '+' means the observed time is from censored subjects.

Data Snapshot: 14OCT2019, Data Cutoff Date: 04SEP2019

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_1753\v01\outputs\tlfs\pgms\t-ae-km-socpt-subgrp.sas Output: t-ae-km-socpt-sub-5-race-safs.rtf (17JUL20:17:19)

Data: adsl, adae, adttesaf

Seattle Genetics Protocol ONT-380-206

Table 2.6.6 Summary of Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Race - Time-to-Event Analysis
Safety Analysis Set

| System Organ Class/ Preferred Term | Parameters | White | | Non-White | |
|---------------------------------------|--|------------------------|------------------------|------------------------|-----------------------|
| | | Tuc+Cap+Tra (N=283) | Pbo+Cap+Tra (N=153) | Tuc+Cap+Tra (N=121) | Pbo+Cap+Tra (N=44) |
| Renal And Urinary Disorders (SOC) | Number of Subjects With at Least One Event, n (%) | 32 (11.3) | 7 (4.6) | 8 (6.6) | 2 (4.5) |
| | Number of Censored Subjects, n (%) | 251 (88.7) | 146 (95.4) | 113 (93.4) | 42 (95.5) |
| | Stratified Hazard Ratio ^{a, b} (95% C.I.) | | 2.403 (1.057, 5.463) | | 1.403 (0.295, 6.660) |
| | P-value ^{b, c} | | 0.03631 | | 0.67014 |
| | Interaction Test P-value ^d | | | 0.53310 | |
| | Median Time to Onset of the First Event (Days) (95% C.I.) ^e | - (-, -) | - (529.0, -) | - (-, -) | - (295.0, -) |
| | 25 th , 75 th Percentile | -, - | 529.0, - | -, - | -, - |
| Observed Min, Max ^f | 2, 945+ | 1, 762+ | 2, 1070+ | 18, 583+ | |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (Presence or history of brain metastases: Yes/No, ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.

c. Two-sided p-value calculated from Cox proportional hazards model.

d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and race.

e. Calculated using the complementary log-log transformation method (Collett, 1994). f. '+' means the observed time is from censored subjects.

Data Snapshot: 14OCT2019, Data Cutoff Date: 04SEP2019

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_1753\v01\outputs\tlfs\pgms\t-ae-km-socpt-subgrp.sas Output: t-ae-km-socpt-sub-5-race-safs.rtf (17JUL20:17:19)

Data: adsl, adae, adttesaf

Seattle Genetics Protocol ONT-380-206

**Table 2.6.6 Summary of Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Race - Time-to-Event Analysis
Safety Analysis Set**

| System Organ Class/ Preferred Term | Parameters | White | | Non-White | |
|---------------------------------------|--|------------------------|------------------------|------------------------|-----------------------|
| | | Tuc+Cap+Tra (N=283) | Pbo+Cap+Tra (N=153) | Tuc+Cap+Tra (N=121) | Pbo+Cap+Tra (N=44) |
| Epistaxis (PT) | Number of Subjects With at Least One Event, n (%) | 36 (12.7) | 8 (5.2) | 11 (9.1) | 2 (4.5) |
| | Number of Censored Subjects, n (%) | 247 (87.3) | 145 (94.8) | 110 (90.9) | 42 (95.5) |
| | Stratified Hazard Ratio ^{a, b} (95% C.I.) | 2.450 (1.137, 5.280) | | 2.096 (0.458, 9.599) | |
| | P-value ^{b, c} | 0.02218 | | 0.34034 | |
| | Interaction Test P-value ^d | 0.75749 | | | |
| | Median Time to Onset of the First Event (Days) (95% C.I.) ^e | - (-, -) | - (-, -) | - (-, -) | - (-, -) |
| | 25 th , 75 th Percentile | -, - | -, - | -, - | -, - |
| Observed Min, Max ^f | 1, 1059+ | 3, 762+ | 4+, 988+ | 5, 583+ | |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (Presence or history of brain metastases: Yes/No, ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.

c. Two-sided p-value calculated from Cox proportional hazards model.

d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and race.

e. Calculated using the complementary log-log transformation method (Collett, 1994). f. '+' means the observed time is from censored subjects.

Data Snapshot: 14OCT2019, Data Cutoff Date: 04SEP2019

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_1753\v01\outputs\tlfs\pgms\t-ae-km-socpt-subgrp.sas Output: t-ae-km-socpt-sub-5-race-safs.rtf (17JUL20:17:19)

Data: adsl, adae, adttesaf

Seattle Genetics Protocol ONT-380-206

Table 2.6.6 Summary of Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Race - Time-to-Event Analysis
Safety Analysis Set

| System Organ Class/ Preferred Term | Parameters | White | | Non-White | |
|---------------------------------------|--|------------------------|------------------------|------------------------|-----------------------|
| | | Tuc+Cap+Tra (N=283) | Pbo+Cap+Tra (N=153) | Tuc+Cap+Tra (N=121) | Pbo+Cap+Tra (N=44) |
| Pleural Effusion (PT) | Number of Subjects With at Least One Event, n (%) | 7 (2.5) | 10 (6.5) | 3 (2.5) | 1 (2.3) |
| | Number of Censored Subjects, n (%) | 276 (97.5) | 143 (93.5) | 118 (97.5) | 43 (97.7) |
| | Stratified Hazard Ratio ^{a, b} (95% C.I.) | 0.288 (0.103, 0.802) | | 1.147 (0.112, 11.741) | |
| | P-value ^{b, c} | 0.01730 | | 0.90777 | |
| | Interaction Test P-value ^d | | | 0.33694 | |
| | Median Time to Onset of the First Event (Days) (95% C.I.) ^e | - (942.0, -) | - (-, -) | - (-, -) | - (-, -) |
| | 25 th , 75 th Percentile | 942.0, - | -, - | -, - | -, - |
| | Observed Min, Max ^f | 6+, 1059+ | 6, 762+ | 4+, 1070+ | 40+, 583+ |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (Presence or history of brain metastases: Yes/No, ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.

c. Two-sided p-value calculated from Cox proportional hazards model.

d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and race.

e. Calculated using the complementary log-log transformation method (Collett, 1994). f. '+' means the observed time is from censored subjects.

Data Snapshot: 14OCT2019, Data Cutoff Date: 04SEP2019

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_1753\v01\outputs\tlfs\pgms\t-ae-km-socpt-subgrp.sas Output: t-ae-km-socpt-sub-5-race-safs.rtf (17JUL20:17:19)

Data: adsl, adae, adttesaf

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Table 2.6.6 Summary of Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Race - Time-to-Event Analysis
Safety Analysis Set

| System Organ Class/ Preferred Term | Parameters | White | | Non-White | |
|--|---|------------------------|-------------------------|------------------------|-------------------------|
| | | Tuc+Cap+Tra (N=283) | Pbo+Cap+Tra (N=153) | Tuc+Cap+Tra (N=121) | Pbo+Cap+Tra (N=44) |
| Palmar-Plantar Erythrodysesthesia Syndrome (PT) | Number of Subjects With at Least One Event, n (%) | 179 (63.3) | 81 (52.9) | 77 (63.6) | 23 (52.3) |
| | Number of Censored Subjects, n (%) | 104 (36.7) | 72 (47.1) | 44 (36.4) | 21 (47.7) |
| | Stratified Hazard Ratio ^{a, b} (95% C.I.) | | 1.296 (0.994, 1.688) | | 1.267 (0.777, 2.066) |
| | P-value ^{b, c} | | 0.05499 | | 0.34228 |
| | Interaction Test P-value ^d | | | 0.88301 | |
| | Median Time to Onset of the First Event (Days) (95% C.I.) ^e | 63.0 (51.0, 83.0) | 92.0 (64.0, 163.0) | 64.0 (42.0, 109.0) | 91.0 (40.0, -) |
| | 25 th , 75 th Percentile | 29.0, 648.0 | 34.0, - | 23.0, 324.0 | 28.5, - |
| Observed Min, Max ^f | 1, 648 | 1, 409+ | 4, 602+ | 1, 279+ | |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (Presence or history of brain metastases: Yes/No, ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.

c. Two-sided p-value calculated from Cox proportional hazards model.

d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and race.

e. Calculated using the complementary log-log transformation method (Collett, 1994). f. '+' means the observed time is from censored subjects.

Data Snapshot: 14OCT2019, Data Cutoff Date: 04SEP2019

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_1753\v01\outputs\tlfs\pgms\t-ae-km-socpt-subgrp.sas Output: t-ae-km-socpt-sub-5-race-safs.rtf (17JUL20:17:19)

Data: adsl, adae, adttesaf

Seattle Genetics Protocol ONT-380-206**Table 2.6.7 Summary of Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Hormone Receptor Status - Time-to-Event Analysis Safety Analysis Set**

| System Organ Class/ Preferred Term | Parameters | Negative for Both | | Positive for ER or PR or Both | |
|---------------------------------------|--|------------------------|-----------------------|-------------------------------|------------------------|
| | | Tuc+Cap+Tra (N=163) | Pbo+Cap+Tra (N=74) | Tuc+Cap+Tra (N=241) | Pbo+Cap+Tra (N=123) |
| Anaemia (PT) | Number of Subjects With at Least One Event, n (%) | 24 (14.7) | 10 (13.5) | 56 (23.2) | 13 (10.6) |
| | Number of Censored Subjects, n (%) | 139 (85.3) | 64 (86.5) | 185 (76.8) | 110 (89.4) |
| | Stratified Hazard Ratio ^{a, b} (95% C.I.) | 1.051 (0.493, 2.241) | | 2.185 (1.191, 4.009) | |
| | P-value ^{b, c} | 0.89799 | | 0.01158 | |
| | Interaction Test P-value ^d | 0.12734 | | | |
| | Median Time to Onset of the First Event (Days) (95% C.I.) ^e | - (924.0, -) | - (-, -) | - (-, -) | - (-, -) |
| | 25 th , 75 th Percentile | 924.0, - | -, - | 266.0, - | -, - |
| | Observed Min, Max ^f | 1, 1070+ | 22, 580+ | 1, 891+ | 12, 762+ |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (Presence or history of brain metastases: Yes/No, ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.

c. Two-sided p-value calculated from Cox proportional hazards model.

d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and hormone receptor status.

e. Calculated using the complementary log-log transformation method (Collett, 1994). f. '+' means the observed time is from censored subjects.

Data Snapshot: 14OCT2019, Data Cutoff Date: 04SEP2019

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_1753\v01\outputs\tlfs\pgms\t-ae-km-socpt-subgrp.sas Output: t-ae-km-socpt-sub-6-hr-safs.rtf (17JUL20:17:19)

Data: adsl, adae, adttesaf

Seattle Genetics Protocol ONT-380-206**Table 2.6.7 Summary of Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Hormone Receptor Status - Time-to-Event Analysis Safety Analysis Set**

| System Organ Class/ Preferred Term | Parameters | Negative for Both | | Positive for ER or PR or Both | |
|---------------------------------------|--|------------------------|-----------------------|-------------------------------|------------------------|
| | | Tuc+Cap+Tra (N=163) | Pbo+Cap+Tra (N=74) | Tuc+Cap+Tra (N=241) | Pbo+Cap+Tra (N=123) |
| Investigations (SOC) | Number of Subjects With at Least One Event, n (%) | 100 (61.3) | 30 (40.5) | 141 (58.5) | 41 (33.3) |
| | Number of Censored Subjects, n (%) | 63 (38.7) | 44 (59.5) | 100 (41.5) | 82 (66.7) |
| | Stratified Hazard Ratio ^{a, b} (95% C.I.) | | 1.457 (0.959, 2.213) | | 2.074 (1.461, 2.944) |
| | P-value ^{b, c} | | 0.07800 | | 0.00004 |
| | Interaction Test P-value ^d | | | 0.25780 | |
| | Median Time to Onset of the First Event (Days) (95% C.I.) ^e | 106.0 (62.0, 181.0) | 317.0 (127.0, -) | 64.0 (43.0, 152.0) | - (255.0, -) |
| | 25 th , 75 th Percentile | 23.0, - | 50.0, - | 22.0, - | 65.0, - |
| Observed Min, Max ^f | 1, 659+ | 7, 453+ | 1, 891+ | 1, 478+ | |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (Presence or history of brain metastases: Yes/No, ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.

c. Two-sided p-value calculated from Cox proportional hazards model.

d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and hormone receptor status.

e. Calculated using the complementary log-log transformation method (Collett, 1994). f. '+' means the observed time is from censored subjects.

Data Snapshot: 14OCT2019, Data Cutoff Date: 04SEP2019

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_1753\v01\outputs\tlfs\pgms\t-ae-km-socpt-subgrp.sas Output: t-ae-km-socpt-sub-6-hr-safs.rtf (17JUL20:17:19)

Data: adsl, adae, adttesaf

Seattle Genetics Protocol ONT-380-206

Table 2.6.7 Summary of Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Hormone Receptor Status - Time-to-Event Analysis Safety Analysis Set

| System Organ Class/ Preferred Term | Parameters | Negative for Both | | Positive for ER or PR or Both | |
|---|--|------------------------|-----------------------|-------------------------------|------------------------|
| | | Tuc+Cap+Tra (N=163) | Pbo+Cap+Tra (N=74) | Tuc+Cap+Tra (N=241) | Pbo+Cap+Tra (N=123) |
| Aspartate Aminotransferase Increased (PT) | Number of Subjects With at Least One Event, n (%) | 33 (20.2) | 9 (12.2) | 53 (22.0) | 13 (10.6) |
| | Number of Censored Subjects, n (%) | 130 (79.8) | 65 (87.8) | 188 (78.0) | 110 (89.4) |
| | Stratified Hazard Ratio ^{a, b} (95% C.I.) | 1.666 (0.791, 3.509) | | 2.208 (1.200, 4.061) | |
| | P-value ^{b, c} | 0.17954 | | 0.01085 | |
| | Interaction Test P-value ^d | 0.50933 | | | |
| | Median Time to Onset of the First Event (Days) (95% C.I.) ^e | - (-, -) | - (335.0, -) | - (-, -) | - (-, -) |
| | 25 th , 75 th Percentile | -, - | -, - | 358.0, - | -, - |
| Observed Min, Max ^f | 4+, 1070+ | 11, 453+ | 6+, 891+ | 1, 762+ | |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.
 b. Computed using stratification factors (Presence or history of brain metastases: Yes/No, ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.
 c. Two-sided p-value calculated from Cox proportional hazards model.
 d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and hormone receptor status.
 e. Calculated using the complementary log-log transformation method (Collett, 1994). f. '+' means the observed time is from censored subjects.
 Data Snapshot: 14OCT2019, Data Cutoff Date: 04SEP2019
 Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_1753\v01\outputs\tlfs\pgms\t-ae-km-socpt-subgrp.sas Output: t-ae-km-socpt-sub-6-hr-safs.rtf (17JUL20:17:19)
 Data: adsl, adae, adttesaf

Seattle Genetics Protocol ONT-380-206**Table 2.6.7 Summary of Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Hormone Receptor Status - Time-to-Event Analysis Safety Analysis Set**

| System Organ Class/ Preferred Term | Parameters | Negative for Both | | Positive for ER or PR or Both | |
|---|--|------------------------|-----------------------|-------------------------------|------------------------|
| | | Tuc+Cap+Tra (N=163) | Pbo+Cap+Tra (N=74) | Tuc+Cap+Tra (N=241) | Pbo+Cap+Tra (N=123) |
| Alanine Aminotransferase Increased (PT) | Number of Subjects With at Least One Event, n (%) | 30 (18.4) | 4 (5.4) | 51 (21.2) | 9 (7.3) |
| | Number of Censored Subjects, n (%) | 133 (81.6) | 70 (94.6) | 190 (78.8) | 114 (92.7) |
| | Stratified Hazard Ratio ^{a, b} (95% C.I.) | | 3.238 (1.131, 9.274) | | 3.164 (1.554, 6.440) |
| | P-value ^{b, c} | | 0.02861 | | 0.00149 |
| | Interaction Test P-value ^d | | | 0.94945 | |
| | Median Time to Onset of the First Event (Days) (95% C.I.) ^e | - (-, -) | - (357.0, -) | - (-, -) | - (-, -) |
| | 25 th , 75 th Percentile | -, - | -, - | 407.0, - | -, - |
| Observed Min, Max ^f | 4+, 1070+ | 22, 453+ | 6+, 891+ | 14, 762+ | |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (Presence or history of brain metastases: Yes/No, ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.

c. Two-sided p-value calculated from Cox proportional hazards model.

d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and hormone receptor status.

e. Calculated using the complementary log-log transformation method (Collett, 1994). f. '+' means the observed time is from censored subjects.

Data Snapshot: 14OCT2019, Data Cutoff Date: 04SEP2019

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_1753\v01\outputs\tlfs\pgms\t-ae-km-socpt-subgrp.sas Output: t-ae-km-socpt-sub-6-hr-safs.rtf (17JUL20:17:19)

Data: adsl, adae, adtesaf

Seattle Genetics Protocol ONT-380-206**Table 2.6.7 Summary of Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Hormone Receptor Status - Time-to-Event Analysis Safety Analysis Set**

| System Organ Class/ Preferred Term | Parameters | Negative for Both | | Positive for ER or PR or Both | |
|---------------------------------------|--|------------------------|-----------------------|-------------------------------|------------------------|
| | | Tuc+Cap+Tra (N=163) | Pbo+Cap+Tra (N=74) | Tuc+Cap+Tra (N=241) | Pbo+Cap+Tra (N=123) |
| Blood Bilirubin Increased (PT) | Number of Subjects With at Least One Event, n (%) | 31 (19.0) | 7 (9.5) | 44 (18.3) | 13 (10.6) |
| | Number of Censored Subjects, n (%) | 132 (81.0) | 67 (90.5) | 197 (81.7) | 110 (89.4) |
| | Stratified Hazard Ratio ^{a, b} (95% C.I.) | 1.924 (0.841, 4.400) | | 1.728 (0.927, 3.221) | |
| | P-value ^{b, c} | 0.12101 | | 0.08503 | |
| | Interaction Test P-value ^d | 0.90773 | | | |
| | Median Time to Onset of the First Event (Days) (95% C.I.) ^e | - (-, -) | - (-, -) | - (-, -) | - (-, -) |
| | 25 th , 75 th Percentile | -, - | -, - | -, - | -, - |
| | Observed Min, Max ^f | 4+, 1070+ | 7, 580+ | 6+, 891+ | 6, 762+ |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (Presence or history of brain metastases: Yes/No, ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.

c. Two-sided p-value calculated from Cox proportional hazards model.

d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and hormone receptor status.

e. Calculated using the complementary log-log transformation method (Collett, 1994). f. '+' means the observed time is from censored subjects.

Data Snapshot: 14OCT2019, Data Cutoff Date: 04SEP2019

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_1753\v01\outputs\tlfs\pgms\t-ae-km-socpt-subgrp.sas Output: t-ae-km-socpt-sub-6-hr-safs.rtf (17JUL20:17:19)

Data: adsl, adae, adttesaf

Seattle Genetics Protocol ONT-380-206

Table 2.6.7 Summary of Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Hormone Receptor Status - Time-to-Event Analysis Safety Analysis Set

| System Organ Class/ Preferred Term | Parameters | Negative for Both | | Positive for ER or PR or Both | |
|---------------------------------------|--|------------------------|-----------------------|-------------------------------|------------------------|
| | | Tuc+Cap+Tra (N=163) | Pbo+Cap+Tra (N=74) | Tuc+Cap+Tra (N=241) | Pbo+Cap+Tra (N=123) |
| Blood Creatinine Increased (PT) | Number of Subjects With at Least One Event, n (%) | 18 (11.0) | 1 (1.4) | 38 (15.8) | 2 (1.6) |
| | Number of Censored Subjects, n (%) | 145 (89.0) | 73 (98.6) | 203 (84.2) | 121 (98.4) |
| | Stratified Hazard Ratio ^{a, b} (95% C.I.) | 6.923 (0.909, 52.749) | | 10.365 (2.496, 43.036) | |
| | P-value ^{b, c} | 0.06185 | | 0.00128 | |
| | Interaction Test P-value ^d | 0.76878 | | | |
| | Median Time to Onset of the First Event (Days) (95% C.I.) ^e | -(747.0, -) | -(356.0, -) | - (-, -) | - (-, -) |
| | 25 th , 75 th Percentile | 747.0, - | -, - | -, - | -, - |
| Observed Min, Max ^f | 4+, 1070+ | 29+, 580+ | 5, 891+ | 13, 762+ | |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.
 b. Computed using stratification factors (Presence or history of brain metastases: Yes/No, ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.
 c. Two-sided p-value calculated from Cox proportional hazards model.
 d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and hormone receptor status.
 e. Calculated using the complementary log-log transformation method (Collett, 1994). f. '+' means the observed time is from censored subjects.
 Data Snapshot: 14OCT2019, Data Cutoff Date: 04SEP2019
 Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_1753\v01\outputs\tlfs\pgms\t-ae-km-socpt-subgrp.sas Output: t-ae-km-socpt-sub-6-hr-safs.rtf (17JUL20:17:19)
 Data: adsl, adae, adttesaf

Seattle Genetics Protocol ONT-380-206**Table 2.6.7 Summary of Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Hormone Receptor Status - Time-to-Event Analysis Safety Analysis Set**

| System Organ Class/ Preferred Term | Parameters | Negative for Both | | Positive for ER or PR or Both | |
|---------------------------------------|--|------------------------|-----------------------|-------------------------------|------------------------|
| | | Tuc+Cap+Tra (N=163) | Pbo+Cap+Tra (N=74) | Tuc+Cap+Tra (N=241) | Pbo+Cap+Tra (N=123) |
| Weight Decreased (PT) | Number of Subjects With at Least One Event, n (%) | 21 (12.9) | 6 (8.1) | 33 (13.7) | 5 (4.1) |
| | Number of Censored Subjects, n (%) | 142 (87.1) | 68 (91.9) | 208 (86.3) | 118 (95.9) |
| | Stratified Hazard Ratio ^{a, b} (95% C.I.) | 1.392 (0.552, 3.508) | | 3.357 (1.307, 8.622) | |
| | P-value ^{b, c} | 0.48311 | | 0.01184 | |
| | Interaction Test P-value ^d | 0.21621 | | | |
| | Median Time to Onset of the First Event (Days) (95% C.I.) ^e | - (-, -) | - (-, -) | - (-, -) | - (-, -) |
| | 25 th , 75 th Percentile | -, - | -, - | -, - | -, - |
| Observed Min, Max ^f | 4+, 1059+ | 25, 580+ | 6, 891+ | 9, 762+ | |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (Presence or history of brain metastases: Yes/No, ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.

c. Two-sided p-value calculated from Cox proportional hazards model.

d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and hormone receptor status.

e. Calculated using the complementary log-log transformation method (Collett, 1994). f. '+' means the observed time is from censored subjects.

Data Snapshot: 14OCT2019, Data Cutoff Date: 04SEP2019

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_1753\v01\outputs\tlfs\pgms\t-ae-km-socpt-subgrp.sas Output: t-ae-km-socpt-sub-6-hr-safs.rtf (17JUL20:17:19)

Data: adsl, adae, adttesaf

Seattle Genetics Protocol ONT-380-206**Table 2.6.7 Summary of Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Hormone Receptor Status - Time-to-Event Analysis Safety Analysis Set**

| System Organ Class/ Preferred Term | Parameters | Negative for Both | | Positive for ER or PR or Both | |
|--|--|------------------------|-----------------------|-------------------------------|------------------------|
| | | Tuc+Cap+Tra (N=163) | Pbo+Cap+Tra (N=74) | Tuc+Cap+Tra (N=241) | Pbo+Cap+Tra (N=123) |
| Metabolism And Nutrition Disorders (SOC) | Number of Subjects With at Least One Event, n (%) | 78 (47.9) | 32 (43.2) | 126 (52.3) | 39 (31.7) |
| | Number of Censored Subjects, n (%) | 85 (52.1) | 42 (56.8) | 115 (47.7) | 84 (68.3) |
| | Stratified Hazard Ratio ^{a, b} (95% C.I.) | | 1.003 (0.658, 1.531) | | 1.929 (1.344, 2.770) |
| | P-value ^{b, c} | | 0.98715 | | 0.00037 |
| | Interaction Test P-value ^d | | | 0.02919 | |
| | Median Time to Onset of the First Event (Days) (95% C.I.) ^e | 399.0 (127.0, -) | 335.0 (80.0, -) | 127.0 (84.0, 365.0) | - (-, -) |
| | 25 th , 75 th Percentile | 34.0, - | 31.0, - | 22.0, - | 85.0, - |
| Observed Min, Max ^f | 1, 849+ | 1, 396+ | 1, 863+ | 3, 762+ | |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (Presence or history of brain metastases: Yes/No, ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.

c. Two-sided p-value calculated from Cox proportional hazards model.

d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and hormone receptor status.

e. Calculated using the complementary log-log transformation method (Collett, 1994). f. '+' means the observed time is from censored subjects.

Data Snapshot: 14OCT2019, Data Cutoff Date: 04SEP2019

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_1753\v01\outputs\tlfs\pgms\t-ae-km-socpt-subgrp.sas Output: t-ae-km-socpt-sub-6-hr-safs.rtf (17JUL20:17:19)

Data: adsl, adae, adtesaf

Seattle Genetics Protocol ONT-380-206**Table 2.6.7 Summary of Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Hormone Receptor Status - Time-to-Event Analysis
Safety Analysis Set**

| System Organ Class/ Preferred Term | Parameters | Negative for Both | | Positive for ER or PR or Both | |
|---------------------------------------|--|------------------------|-----------------------|-------------------------------|------------------------|
| | | Tuc+Cap+Tra (N=163) | Pbo+Cap+Tra (N=74) | Tuc+Cap+Tra (N=241) | Pbo+Cap+Tra (N=123) |
| Hyperglycaemia (PT) | Number of Subjects With at Least One Event, n (%) | 8 (4.9) | 1 (1.4) | 15 (6.2) | 2 (1.6) |
| | Number of Censored Subjects, n (%) | 155 (95.1) | 73 (98.6) | 226 (93.8) | 121 (98.4) |
| | Stratified Hazard Ratio ^{a, b} (95% C.I.) | 3.480 (0.431, 28.127) | | 3.354 (0.765, 14.701) | |
| | P-value ^{b, c} | 0.24217 | | 0.10847 | |
| | Interaction Test P-value ^d | 0.95569 | | | |
| | Median Time to Onset of the First Event (Days) (95% C.I.) ^e | - (-, -) | - (-, -) | - (-, -) | - (-, -) |
| | 25 th , 75 th Percentile | -, - | -, - | -, - | -, - |
| Observed Min, Max ^f | 4+, 1070+ | 13, 580+ | 2, 891+ | 12, 762+ | |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (Presence or history of brain metastases: Yes/No, ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.

c. Two-sided p-value calculated from Cox proportional hazards model.

d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and hormone receptor status.

e. Calculated using the complementary log-log transformation method (Collett, 1994). f. '+' means the observed time is from censored subjects.

Data Snapshot: 14OCT2019, Data Cutoff Date: 04SEP2019

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_1753\v01\outputs\tlfs\pgms\t-ae-km-socpt-subgrp.sas Output: t-ae-km-socpt-sub-6-hr-safs.rtf (17JUL20:17:19)

Data: adsl, adae, adttesaf

Seattle Genetics Protocol ONT-380-206**Table 2.6.7 Summary of Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Hormone Receptor Status - Time-to-Event Analysis Safety Analysis Set**

| System Organ Class/ Preferred Term | Parameters | Negative for Both | | Positive for ER or PR or Both | |
|--|---|-------------------------|-----------------------|-------------------------------|------------------------|
| | | Tuc+Cap+Tra (N=163) | Pbo+Cap+Tra (N=74) | Tuc+Cap+Tra (N=241) | Pbo+Cap+Tra (N=123) |
| Musculoskeletal And Connective Tissue Disorders (SOC) | Number of Subjects With at Least One Event, n (%) | 66 (40.5) | 23 (31.1) | 117 (48.5) | 44 (35.8) |
| | Number of Censored Subjects, n (%) | 97 (59.5) | 51 (68.9) | 124 (51.5) | 79 (64.2) |
| | Stratified Hazard Ratio ^{a, b} (95% C.I.) | 1.230 (0.752, 2.014) | | 1.413 (0.995, 2.005) | |
| | P-value ^{b, c} | 0.40970 | | 0.05327 | |
| | Interaction Test P-value ^d | 0.53428 | | | |
| | Median Time to Onset of the First Event (Days) (95% C.I.) ^e | 446.0 (213.0, 721.0) | 253.0 (148.0, -) | 211.0 (138.0, 280.0) | 399.0 (275.0, -) |
| | 25 th , 75 th Percentile | 64.0, - | 123.0, - | 61.0, 787.0 | 99.0, - |
| Observed Min, Max ^f | 1, 849+ | 1, 386+ | 1, 830+ | 2, 760+ | |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (Presence or history of brain metastases: Yes/No, ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.

c. Two-sided p-value calculated from Cox proportional hazards model.

d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and hormone receptor status.

e. Calculated using the complementary log-log transformation method (Collett, 1994). f. '+' means the observed time is from censored subjects.

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Data: adsl, adae, adttesaf

Seattle Genetics Protocol ONT-380-206

Table 2.6.7 Summary of Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Hormone Receptor Status - Time-to-Event Analysis Safety Analysis Set

| System Organ Class/ Preferred Term | Parameters | Negative for Both | | Positive for ER or PR or Both | |
|---------------------------------------|--|------------------------|-----------------------|-------------------------------|------------------------|
| | | Tuc+Cap+Tra (N=163) | Pbo+Cap+Tra (N=74) | Tuc+Cap+Tra (N=241) | Pbo+Cap+Tra (N=123) |
| Arthralgia (PT) | Number of Subjects With at Least One Event, n (%) | 27 (16.6) | 1 (1.4) | 32 (13.3) | 8 (6.5) |
| | Number of Censored Subjects, n (%) | 136 (83.4) | 73 (98.6) | 209 (86.7) | 115 (93.5) |
| | Stratified Hazard Ratio ^{a, b} (95% C.I.) | 9.684 (1.296, 72.365) | | 1.983 (0.910, 4.323) | |
| | P-value ^{b, c} | 0.02693 | | 0.08498 | |
| | Interaction Test P-value ^d | 0.11530 | | | |
| | Median Time to Onset of the First Event (Days) (95% C.I.) ^e | - (602.0, -) | - (320.0, -) | - (707.0, -) | - (-, -) |
| | 25 th , 75 th Percentile | 446.0, - | -, - | 707.0, - | -, - |
| Observed Min, Max ^f | 1, 1070+ | 29+, 580+ | 1, 891+ | 4, 762+ | |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.
 b. Computed using stratification factors (Presence or history of brain metastases: Yes/No, ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.
 c. Two-sided p-value calculated from Cox proportional hazards model.
 d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and hormone receptor status.
 e. Calculated using the complementary log-log transformation method (Collett, 1994). f. '+' means the observed time is from censored subjects.
 Data Snapshot: 14OCT2019, Data Cutoff Date: 04SEP2019
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 Data: adsl, adae, adttesaf

Seattle Genetics Protocol ONT-380-206**Table 2.6.7 Summary of Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Hormone Receptor Status - Time-to-Event Analysis Safety Analysis Set**

| System Organ Class/ Preferred Term | Parameters | Negative for Both | | Positive for ER or PR or Both | |
|---------------------------------------|--|-----------------------------|-----------------------|-------------------------------|------------------------|
| | | Tuc+Cap+Tra (N=163) | Pbo+Cap+Tra (N=74) | Tuc+Cap+Tra (N=241) | Pbo+Cap+Tra (N=123) |
| Muscle Spasms (PT) | Number of Subjects With at Least One Event, n (%) | 9 (5.5) | 0 | 29 (12.0) | 5 (4.1) |
| | Number of Censored Subjects, n (%) | 154 (94.5) | 74 (100) | 212 (88.0) | 118 (95.9) |
| | Stratified Hazard Ratio ^{a, b} (95% C.I.) | 16005153.41 5 (0.000, -) | | 3.021 (1.162, 7.858) | |
| | P-value ^{b, c} | 0.99450 | | 0.02337 | |
| | Interaction Test P-value ^d | | | 0.98857 | |
| | Median Time to Onset of the First Event (Days) (95% C.I.) ^e | 966.0 (966.0, -) | - (-, -) | - (787.0, -) | - (-, -) |
| | 25 th , 75 th Percentile | 966.0, - | -, - | 787.0, - | -, - |
| Observed Min, Max ^f | 1, 1059+ | 29+, 580+ | 2, 875+ | 21, 762+ | |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (Presence or history of brain metastases: Yes/No, ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.

c. Two-sided p-value calculated from Cox proportional hazards model.

d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and hormone receptor status.

e. Calculated using the complementary log-log transformation method (Collett, 1994). f. '+' means the observed time is from censored subjects.

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Data: adsl, adae, adttesaf

Seattle Genetics Protocol ONT-380-206**Table 2.6.7 Summary of Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Hormone Receptor Status - Time-to-Event Analysis Safety Analysis Set**

| System Organ Class/ Preferred Term | Parameters | Negative for Both | | Positive for ER or PR or Both | |
|---------------------------------------|--|------------------------|-----------------------|-------------------------------|------------------------|
| | | Tuc+Cap+Tra (N=163) | Pbo+Cap+Tra (N=74) | Tuc+Cap+Tra (N=241) | Pbo+Cap+Tra (N=123) |
| Dysgeusia (PT) | Number of Subjects With at Least One Event, n (%) | 14 (8.6) | 2 (2.7) | 16 (6.6) | 3 (2.4) |
| | Number of Censored Subjects, n (%) | 149 (91.4) | 72 (97.3) | 225 (93.4) | 120 (97.6) |
| | Stratified Hazard Ratio ^{a, b} (95% C.I.) | 3.327 (0.750, 14.750) | | 2.333 (0.671, 8.113) | |
| | P-value ^{b, c} | 0.11361 | | 0.18282 | |
| | Interaction Test P-value ^d | 0.82317 | | | |
| | Median Time to Onset of the First Event (Days) (95% C.I.) ^e | - (-, -) | - (-, -) | - (-, -) | - (-, -) |
| | 25 th , 75 th Percentile | -, - | -, - | -, - | -, - |
| Observed Min, Max ^f | 3, 1059+ | 12, 580+ | 1, 891+ | 11, 762+ | |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (Presence or history of brain metastases: Yes/No, ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.

c. Two-sided p-value calculated from Cox proportional hazards model.

d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and hormone receptor status.

e. Calculated using the complementary log-log transformation method (Collett, 1994). f. '+' means the observed time is from censored subjects.

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Data: adsl, adae, adttesaf

Seattle Genetics Protocol ONT-380-206

Table 2.6.7 Summary of Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Hormone Receptor Status - Time-to-Event Analysis Safety Analysis Set

| System Organ Class/ Preferred Term | Parameters | Negative for Both | | Positive for ER or PR or Both | |
|---------------------------------------|--|------------------------|-----------------------|-------------------------------|------------------------|
| | | Tuc+Cap+Tra (N=163) | Pbo+Cap+Tra (N=74) | Tuc+Cap+Tra (N=241) | Pbo+Cap+Tra (N=123) |
| Renal And Urinary Disorders (SOC) | Number of Subjects With at Least One Event, n (%) | 13 (8.0) | 1 (1.4) | 27 (11.2) | 8 (6.5) |
| | Number of Censored Subjects, n (%) | 150 (92.0) | 73 (98.6) | 214 (88.8) | 115 (93.5) |
| | Stratified Hazard Ratio ^{a, b} (95% C.I.) | 5.588 (0.725, 43.078) | | 1.716 (0.777, 3.791) | |
| | P-value ^{b, c} | 0.09873 | | 0.18182 | |
| | Interaction Test P-value ^d | | | 0.30154 | |
| | Median Time to Onset of the First Event (Days) (95% C.I.) ^e | - (-, -) | - (-, -) | - (-, -) | - (529.0, -) |
| | 25 th , 75 th Percentile | -, - | -, - | -, - | 529.0, - |
| Observed Min, Max ^f | 2, 1070+ | 29+, 580+ | 2, 891+ | 1, 762+ | |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (Presence or history of brain metastases: Yes/No, ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.

c. Two-sided p-value calculated from Cox proportional hazards model.

d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and hormone receptor status.

e. Calculated using the complementary log-log transformation method (Collett, 1994). f. '+' means the observed time is from censored subjects.

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Data: adsl, adae, adttesaf

Seattle Genetics Protocol ONT-380-206**Table 2.6.7 Summary of Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Hormone Receptor Status - Time-to-Event Analysis Safety Analysis Set**

| System Organ Class/ Preferred Term | Parameters | Negative for Both | | Positive for ER or PR or Both | |
|---------------------------------------|--|------------------------|-----------------------|-------------------------------|------------------------|
| | | Tuc+Cap+Tra (N=163) | Pbo+Cap+Tra (N=74) | Tuc+Cap+Tra (N=241) | Pbo+Cap+Tra (N=123) |
| Epistaxis (PT) | Number of Subjects With at Least One Event, n (%) | 14 (8.6) | 4 (5.4) | 33 (13.7) | 6 (4.9) |
| | Number of Censored Subjects, n (%) | 149 (91.4) | 70 (94.6) | 208 (86.3) | 117 (95.1) |
| | Stratified Hazard Ratio ^{a, b} (95% C.I.) | 1.569 (0.506, 4.867) | | 2.647 (1.105, 6.340) | |
| | P-value ^{b, c} | 0.43586 | | 0.02891 | |
| | Interaction Test P-value ^d | 0.42898 | | | |
| | Median Time to Onset of the First Event (Days) (95% C.I.) ^e | - (-, -) | - (-, -) | - (-, -) | - (-, -) |
| | 25 th , 75 th Percentile | -, - | -, - | -, - | -, - |
| | Observed Min, Max ^f | 1, 1059+ | 13, 580+ | 1, 875+ | 3, 762+ |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (Presence or history of brain metastases: Yes/No, ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.

c. Two-sided p-value calculated from Cox proportional hazards model.

d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and hormone receptor status.

e. Calculated using the complementary log-log transformation method (Collett, 1994). f. '+' means the observed time is from censored subjects.

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Data: adsl, adae, adttesaf

Seattle Genetics Protocol ONT-380-206**Table 2.6.7 Summary of Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Hormone Receptor Status - Time-to-Event Analysis Safety Analysis Set**

| System Organ Class/ Preferred Term | Parameters | Negative for Both | | Positive for ER or PR or Both | |
|--|--|------------------------|-----------------------|-------------------------------|------------------------|
| | | Tuc+Cap+Tra (N=163) | Pbo+Cap+Tra (N=74) | Tuc+Cap+Tra (N=241) | Pbo+Cap+Tra (N=123) |
| Pleural Effusion (PT) | Number of Subjects With at Least One Event, n (%) | 7 (4.3) | 4 (5.4) | 3 (1.2) | 7 (5.7) |
| | Number of Censored Subjects, n (%) | 156 (95.7) | 70 (94.6) | 238 (98.8) | 116 (94.3) |
| | Stratified Hazard Ratio ^{a, b} (95% C.I.) | 0.564 (0.151, 2.110) | | 0.231 (0.060, 0.894) | |
| | P-value ^{b, c} | 0.39449 | | 0.03387 | |
| | Interaction Test P-value ^d | 0.23042 | | | |
| | Median Time to Onset of the First Event (Days) (95% C.I.) ^e | - (942.0, -) | - (-, -) | - (-, -) | - (-, -) |
| 25 th , 75 th Percentile | 942.0, - | -, - | -, - | -, - | |
| Observed Min, Max ^f | 4+, 1070+ | 6, 580+ | 6+, 891+ | 8, 762+ | |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (Presence or history of brain metastases: Yes/No, ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.

c. Two-sided p-value calculated from Cox proportional hazards model.

d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and hormone receptor status.

e. Calculated using the complementary log-log transformation method (Collett, 1994). f. '+' means the observed time is from censored subjects.

Data Snapshot: 14OCT2019, Data Cutoff Date: 04SEP2019

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_1753\v01\outputs\tlfs\pgms\t-ae-km-socpt-subgrp.sas Output: t-ae-km-socpt-sub-6-hr-safs.rtf (17JUL20:17:19)

Data: adsl, adae, adttesaf

Seattle Genetics Protocol ONT-380-206

Table 2.6.7 Summary of Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Hormone Receptor Status - Time-to-Event Analysis Safety Analysis Set

| System Organ Class/ Preferred Term | Parameters | Negative for Both | | Positive for ER or PR or Both | |
|---|--|------------------------|-----------------------|-------------------------------|------------------------|
| | | Tuc+Cap+Tra (N=163) | Pbo+Cap+Tra (N=74) | Tuc+Cap+Tra (N=241) | Pbo+Cap+Tra (N=123) |
| Palmar-Plantar Erythrodysesthesia Syndrome (PT) | Number of Subjects With at Least One Event, n (%) | 105 (64.4) | 34 (45.9) | 151 (62.7) | 70 (56.9) |
| | Number of Censored Subjects, n (%) | 58 (35.6) | 40 (54.1) | 90 (37.3) | 53 (43.1) |
| | Stratified Hazard Ratio ^{a, b} (95% C.I.) | 1.674 (1.126, 2.487) | | 1.122 (0.843, 1.493) | |
| | P-value ^{b, c} | 0.01082 | | 0.43127 | |
| | Interaction Test P-value ^d | 0.17191 | | | |
| | Median Time to Onset of the First Event (Days) (95% C.I.) ^e | 62.0 (43.0, 84.0) | 141.0 (86.0, -) | 64.0 (46.0, 85.0) | 71.0 (57.0, 127.0) |
| | 25 th , 75 th Percentile | 30.0, - | 36.0, - | 27.0, 337.0 | 32.0, - |
| Observed Min, Max ^f | 1, 605+ | 1, 343+ | 1, 648 | 1, 409+ | |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.
 b. Computed using stratification factors (Presence or history of brain metastases: Yes/No, ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.
 c. Two-sided p-value calculated from Cox proportional hazards model.
 d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and hormone receptor status.
 e. Calculated using the complementary log-log transformation method (Collett, 1994). f. '+' means the observed time is from censored subjects.
 Data Snapshot: 14OCT2019, Data Cutoff Date: 04SEP2019
 Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_1753\v01\outputs\tlfs\pgms\t-ae-km-socpt-subgrp.sas Output: t-ae-km-socpt-sub-6-hr-safs.rtf (17JUL20:17:19)
 Data: adsl, adae, adttesaf

Seagen Protocol ONT-380-206**Table 2.2.1 Summary of Gastrointestinal Adverse Events by System Organ Class, Preferred Term and History of Brain Metastases at Baseline
Safety Analysis Set**

| System Organ Class/ Preferred Term | Parameters | With Brian Metastases | | Without Brain Metastases | |
|---------------------------------------|--|------------------------|-----------------------|--------------------------|------------------------|
| | | Tuc+Cap+Tra (N=194) | Pbo+Cap+Tra (N=91) | Tuc+Cap+Tra (N=209) | Pbo+Cap+Tra (N=105) |
| Gastrointestinal Disorders | Number of Subjects With at Least One Event, n (%) | 183 (94.3) | 73 (80.2) | 198 (94.7) | 91 (86.7) |
| | Number of Censored Subjects, n (%) | 11 (5.7) | 18 (19.8) | 11 (5.3) | 14 (13.3) |
| | Stratified Hazard Ratio ^{a, b} (95% C.I.) | | 2.126 (1.602, 2.821) | | 1.713 (1.328, 2.211) |
| | P-value ^{b, c} | | <.00001 | | 0.00003 |
| | Interaction Test P-value ^d | | | 0.37640 | |
| | Median Time to Onset of the First Event (Days) (95% C.I.) ^e | 7.0 (5.0, 8.0) | 19.0 (11.0, 26.0) | 7.0 (5.0, 8.0) | 15.0 (12.0, 25.0) |
| | 25 th , 75 th Percentile | 2.0, 15.0 | 8.0, 125.0 | 3.0, 14.0 | 5.0, 60.0 |
| Observed Min, Max ^f | 1, 420 | 1, 345+ | 1, 436+ | 1, 409+ | |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.

c. Two-sided p-value calculated from Cox proportional hazards model.

d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and history of brain metastases at baseline.

e. Calculated using the complementary log-log transformation method (Collett, 1994).

f. '+' means the observed time is from censored subjects.

Snapshot date: 10SEP2020, data cutoff date: 29MAY2020.

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_may2020_dco_1943\v01\outputs\tlfs\pgms\t-ae-km-gisoc-subgrp.sas Output: t02-02-01-ae-km-gisoc-sub-1-bm-safs.rtf (14DEC20:17:13) Data: adsl, adae, adttesaf

Seagen Protocol ONT-380-206**Table 2.2.1 Summary of Gastrointestinal Adverse Events by System Organ Class, Preferred Term and History of Brain Metastases at Baseline
Safety Analysis Set**

| System Organ Class/ Preferred Term | Parameters | With Brain Metastases | | Without Brain Metastases | |
|---------------------------------------|--|------------------------|-----------------------|--------------------------|------------------------|
| | | Tuc+Cap+Tra (N=194) | Pbo+Cap+Tra (N=91) | Tuc+Cap+Tra (N=209) | Pbo+Cap+Tra (N=105) |
| Diarrhoea | Number of Subjects With at Least One Event, n (%) | 161 (83.0) | 46 (50.5) | 169 (80.9) | 60 (57.1) |
| | Number of Censored Subjects, n (%) | 33 (17.0) | 45 (49.5) | 40 (19.1) | 45 (42.9) |
| | Stratified Hazard Ratio ^{a, b} (95% C.I.) | | 2.625 (1.882, 3.660) | | 2.221 (1.648, 2.994) |
| | P-value ^{b, c} | | <.00001 | | <.00001 |
| | Interaction Test P-value ^d | | | 0.50750 | |
| | Median Time to Onset of the First Event (Days) (95% C.I.) ^e | 15.0 (13.0, 16.0) | 157.0 (56.0, -) | 14.0 (12.0, 18.0) | 96.0 (60.0, 169.0) |
| | 25 th , 75 th Percentile | 8.0, 60.0 | 19.0, - | 7.0, 68.0 | 22.0, - |
| Observed Min, Max ^f | 1, 686+ | 1, 599+ | 1, 656+ | 1, 839+ | |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.

c. Two-sided p-value calculated from Cox proportional hazards model.

d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and history of brain metastases at baseline.

e. Calculated using the complementary log-log transformation method (Collett, 1994).

f. '+' means the observed time is from censored subjects.

Snapshot date: 10SEP2020, data cutoff date: 29MAY2020.

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_may2020_dco_1943\v01\outputs\tlfs\pgms\t-ae-km-gisoc-subgrp.sas Output: t02-02-01-ae-km-gisoc-sub-1-bm-safs.rtf (14DEC20:17:13) Data: adsl, adae, adttesaf

Seagen Protocol ONT-380-206**Table 2.2.1 Summary of Gastrointestinal Adverse Events by System Organ Class, Preferred Term and History of Brain Metastases at Baseline
Safety Analysis Set**

| System Organ Class/ Preferred Term | Parameters | With Brain Metastases | | Without Brain Metastases | |
|---------------------------------------|--|------------------------|-----------------------|--------------------------|------------------------|
| | | Tuc+Cap+Tra (N=194) | Pbo+Cap+Tra (N=91) | Tuc+Cap+Tra (N=209) | Pbo+Cap+Tra (N=105) |
| Nausea | Number of Subjects With at Least One Event, n (%) | 117 (60.3) | 37 (40.7) | 123 (58.9) | 51 (48.6) |
| | Number of Censored Subjects, n (%) | 77 (39.7) | 54 (59.3) | 86 (41.1) | 54 (51.4) |
| | Stratified Hazard Ratio ^{a, b} (95% C.I.) | | 1.741 (1.200, 2.528) | | 1.285 (0.925, 1.785) |
| | P-value ^{b, c} | | 0.00352 | | 0.13446 |
| | Interaction Test P-value ^d | | | 0.25692 | |
| | Median Time to Onset of the First Event (Days) (95% C.I.) ^e | 43.0 (22.0, 160.0) | - (146.0, -) | 43.0 (15.0, 171.0) | 197.0 (50.0, -) |
| | 25 th , 75 th Percentile | 7.0, - | 15.0, - | 6.0, - | 15.0, - |
| Observed Min, Max ^f | 1, 718+ | 1, 599+ | 1, 1327+ | 1, 762+ | |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.

c. Two-sided p-value calculated from Cox proportional hazards model.

d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and history of brain metastases at baseline.

e. Calculated using the complementary log-log transformation method (Collett, 1994).

f. '+' means the observed time is from censored subjects.

Snapshot date: 10SEP2020, data cutoff date: 29MAY2020.

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_may2020_dco_1943\v01\outputs\tlfs\pgms\t-ae-km-gisoc-subgrp.sas Output: t02-02-01-ae-km-gisoc-sub-1-bm-safs.rtf (14DEC20:17:13) Data: adsl, adae, adttesaf

Seagen Protocol ONT-380-206**Table 2.2.1 Summary of Gastrointestinal Adverse Events by System Organ Class, Preferred Term and History of Brain Metastases at Baseline
Safety Analysis Set**

| System Organ Class/ Preferred Term | Parameters | With Brian Metastases | | Without Brain Metastases | |
|---------------------------------------|--|------------------------|-----------------------|--------------------------|------------------------|
| | | Tuc+Cap+Tra (N=194) | Pbo+Cap+Tra (N=91) | Tuc+Cap+Tra (N=209) | Pbo+Cap+Tra (N=105) |
| Vomiting | Number of Subjects With at Least One Event, n (%) | 81 (41.8) | 22 (24.2) | 67 (32.1) | 29 (27.6) |
| | Number of Censored Subjects, n (%) | 113 (58.2) | 69 (75.8) | 142 (67.9) | 76 (72.4) |
| | Stratified Hazard Ratio ^{a, b} (95% C.I.) | | 1.789 (1.114, 2.872) | | 1.170 (0.755, 1.812) |
| | P-value ^{b, c} | | 0.01601 | | 0.48243 |
| | Interaction Test P-value ^d | | | 0.17897 | |
| | Median Time to Onset of the First Event (Days) (95% C.I.) ^e | 599.0 (304.0, -) | - (-, -) | - (686.0, -) | - (333.0, -) |
| | 25 th , 75 th Percentile | 40.0, - | 173.0, - | 52.0, - | 119.0, - |
| Observed Min, Max ^f | 1, 899+ | 1, 599+ | 1, 1327+ | 1, 839+ | |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.

c. Two-sided p-value calculated from Cox proportional hazards model.

d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and history of brain metastases at baseline.

e. Calculated using the complementary log-log transformation method (Collett, 1994).

f. '+' means the observed time is from censored subjects.

Snapshot date: 10SEP2020, data cutoff date: 29MAY2020.

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_may2020_dco_1943\v01\outputs\tlfs\pgms\t-ae-km-gisoc-subgrp.sas Output: t02-02-01-ae-km-gisoc-sub-1-bm-safs.rtf (14DEC20:17:13) Data: adsl, adae, adttesaf

Seagen Protocol ONT-380-206**Table 2.2.1 Summary of Gastrointestinal Adverse Events by System Organ Class, Preferred Term and History of Brain Metastases at Baseline
Safety Analysis Set**

| System Organ Class/ Preferred Term | Parameters | With Brian Metastases | | Without Brain Metastases | |
|---------------------------------------|--|------------------------|-----------------------|--------------------------|------------------------|
| | | Tuc+Cap+Tra (N=194) | Pbo+Cap+Tra (N=91) | Tuc+Cap+Tra (N=209) | Pbo+Cap+Tra (N=105) |
| Stomatitis | Number of Subjects With at Least One Event, n (%) | 52 (26.8) | 12 (13.2) | 52 (24.9) | 16 (15.2) |
| | Number of Censored Subjects, n (%) | 142 (73.2) | 79 (86.8) | 157 (75.1) | 89 (84.8) |
| | Stratified Hazard Ratio ^{a, b} (95% C.I.) | | 2.046 (1.088, 3.848) | | 1.669 (0.950, 2.931) |
| | P-value ^{b, c} | | 0.02624 | | 0.07460 |
| | Interaction Test P-value ^d | | | 0.55040 | |
| | Median Time to Onset of the First Event (Days) (95% C.I.) ^e | - (-, -) | - (-, -) | - (-, -) | - (-, -) |
| | 25 th , 75 th Percentile Observed Min, Max ^f | 190.0, - 1, 1011+ | - , - 7, 599+ | 271.0, - 1, 1327+ | - , - 7, 839+ |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.

c. Two-sided p-value calculated from Cox proportional hazards model.

d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and history of brain metastases at baseline.

e. Calculated using the complementary log-log transformation method (Collett, 1994).

f. '+' means the observed time is from censored subjects.

Snapshot date: 10SEP2020, data cutoff date: 29MAY2020.

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_may2020_dco_1943\v01\outputs\tlfs\pgms\t-ae-km-gisoc-subgrp.sas Output:
t02-02-01-ae-km-gisoc-sub-1-bm-safs.rtf (14DEC20:17:13) Data: adsl, adae, adttesaf

Seagen Protocol ONT-380-206**Table 2.2.1 Summary of Gastrointestinal Adverse Events by System Organ Class, Preferred Term and History of Brain Metastases at Baseline
Safety Analysis Set**

| System Organ Class/ Preferred Term | Parameters | With Brian Metastases | | Without Brain Metastases | |
|---------------------------------------|--|------------------------|-----------------------|--------------------------|------------------------|
| | | Tuc+Cap+Tra (N=194) | Pbo+Cap+Tra (N=91) | Tuc+Cap+Tra (N=209) | Pbo+Cap+Tra (N=105) |
| Constipation | Number of Subjects With at Least One Event, n (%) | 42 (21.6) | 18 (19.8) | 24 (11.5) | 24 (22.9) |
| | Number of Censored Subjects, n (%) | 152 (78.4) | 73 (80.2) | 185 (88.5) | 81 (77.1) |
| | Stratified Hazard Ratio ^{a, b} (95% C.I.) | | 0.891 (0.507, 1.564) | | 0.376 (0.209, 0.676) |
| | P-value ^{b, c} | | 0.68707 | | 0.00108 |
| | Interaction Test P-value ^d | | | 0.04876 | |
| | Median Time to Onset of the First Event (Days) (95% C.I.) ^e | - (709.0, -) | - (-, -) | - (-, -) | - (398.0, -) |
| | 25 th , 75 th Percentile | 403.0, - | -, - | -, - | 313.0, - |
| | Observed Min, Max ^f | 1, 1011+ | 3, 598+ | 1, 1327+ | 1, 839+ |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.

c. Two-sided p-value calculated from Cox proportional hazards model.

d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and history of brain metastases at baseline.

e. Calculated using the complementary log-log transformation method (Collett, 1994).

f. '+' means the observed time is from censored subjects.

Snapshot date: 10SEP2020, data cutoff date: 29MAY2020.

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_may2020_dco_1943\v01\outputs\tlfs\pgms\t-ae-km-gisoc-subgrp.sas Output: t02-02-01-ae-km-gisoc-sub-1-bm-safs.rtf (14DEC20:17:13) Data: adsl, adae, adttesaf

Seagen Protocol ONT-380-206**Table 2.2.2 Summary of Gastrointestinal Adverse Events by System Organ Class, Preferred Term and Geographic Region
Safety Analysis Set**

| System Organ Class/ Preferred Term | Parameters | North America | | Rest of World | |
|---------------------------------------|--|------------------------|------------------------|------------------------|-----------------------|
| | | Tuc+Cap+Tra (N=241) | Pbo+Cap+Tra (N=119) | Tuc+Cap+Tra (N=163) | Pbo+Cap+Tra (N=78) |
| Gastrointestinal Disorders | Number of Subjects With at Least One Event, n (%) | 231 (95.9) | 101 (84.9) | 151 (92.6) | 63 (80.8) |
| | Number of Censored Subjects, n (%) | 10 (4.1) | 18 (15.1) | 12 (7.4) | 15 (19.2) |
| | Stratified Hazard Ratio ^{a, b} (95% C.I.) | | 1.896 (1.488, 2.416) | | 1.940 (1.430, 2.633) |
| | P-value ^{b, c} | | <.00001 | | 0.00002 |
| | Interaction Test P-value ^d | | | 0.52863 | |
| | Median Time to Onset of the First Event (Days) (95% C.I.) ^e | 8.0 (7.0, 9.0) | 15.0 (12.0, 22.0) | 5.0 (4.0, 7.0) | 15.0 (11.0, 35.0) |
| | 25 th , 75 th Percentile | 3.0, 14.0 | 7.0, 55.0 | 2.0, 13.0 | 3.0, 114.0 |
| Observed Min, Max ^f | 1, 436+ | 1, 345+ | 1, 389+ | 1, 409+ | |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (Presence or history of brain metastases: Yes/No and ECOG performance status: 0/1) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.

c. Two-sided p-value calculated from Cox proportional hazards model.

d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and geographic region.

e. Calculated using the complementary log-log transformation method (Collett, 1994).

f. '+' means the observed time is from censored subjects.

Snapshot date: 10SEP2020, data cutoff date: 29MAY2020.

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_may2020_dco_1943\v01\outputs\tlfs\pgms\t-ae-km-gisoc-subgrp.sas Output: t02-02-02-ae-km-gisoc-sub-2-reg-safs.rtf (14DEC20:17:13) Data: adsl, adae, adttesaf

Seagen Protocol ONT-380-206**Table 2.2.2 Summary of Gastrointestinal Adverse Events by System Organ Class, Preferred Term and Geographic Region
Safety Analysis Set**

| System Organ Class/ Preferred Term | Parameters | North America | | Rest of World | |
|---------------------------------------|--|------------------------|------------------------|------------------------|-----------------------|
| | | Tuc+Cap+Tra (N=241) | Pbo+Cap+Tra (N=119) | Tuc+Cap+Tra (N=163) | Pbo+Cap+Tra (N=78) |
| Diarrhoea | Number of Subjects With at Least One Event, n (%) | 201 (83.4) | 68 (57.1) | 130 (79.8) | 38 (48.7) |
| | Number of Censored Subjects, n (%) | 40 (16.6) | 51 (42.9) | 33 (20.2) | 40 (51.3) |
| | Stratified Hazard Ratio ^{a, b} (95% C.I.) | | 2.365 (1.789, 3.126) | | 2.533 (1.756, 3.655) |
| | P-value ^{b, c} | | <.00001 | | <.00001 |
| | Interaction Test P-value ^d | | | 0.57515 | |
| | Median Time to Onset of the First Event (Days) (95% C.I.) ^e | 15.0 (13.0, 16.0) | 80.0 (43.0, 167.0) | 15.0 (12.0, 18.0) | 169.0 (62.0, -) |
| | 25 th , 75 th Percentile | 8.0, 49.0 | 22.0, - | 5.0, 118.0 | 21.0, - |
| Observed Min, Max ^f | 1, 686+ | 1, 407+ | 1, 455+ | 1, 839+ | |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (Presence or history of brain metastases: Yes/No and ECOG performance status: 0/1) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.

c. Two-sided p-value calculated from Cox proportional hazards model.

d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and geographic region.

e. Calculated using the complementary log-log transformation method (Collett, 1994).

f. '+' means the observed time is from censored subjects.

Snapshot date: 10SEP2020, data cutoff date: 29MAY2020.

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_may2020_dco_1943\v01\outputs\tlfs\pgms\t-ae-km-gisoc-subgrp.sas Output: t02-02-02-ae-km-gisoc-sub-2-reg-safs.rtf (14DEC20:17:13) Data: adsl, adae, adttesaf

Seagen Protocol ONT-380-206**Table 2.2.2 Summary of Gastrointestinal Adverse Events by System Organ Class, Preferred Term and Geographic Region
Safety Analysis Set**

| System Organ Class/ Preferred Term | Parameters | North America | | Rest of World | |
|---------------------------------------|--|------------------------|------------------------|------------------------|-----------------------|
| | | Tuc+Cap+Tra (N=241) | Pbo+Cap+Tra (N=119) | Tuc+Cap+Tra (N=163) | Pbo+Cap+Tra (N=78) |
| Nausea | Number of Subjects With at Least One Event, n (%) | 148 (61.4) | 57 (47.9) | 93 (57.1) | 31 (39.7) |
| | Number of Censored Subjects, n (%) | 93 (38.6) | 62 (52.1) | 70 (42.9) | 47 (60.3) |
| | Stratified Hazard Ratio ^{a, b} (95% C.I.) | 1.461 (1.075, 1.985) | | 1.553 (1.031, 2.339) | |
| | P-value ^{b, c} | 0.01553 | | 0.03524 | |
| | Interaction Test P-value ^d | 0.79561 | | | |
| | Median Time to Onset of the First Event (Days) (95% C.I.) ^e | 31.0 (16.0, 66.0) | 197.0 (64.0, -) | 82.0 (36.0, 225.0) | 499.0 (160.0, -) |
| | 25 th , 75 th Percentile | 7.0, - | 15.0, - | 6.0, - | 14.0, - |
| Observed Min, Max ^f | 1, 1327+ | 1, 762+ | 1, 873+ | 1, 599+ | |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (Presence or history of brain metastases: Yes/No and ECOG performance status: 0/1) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.

c. Two-sided p-value calculated from Cox proportional hazards model.

d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and geographic region.

e. Calculated using the complementary log-log transformation method (Collett, 1994).

f. '+' means the observed time is from censored subjects.

Snapshot date: 10SEP2020, data cutoff date: 29MAY2020.

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_may2020_dco_1943\v01\outputs\tlfs\pgms\t-ae-km-gisoc-subgrp.sas Output: t02-02-02-ae-km-gisoc-sub-2-reg-safs.rtf (14DEC20:17:13) Data: adsl, adae, adttesaf

Seagen Protocol ONT-380-206**Table 2.2.2 Summary of Gastrointestinal Adverse Events by System Organ Class, Preferred Term and Geographic Region
Safety Analysis Set**

| System Organ Class/ Preferred Term | Parameters | North America | | Rest of World | |
|---------------------------------------|--|------------------------|------------------------|------------------------|-----------------------|
| | | Tuc+Cap+Tra (N=241) | Pbo+Cap+Tra (N=119) | Tuc+Cap+Tra (N=163) | Pbo+Cap+Tra (N=78) |
| Vomiting | Number of Subjects With at Least One Event, n (%) | 94 (39.0) | 29 (24.4) | 55 (33.7) | 22 (28.2) |
| | Number of Censored Subjects, n (%) | 147 (61.0) | 90 (75.6) | 108 (66.3) | 56 (71.8) |
| | Stratified Hazard Ratio ^{a, b} (95% C.I.) | | 1.729 (1.138, 2.627) | | 1.164 (0.708, 1.914) |
| | P-value ^{b, c} | | 0.01023 | | 0.54840 |
| | Interaction Test P-value ^d | | | 0.26535 | |
| | Median Time to Onset of the First Event (Days) (95% C.I.) ^e | 1025.0 (359.0, -) | - (-, -) | 686.0 (599.0, -) | - (332.0, -) |
| | 25 th , 75 th Percentile | 34.0, - | 119.0, - | 52.0, - | 240.0, - |
| Observed Min, Max ^f | 1, 1327+ | 1, 762+ | 1, 855+ | 1, 839+ | |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (Presence or history of brain metastases: Yes/No and ECOG performance status: 0/1) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.

c. Two-sided p-value calculated from Cox proportional hazards model.

d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and geographic region.

e. Calculated using the complementary log-log transformation method (Collett, 1994).

f. '+' means the observed time is from censored subjects.

Snapshot date: 10SEP2020, data cutoff date: 29MAY2020.

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_may2020_dco_1943\v01\outputs\tlfs\pgms\t-ae-km-gisoc-subgrp.sas Output: t02-02-02-ae-km-gisoc-sub-2-reg-safs.rtf (14DEC20:17:13) Data: adsl, adae, adttesaf

Seagen Protocol ONT-380-206**Table 2.2.2 Summary of Gastrointestinal Adverse Events by System Organ Class, Preferred Term and Geographic Region
Safety Analysis Set**

| System Organ Class/ Preferred Term | Parameters | North America | | Rest of World | |
|---------------------------------------|--|------------------------|------------------------|------------------------|-----------------------|
| | | Tuc+Cap+Tra (N=241) | Pbo+Cap+Tra (N=119) | Tuc+Cap+Tra (N=163) | Pbo+Cap+Tra (N=78) |
| Stomatitis | Number of Subjects With at Least One Event, n (%) | 68 (28.2) | 23 (19.3) | 37 (22.7) | 5 (6.4) |
| | Number of Censored Subjects, n (%) | 173 (71.8) | 96 (80.7) | 126 (77.3) | 73 (93.6) |
| | Stratified Hazard Ratio ^{a, b} (95% C.I.) | 1.441 (0.896, 2.319) | | 4.077 (1.599, 10.397) | |
| | P-value ^{b, c} | 0.13195 | | 0.00326 | |
| | Interaction Test P-value ^d | | | 0.07072 | |
| | Median Time to Onset of the First Event (Days) (95% C.I.) ^e | - (-, -) | - (-, -) | - (-, -) | - (-, -) |
| | 25 th , 75 th Percentile | 176.0, - | -, - | 271.0, - | -, - |
| Observed Min, Max ^f | 1, 1327+ | 7, 762+ | 2, 873+ | 8, 839+ | |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (Presence or history of brain metastases: Yes/No and ECOG performance status: 0/1) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.

c. Two-sided p-value calculated from Cox proportional hazards model.

d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and geographic region.

e. Calculated using the complementary log-log transformation method (Collett, 1994).

f. '+' means the observed time is from censored subjects.

Snapshot date: 10SEP2020, data cutoff date: 29MAY2020.

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_may2020_dco_1943\v01\outputs\tlfs\pgms\t-ae-km-gisoc-subgrp.sas Output: t02-02-02-ae-km-gisoc-sub-2-reg-safs.rtf (14DEC20:17:13) Data: adsl, adae, adttesaf

Seagen Protocol ONT-380-206**Table 2.2.2 Summary of Gastrointestinal Adverse Events by System Organ Class, Preferred Term and Geographic Region
Safety Analysis Set**

| System Organ Class/ Preferred Term | Parameters | North America | | Rest of World | |
|---------------------------------------|--|------------------------|------------------------|------------------------|-----------------------|
| | | Tuc+Cap+Tra (N=241) | Pbo+Cap+Tra (N=119) | Tuc+Cap+Tra (N=163) | Pbo+Cap+Tra (N=78) |
| Constipation | Number of Subjects With at Least One Event, n (%) | 41 (17.0) | 23 (19.3) | 25 (15.3) | 19 (24.4) |
| | Number of Censored Subjects, n (%) | 200 (83.0) | 96 (80.7) | 138 (84.7) | 59 (75.6) |
| | Stratified Hazard Ratio ^{a, b} (95% C.I.) | | 0.761 (0.453, 1.280) | | 0.441 (0.238, 0.816) |
| | P-value ^{b, c} | | 0.30365 | | 0.00917 |
| | Interaction Test P-value ^d | | | 0.32726 | |
| | Median Time to Onset of the First Event (Days) (95% C.I.) ^e | - (709.0, -) | - (398.0, -) | - (-, -) | 500.0 (342.0, -) |
| | 25 th , 75 th Percentile | 660.0, - | 398.0, - | 500.0, - | 294.0, - |
| Observed Min, Max ^f | 1, 1327+ | 3, 762+ | 1, 873+ | 1, 839+ | |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (Presence or history of brain metastases: Yes/No and ECOG performance status: 0/1) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.

c. Two-sided p-value calculated from Cox proportional hazards model.

d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and geographic region.

e. Calculated using the complementary log-log transformation method (Collett, 1994).

f. '+' means the observed time is from censored subjects.

Snapshot date: 10SEP2020, data cutoff date: 29MAY2020.

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_may2020_dco_1943\v01\outputs\tlfs\pgms\t-ae-km-gisoc-subgrp.sas Output: t02-02-02-ae-km-gisoc-sub-2-reg-safs.rtf (14DEC20:17:13) Data: adsl, adae, adttesaf

Seagen Protocol ONT-380-206**Table 2.2.3 Summary of Gastrointestinal Adverse Events by System Organ Class, Preferred Term and Baseline ECOG Score
Safety Analysis Set**

| System Organ Class/ Preferred Term | Parameters | ECOG=0 | | ECOG=1 | |
|---------------------------------------|--|------------------------|-----------------------|------------------------|------------------------|
| | | Tuc+Cap+Tra (N=203) | Pbo+Cap+Tra (N=91) | Tuc+Cap+Tra (N=201) | Pbo+Cap+Tra (N=106) |
| Gastrointestinal Disorders | Number of Subjects With at Least One Event, n (%) | 190 (93.6) | 77 (84.6) | 192 (95.5) | 87 (82.1) |
| | Number of Censored Subjects, n (%) | 13 (6.4) | 14 (15.4) | 9 (4.5) | 19 (17.9) |
| | Stratified Hazard Ratio ^{a, b} (95% C.I.) | | 1.730 (1.313, 2.281) | | 2.194 (1.682, 2.863) |
| | P-value ^{b, c} | | 0.00010 | | <.00001 |
| | Interaction Test P-value ^d | | | 0.32491 | |
| | Median Time to Onset of the First Event (Days) (95% C.I.) ^e | 7.0 (5.0, 8.0) | 14.0 (9.0, 21.0) | 7.0 (5.0, 9.0) | 21.0 (14.0, 35.0) |
| | 25 th , 75 th Percentile | 2.0, 14.0 | 4.0, 61.0 | 3.0, 14.0 | 8.0, 77.0 |
| Observed Min, Max ^f | 1, 436+ | 1, 409+ | 1, 433+ | 1, 345+ | |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (Presence or history of brain metastases: Yes/No and Region of world: North America /Rest of World) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.

c. Two-sided p-value calculated from Cox proportional hazards model.

d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and baseline ECOG score.

e. Calculated using the complementary log-log transformation method (Collett, 1994).

f. '+' means the observed time is from censored subjects.

Snapshot date: 10SEP2020, data cutoff date: 29MAY2020.

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_may2020_dco_1943\v01\outputs\tlfs\pgms\t-ae-km-gisoc-subgrp.sas Output: t02-02-03-ae-km-gisoc-sub-3-ecog-safs.rtf (14DEC20:17:13) Data: adsl, adae, adttesaf

Seagen Protocol ONT-380-206**Table 2.2.3 Summary of Gastrointestinal Adverse Events by System Organ Class, Preferred Term and Baseline ECOG Score
Safety Analysis Set**

| System Organ Class/ Preferred Term | Parameters | ECOG=0 | | ECOG=1 | |
|---------------------------------------|--|------------------------|-----------------------|------------------------|------------------------|
| | | Tuc+Cap+Tra (N=203) | Pbo+Cap+Tra (N=91) | Tuc+Cap+Tra (N=201) | Pbo+Cap+Tra (N=106) |
| Diarrhoea | Number of Subjects With at Least One Event, n (%) | 167 (82.3) | 53 (58.2) | 164 (81.6) | 53 (50.0) |
| | Number of Censored Subjects, n (%) | 36 (17.7) | 38 (41.8) | 37 (18.4) | 53 (50.0) |
| | Stratified Hazard Ratio ^{a, b} (95% C.I.) | | 2.371 (1.727, 3.257) | | 2.497 (1.826, 3.415) |
| | P-value ^{b, c} | | <.00001 | | <.00001 |
| | Interaction Test P-value ^d | | | 0.74346 | |
| | Median Time to Onset of the First Event (Days) (95% C.I.) ^e | 15.0 (13.0, 17.0) | 114.0 (43.0, 194.0) | 15.0 (13.0, 19.0) | 98.0 (61.0, -) |
| | 25 th , 75 th Percentile | 7.0, 59.0 | 16.0, - | 7.0, 86.0 | 25.0, - |
| Observed Min, Max ^f | 1, 686+ | 1, 839+ | 1, 433+ | 1, 599+ | |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (Presence or history of brain metastases: Yes/No and Region of world: North America /Rest of World) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.

c. Two-sided p-value calculated from Cox proportional hazards model.

d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and baseline ECOG score.

e. Calculated using the complementary log-log transformation method (Collett, 1994).

f. '+' means the observed time is from censored subjects.

Snapshot date: 10SEP2020, data cutoff date: 29MAY2020.

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_may2020_dco_1943\v01\outputs\tlfs\pgms\t-ae-km-gisoc-subgrp.sas Output: t02-02-03-ae-km-gisoc-sub-3-ecog-safs.rtf (14DEC20:17:13) Data: adsl, adae, adttesaf

Seagen Protocol ONT-380-206**Table 2.2.3 Summary of Gastrointestinal Adverse Events by System Organ Class, Preferred Term and Baseline ECOG Score
Safety Analysis Set**

| System Organ Class/ Preferred Term | Parameters | ECOG=0 | | ECOG=1 | |
|---------------------------------------|--|------------------------|-----------------------|------------------------|------------------------|
| | | Tuc+Cap+Tra (N=203) | Pbo+Cap+Tra (N=91) | Tuc+Cap+Tra (N=201) | Pbo+Cap+Tra (N=106) |
| Nausea | Number of Subjects With at Least One Event, n (%) | 122 (60.1) | 42 (46.2) | 119 (59.2) | 46 (43.4) |
| | Number of Censored Subjects, n (%) | 81 (39.9) | 49 (53.8) | 82 (40.8) | 60 (56.6) |
| | Stratified Hazard Ratio ^{a, b} (95% C.I.) | | 1.419 (0.997, 2.020) | | 1.544 (1.096, 2.174) |
| | P-value ^{b, c} | | 0.05176 | | 0.01297 |
| | Interaction Test P-value ^d | | | 0.74498 | |
| | Median Time to Onset of the First Event (Days) (95% C.I.) ^e | 43.0 (17.0, 171.0) | 342.0 (75.0, -) | 49.0 (22.0, 160.0) | -(104.0, -) |
| | 25 th , 75 th Percentile | 6.0, - | 12.0, 499.0 | 7.0, - | 21.0, - |
| Observed Min, Max ^f | 1, 1327+ | 1, 546+ | 1, 945+ | 1, 762+ | |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (Presence or history of brain metastases: Yes/No and Region of world: North America /Rest of World) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.

c. Two-sided p-value calculated from Cox proportional hazards model.

d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and baseline ECOG score.

e. Calculated using the complementary log-log transformation method (Collett, 1994).

f. '+' means the observed time is from censored subjects.

Snapshot date: 10SEP2020, data cutoff date: 29MAY2020.

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_may2020_dco_1943\v01\outputs\tlfs\pgms\t-ae-km-gisoc-subgrp.sas Output: t02-02-03-ae-km-gisoc-sub-3-ecog-safs.rtf (14DEC20:17:13) Data: adsl, adae, adttesaf

Seagen Protocol ONT-380-206**Table 2.2.3 Summary of Gastrointestinal Adverse Events by System Organ Class, Preferred Term and Baseline ECOG Score
Safety Analysis Set**

| System Organ Class/ Preferred Term | Parameters | ECOG=0 | | ECOG=1 | |
|---------------------------------------|--|------------------------|-----------------------|------------------------|------------------------|
| | | Tuc+Cap+Tra (N=203) | Pbo+Cap+Tra (N=91) | Tuc+Cap+Tra (N=201) | Pbo+Cap+Tra (N=106) |
| Vomiting | Number of Subjects With at Least One Event, n (%) | 73 (36.0) | 26 (28.6) | 76 (37.8) | 25 (23.6) |
| | Number of Censored Subjects, n (%) | 130 (64.0) | 65 (71.4) | 125 (62.2) | 81 (76.4) |
| | Stratified Hazard Ratio ^{a, b} (95% C.I.) | | 1.293 (0.824, 2.029) | | 1.674 (1.064, 2.633) |
| | P-value ^{b, c} | | 0.26361 | | 0.02590 |
| | Interaction Test P-value ^d | | | 0.41959 | |
| | Median Time to Onset of the First Event (Days) (95% C.I.) ^e | 1025.0 (686.0, -) | - (332.0, -) | 599.0 (520.0, -) | - (-, -) |
| | 25 th , 75 th Percentile | 45.0, - | 173.0, - | 42.0, - | 266.0, - |
| Observed Min, Max ^f | 1, 1327+ | 1, 839+ | 1, 899+ | 3, 762+ | |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (Presence or history of brain metastases: Yes/No and Region of world: North America /Rest of World) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.

c. Two-sided p-value calculated from Cox proportional hazards model.

d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and baseline ECOG score.

e. Calculated using the complementary log-log transformation method (Collett, 1994).

f. '+' means the observed time is from censored subjects.

Snapshot date: 10SEP2020, data cutoff date: 29MAY2020.

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_may2020_dco_1943\v01\outputs\tlfs\pgms\t-ae-km-gisoc-subgrp.sas Output:
t02-02-03-ae-km-gisoc-sub-3-ecog-safs.rtf (14DEC20:17:13) Data: adsl, adae, adttesaf

Seagen Protocol ONT-380-206**Table 2.2.3 Summary of Gastrointestinal Adverse Events by System Organ Class, Preferred Term and Baseline ECOG Score
Safety Analysis Set**

| System Organ Class/ Preferred Term | Parameters | ECOG=0 | | ECOG=1 | |
|---------------------------------------|--|------------------------|-----------------------|------------------------|------------------------|
| | | Tuc+Cap+Tra (N=203) | Pbo+Cap+Tra (N=91) | Tuc+Cap+Tra (N=201) | Pbo+Cap+Tra (N=106) |
| Stomatitis | Number of Subjects With at Least One Event, n (%) | 51 (25.1) | 15 (16.5) | 54 (26.9) | 13 (12.3) |
| | Number of Censored Subjects, n (%) | 152 (74.9) | 76 (83.5) | 147 (73.1) | 93 (87.7) |
| | Stratified Hazard Ratio ^{a, b} (95% C.I.) | | 1.637 (0.919, 2.915) | | 2.246 (1.222, 4.128) |
| | P-value ^{b, c} | | 0.09443 | | 0.00914 |
| | Interaction Test P-value ^d | | | 0.38466 | |
| | Median Time to Onset of the First Event (Days) (95% C.I.) ^e | - (-, -) | - (-, -) | - (615.0, -) | - (-, -) |
| | 25 th , 75 th Percentile | 206.0, - | -, - | 176.0, - | -, - |
| Observed Min, Max ^f | 1, 1327+ | 7, 839+ | 1, 945+ | 8, 762+ | |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (Presence or history of brain metastases: Yes/No and Region of world: North America /Rest of World) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.

c. Two-sided p-value calculated from Cox proportional hazards model.

d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and baseline ECOG score.

e. Calculated using the complementary log-log transformation method (Collett, 1994).

f. '+' means the observed time is from censored subjects.

Snapshot date: 10SEP2020, data cutoff date: 29MAY2020.

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_may2020_dco_1943\v01\outputs\tlfs\pgms\t-ae-km-gisoc-subgrp.sas Output: t02-02-03-ae-km-gisoc-sub-3-ecog-safs.rtf (14DEC20:17:13) Data: adsl, adae, adttesaf

Seagen Protocol ONT-380-206**Table 2.2.3 Summary of Gastrointestinal Adverse Events by System Organ Class, Preferred Term and Baseline ECOG Score
Safety Analysis Set**

| System Organ Class/ Preferred Term | Parameters | ECOG=0 | | ECOG=1 | |
|---------------------------------------|--|------------------------|-----------------------|------------------------|------------------------|
| | | Tuc+Cap+Tra (N=203) | Pbo+Cap+Tra (N=91) | Tuc+Cap+Tra (N=201) | Pbo+Cap+Tra (N=106) |
| Constipation | Number of Subjects With at Least One Event, n (%) | 21 (10.3) | 21 (23.1) | 45 (22.4) | 21 (19.8) |
| | Number of Censored Subjects, n (%) | 182 (89.7) | 70 (76.9) | 156 (77.6) | 85 (80.2) |
| | Stratified Hazard Ratio ^{a, b} (95% C.I.) | | 0.361 (0.193, 0.676) | | 0.910 (0.537, 1.544) |
| | P-value ^{b, c} | | 0.00144 | | 0.72694 |
| | Interaction Test P-value ^d | | | 0.01089 | |
| | Median Time to Onset of the First Event (Days) (95% C.I.) ^e | - (-, -) | - (500.0, -) | - (643.0, -) | - (398.0, -) |
| | 25 th , 75 th Percentile | -, - | 313.0, - | 295.0, - | 398.0, - |
| Observed Min, Max ^f | 1, 1327+ | 1, 839+ | 1, 945+ | 1, 762+ | |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (Presence or history of brain metastases: Yes/No and Region of world: North America /Rest of World) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.

c. Two-sided p-value calculated from Cox proportional hazards model.

d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and baseline ECOG score.

e. Calculated using the complementary log-log transformation method (Collett, 1994).

f. '+' means the observed time is from censored subjects.

Snapshot date: 10SEP2020, data cutoff date: 29MAY2020.

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_may2020_dco_1943\v01\outputs\tlfs\pgms\t-ae-km-gisoc-subgrp.sas Output: t02-02-03-ae-km-gisoc-sub-3-ecog-safs.rtf (14DEC20:17:13) Data: adsl, adae, adttesaf

Seagen Protocol ONT-380-206**Table 2.2.4 Summary of Gastrointestinal Adverse Events by System Organ Class, Preferred Term and Age Safety Analysis Set**

| System Organ Class/ Preferred Term | Parameters | Age < 65 Years | | Age ≥ 65 Years | |
|---------------------------------------|--|------------------------|------------------------|-----------------------|-----------------------|
| | | Tuc+Cap+Tra (N=322) | Pbo+Cap+Tra (N=164) | Tuc+Cap+Tra (N=82) | Pbo+Cap+Tra (N=33) |
| Gastrointestinal Disorders | Number of Subjects With at Least One Event, n (%) | 303 (94.1) | 139 (84.8) | 79 (96.3) | 25 (75.8) |
| | Number of Censored Subjects, n (%) | 19 (5.9) | 25 (15.2) | 3 (3.7) | 8 (24.2) |
| | Stratified Hazard Ratio ^{a, b} (95% C.I.) | | 1.687 (1.371, 2.075) | | 3.951 (2.210, 7.062) |
| | P-value ^{b, c} | | <.00001 | | <.00001 |
| | Interaction Test P-value ^d | | | 0.01812 | |
| | Median Time to Onset of the First Event (Days) (95% C.I.) ^e | 7.0 (5.0, 8.0) | 15.0 (11.0, 21.0) | 7.0 (5.0, 9.0) | 41.0 (14.0, 77.0) |
| | 25 th , 75 th Percentile | 2.0, 15.0 | 5.0, 55.0 | 3.0, 13.0 | 13.0, 125.0 |
| Observed Min, Max ^f | 1, 436+ | 1, 345+ | 1, 282+ | 1, 409+ | |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (Presence or history of brain metastases: Yes/No, ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.

c. Two-sided p-value calculated from Cox proportional hazards model.

d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and age.

e. Calculated using the complementary log-log transformation method (Collett, 1994).

f. '+' means the observed time is from censored subjects.

Snapshot date: 10SEP2020, data cutoff date: 29MAY2020.

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_may2020_dco_1943\v01\outputs\tlfs\pgms\t-ae-km-gisoc-subgrp.sas Output: t02-02-04-ae-km-gisoc-sub-4-age-safs.rtf (14DEC20:17:13) Data: adsl, adae, adttesaf

Seagen Protocol ONT-380-206**Table 2.2.4 Summary of Gastrointestinal Adverse Events by System Organ Class, Preferred Term and Age Safety Analysis Set**

| System Organ Class/ Preferred Term | Parameters | Age < 65 Years | | Age ≥ 65 Years | |
|---------------------------------------|--|------------------------|------------------------|-----------------------|-----------------------|
| | | Tuc+Cap+Tra (N=322) | Pbo+Cap+Tra (N=164) | Tuc+Cap+Tra (N=82) | Pbo+Cap+Tra (N=33) |
| Diarrhoea | Number of Subjects With at Least One Event, n (%) | 260 (80.7) | 91 (55.5) | 71 (86.6) | 15 (45.5) |
| | Number of Censored Subjects, n (%) | 62 (19.3) | 73 (44.5) | 11 (13.4) | 18 (54.5) |
| | Stratified Hazard Ratio ^{a, b} (95% C.I.) | | 2.173 (1.705, 2.770) | | 4.410 (2.386, 8.152) |
| | P-value ^{b, c} | | <.00001 | | <.00001 |
| | Interaction Test P-value ^d | | | 0.03417 | |
| | Median Time to Onset of the First Event (Days) (95% C.I.) ^e | 16.0 (14.0, 19.0) | 96.0 (59.0, 183.0) | 12.0 (10.0, 14.0) | 129.0 (64.0, -) |
| | 25 th , 75 th Percentile | 7.0, 94.0 | 20.0, - | 6.0, 21.0 | 41.0, - |
| Observed Min, Max ^f | 1, 686+ | 1, 839+ | 1, 455+ | 2, 409+ | |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (Presence or history of brain metastases: Yes/No, ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.

c. Two-sided p-value calculated from Cox proportional hazards model.

d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and age.

e. Calculated using the complementary log-log transformation method (Collett, 1994).

f. '+' means the observed time is from censored subjects.

Snapshot date: 10SEP2020, data cutoff date: 29MAY2020.

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_may2020_dco_1943\v01\outputs\tlfs\pgms\t-ae-km-gisoc-subgrp.sas Output: t02-02-04-ae-km-gisoc-sub-4-age-safs.rtf (14DEC20:17:13) Data: adsl, adae, adttesaf

Seagen Protocol ONT-380-206**Table 2.2.4 Summary of Gastrointestinal Adverse Events by System Organ Class, Preferred Term and Age Safety Analysis Set**

| System Organ Class/ Preferred Term | Parameters | Age < 65 Years | | Age ≥ 65 Years | |
|---------------------------------------|--|------------------------|------------------------|-----------------------|-----------------------|
| | | Tuc+Cap+Tra (N=322) | Pbo+Cap+Tra (N=164) | Tuc+Cap+Tra (N=82) | Pbo+Cap+Tra (N=33) |
| Nausea | Number of Subjects With at Least One Event, n (%) | 190 (59.0) | 78 (47.6) | 51 (62.2) | 10 (30.3) |
| | Number of Censored Subjects, n (%) | 132 (41.0) | 86 (52.4) | 31 (37.8) | 23 (69.7) |
| | Stratified Hazard Ratio ^{a, b} (95% C.I.) | | 1.337 (1.025, 1.743) | | 2.767 (1.377, 5.563) |
| | P-value ^{b, c} | | 0.03225 | | 0.00427 |
| | Interaction Test P-value ^d | | | 0.06526 | |
| | Median Time to Onset of the First Event (Days) (95% C.I.) ^e | 43.0 (21.0, 160.0) | 205.0 (75.0, -) | 53.0 (22.0, 136.0) | -(119.0, -) |
| | 25 th , 75 th Percentile | 6.0, - | 12.0, - | 9.0, - | 104.0, - |
| Observed Min, Max ^f | 1, 1327+ | 1, 762+ | 1, 945+ | 7, 428+ | |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (Presence or history of brain metastases: Yes/No, ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.

c. Two-sided p-value calculated from Cox proportional hazards model.

d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and age.

e. Calculated using the complementary log-log transformation method (Collett, 1994).

f. '+' means the observed time is from censored subjects.

Snapshot date: 10SEP2020, data cutoff date: 29MAY2020.

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_may2020_dco_1943\v01\outputs\tlfs\pgms\t-ae-km-gisoc-subgrp.sas Output: t02-02-04-ae-km-gisoc-sub-4-age-safs.rtf (14DEC20:17:13) Data: adsl, adae, adttesaf

Seagen Protocol ONT-380-206**Table 2.2.4 Summary of Gastrointestinal Adverse Events by System Organ Class, Preferred Term and Age Safety Analysis Set**

| System Organ Class/ Preferred Term | Parameters | Age < 65 Years | | Age ≥ 65 Years | |
|---------------------------------------|--|------------------------|------------------------|-----------------------|-----------------------|
| | | Tuc+Cap+Tra (N=322) | Pbo+Cap+Tra (N=164) | Tuc+Cap+Tra (N=82) | Pbo+Cap+Tra (N=33) |
| Vomiting | Number of Subjects With at Least One Event, n (%) | 114 (35.4) | 43 (26.2) | 35 (42.7) | 8 (24.2) |
| | Number of Censored Subjects, n (%) | 208 (64.6) | 121 (73.8) | 47 (57.3) | 25 (75.8) |
| | Stratified Hazard Ratio ^{a, b} (95% C.I.) | | 1.337 (0.939, 1.904) | | 2.117 (0.968, 4.630) |
| | P-value ^{b, c} | | 0.10701 | | 0.06034 |
| | Interaction Test P-value ^d | | | 0.30635 | |
| | Median Time to Onset of the First Event (Days) (95% C.I.) ^e | 1025.0 (686.0, -) | - (-, -) | 520.0 (73.0, -) | - (266.0, -) |
| | 25 th , 75 th Percentile | 48.0, - | 173.0, - | 34.0, - | 266.0, - |
| Observed Min, Max ^f | 1, 1327+ | 1, 839+ | 1, 585+ | 5, 428+ | |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (Presence or history of brain metastases: Yes/No, ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.

c. Two-sided p-value calculated from Cox proportional hazards model.

d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and age.

e. Calculated using the complementary log-log transformation method (Collett, 1994).

f. '+' means the observed time is from censored subjects.

Snapshot date: 10SEP2020, data cutoff date: 29MAY2020.

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_may2020_dco_1943\v01\outputs\tlfs\pgms\t-ae-km-gisoc-subgrp.sas Output: t02-02-04-ae-km-gisoc-sub-4-age-safs.rtf (14DEC20:17:13) Data: adsl, adae, adttesaf

Seagen Protocol ONT-380-206**Table 2.2.4 Summary of Gastrointestinal Adverse Events by System Organ Class, Preferred Term and Age Safety Analysis Set**

| System Organ Class/ Preferred Term | Parameters | Age < 65 Years | | Age ≥ 65 Years | |
|---------------------------------------|--|------------------------|------------------------|-----------------------|-----------------------|
| | | Tuc+Cap+Tra (N=322) | Pbo+Cap+Tra (N=164) | Tuc+Cap+Tra (N=82) | Pbo+Cap+Tra (N=33) |
| Stomatitis | Number of Subjects With at Least One Event, n (%) | 82 (25.5) | 21 (12.8) | 23 (28.0) | 7 (21.2) |
| | Number of Censored Subjects, n (%) | 240 (74.5) | 143 (87.2) | 59 (72.0) | 26 (78.8) |
| | Stratified Hazard Ratio ^{a, b} (95% C.I.) | | 2.040 (1.260, 3.304) | | 1.404 (0.590, 3.339) |
| | P-value ^{b, c} | | 0.00374 | | 0.44320 |
| | Interaction Test P-value ^d | | | 0.38035 | |
| | Median Time to Onset of the First Event (Days) (95% C.I.) ^e | - (-, -) | - (-, -) | - (-, -) | - (-, -) |
| | 25 th , 75 th Percentile | 206.0, - | -, - | 72.0, - | 186.0, - |
| Observed Min, Max ^f | 2, 1327+ | 7, 839+ | 1, 945+ | 7, 428+ | |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (Presence or history of brain metastases: Yes/No, ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.

c. Two-sided p-value calculated from Cox proportional hazards model.

d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and age.

e. Calculated using the complementary log-log transformation method (Collett, 1994).

f. '+' means the observed time is from censored subjects.

Snapshot date: 10SEP2020, data cutoff date: 29MAY2020.

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_may2020_dco_1943\v01\outputs\tlfs\pgms\t-ae-km-gisoc-subgrp.sas Output: t02-02-04-ae-km-gisoc-sub-4-age-safs.rtf (14DEC20:17:13) Data: adsl, adae, adttesaf

Seagen Protocol ONT-380-206**Table 2.2.4 Summary of Gastrointestinal Adverse Events by System Organ Class, Preferred Term and Age Safety Analysis Set**

| System Organ Class/ Preferred Term | Parameters | Age < 65 Years | | Age ≥ 65 Years | |
|---------------------------------------|--|------------------------|------------------------|-----------------------|-----------------------|
| | | Tuc+Cap+Tra (N=322) | Pbo+Cap+Tra (N=164) | Tuc+Cap+Tra (N=82) | Pbo+Cap+Tra (N=33) |
| Constipation | Number of Subjects With at Least One Event, n (%) | 53 (16.5) | 36 (22.0) | 13 (15.9) | 6 (18.2) |
| | Number of Censored Subjects, n (%) | 269 (83.5) | 128 (78.0) | 69 (84.1) | 27 (81.8) |
| | Stratified Hazard Ratio ^{a, b} (95% C.I.) | | 0.571 (0.368, 0.887) | | 0.974 (0.358, 2.651) |
| | P-value ^{b, c} | | 0.01254 | | 0.95935 |
| | Interaction Test P-value ^d | | | 0.51368 | |
| | Median Time to Onset of the First Event (Days) (95% C.I.) ^e | - (-, -) | - (500.0, -) | - (-, -) | 398.0 (398.0, -) |
| | 25 th , 75 th Percentile | 643.0, - | 313.0, - | -, - | 398.0, - |
| Observed Min, Max ^f | 1, 1327+ | 1, 839+ | 4+, 945+ | 9, 409+ | |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (Presence or history of brain metastases: Yes/No, ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.

c. Two-sided p-value calculated from Cox proportional hazards model.

d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and age.

e. Calculated using the complementary log-log transformation method (Collett, 1994).

f. '+' means the observed time is from censored subjects.

Snapshot date: 10SEP2020, data cutoff date: 29MAY2020.

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_may2020_dco_1943\v01\outputs\tlfs\pgms\t-ae-km-gisoc-subgrp.sas Output: t02-02-04-ae-km-gisoc-sub-4-age-safs.rtf (14DEC20:17:13) Data: adsl, adae, adttesaf

Seagen Protocol ONT-380-206**Table 2.2.5 Summary of Gastrointestinal Adverse Events by System Organ Class, Preferred Term and Race Safety Analysis Set**

| System Organ Class/ Preferred Term | Parameters | White | | Non-White | |
|---------------------------------------|--|------------------------|------------------------|------------------------|-----------------------|
| | | Tuc+Cap+Tra (N=283) | Pbo+Cap+Tra (N=153) | Tuc+Cap+Tra (N=121) | Pbo+Cap+Tra (N=44) |
| Gastrointestinal Disorders | Number of Subjects With at Least One Event, n (%) | 267 (94.3) | 128 (83.7) | 115 (95.0) | 36 (81.8) |
| | Number of Censored Subjects, n (%) | 16 (5.7) | 25 (16.3) | 6 (5.0) | 8 (18.2) |
| | Stratified Hazard Ratio ^{a, b} (95% C.I.) | | 1.812 (1.455, 2.256) | | 2.634 (1.715, 4.045) |
| | P-value ^{b, c} | | <.00001 | | <.00001 |
| | Interaction Test P-value ^d | | | 0.30821 | |
| | Median Time to Onset of the First Event (Days) (95% C.I.) ^e | 7.0 (6.0, 8.0) | 15.0 (12.0, 21.0) | 7.0 (5.0, 8.0) | 24.0 (10.0, 49.0) |
| | 25 th , 75 th Percentile | 3.0, 14.0 | 5.0, 68.0 | 2.0, 14.0 | 8.5, 64.0 |
| Observed Min, Max ^f | 1, 433+ | 1, 409+ | 1, 436+ | 1, 205+ | |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (Presence or history of brain metastases: Yes/No, ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.

c. Two-sided p-value calculated from Cox proportional hazards model.

d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and race.

e. Calculated using the complementary log-log transformation method (Collett, 1994).

f. '+' means the observed time is from censored subjects.

Snapshot date: 10SEP2020, data cutoff date: 29MAY2020.

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_may2020_dco_1943\v01\outputs\tlfs\pgms\t-ae-km-gisoc-subgrp.sas Output: t02-02-05-ae-km-gisoc-sub-5-race-safs.rtf (14DEC20:17:13) Data: adsl, adae, adttesaf

Seagen Protocol ONT-380-206**Table 2.2.5 Summary of Gastrointestinal Adverse Events by System Organ Class, Preferred Term and Race Safety Analysis Set**

| System Organ Class/ Preferred Term | Parameters | White | | Non-White | |
|---------------------------------------|--|------------------------|------------------------|------------------------|-----------------------|
| | | Tuc+Cap+Tra (N=283) | Pbo+Cap+Tra (N=153) | Tuc+Cap+Tra (N=121) | Pbo+Cap+Tra (N=44) |
| Diarrhoea | Number of Subjects With at Least One Event, n (%) | 230 (81.3) | 87 (56.9) | 101 (83.5) | 19 (43.2) |
| | Number of Censored Subjects, n (%) | 53 (18.7) | 66 (43.1) | 20 (16.5) | 25 (56.8) |
| | Stratified Hazard Ratio ^{a, b} (95% C.I.) | | 2.229 (1.736, 2.861) | | 3.533 (2.107, 5.923) |
| | P-value ^{b, c} | | <.00001 | | <.00001 |
| | Interaction Test P-value ^d | | | 0.14119 | |
| | Median Time to Onset of the First Event (Days) (95% C.I.) ^e | 15.0 (13.0, 16.0) | 89.0 (57.0, 167.0) | 15.0 (11.0, 21.0) | - (64.0, -) |
| | 25 th , 75 th Percentile | 7.0, 71.0 | 18.0, - | 7.0, 60.0 | 35.0, - |
| Observed Min, Max ^f | 1, 686+ | 1, 839+ | 1, 436+ | 1, 599+ | |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (Presence or history of brain metastases: Yes/No, ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.

c. Two-sided p-value calculated from Cox proportional hazards model.

d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and race.

e. Calculated using the complementary log-log transformation method (Collett, 1994).

f. '+' means the observed time is from censored subjects.

Snapshot date: 10SEP2020, data cutoff date: 29MAY2020.

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_may2020_dco_1943\v01\outputs\tlfs\pgms\t-ae-km-gisoc-subgrp.sas Output: t02-02-05-ae-km-gisoc-sub-5-race-safs.rtf (14DEC20:17:13) Data: adsl, adae, adttesaf

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Table 2.2.5 Summary of Gastrointestinal Adverse Events by System Organ Class, Preferred Term and Race Safety Analysis Set

| System Organ Class/ Preferred Term | Parameters | White | | Non-White | |
|---------------------------------------|--|------------------------|------------------------|------------------------|-----------------------|
| | | Tuc+Cap+Tra (N=283) | Pbo+Cap+Tra (N=153) | Tuc+Cap+Tra (N=121) | Pbo+Cap+Tra (N=44) |
| Nausea | Number of Subjects With at Least One Event, n (%) | 168 (59.4) | 74 (48.4) | 73 (60.3) | 14 (31.8) |
| | Number of Censored Subjects, n (%) | 115 (40.6) | 79 (51.6) | 48 (39.7) | 30 (68.2) |
| | Stratified Hazard Ratio ^{a, b} (95% C.I.) | | 1.338 (1.015, 1.764) | | 2.342 (1.310, 4.185) |
| | P-value ^{b, c} | | 0.03860 | | 0.00408 |
| | Interaction Test P-value ^d | | | 0.08296 | |
| | Median Time to Onset of the First Event (Days) (95% C.I.) ^e | 43.0 (21.0, 148.0) | 197.0 (64.0, -) | 49.0 (21.0, 228.0) | -(172.0, -) |
| | 25 th , 75 th Percentile | 5.0, - | 13.0, - | 7.0, - | 65.0, - |
| Observed Min, Max ^f | 1, 1327+ | 1, 762+ | 1, 674+ | 1, 599+ | |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (Presence or history of brain metastases: Yes/No, ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.

c. Two-sided p-value calculated from Cox proportional hazards model.

d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and race.

e. Calculated using the complementary log-log transformation method (Collett, 1994).

f. '+' means the observed time is from censored subjects.

Snapshot date: 10SEP2020, data cutoff date: 29MAY2020.

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Seagen Protocol ONT-380-206**Table 2.2.5 Summary of Gastrointestinal Adverse Events by System Organ Class, Preferred Term and Race Safety Analysis Set**

| System Organ Class/ Preferred Term | Parameters | White | | Non-White | |
|---------------------------------------|--|------------------------|------------------------|------------------------|-----------------------|
| | | Tuc+Cap+Tra (N=283) | Pbo+Cap+Tra (N=153) | Tuc+Cap+Tra (N=121) | Pbo+Cap+Tra (N=44) |
| Vomiting | Number of Subjects With at Least One Event, n (%) | 106 (37.5) | 41 (26.8) | 43 (35.5) | 10 (22.7) |
| | Number of Censored Subjects, n (%) | 177 (62.5) | 112 (73.2) | 78 (64.5) | 34 (77.3) |
| | Stratified Hazard Ratio ^{a, b} (95% C.I.) | | 1.463 (1.016, 2.105) | | 1.593 (0.793, 3.199) |
| | P-value ^{b, c} | | 0.04058 | | 0.19092 |
| | Interaction Test P-value ^d | | | 0.76299 | |
| | Median Time to Onset of the First Event (Days) (95% C.I.) ^e | 1025.0 (686.0, -) | - (-, -) | 599.0 (520.0, -) | - (-, -) |
| | 25 th , 75 th Percentile | 40.0, - | 146.0, - | 62.0, - | 173.0, - |
| Observed Min, Max ^f | 1, 1327+ | 1, 839+ | 1, 1051+ | 1, 599+ | |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (Presence or history of brain metastases: Yes/No, ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.

c. Two-sided p-value calculated from Cox proportional hazards model.

d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and race.

e. Calculated using the complementary log-log transformation method (Collett, 1994).

f. '+' means the observed time is from censored subjects.

Snapshot date: 10SEP2020, data cutoff date: 29MAY2020.

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Seagen Protocol ONT-380-206**Table 2.2.5 Summary of Gastrointestinal Adverse Events by System Organ Class, Preferred Term and Race Safety Analysis Set**

| System Organ Class/ Preferred Term | Parameters | White | | Non-White | |
|---------------------------------------|--|------------------------|------------------------|------------------------|-----------------------|
| | | Tuc+Cap+Tra (N=283) | Pbo+Cap+Tra (N=153) | Tuc+Cap+Tra (N=121) | Pbo+Cap+Tra (N=44) |
| Stomatitis | Number of Subjects With at Least One Event, n (%) | 65 (23.0) | 24 (15.7) | 40 (33.1) | 4 (9.1) |
| | Number of Censored Subjects, n (%) | 218 (77.0) | 129 (84.3) | 81 (66.9) | 40 (90.9) |
| | Stratified Hazard Ratio ^{a, b} (95% C.I.) | | 1.501 (0.938, 2.403) | | 4.414 (1.536, 12.685) |
| | P-value ^{b, c} | | 0.09078 | | 0.00584 |
| | Interaction Test P-value ^d | | | 0.07691 | |
| | Median Time to Onset of the First Event (Days) (95% C.I.) ^e | - (-, -) | - (-, -) | - (274.0, -) | - (-, -) |
| | 25 th , 75 th Percentile | 615.0, - | -, - | 120.0, - | -, - |
| Observed Min, Max ^f | 1, 1327+ | 7, 839+ | 2, 785+ | 11, 599+ | |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (Presence or history of brain metastases: Yes/No, ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.

c. Two-sided p-value calculated from Cox proportional hazards model.

d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and race.

e. Calculated using the complementary log-log transformation method (Collett, 1994).

f. '+' means the observed time is from censored subjects.

Snapshot date: 10SEP2020, data cutoff date: 29MAY2020.

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Seagen Protocol ONT-380-206**Table 2.2.5 Summary of Gastrointestinal Adverse Events by System Organ Class, Preferred Term and Race Safety Analysis Set**

| System Organ Class/ Preferred Term | Parameters | White | | Non-White | |
|---------------------------------------|--|------------------------|------------------------|------------------------|-----------------------|
| | | Tuc+Cap+Tra (N=283) | Pbo+Cap+Tra (N=153) | Tuc+Cap+Tra (N=121) | Pbo+Cap+Tra (N=44) |
| Constipation | Number of Subjects With at Least One Event, n (%) | 46 (16.3) | 34 (22.2) | 20 (16.5) | 8 (18.2) |
| | Number of Censored Subjects, n (%) | 237 (83.7) | 119 (77.8) | 101 (83.5) | 36 (81.8) |
| | Stratified Hazard Ratio ^{a, b} (95% C.I.) | | 0.576 (0.365, 0.909) | | 0.850 (0.361, 2.000) |
| | P-value ^{b, c} | | 0.01786 | | 0.70910 |
| | Interaction Test P-value ^d | | | 0.55319 | |
| | Median Time to Onset of the First Event (Days) (95% C.I.) ^e | - (-, -) | - (500.0, -) | - (709.0, -) | - (313.0, -) |
| | 25 th , 75 th Percentile | 643.0, - | 295.0, - | 709.0, - | 313.0, - |
| Observed Min, Max ^f | 1, 1327+ | 1, 839+ | 1, 1051+ | 1, 583+ | |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (Presence or history of brain metastases: Yes/No, ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.

c. Two-sided p-value calculated from Cox proportional hazards model.

d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and race.

e. Calculated using the complementary log-log transformation method (Collett, 1994).

f. '+' means the observed time is from censored subjects.

Snapshot date: 10SEP2020, data cutoff date: 29MAY2020.

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_may2020_dco_1943\v01\outputs\tlfs\pgms\t-ae-km-gisoc-subgrp.sas Output: t02-02-05-ae-km-gisoc-sub-5-race-safs.rtf (14DEC20:17:13) Data: adsl, adae, adttesaf

Seagen Protocol ONT-380-206**Table 2.2.6 Summary of Gastrointestinal Adverse Events by System Organ Class, Preferred Term and Hormone Receptor Status Safety Analysis Set**

| System Organ Class/ Preferred Term | Parameters | Negative for Both | | Positive for ER or PR or Both | |
|---------------------------------------|--|------------------------|-----------------------|-------------------------------|------------------------|
| | | Tuc+Cap+Tra (N=163) | Pbo+Cap+Tra (N=74) | Tuc+Cap+Tra (N=241) | Pbo+Cap+Tra (N=123) |
| Gastrointestinal Disorders | Number of Subjects With at Least One Event, n (%) | 152 (93.3) | 59 (79.7) | 230 (95.4) | 105 (85.4) |
| | Number of Censored Subjects, n (%) | 11 (6.7) | 15 (20.3) | 11 (4.6) | 18 (14.6) |
| | Stratified Hazard Ratio ^{a, b} (95% C.I.) | | 1.753 (1.283, 2.394) | | 2.072 (1.620, 2.649) |
| | P-value ^{b, c} | | 0.00042 | | <.00001 |
| | Interaction Test P-value ^d | | | 0.64195 | |
| | Median Time to Onset of the First Event (Days) (95% C.I.) ^e | 7.0 (5.0, 8.0) | 15.5 (11.0, 22.0) | 7.0 (6.0, 8.0) | 15.0 (13.0, 26.0) |
| | 25 th , 75 th Percentile | 2.0, 15.0 | 7.0, 66.0 | 3.0, 14.0 | 6.0, 77.0 |
| Observed Min, Max ^f | 1, 433+ | 1, 345+ | 1, 436+ | 1, 409+ | |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (Presence or history of brain metastases: Yes/No, ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.

c. Two-sided p-value calculated from Cox proportional hazards model.

d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and hormone receptor status.

e. Calculated using the complementary log-log transformation method (Collett, 1994).

f. '+' means the observed time is from censored subjects.

Snapshot date: 10SEP2020, data cutoff date: 29MAY2020.

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_may2020_dco_1943\v01\outputs\tlfs\pgms\t-ae-km-gisoc-subgrp.sas Output: t02-02-06-ae-km-gisoc-sub-6-hr-safs.rtf (14DEC20:17:13) Data: adsl, adae, adttesaf

Seagen Protocol ONT-380-206**Table 2.2.6 Summary of Gastrointestinal Adverse Events by System Organ Class, Preferred Term and Hormone Receptor Status Safety Analysis Set**

| System Organ Class/ Preferred Term | Parameters | Negative for Both | | Positive for ER or PR or Both | |
|---------------------------------------|--|------------------------|-----------------------|-------------------------------|------------------------|
| | | Tuc+Cap+Tra (N=163) | Pbo+Cap+Tra (N=74) | Tuc+Cap+Tra (N=241) | Pbo+Cap+Tra (N=123) |
| Diarrhoea | Number of Subjects With at Least One Event, n (%) | 137 (84.0) | 37 (50.0) | 194 (80.5) | 69 (56.1) |
| | Number of Censored Subjects, n (%) | 26 (16.0) | 37 (50.0) | 47 (19.5) | 54 (43.9) |
| | Stratified Hazard Ratio ^{a, b} (95% C.I.) | | 2.560 (1.768, 3.708) | | 2.305 (1.742, 3.050) |
| | P-value ^{b, c} | | <.00001 | | <.00001 |
| | Interaction Test P-value ^d | | | 0.77332 | |
| | Median Time to Onset of the First Event (Days) (95% C.I.) ^e | 15.0 (13.0, 20.0) | 129.0 (43.0, -) | 14.0 (13.0, 16.0) | 89.0 (57.0, 205.0) |
| | 25 th , 75 th Percentile | 7.0, 87.0 | 22.0, - | 7.0, 60.0 | 19.0, - |
| Observed Min, Max ^f | 1, 656+ | 2, 386+ | 1, 686+ | 1, 839+ | |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (Presence or history of brain metastases: Yes/No, ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.

c. Two-sided p-value calculated from Cox proportional hazards model.

d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and hormone receptor status.

e. Calculated using the complementary log-log transformation method (Collett, 1994).

f. '+' means the observed time is from censored subjects.

Snapshot date: 10SEP2020, data cutoff date: 29MAY2020.

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_may2020_dco_1943\v01\outputs\tlfs\pgms\t-ae-km-gisoc-subgrp.sas Output: t02-02-06-ae-km-gisoc-sub-6-hr-safs.rtf (14DEC20:17:13) Data: adsl, adae, adttesaf

Seagen Protocol ONT-380-206**Table 2.2.6 Summary of Gastrointestinal Adverse Events by System Organ Class, Preferred Term and Hormone Receptor Status Safety Analysis Set**

| System Organ Class/ Preferred Term | Parameters | Negative for Both | | Positive for ER or PR or Both | |
|---------------------------------------|--|------------------------|-----------------------|-------------------------------|------------------------|
| | | Tuc+Cap+Tra (N=163) | Pbo+Cap+Tra (N=74) | Tuc+Cap+Tra (N=241) | Pbo+Cap+Tra (N=123) |
| Nausea | Number of Subjects With at Least One Event, n (%) | 91 (55.8) | 30 (40.5) | 150 (62.2) | 58 (47.2) |
| | Number of Censored Subjects, n (%) | 72 (44.2) | 44 (59.5) | 91 (37.8) | 65 (52.8) |
| | Stratified Hazard Ratio ^{a, b} (95% C.I.) | | 1.549 (1.015, 2.363) | | 1.490 (1.098, 2.022) |
| | P-value ^{b, c} | | 0.04236 | | 0.01043 |
| | Interaction Test P-value ^d | | | 0.94910 | |
| | Median Time to Onset of the First Event (Days) (95% C.I.) ^e | 148.0 (36.0, 378.0) | 499.0 (110.0, -) | 30.0 (15.0, 63.0) | 205.0 (63.0, -) |
| | 25 th , 75 th Percentile | 7.0, - | 21.0, - | 6.0, - | 13.0, - |
| Observed Min, Max ^f | 1, 1327+ | 1, 580+ | 1, 822+ | 1, 762+ | |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (Presence or history of brain metastases: Yes/No, ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.

c. Two-sided p-value calculated from Cox proportional hazards model.

d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and hormone receptor status.

e. Calculated using the complementary log-log transformation method (Collett, 1994).

f. '+' means the observed time is from censored subjects.

Snapshot date: 10SEP2020, data cutoff date: 29MAY2020.

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_may2020_dco_1943\v01\outputs\tlfs\pgms\t-ae-km-gisoc-subgrp.sas Output: t02-02-06-ae-km-gisoc-sub-6-hr-safs.rtf (14DEC20:17:13) Data: adsl, adae, adttesaf

Seagen Protocol ONT-380-206**Table 2.2.6 Summary of Gastrointestinal Adverse Events by System Organ Class, Preferred Term and Hormone Receptor Status Safety Analysis Set**

| System Organ Class/ Preferred Term | Parameters | Negative for Both | | Positive for ER or PR or Both | |
|---------------------------------------|--|------------------------|-----------------------|-------------------------------|------------------------|
| | | Tuc+Cap+Tra (N=163) | Pbo+Cap+Tra (N=74) | Tuc+Cap+Tra (N=241) | Pbo+Cap+Tra (N=123) |
| Vomiting | Number of Subjects With at Least One Event, n (%) | 66 (40.5) | 20 (27.0) | 83 (34.4) | 31 (25.2) |
| | Number of Censored Subjects, n (%) | 97 (59.5) | 54 (73.0) | 158 (65.6) | 92 (74.8) |
| | Stratified Hazard Ratio ^{a, b} (95% C.I.) | | 1.515 (0.910, 2.523) | | 1.449 (0.957, 2.194) |
| | P-value ^{b, c} | | 0.11007 | | 0.07941 |
| | Interaction Test P-value ^d | | | 0.90449 | |
| | Median Time to Onset of the First Event (Days) (95% C.I.) ^e | 1025.0 (304.0, -) | - (332.0, -) | - (686.0, -) | - (-, -) |
| | 25 th , 75 th Percentile | 43.0, - | 173.0, - | 42.0, - | 240.0, - |
| Observed Min, Max ^f | 1, 1327+ | 1, 580+ | 1, 1131+ | 1, 839+ | |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (Presence or history of brain metastases: Yes/No, ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.

c. Two-sided p-value calculated from Cox proportional hazards model.

d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and hormone receptor status.

e. Calculated using the complementary log-log transformation method (Collett, 1994).

f. '+' means the observed time is from censored subjects.

Snapshot date: 10SEP2020, data cutoff date: 29MAY2020.

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_may2020_dco_1943\v01\outputs\tlfs\pgms\t-ae-km-gisoc-subgrp.sas Output: t02-02-06-ae-km-gisoc-sub-6-hr-safs.rtf (14DEC20:17:13) Data: adsl, adae, adttesaf

Seagen Protocol ONT-380-206**Table 2.2.6 Summary of Gastrointestinal Adverse Events by System Organ Class, Preferred Term and Hormone Receptor Status Safety Analysis Set**

| System Organ Class/ Preferred Term | Parameters | Negative for Both | | Positive for ER or PR or Both | |
|---------------------------------------|--|------------------------|-----------------------|-------------------------------|------------------------|
| | | Tuc+Cap+Tra (N=163) | Pbo+Cap+Tra (N=74) | Tuc+Cap+Tra (N=241) | Pbo+Cap+Tra (N=123) |
| Stomatitis | Number of Subjects With at Least One Event, n (%) | 36 (22.1) | 10 (13.5) | 69 (28.6) | 18 (14.6) |
| | Number of Censored Subjects, n (%) | 127 (77.9) | 64 (86.5) | 172 (71.4) | 105 (85.4) |
| | Stratified Hazard Ratio ^{a, b} (95% C.I.) | | 1.601 (0.784, 3.269) | | 2.026 (1.202, 3.413) |
| | P-value ^{b, c} | | 0.19639 | | 0.00803 |
| | Interaction Test P-value ^d | | | 0.68037 | |
| | Median Time to Onset of the First Event (Days) (95% C.I.) ^e | - (-, -) | - (-, -) | - (615.0, -) | - (-, -) |
| | 25 th , 75 th Percentile | 347.0, - | -, - | 148.0, - | -, - |
| Observed Min, Max ^f | 1, 1327+ | 7, 580+ | 1, 1131+ | 7, 839+ | |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (Presence or history of brain metastases: Yes/No, ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.

c. Two-sided p-value calculated from Cox proportional hazards model.

d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and hormone receptor status.

e. Calculated using the complementary log-log transformation method (Collett, 1994).

f. '+' means the observed time is from censored subjects.

Snapshot date: 10SEP2020, data cutoff date: 29MAY2020.

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_may2020_dco_1943\v01\outputs\tlfs\pgms\t-ae-km-gisoc-subgrp.sas Output: t02-02-06-ae-km-gisoc-sub-6-hr-safs.rtf (14DEC20:17:13) Data: adsl, adae, adttesaf

Seagen Protocol ONT-380-206**Table 2.2.6 Summary of Gastrointestinal Adverse Events by System Organ Class, Preferred Term and Hormone Receptor Status Safety Analysis Set**

| System Organ Class/ Preferred Term | Parameters | Negative for Both | | Positive for ER or PR or Both | |
|---------------------------------------|--|------------------------|-----------------------|-------------------------------|------------------------|
| | | Tuc+Cap+Tra (N=163) | Pbo+Cap+Tra (N=74) | Tuc+Cap+Tra (N=241) | Pbo+Cap+Tra (N=123) |
| Constipation | Number of Subjects With at Least One Event, n (%) | 30 (18.4) | 20 (27.0) | 36 (14.9) | 22 (17.9) |
| | Number of Censored Subjects, n (%) | 133 (81.6) | 54 (73.0) | 205 (85.1) | 101 (82.1) |
| | Stratified Hazard Ratio ^{a, b} (95% C.I.) | | 0.560 (0.310, 1.012) | | 0.684 (0.396, 1.180) |
| | P-value ^{b, c} | | 0.05469 | | 0.17243 |
| | Interaction Test P-value ^d | | | 0.51859 | |
| | Median Time to Onset of the First Event (Days) (95% C.I.) ^e | - (709.0, -) | 398.0 (342.0, -) | - (-, -) | - (-, -) |
| | 25 th , 75 th Percentile | 643.0, - | 294.0, - | 660.0, - | -, - |
| Observed Min, Max ^f | 1, 1327+ | 1, 580+ | 1, 1131+ | 3, 839+ | |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (Presence or history of brain metastases: Yes/No, ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.

c. Two-sided p-value calculated from Cox proportional hazards model.

d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and hormone receptor status.

e. Calculated using the complementary log-log transformation method (Collett, 1994).

f. '+' means the observed time is from censored subjects.

Snapshot date: 10SEP2020, data cutoff date: 29MAY2020.

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_may2020_dco_1943\v01\outputs\tlfs\pgms\t-ae-km-gisoc-subgrp.sas Output: t02-02-06-ae-km-gisoc-sub-6-hr-safs.rtf (14DEC20:17:13) Data: adsl, adae, adttesaf

Seagen Protocol ONT-380-206**Table 2.6.2 Summary of Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and History of Brain Metastases at Baseline - Time-to-Event Analysis
Safety Analysis Set**

| System Organ Class/ Preferred Term | Parameters | With Brian Metastases | | Without Brain Metastases | |
|---------------------------------------|--|------------------------|-----------------------|--------------------------|------------------------|
| | | Tuc+Cap+Tra (N=194) | Pbo+Cap+Tra (N=91) | Tuc+Cap+Tra (N=209) | Pbo+Cap+Tra (N=105) |
| Anaemia (PT) | Number of Subjects With at Least One Event, n (%) | 39 (20.1) | 11 (12.1) | 46 (22.0) | 13 (12.4) |
| | Number of Censored Subjects, n (%) | 155 (79.9) | 80 (87.9) | 163 (78.0) | 92 (87.6) |
| | Stratified Hazard Ratio ^{a, b} (95% C.I.) | 1.510 (0.768, 2.970) | | 1.697 (0.914, 3.150) | |
| | P-value ^{b, c} | 0.23242 | | 0.09383 | |
| | Interaction Test P-value ^d | | | 0.84895 | |
| | Median Time to Onset of the First Event (Days) (95% C.I.) ^e | - (924.0, -) | - (-, -) | - (-, -) | - (-, -) |
| | 25 th , 75 th Percentile | 536.0, - | -, - | 435.0, - | -, - |
| | Observed Min, Max ^f | 4+, 1156+ | 12, 599+ | 1, 1327+ | 12, 839+ |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.

c. Two-sided p-value calculated from Cox proportional hazards model.

d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and history of brain metastases at baseline.

e. Calculated using the complementary log-log transformation method (Collett, 1994). f. '+' means the observed time is from censored subjects.

Snapshot date: 10SEP2020, data cutoff date: 29MAY2020.

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_may2020_dco_1943\v01\outputs\tlfs\pgms\t-ae-km-socpt-subgrp.sas Output: t02-06-02-ae-km-socpt-sub-1-bm-safs.rtf (14DEC20:17:14) Data: adsl, adae, adttesaf

Seagen Protocol ONT-380-206**Table 2.6.2 Summary of Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and History of Brain Metastases at Baseline - Time-to-Event Analysis Safety Analysis Set**

| System Organ Class/ Preferred Term | Parameters | With Brian Metastases | | Without Brain Metastases | |
|---------------------------------------|--|------------------------|-----------------------|--------------------------|------------------------|
| | | Tuc+Cap+Tra (N=194) | Pbo+Cap+Tra (N=91) | Tuc+Cap+Tra (N=209) | Pbo+Cap+Tra (N=105) |
| Investigations (SOC) | Number of Subjects With at Least One Event, n (%) | 129 (66.5) | 29 (31.9) | 125 (59.8) | 45 (42.9) |
| | Number of Censored Subjects, n (%) | 65 (33.5) | 62 (68.1) | 84 (40.2) | 60 (57.1) |
| | Stratified Hazard Ratio ^{a, b} (95% C.I.) | | 2.378 (1.585, 3.568) | | 1.570 (1.115, 2.213) |
| | P-value ^{b, c} | | 0.00003 | | 0.00986 |
| | Interaction Test P-value ^d | | | 0.14636 | |
| | Median Time to Onset of the First Event (Days) (95% C.I.) ^e | 64.0 (43.0, 112.0) | - (283.0, -) | 105.0 (48.0, 197.0) | 317.0 (200.0, -) |
| | 25 th , 75 th Percentile | 22.0, 356.0 | 64.0, - | 23.0, 757.0 | 63.0, - |
| Observed Min, Max ^f | 1, 899+ | 1, 598+ | 1, 765+ | 6, 562+ | |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.

c. Two-sided p-value calculated from Cox proportional hazards model.

d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and history of brain metastases at baseline.

e. Calculated using the complementary log-log transformation method (Collett, 1994). f. '+' means the observed time is from censored subjects.

Snapshot date: 10SEP2020, data cutoff date: 29MAY2020.

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_may2020_dco_1943\v01\outputs\tlfs\pgms\t-ae-km-socpt-subgrp.sas Output: t02-06-02-ae-km-socpt-sub-1-bm-safs.rtf (14DEC20:17:14) Data: adsl, adae, adttesaf

Seagen Protocol ONT-380-206**Table 2.6.2 Summary of Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and History of Brain Metastases at Baseline - Time-to-Event Analysis
Safety Analysis Set**

| System Organ Class/ Preferred Term | Parameters | With Brian Metastases | | Without Brain Metastases | |
|---|---|-------------------------|-----------------------|--------------------------|------------------------|
| | | Tuc+Cap+Tra (N=194) | Pbo+Cap+Tra (N=91) | Tuc+Cap+Tra (N=209) | Pbo+Cap+Tra (N=105) |
| Aspartate Aminotransferase Increased (PT) | Number of Subjects With at Least One Event, n (%) | 39 (20.1) | 9 (9.9) | 50 (23.9) | 13 (12.4) |
| | Number of Censored Subjects, n (%) | 155 (79.9) | 82 (90.1) | 159 (76.1) | 92 (87.6) |
| | Stratified Hazard Ratio ^{a, b} (95% C.I.) | 2.039 (0.985, 4.217) | | 1.941 (1.053, 3.579) | |
| | P-value ^{b, c} | 0.05485 | | 0.03368 | |
| | Interaction Test P-value ^d | 0.96932 | | | |
| | Median Time to Onset of the First Event (Days) (95% C.I.) ^e | - (-, -) | - (-, -) | - (677.0, -) | - (-, -) |
| | 25 th , 75 th Percentile | -, - | -, - | 337.0, - | -, - |
| Observed Min, Max ^f | 4+, 1156+ | 1, 599+ | 11, 1117+ | 11, 839+ | |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.

c. Two-sided p-value calculated from Cox proportional hazards model.

d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and history of brain metastases at baseline.

e. Calculated using the complementary log-log transformation method (Collett, 1994). f. '+' means the observed time is from censored subjects.

Snapshot date: 10SEP2020, data cutoff date: 29MAY2020.

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_may2020_dco_1943\v01\outputs\tlfs\pgms\t-ae-km-socpt-subgrp.sas Output:
t02-06-02-ae-km-socpt-sub-1-bm-safs.rtf (14DEC20:17:14) Data: adsl, adae, adttesaf

Seagen Protocol ONT-380-206**Table 2.6.2 Summary of Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and History of Brain Metastases at Baseline - Time-to-Event Analysis
Safety Analysis Set**

| System Organ Class/ Preferred Term | Parameters | With Brian Metastases | | Without Brain Metastases | |
|---|--|------------------------|-----------------------|--------------------------|------------------------|
| | | Tuc+Cap+Tra (N=194) | Pbo+Cap+Tra (N=91) | Tuc+Cap+Tra (N=209) | Pbo+Cap+Tra (N=105) |
| Alanine Aminotransferase Increased (PT) | Number of Subjects With at Least One Event, n (%) | 36 (18.6) | 8 (8.8) | 49 (23.4) | 5 (4.8) |
| | Number of Censored Subjects, n (%) | 158 (81.4) | 83 (91.2) | 160 (76.6) | 100 (95.2) |
| | Stratified Hazard Ratio ^{a, b} (95% C.I.) | | 2.010 (0.930, 4.343) | | 5.289 (2.106, 13.284) |
| | P-value ^{b, c} | | 0.07562 | | 0.00039 |
| | Interaction Test P-value ^d | | | 0.10622 | |
| | Median Time to Onset of the First Event (Days) (95% C.I.) ^e | - (-, -) | - (357.0, -) | - (-, -) | - (-, -) |
| | 25 th , 75 th Percentile | -, - | -, - | 337.0, - | -, - |
| Observed Min, Max ^f | 4+, 1156+ | 21, 599+ | 11, 1131+ | 14, 839+ | |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.

c. Two-sided p-value calculated from Cox proportional hazards model.

d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and history of brain metastases at baseline.

e. Calculated using the complementary log-log transformation method (Collett, 1994). f. '+' means the observed time is from censored subjects.

Snapshot date: 10SEP2020, data cutoff date: 29MAY2020.

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_may2020_dco_1943\v01\outputs\tlfs\pgms\t-ae-km-socpt-subgrp.sas Output:
t02-06-02-ae-km-socpt-sub-1-bm-safs.rtf (14DEC20:17:14) Data: adsl, adae, adttesaf

Seagen Protocol ONT-380-206**Table 2.6.2 Summary of Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and History of Brain Metastases at Baseline - Time-to-Event Analysis Safety Analysis Set**

| System Organ Class/ Preferred Term | Parameters | With Brian Metastases | | Without Brain Metastases | |
|---------------------------------------|--|------------------------|-----------------------|--------------------------|------------------------|
| | | Tuc+Cap+Tra (N=194) | Pbo+Cap+Tra (N=91) | Tuc+Cap+Tra (N=209) | Pbo+Cap+Tra (N=105) |
| Blood Bilirubin Increased (PT) | Number of Subjects With at Least One Event, n (%) | 39 (20.1) | 8 (8.8) | 41 (19.6) | 13 (12.4) |
| | Number of Censored Subjects, n (%) | 155 (79.9) | 83 (91.2) | 168 (80.4) | 92 (87.6) |
| | Stratified Hazard Ratio ^{a, b} (95% C.I.) | 2.153 (1.002, 4.626) | | 1.590 (0.851, 2.971) | |
| | P-value ^{b, c} | 0.04931 | | 0.14613 | |
| | Interaction Test P-value ^d | 0.52971 | | | |
| | Median Time to Onset of the First Event (Days) (95% C.I.) ^e | - (-, -) | - (-, -) | - (-, -) | - (-, -) |
| | 25 th , 75 th Percentile | 429.0, - | -, - | 364.0, - | -, - |
| | Observed Min, Max ^f | 4+, 1156+ | 7, 599+ | 11, 1131+ | 6, 839+ |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.

c. Two-sided p-value calculated from Cox proportional hazards model.

d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and history of brain metastases at baseline.

e. Calculated using the complementary log-log transformation method (Collett, 1994). f. '+' means the observed time is from censored subjects.

Snapshot date: 10SEP2020, data cutoff date: 29MAY2020.

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_may2020_dco_1943\v01\outputs\tlfs\pgms\t-ae-km-socpt-subgrp.sas Output: t02-06-02-ae-km-socpt-sub-1-bm-safs.rtf (14DEC20:17:14) Data: adsl, adae, adttesaf

Seagen Protocol ONT-380-206**Table 2.6.2 Summary of Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and History of Brain Metastases at Baseline - Time-to-Event Analysis
Safety Analysis Set**

| System Organ Class/ Preferred Term | Parameters | With Brian Metastases | | Without Brain Metastases | |
|---------------------------------------|--|--------------------------|-----------------------|-------------------------------|------------------------|
| | | Tuc+Cap+Tra (N=194) | Pbo+Cap+Tra (N=91) | Tuc+Cap+Tra (N=209) | Pbo+Cap+Tra (N=105) |
| Blood Creatinine Increased (PT) | Number of Subjects With at Least One Event, n (%) | 28 (14.4) | 2 (2.2) | 34 (16.3) | 1 (1.0) |
| | Number of Censored Subjects, n (%) | 166 (85.6) | 89 (97.8) | 175 (83.7) | 104 (99.0) |
| | Stratified Hazard Ratio ^{a, b} (95% C.I.) | 5.810 (1.376, 24.530) | | 16.759 (2.291, 122.586) | |
| | P-value ^{b, c} | 0.01664 | | 0.00549 | |
| | Interaction Test P-value ^d | | | 0.37403 | |
| | Median Time to Onset of the First Event (Days) (95% C.I.) ^e | -(747.0, -) | - (-, -) | - (-, -) | - (-, -) |
| | 25 th , 75 th Percentile Observed Min, Max ^f | 747.0, - 4+, 1154+ | -, - 13, 599+ | -, - 5, 1131+ | -, - 29+, 839+ |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.

c. Two-sided p-value calculated from Cox proportional hazards model.

d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and history of brain metastases at baseline.

e. Calculated using the complementary log-log transformation method (Collett, 1994). f. '+' means the observed time is from censored subjects.

Snapshot date: 10SEP2020, data cutoff date: 29MAY2020.

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_may2020_dco_1943\v01\outputs\tlfs\pgms\t-ae-km-socpt-subgrp.sas Output:
t02-06-02-ae-km-socpt-sub-1-bm-safs.rtf (14DEC20:17:14) Data: adsl, adae, adttesaf

Seagen Protocol ONT-380-206**Table 2.6.2 Summary of Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and History of Brain Metastases at Baseline - Time-to-Event Analysis Safety Analysis Set**

| System Organ Class/ Preferred Term | Parameters | With Brian Metastases | | Without Brain Metastases | |
|---------------------------------------|--|------------------------|-----------------------|--------------------------|------------------------|
| | | Tuc+Cap+Tra (N=194) | Pbo+Cap+Tra (N=91) | Tuc+Cap+Tra (N=209) | Pbo+Cap+Tra (N=105) |
| Weight Decreased (PT) | Number of Subjects With at Least One Event, n (%) | 38 (19.6) | 7 (7.7) | 24 (11.5) | 5 (4.8) |
| | Number of Censored Subjects, n (%) | 156 (80.4) | 84 (92.3) | 185 (88.5) | 100 (95.2) |
| | Stratified Hazard Ratio ^{a, b} (95% C.I.) | 2.360 (1.049, 5.312) | | 2.174 (0.827, 5.716) | |
| | P-value ^{b, c} | 0.03801 | | 0.11521 | |
| | Interaction Test P-value ^d | 0.97111 | | | |
| | Median Time to Onset of the First Event (Days) (95% C.I.) ^e | - (-, -) | - (-, -) | - (-, -) | - (-, -) |
| | 25 th , 75 th Percentile | -, - | -, - | -, - | -, - |
| | Observed Min, Max ^f | 4+, 1011+ | 9, 599+ | 6, 1327+ | 25, 839+ |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.

c. Two-sided p-value calculated from Cox proportional hazards model.

d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and history of brain metastases at baseline.

e. Calculated using the complementary log-log transformation method (Collett, 1994). f. '+' means the observed time is from censored subjects.

Snapshot date: 10SEP2020, data cutoff date: 29MAY2020.

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_may2020_dco_1943\v01\outputs\tlfs\pgms\t-ae-km-socpt-subgrp.sas Output: t02-06-02-ae-km-socpt-sub-1-bm-safs.rtf (14DEC20:17:14) Data: adsl, adae, adttesaf

Seagen Protocol ONT-380-206**Table 2.6.2 Summary of Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and History of Brain Metastases at Baseline - Time-to-Event Analysis
Safety Analysis Set**

| System Organ Class/ Preferred Term | Parameters | With Brian Metastases | | Without Brain Metastases | |
|--|---|------------------------|-------------------------|--------------------------|-------------------------|
| | | Tuc+Cap+Tra (N=194) | Pbo+Cap+Tra (N=91) | Tuc+Cap+Tra (N=209) | Pbo+Cap+Tra (N=105) |
| Metabolism And Nutrition Disorders (SOC) | Number of Subjects With at Least One Event, n (%) | 105 (54.1) | 34 (37.4) | 106 (50.7) | 40 (38.1) |
| | Number of Censored Subjects, n (%) | 89 (45.9) | 57 (62.6) | 103 (49.3) | 65 (61.9) |
| | Stratified Hazard Ratio ^{a, b} (95% C.I.) | | 1.564 (1.059, 2.311) | | 1.387 (0.962, 1.998) |
| | P-value ^{b, c} | | 0.02468 | | 0.07953 |
| | Interaction Test P-value ^d | | | 0.63101 | |
| | Median Time to Onset of the First Event (Days) (95% C.I.) ^e | 127.0 (79.0, 317.0) | 335.0 (216.0, -) | 211.0 (120.0, 539.0) | - (201.0, -) |
| | 25 th , 75 th Percentile | 22.0, - | 45.0, 526.0 | 23.0, - | 43.0, - |
| Observed Min, Max ^f | 1, 718+ | 7, 598+ | 1, 1131+ | 1, 839+ | |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.

c. Two-sided p-value calculated from Cox proportional hazards model.

d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and history of brain metastases at baseline.

e. Calculated using the complementary log-log transformation method (Collett, 1994). f. '+' means the observed time is from censored subjects.

Snapshot date: 10SEP2020, data cutoff date: 29MAY2020.

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_may2020_dco_1943\v01\outputs\tlfs\pgms\t-ae-km-socpt-subgrp.sas Output:
t02-06-02-ae-km-socpt-sub-1-bm-safs.rtf (14DEC20:17:14) Data: adsl, adae, adttesaf

Seagen Protocol ONT-380-206**Table 2.6.2 Summary of Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and History of Brain Metastases at Baseline - Time-to-Event Analysis Safety Analysis Set**

| System Organ Class/ Preferred Term | Parameters | With Brian Metastases | | Without Brain Metastases | |
|---------------------------------------|--|-----------------------------|-----------------------|--------------------------|------------------------|
| | | Tuc+Cap+Tra (N=194) | Pbo+Cap+Tra (N=91) | Tuc+Cap+Tra (N=209) | Pbo+Cap+Tra (N=105) |
| Hyperglycaemia (PT) | Number of Subjects With at Least One Event, n (%) | 10 (5.2) | 0 | 13 (6.2) | 3 (2.9) |
| | Number of Censored Subjects, n (%) | 184 (94.8) | 91 (100) | 196 (93.8) | 102 (97.1) |
| | Stratified Hazard Ratio ^{a, b} (95% C.I.) | 16570262.93 6 (0.000, -) | | 1.869 (0.531, 6.574) | |
| | P-value ^{b, c} | 0.99304 | | 0.32978 | |
| | Interaction Test P-value ^d | | | 0.98796 | |
| | Median Time to Onset of the First Event (Days) (95% C.I.) ^e | - (-, -) | - (-, -) | - (-, -) | - (-, -) |
| | 25 th , 75 th Percentile | -, - | -, - | -, - | -, - |
| | Observed Min, Max ^f | 2, 1156+ | 26+, 599+ | 10, 1327+ | 12, 839+ |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.

c. Two-sided p-value calculated from Cox proportional hazards model.

d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and history of brain metastases at baseline.

e. Calculated using the complementary log-log transformation method (Collett, 1994). f. '+' means the observed time is from censored subjects.

Snapshot date: 10SEP2020, data cutoff date: 29MAY2020.

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_may2020_dco_1943\v01\outputs\tlfs\pgms\t-ae-km-socpt-subgrp.sas Output: t02-06-02-ae-km-socpt-sub-1-bm-safs.rtf (14DEC20:17:14) Data: adsl, adae, adttesaf

Seagen Protocol ONT-380-206**Table 2.6.2 Summary of Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and History of Brain Metastases at Baseline - Time-to-Event Analysis Safety Analysis Set**

| System Organ Class/ Preferred Term | Parameters | With Brian Metastases | | Without Brain Metastases | | |
|--|---|-------------------------|-----------------------|--------------------------|------------------------|--|
| | | Tuc+Cap+Tra (N=194) | Pbo+Cap+Tra (N=91) | Tuc+Cap+Tra (N=209) | Pbo+Cap+Tra (N=105) | |
| Musculoskeletal And Connective Tissue Disorders (SOC) | Number of Subjects With at Least One Event, n (%) | 100 (51.5) | 32 (35.2) | 97 (46.4) | 37 (35.2) | |
| | Number of Censored Subjects, n (%) | 94 (48.5) | 59 (64.8) | 112 (53.6) | 68 (64.8) | |
| | Stratified Hazard Ratio ^{a, b} (95% C.I.) | 1.312 (0.875, 1.969) | | 1.365 (0.932, 2.000) | | |
| | P-value ^{b, c} | 0.18917 | | 0.10952 | | |
| | Interaction Test P-value ^d | 0.88407 | | | | |
| | Median Time to Onset of the First Event (Days) (95% C.I.) ^e | 226.0 (158.0, 307.0) | 291.0 (253.0, -) | 212.0 (149.0, 508.0) | - (148.0, -) | |
| | 25 th , 75 th Percentile | 64.0, 721.0 | 92.0, 355.0 | 61.0, - | 102.0, - | |
| Observed Min, Max ^f | 1, 1011+ | 2, 405+ | 1, 1117+ | 1, 839+ | | |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.

c. Two-sided p-value calculated from Cox proportional hazards model.

d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and history of brain metastases at baseline.

e. Calculated using the complementary log-log transformation method (Collett, 1994). f. '+' means the observed time is from censored subjects.

Snapshot date: 10SEP2020, data cutoff date: 29MAY2020.

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_may2020_dco_1943\v01\outputs\tlfs\pgms\t-ae-km-socpt-subgrp.sas Output:
t02-06-02-ae-km-socpt-sub-1-bm-safs.rtf (14DEC20:17:14) Data: adsl, adae, adttesaf

Seagen Protocol ONT-380-206**Table 2.6.2 Summary of Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and History of Brain Metastases at Baseline - Time-to-Event Analysis Safety Analysis Set**

| System Organ Class/ Preferred Term | Parameters | With Brain Metastases | | Without Brain Metastases | |
|---------------------------------------|--|------------------------|-----------------------|--------------------------|------------------------|
| | | Tuc+Cap+Tra (N=194) | Pbo+Cap+Tra (N=91) | Tuc+Cap+Tra (N=209) | Pbo+Cap+Tra (N=105) |
| Arthralgia (PT) | Number of Subjects With at Least One Event, n (%) | 32 (16.5) | 8 (8.8) | 32 (15.3) | 4 (3.8) |
| | Number of Censored Subjects, n (%) | 162 (83.5) | 83 (91.2) | 177 (84.7) | 101 (96.2) |
| | Stratified Hazard Ratio ^{a, b} (95% C.I.) | 1.498 (0.683, 3.285) | | 3.407 (1.196, 9.699) | |
| | P-value ^{b, c} | 0.31370 | | 0.02168 | |
| | Interaction Test P-value ^d | 0.18341 | | | |
| | Median Time to Onset of the First Event (Days) (95% C.I.) ^e | - (-, -) | -(355.0, -) | -(959.0, -) | - (-, -) |
| | 25 th , 75 th Percentile | -, - | 355.0, - | 707.0, - | -, - |
| | Observed Min, Max ^f | 1, 1156+ | 7, 599+ | 2, 1131+ | 4, 839+ |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.

c. Two-sided p-value calculated from Cox proportional hazards model.

d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and history of brain metastases at baseline.

e. Calculated using the complementary log-log transformation method (Collett, 1994). f. '+' means the observed time is from censored subjects.

Snapshot date: 10SEP2020, data cutoff date: 29MAY2020.

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_may2020_dco_1943\v01\outputs\tlfs\pgms\t-ae-km-socpt-subgrp.sas Output: t02-06-02-ae-km-socpt-sub-1-bm-safs.rtf (14DEC20:17:14) Data: adsl, adae, adttesaf

Seagen Protocol ONT-380-206**Table 2.6.2 Summary of Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and History of Brain Metastases at Baseline - Time-to-Event Analysis Safety Analysis Set**

| System Organ Class/ Preferred Term | Parameters | With Brian Metastases | | Without Brain Metastases | |
|---------------------------------------|--|------------------------|-----------------------|--------------------------|------------------------|
| | | Tuc+Cap+Tra (N=194) | Pbo+Cap+Tra (N=91) | Tuc+Cap+Tra (N=209) | Pbo+Cap+Tra (N=105) |
| Muscle Spasms (PT) | Number of Subjects With at Least One Event, n (%) | 24 (12.4) | 2 (2.2) | 19 (9.1) | 4 (3.8) |
| | Number of Censored Subjects, n (%) | 170 (87.6) | 89 (97.8) | 190 (90.9) | 101 (96.2) |
| | Stratified Hazard Ratio ^{a, b} (95% C.I.) | 4.540 (1.063, 19.394) | | 1.878 (0.627, 5.623) | |
| | P-value ^{b, c} | 0.04115 | | 0.26034 | |
| | Interaction Test P-value ^d | | | 0.33194 | |
| | Median Time to Onset of the First Event (Days) (95% C.I.) ^e | - (966.0, -) | - (-, -) | - (826.0, -) | - (-, -) |
| | 25 th , 75 th Percentile | 966.0, - | -, - | 826.0, - | -, - |
| Observed Min, Max ^f | 1, 1156+ | 21, 599+ | 8, 1327+ | 29+, 839+ | |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.

c. Two-sided p-value calculated from Cox proportional hazards model.

d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and history of brain metastases at baseline.

e. Calculated using the complementary log-log transformation method (Collett, 1994). f. '+' means the observed time is from censored subjects.

Snapshot date: 10SEP2020, data cutoff date: 29MAY2020.

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_may2020_dco_1943\v01\outputs\tlfs\pgms\t-ae-km-socpt-subgrp.sas Output: t02-06-02-ae-km-socpt-sub-1-bm-safs.rtf (14DEC20:17:14) Data: adsl, adae, adttesaf

Seagen Protocol ONT-380-206**Table 2.6.2 Summary of Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and History of Brain Metastases at Baseline - Time-to-Event Analysis
Safety Analysis Set**

| System Organ Class/ Preferred Term | Parameters | With Brian Metastases | | Without Brain Metastases | |
|---------------------------------------|--|------------------------|-----------------------|--------------------------|------------------------|
| | | Tuc+Cap+Tra (N=194) | Pbo+Cap+Tra (N=91) | Tuc+Cap+Tra (N=209) | Pbo+Cap+Tra (N=105) |
| Peripheral Sensory Neuropathy (PT) | Number of Subjects With at Least One Event, n (%) | 19 (9.8) | 4 (4.4) | 31 (14.8) | 8 (7.6) |
| | Number of Censored Subjects, n (%) | 175 (90.2) | 87 (95.6) | 178 (85.2) | 97 (92.4) |
| | Stratified Hazard Ratio ^{a, b} (95% C.I.) | 1.948 (0.653, 5.817) | | 1.873 (0.859, 4.087) | |
| | P-value ^{b, c} | 0.23203 | | 0.11480 | |
| | Interaction Test P-value ^d | 0.93676 | | | |
| | Median Time to Onset of the First Event (Days) (95% C.I.) ^e | - (-, -) | - (-, -) | - (-, -) | - (509.0, -) |
| | 25 th , 75 th Percentile | -, - | -, - | -, - | 509.0, - |
| Observed Min, Max ^f | 2, 1154+ | 21, 599+ | 4, 1327+ | 12, 839+ | |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.

c. Two-sided p-value calculated from Cox proportional hazards model.

d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and history of brain metastases at baseline.

e. Calculated using the complementary log-log transformation method (Collett, 1994). f. '+' means the observed time is from censored subjects.

Snapshot date: 10SEP2020, data cutoff date: 29MAY2020.

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_may2020_dco_1943\v01\outputs\tlfs\pgms\t-ae-km-socpt-subgrp.sas Output:

t02-06-02-ae-km-socpt-sub-1-bm-safs.rtf (14DEC20:17:14) Data: adsl, adae, adttesaf

Seagen Protocol ONT-380-206**Table 2.6.2 Summary of Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and History of Brain Metastases at Baseline - Time-to-Event Analysis
Safety Analysis Set**

| System Organ Class/ Preferred Term | Parameters | With Brian Metastases | | Without Brain Metastases | |
|---------------------------------------|--|------------------------|-----------------------|--------------------------|------------------------|
| | | Tuc+Cap+Tra (N=194) | Pbo+Cap+Tra (N=91) | Tuc+Cap+Tra (N=209) | Pbo+Cap+Tra (N=105) |
| Dysgeusia (PT) | Number of Subjects With at Least One Event, n (%) | 16 (8.2) | 5 (5.5) | 17 (8.1) | 1 (1.0) |
| | Number of Censored Subjects, n (%) | 178 (91.8) | 86 (94.5) | 192 (91.9) | 104 (99.0) |
| | Stratified Hazard Ratio ^{a, b} (95% C.I.) | 1.242 (0.444, 3.472) | | 8.785 (1.169, 66.044) | |
| | P-value ^{b, c} | 0.67903 | | 0.03474 | |
| | Interaction Test P-value ^d | 0.11025 | | | |
| | Median Time to Onset of the First Event (Days) (95% C.I.) ^e | - (-, -) | - (-, -) | - (-, -) | - (-, -) |
| | 25 th , 75 th Percentile | -, - | -, - | -, - | -, - |
| | Observed Min, Max ^f | 1, 1011+ | 11, 599+ | 2, 1327+ | 29+, 839+ |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.

c. Two-sided p-value calculated from Cox proportional hazards model.

d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and history of brain metastases at baseline.

e. Calculated using the complementary log-log transformation method (Collett, 1994). f. '+' means the observed time is from censored subjects.

Snapshot date: 10SEP2020, data cutoff date: 29MAY2020.

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_may2020_dco_1943\v01\outputs\tlfs\pgms\t-ae-km-socpt-subgrp.sas Output: t02-06-02-ae-km-socpt-sub-1-bm-safs.rtf (14DEC20:17:14) Data: adsl, adae, adttesaf

Seagen Protocol ONT-380-206**Table 2.6.2 Summary of Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and History of Brain Metastases at Baseline - Time-to-Event Analysis Safety Analysis Set**

| System Organ Class/ Preferred Term | Parameters | With Brian Metastases | | Without Brain Metastases | |
|---------------------------------------|--|------------------------|-----------------------|--------------------------|------------------------|
| | | Tuc+Cap+Tra (N=194) | Pbo+Cap+Tra (N=91) | Tuc+Cap+Tra (N=209) | Pbo+Cap+Tra (N=105) |
| Epistaxis (PT) | Number of Subjects With at Least One Event, n (%) | 21 (10.8) | 2 (2.2) | 29 (13.9) | 8 (7.6) |
| | Number of Censored Subjects, n (%) | 173 (89.2) | 89 (97.8) | 180 (86.1) | 97 (92.4) |
| | Stratified Hazard Ratio ^{a, b} (95% C.I.) | 4.777 (1.116, 20.456) | | 1.690 (0.768, 3.715) | |
| | P-value ^{b, c} | 0.03508 | | 0.19198 | |
| | Interaction Test P-value ^d | | | 0.23769 | |
| | Median Time to Onset of the First Event (Days) (95% C.I.) ^e | - (-, -) | - (-, -) | - (-, -) | - (-, -) |
| | 25 th , 75 th Percentile | -, - | -, - | -, - | -, - |
| | Observed Min, Max ^f | 2, 1156+ | 19, 599+ | 1, 1327+ | 3, 839+ |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.

c. Two-sided p-value calculated from Cox proportional hazards model.

d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and history of brain metastases at baseline.

e. Calculated using the complementary log-log transformation method (Collett, 1994). f. '+' means the observed time is from censored subjects.

Snapshot date: 10SEP2020, data cutoff date: 29MAY2020.

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_may2020_dco_1943\v01\outputs\tlfs\pgms\t-ae-km-socpt-subgrp.sas Output: t02-06-02-ae-km-socpt-sub-1-bm-safs.rtf (14DEC20:17:14) Data: adsl, adae, adttesaf

Seagen Protocol ONT-380-206**Table 2.6.2 Summary of Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and History of Brain Metastases at Baseline - Time-to-Event Analysis Safety Analysis Set**

| System Organ Class/ Preferred Term | Parameters | With Brian Metastases | | Without Brain Metastases | |
|---------------------------------------|--|------------------------|-----------------------|--------------------------|------------------------|
| | | Tuc+Cap+Tra (N=194) | Pbo+Cap+Tra (N=91) | Tuc+Cap+Tra (N=209) | Pbo+Cap+Tra (N=105) |
| Pleural Effusion (PT) | Number of Subjects With at Least One Event, n (%) | 7 (3.6) | 4 (4.4) | 3 (1.4) | 7 (6.7) |
| | Number of Censored Subjects, n (%) | 187 (96.4) | 87 (95.6) | 206 (98.6) | 98 (93.3) |
| | Stratified Hazard Ratio ^{a, b} (95% C.I.) | 0.708 (0.203, 2.463) | | 0.140 (0.029, 0.674) | |
| | P-value ^{b, c} | 0.58722 | | 0.01421 | |
| | Interaction Test P-value ^d | 0.19459 | | | |
| | Median Time to Onset of the First Event (Days) (95% C.I.) ^e | - (-, -) | - (-, -) | - (942.0, -) | - (-, -) |
| | 25 th , 75 th Percentile | -, - | -, - | -, - | -, - |
| Observed Min, Max ^f | 4+, 1156+ | 21, 599+ | 24+, 1327+ | 6, 839+ | |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.

c. Two-sided p-value calculated from Cox proportional hazards model.

d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and history of brain metastases at baseline.

e. Calculated using the complementary log-log transformation method (Collett, 1994). f. '+' means the observed time is from censored subjects.

Snapshot date: 10SEP2020, data cutoff date: 29MAY2020.

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_may2020_dco_1943\v01\outputs\tlfs\pgms\t-ae-km-socpt-subgrp.sas Output: t02-06-02-ae-km-socpt-sub-1-bm-safs.rtf (14DEC20:17:14) Data: adsl, adae, adttesaf

Seagen Protocol ONT-380-206**Table 2.6.2 Summary of Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and History of Brain Metastases at Baseline - Time-to-Event Analysis Safety Analysis Set**

| System Organ Class/ Preferred Term | Parameters | With Brian Metastases | | Without Brain Metastases | |
|---|--|------------------------|-----------------------|--------------------------|------------------------|
| | | Tuc+Cap+Tra (N=194) | Pbo+Cap+Tra (N=91) | Tuc+Cap+Tra (N=209) | Pbo+Cap+Tra (N=105) |
| Palmar-Plantar Erythrodyssaesthesia Syndrome (PT) | Number of Subjects With at Least One Event, n (%) | 129 (66.5) | 44 (48.4) | 132 (63.2) | 61 (58.1) |
| | Number of Censored Subjects, n (%) | 65 (33.5) | 47 (51.6) | 77 (36.8) | 44 (41.9) |
| | Stratified Hazard Ratio ^{a, b} (95% C.I.) | 1.425 (1.007, 2.017) | | 1.134 (0.836, 1.540) | |
| | P-value ^{b, c} | 0.04543 | | 0.41903 | |
| | Interaction Test P-value ^d | 0.31112 | | | |
| | Median Time to Onset of the First Event (Days) (95% C.I.) ^e | 61.0 (46.0, 85.0) | 141.0 (71.0, -) | 64.0 (43.0, 85.0) | 72.0 (63.0, 127.0) |
| | 25 th , 75 th Percentile | 31.0, 267.0 | 35.0, - | 25.0, 648.0 | 33.0, - |
| Observed Min, Max ^f | 1, 785+ | 1, 405+ | 1, 873+ | 1, 457+ | |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.

c. Two-sided p-value calculated from Cox proportional hazards model.

d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and history of brain metastases at baseline.

e. Calculated using the complementary log-log transformation method (Collett, 1994). f. '+' means the observed time is from censored subjects.

Snapshot date: 10SEP2020, data cutoff date: 29MAY2020.

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_may2020_dco_1943\v01\outputs\tlfs\pgms\t-ae-km-socpt-subgrp.sas Output: t02-06-02-ae-km-socpt-sub-1-bm-safs.rtf (14DEC20:17:14) Data: adsl, adae, adttesaf

Seagen Protocol ONT-380-206**Table 2.6.3 Summary of Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Geographic Region - Time-to-Event Analysis Safety Analysis Set**

| System Organ Class/ Preferred Term | Parameters | North America | | Rest of World | |
|---------------------------------------|--|------------------------|------------------------|------------------------|-----------------------|
| | | Tuc+Cap+Tra (N=241) | Pbo+Cap+Tra (N=119) | Tuc+Cap+Tra (N=163) | Pbo+Cap+Tra (N=78) |
| Anaemia (PT) | Number of Subjects With at Least One Event, n (%) | 51 (21.2) | 14 (11.8) | 35 (21.5) | 10 (12.8) |
| | Number of Censored Subjects, n (%) | 190 (78.8) | 105 (88.2) | 128 (78.5) | 68 (87.2) |
| | Stratified Hazard Ratio ^{a, b} (95% C.I.) | 1.636 (0.901, 2.969) | | 1.669 (0.824, 3.379) | |
| | P-value ^{b, c} | 0.10587 | | 0.15497 | |
| | Interaction Test P-value ^d | 0.99954 | | | |
| | Median Time to Onset of the First Event (Days) (95% C.I.) ^e | - (924.0, -) | - (-, -) | - (-, -) | - (-, -) |
| | 25 th , 75 th Percentile | 472.0, - | -, - | 298.0, - | -, - |
| | Observed Min, Max ^f | 1, 1327+ | 12, 762+ | 1, 954+ | 12, 839+ |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (Presence or history of brain metastases: Yes/No and ECOG performance status: 0/1) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.

c. Two-sided p-value calculated from Cox proportional hazards model.

d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and geographic region.

e. Calculated using the complementary log-log transformation method (Collett, 1994). f. '+' means the observed time is from censored subjects.

Snapshot date: 10SEP2020, data cutoff date: 29MAY2020.

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_may2020_dco_1943\v01\outputs\tlfs\pgms\t-ae-km-socpt-subgrp.sas Output: t02-06-03-ae-km-socpt-sub-2-reg-safs.rtf (14DEC20:17:14) Data: adsl, adae, adttesaf

Seagen Protocol ONT-380-206**Table 2.6.3 Summary of Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Geographic Region - Time-to-Event Analysis Safety Analysis Set**

| System Organ Class/ Preferred Term | Parameters | North America | | Rest of World | |
|---------------------------------------|--|------------------------|------------------------|------------------------|-----------------------|
| | | Tuc+Cap+Tra (N=241) | Pbo+Cap+Tra (N=119) | Tuc+Cap+Tra (N=163) | Pbo+Cap+Tra (N=78) |
| Investigations (SOC) | Number of Subjects With at Least One Event, n (%) | 148 (61.4) | 49 (41.2) | 106 (65.0) | 25 (32.1) |
| | Number of Censored Subjects, n (%) | 93 (38.6) | 70 (58.8) | 57 (35.0) | 53 (67.9) |
| | Stratified Hazard Ratio ^{a, b} (95% C.I.) | 1.629 (1.178, 2.252) | | 2.434 (1.569, 3.777) | |
| | P-value ^{b, c} | 0.00317 | | 0.00007 | |
| | Interaction Test P-value ^d | 0.12991 | | | |
| | Median Time to Onset of the First Event (Days) (95% C.I.) ^e | 64.0 (44.0, 148.0) | 356.0 (133.0, -) | 88.0 (50.0, 173.0) | 409.0 (283.0, -) |
| | 25 th , 75 th Percentile | 22.0, - | 43.0, - | 29.0, 520.0 | 147.0, - |
| Observed Min, Max ^f | 1, 899+ | 1, 562+ | 2, 765+ | 6, 598+ | |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (Presence or history of brain metastases: Yes/No and ECOG performance status: 0/1) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.

c. Two-sided p-value calculated from Cox proportional hazards model.

d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and geographic region.

e. Calculated using the complementary log-log transformation method (Collett, 1994). f. '+' means the observed time is from censored subjects.

Snapshot date: 10SEP2020, data cutoff date: 29MAY2020.

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_may2020_dco_1943\v01\outputs\tlfs\pgms\t-ae-km-socpt-subgrp.sas Output: t02-06-03-ae-km-socpt-sub-2-reg-safs.rtf (14DEC20:17:14) Data: adsl, adae, adttesaf

Seagen Protocol ONT-380-206**Table 2.6.3 Summary of Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Geographic Region - Time-to-Event Analysis Safety Analysis Set**

| System Organ Class/ Preferred Term | Parameters | North America | | Rest of World | |
|---|---|-------------------------|------------------------|-------------------------|-----------------------|
| | | Tuc+Cap+Tra (N=241) | Pbo+Cap+Tra (N=119) | Tuc+Cap+Tra (N=163) | Pbo+Cap+Tra (N=78) |
| Aspartate Aminotransferase Increased (PT) | Number of Subjects With at Least One Event, n (%) | 53 (22.0) | 17 (14.3) | 36 (22.1) | 5 (6.4) |
| | Number of Censored Subjects, n (%) | 188 (78.0) | 102 (85.7) | 127 (77.9) | 73 (93.6) |
| | Stratified Hazard Ratio ^{a, b} (95% C.I.) | 1.532 (0.886, 2.647) | | 3.473 (1.360, 8.869) | |
| | P-value ^{b, c} | 0.12658 | | 0.00925 | |
| | Interaction Test P-value ^d | 0.12118 | | | |
| | Median Time to Onset of the First Event (Days) (95% C.I.) ^e | - (-, -) | - (-, -) | - (-, -) | - (-, -) |
| | 25 th , 75 th Percentile | 677.0, - | -, - | 337.0, - | -, - |
| Observed Min, Max ^f | 4+, 1156+ | 1, 762+ | 6+, 954+ | 14, 839+ | |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (Presence or history of brain metastases: Yes/No and ECOG performance status: 0/1) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.

c. Two-sided p-value calculated from Cox proportional hazards model.

d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and geographic region.

e. Calculated using the complementary log-log transformation method (Collett, 1994). f. '+' means the observed time is from censored subjects.

Snapshot date: 10SEP2020, data cutoff date: 29MAY2020.

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_may2020_dco_1943\v01\outputs\tlfs\pgms\t-ae-km-socpt-subgrp.sas Output:

t02-06-03-ae-km-socpt-sub-2-reg-safs.rtf (14DEC20:17:14) Data: adsl, adae, adttesaf

Seagen Protocol ONT-380-206**Table 2.6.3 Summary of Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Geographic Region - Time-to-Event Analysis Safety Analysis Set**

| System Organ Class/ Preferred Term | Parameters | North America | | Rest of World | |
|---|--|------------------------|------------------------|------------------------|-----------------------|
| | | Tuc+Cap+Tra (N=241) | Pbo+Cap+Tra (N=119) | Tuc+Cap+Tra (N=163) | Pbo+Cap+Tra (N=78) |
| Alanine Aminotransferase Increased (PT) | Number of Subjects With at Least One Event, n (%) | 45 (18.7) | 9 (7.6) | 40 (24.5) | 4 (5.1) |
| | Number of Censored Subjects, n (%) | 196 (81.3) | 110 (92.4) | 123 (75.5) | 74 (94.9) |
| | Stratified Hazard Ratio ^{a, b} (95% C.I.) | | 2.536 (1.239, 5.190) | | 4.817 (1.718, 13.508) |
| | P-value ^{b, c} | | 0.01087 | | 0.00281 |
| | Interaction Test P-value ^d | | | 0.25781 | |
| | Median Time to Onset of the First Event (Days) (95% C.I.) ^e | - (-, -) | - (-, -) | - (-, -) | - (-, -) |
| | 25 th , 75 th Percentile | -, - | -, - | 295.0, - | -, - |
| Observed Min, Max ^f | 4+, 1156+ | 14, 762+ | 6+, 954+ | 22, 839+ | |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (Presence or history of brain metastases: Yes/No and ECOG performance status: 0/1) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.

c. Two-sided p-value calculated from Cox proportional hazards model.

d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and geographic region.

e. Calculated using the complementary log-log transformation method (Collett, 1994). f. '+' means the observed time is from censored subjects.

Snapshot date: 10SEP2020, data cutoff date: 29MAY2020.

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_may2020_dco_1943\v01\outputs\tlfs\pgms\t-ae-km-socpt-subgrp.sas Output: t02-06-03-ae-km-socpt-sub-2-reg-safs.rtf (14DEC20:17:14) Data: adsl, adae, addtesaf

Seagen Protocol ONT-380-206**Table 2.6.3 Summary of Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Geographic Region - Time-to-Event Analysis
Safety Analysis Set**

| System Organ Class/ Preferred Term | Parameters | North America | | Rest of World | |
|---------------------------------------|--|------------------------|------------------------|------------------------|-----------------------|
| | | Tuc+Cap+Tra (N=241) | Pbo+Cap+Tra (N=119) | Tuc+Cap+Tra (N=163) | Pbo+Cap+Tra (N=78) |
| Blood Bilirubin Increased (PT) | Number of Subjects With at Least One Event, n (%) | 48 (19.9) | 14 (11.8) | 32 (19.6) | 7 (9.0) |
| | Number of Censored Subjects, n (%) | 193 (80.1) | 105 (88.2) | 131 (80.4) | 71 (91.0) |
| | Stratified Hazard Ratio ^{a, b} (95% C.I.) | 1.614 (0.888, 2.931) | | 2.206 (0.972, 5.009) | |
| | P-value ^{b, c} | 0.11616 | | 0.05859 | |
| | Interaction Test P-value ^d | 0.54789 | | | |
| | Median Time to Onset of the First Event (Days) (95% C.I.) ^e | - (-, -) | - (-, -) | - (-, -) | - (-, -) |
| | 25 th , 75 th Percentile | -, - | -, - | 364.0, - | -, - |
| | Observed Min, Max ^f | 4+, 1156+ | 7, 762+ | 6+, 873+ | 6, 839+ |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (Presence or history of brain metastases: Yes/No and ECOG performance status: 0/1) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.

c. Two-sided p-value calculated from Cox proportional hazards model.

d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and geographic region.

e. Calculated using the complementary log-log transformation method (Collett, 1994). f. '+' means the observed time is from censored subjects.

Snapshot date: 10SEP2020, data cutoff date: 29MAY2020.

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Seagen Protocol ONT-380-206**Table 2.6.3 Summary of Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Geographic Region - Time-to-Event Analysis
Safety Analysis Set**

| System Organ Class/ Preferred Term | Parameters | North America | | Rest of World | |
|---------------------------------------|--|------------------------|------------------------|------------------------|-----------------------|
| | | Tuc+Cap+Tra (N=241) | Pbo+Cap+Tra (N=119) | Tuc+Cap+Tra (N=163) | Pbo+Cap+Tra (N=78) |
| Blood Creatinine Increased (PT) | Number of Subjects With at Least One Event, n (%) | 37 (15.4) | 2 (1.7) | 25 (15.3) | 1 (1.3) |
| | Number of Censored Subjects, n (%) | 204 (84.6) | 117 (98.3) | 138 (84.7) | 77 (98.7) |
| | Stratified Hazard Ratio ^{a, b} (95% C.I.) | 8.387 (2.016, 34.892) | | 11.842 (1.600, 87.637) | |
| | P-value ^{b, c} | 0.00346 | | 0.01551 | |
| | Interaction Test P-value ^d | | | 0.81800 | |
| | Median Time to Onset of the First Event (Days) (95% C.I.) ^e | - (-, -) | - (-, -) | - (-, -) | - (-, -) |
| | 25 th , 75 th Percentile | 747.0, - | -, - | -, - | -, - |
| Observed Min, Max ^f | 4+, 1154+ | 13, 762+ | 5, 954+ | 34+, 839+ | |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (Presence or history of brain metastases: Yes/No and ECOG performance status: 0/1) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.

c. Two-sided p-value calculated from Cox proportional hazards model.

d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and geographic region.

e. Calculated using the complementary log-log transformation method (Collett, 1994). f. '+' means the observed time is from censored subjects.

Snapshot date: 10SEP2020, data cutoff date: 29MAY2020.

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_may2020_dco_1943\v01\outputs\tlfs\pgms\t-ae-km-socpt-subgrp.sas Output: t02-06-03-ae-km-socpt-sub-2-reg-safs.rtf (14DEC20:17:14) Data: adsl, adae, adttesaf

Seagen Protocol ONT-380-206**Table 2.6.3 Summary of Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Geographic Region - Time-to-Event Analysis Safety Analysis Set**

| System Organ Class/ Preferred Term | Parameters | North America | | Rest of World | |
|---------------------------------------|--|------------------------|------------------------|-------------------------|-----------------------|
| | | Tuc+Cap+Tra (N=241) | Pbo+Cap+Tra (N=119) | Tuc+Cap+Tra (N=163) | Pbo+Cap+Tra (N=78) |
| Weight Decreased (PT) | Number of Subjects With at Least One Event, n (%) | 40 (16.6) | 12 (10.1) | 22 (13.5) | 0 |
| | Number of Censored Subjects, n (%) | 201 (83.4) | 107 (89.9) | 141 (86.5) | 78 (100) |
| | Stratified Hazard Ratio ^{a, b} (95% C.I.) | 1.508 (0.787, 2.891) | | 16903925.154 (0.000, -) | |
| | P-value ^{b, c} | 0.21566 | | 0.98968 | |
| | Interaction Test P-value ^d | | | 0.98122 | |
| | Median Time to Onset of the First Event (Days) (95% C.I.) ^e | - (-, -) | - (-, -) | - (-, -) | - (-, -) |
| | 25 th , 75 th Percentile | 705.0, - | -, - | -, - | -, - |
| | Observed Min, Max ^f | 4+, 1327+ | 9, 762+ | 6+, 954+ | 34+, 839+ |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (Presence or history of brain metastases: Yes/No and ECOG performance status: 0/1) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.

c. Two-sided p-value calculated from Cox proportional hazards model.

d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and geographic region.

e. Calculated using the complementary log-log transformation method (Collett, 1994). f. '+' means the observed time is from censored subjects.

Snapshot date: 10SEP2020, data cutoff date: 29MAY2020.

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_may2020_dco_1943\v01\outputs\tlfs\pgms\t-ae-km-socpt-subgrp.sas Output: t02-06-03-ae-km-socpt-sub-2-reg-safs.rtf (14DEC20:17:14) Data: adsl, adae, adttesaf

Seagen Protocol ONT-380-206**Table 2.6.3 Summary of Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Geographic Region - Time-to-Event Analysis Safety Analysis Set**

| System Organ Class/ Preferred Term | Parameters | North America | | Rest of World | |
|--|---|-------------------------|------------------------|-------------------------|-----------------------|
| | | Tuc+Cap+Tra (N=241) | Pbo+Cap+Tra (N=119) | Tuc+Cap+Tra (N=163) | Pbo+Cap+Tra (N=78) |
| Metabolism And Nutrition Disorders (SOC) | Number of Subjects With at Least One Event, n (%) | 141 (58.5) | 50 (42.0) | 71 (43.6) | 24 (30.8) |
| | Number of Censored Subjects, n (%) | 100 (41.5) | 69 (58.0) | 92 (56.4) | 54 (69.2) |
| | Stratified Hazard Ratio ^{a, b} (95% C.I.) | 1.549 (1.121, 2.142) | | 1.360 (0.853, 2.170) | |
| | P-value ^{b, c} | 0.00803 | | 0.19640 | |
| | Interaction Test P-value ^d | 0.76985 | | | |
| | Median Time to Onset of the First Event (Days) (95% C.I.) ^e | 94.0 (64.0, 147.0) | 526.0 (147.0, -) | 422.0 (190.0, -) | - (333.0, -) |
| | 25 th , 75 th Percentile | 22.0, 630.0 | 36.0, - | 41.0, - | 104.0, - |
| Observed Min, Max ^f | 1, 1131+ | 4, 762+ | 1, 873+ | 1, 839+ | |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (Presence or history of brain metastases: Yes/No and ECOG performance status: 0/1) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.

c. Two-sided p-value calculated from Cox proportional hazards model.

d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and geographic region.

e. Calculated using the complementary log-log transformation method (Collett, 1994). f. '+' means the observed time is from censored subjects.

Snapshot date: 10SEP2020, data cutoff date: 29MAY2020.

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_may2020_dco_1943\v01\outputs\tlfs\pgms\t-ae-km-socpt-subgrp.sas Output:

t02-06-03-ae-km-socpt-sub-2-reg-safs.rtf (14DEC20:17:14) Data: adsl, adae, adttesaf

Seagen Protocol ONT-380-206**Table 2.6.3 Summary of Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Geographic Region - Time-to-Event Analysis Safety Analysis Set**

| System Organ Class/ Preferred Term | Parameters | North America | | Rest of World | |
|---------------------------------------|--|------------------------|------------------------|------------------------|-----------------------|
| | | Tuc+Cap+Tra (N=241) | Pbo+Cap+Tra (N=119) | Tuc+Cap+Tra (N=163) | Pbo+Cap+Tra (N=78) |
| Hyperglycaemia (PT) | Number of Subjects With at Least One Event, n (%) | 20 (8.3) | 2 (1.7) | 3 (1.8) | 1 (1.3) |
| | Number of Censored Subjects, n (%) | 221 (91.7) | 117 (98.3) | 160 (98.2) | 77 (98.7) |
| | Stratified Hazard Ratio ^{a, b} (95% C.I.) | 4.524 (1.056, 19.382) | | 1.317 (0.136, 12.702) | |
| | P-value ^{b, c} | 0.04199 | | 0.81205 | |
| | Interaction Test P-value ^d | 0.36068 | | | |
| | Median Time to Onset of the First Event (Days) (95% C.I.) ^e | - (-, -) | - (-, -) | - (-, -) | - (-, -) |
| | 25 th , 75 th Percentile | -, - | -, - | -, - | -, - |
| Observed Min, Max ^f | 4+, 1327+ | 13, 762+ | 2, 954+ | 12, 839+ | |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (Presence or history of brain metastases: Yes/No and ECOG performance status: 0/1) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.

c. Two-sided p-value calculated from Cox proportional hazards model.

d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and geographic region.

e. Calculated using the complementary log-log transformation method (Collett, 1994). f. '+' means the observed time is from censored subjects.

Snapshot date: 10SEP2020, data cutoff date: 29MAY2020.

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_may2020_dco_1943\v01\outputs\tlfs\pgms\t-ae-km-socpt-subgrp.sas Output: t02-06-03-ae-km-socpt-sub-2-reg-safs.rtf (14DEC20:17:14) Data: adsl, adae, adttesaf

Seagen Protocol ONT-380-206**Table 2.6.3 Summary of Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Geographic Region - Time-to-Event Analysis Safety Analysis Set**

| System Organ Class/ Preferred Term | Parameters | North America | | Rest of World | |
|--|---|-------------------------|------------------------|-------------------------|-----------------------|
| | | Tuc+Cap+Tra (N=241) | Pbo+Cap+Tra (N=119) | Tuc+Cap+Tra (N=163) | Pbo+Cap+Tra (N=78) |
| Musculoskeletal And Connective Tissue Disorders (SOC) | Number of Subjects With at Least One Event, n (%) | 134 (55.6) | 40 (33.6) | 63 (38.7) | 29 (37.2) |
| | Number of Censored Subjects, n (%) | 107 (44.4) | 79 (66.4) | 100 (61.3) | 49 (62.8) |
| | Stratified Hazard Ratio ^{a, b} (95% C.I.) | 1.655 (1.158, 2.364) | | 0.970 (0.620, 1.518) | |
| | P-value ^{b, c} | 0.00564 | | 0.89325 | |
| | Interaction Test P-value ^d | 0.04203 | | | |
| | Median Time to Onset of the First Event (Days) (95% C.I.) ^e | 159.0 (127.0, 226.0) | 399.0 (215.0, -) | 455.0 (239.0, -) | 355.0 (138.0, -) |
| | 25 th , 75 th Percentile | 43.0, 538.0 | 92.0, - | 85.0, - | 109.0, - |
| Observed Min, Max ^f | 1, 1117+ | 1, 760+ | 1, 873+ | 1, 839+ | |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (Presence or history of brain metastases: Yes/No and ECOG performance status: 0/1) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.

c. Two-sided p-value calculated from Cox proportional hazards model.

d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and geographic region.

e. Calculated using the complementary log-log transformation method (Collett, 1994). f. '+' means the observed time is from censored subjects.

Snapshot date: 10SEP2020, data cutoff date: 29MAY2020.

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_may2020_dco_1943\v01\outputs\tlfs\pgms\t-ae-km-socpt-subgrp.sas Output:
t02-06-03-ae-km-socpt-sub-2-reg-safs.rtf (14DEC20:17:14) Data: adsl, adae, adttesaf

Seagen Protocol ONT-380-206**Table 2.6.3 Summary of Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Geographic Region - Time-to-Event Analysis Safety Analysis Set**

| System Organ Class/ Preferred Term | Parameters | North America | | Rest of World | |
|---------------------------------------|--|------------------------|------------------------|------------------------|-----------------------|
| | | Tuc+Cap+Tra (N=241) | Pbo+Cap+Tra (N=119) | Tuc+Cap+Tra (N=163) | Pbo+Cap+Tra (N=78) |
| Arthralgia (PT) | Number of Subjects With at Least One Event, n (%) | 42 (17.4) | 7 (5.9) | 22 (13.5) | 5 (6.4) |
| | Number of Censored Subjects, n (%) | 199 (82.6) | 112 (94.1) | 141 (86.5) | 73 (93.6) |
| | Stratified Hazard Ratio ^{a, b} (95% C.I.) | 2.518 (1.120, 5.657) | | 1.676 (0.630, 4.455) | |
| | P-value ^{b, c} | 0.02542 | | 0.30070 | |
| | Interaction Test P-value ^d | 0.59668 | | | |
| | Median Time to Onset of the First Event (Days) (95% C.I.) ^e | - (959.0, -) | - (-, -) | - (-, -) | - (-, -) |
| | 25 th , 75 th Percentile | 602.0, - | -, - | -, - | -, - |
| Observed Min, Max ^f | 1, 1156+ | 4, 762+ | 1, 954+ | 7, 839+ | |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (Presence or history of brain metastases: Yes/No and ECOG performance status: 0/1) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.

c. Two-sided p-value calculated from Cox proportional hazards model.

d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and geographic region.

e. Calculated using the complementary log-log transformation method (Collett, 1994). f. '+' means the observed time is from censored subjects.

Snapshot date: 10SEP2020, data cutoff date: 29MAY2020.

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_may2020_dco_1943\v01\outputs\tlfs\pgms\t-ae-km-socpt-subgrp.sas Output: t02-06-03-ae-km-socpt-sub-2-reg-safs.rtf (14DEC20:17:14) Data: adsl, adae, adttesaf

Seagen Protocol ONT-380-206**Table 2.6.3 Summary of Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Geographic Region - Time-to-Event Analysis Safety Analysis Set**

| System Organ Class/ Preferred Term | Parameters | North America | | Rest of World | |
|---------------------------------------|--|------------------------|------------------------|------------------------|-----------------------|
| | | Tuc+Cap+Tra (N=241) | Pbo+Cap+Tra (N=119) | Tuc+Cap+Tra (N=163) | Pbo+Cap+Tra (N=78) |
| Muscle Spasms (PT) | Number of Subjects With at Least One Event, n (%) | 27 (11.2) | 3 (2.5) | 16 (9.8) | 3 (3.8) |
| | Number of Censored Subjects, n (%) | 214 (88.8) | 116 (97.5) | 147 (90.2) | 75 (96.2) |
| | Stratified Hazard Ratio ^{a, b} (95% C.I.) | 3.542 (1.061, 11.819) | | 2.188 (0.628, 7.620) | |
| | P-value ^{b, c} | 0.03969 | | 0.21895 | |
| | Interaction Test P-value ^d | 0.61735 | | | |
| | Median Time to Onset of the First Event (Days) (95% C.I.) ^e | - (966.0, -) | - (-, -) | 841.0 (826.0, -) | - (-, -) |
| | 25 th , 75 th Percentile | 787.0, - | -, - | 826.0, - | -, - |
| | Observed Min, Max ^f | 2, 1327+ | 21, 762+ | 1, 873+ | 34+, 839+ |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (Presence or history of brain metastases: Yes/No and ECOG performance status: 0/1) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.

c. Two-sided p-value calculated from Cox proportional hazards model.

d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and geographic region.

e. Calculated using the complementary log-log transformation method (Collett, 1994). f. '+' means the observed time is from censored subjects.

Snapshot date: 10SEP2020, data cutoff date: 29MAY2020.

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_may2020_dco_1943\v01\outputs\tlfs\pgms\t-ae-km-socpt-subgrp.sas Output: t02-06-03-ae-km-socpt-sub-2-reg-safs.rtf (14DEC20:17:14) Data: adsl, adae, adttesaf

Seagen Protocol ONT-380-206

Table 2.6.3 Summary of Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Geographic Region - Time-to-Event Analysis Safety Analysis Set

| | | North America | | Rest of World | |
|---------------------------------------|--|------------------------|------------------------|------------------------|-----------------------|
| System Organ Class/ Preferred Term | Parameters | Tuc+Cap+Tra (N=241) | Pbo+Cap+Tra (N=119) | Tuc+Cap+Tra (N=163) | Pbo+Cap+Tra (N=78) |
| Peripheral Sensory Neuropathy (PT) | Number of Subjects With at Least One Event, n (%) | 37 (15.4) | 10 (8.4) | 14 (8.6) | 2 (2.6) |
| | Number of Censored Subjects, n (%) | 204 (84.6) | 109 (91.6) | 149 (91.4) | 76 (97.4) |
| | Stratified Hazard Ratio ^{a, b} (95% C.I.) | | 1.667 (0.825, 3.370) | | 3.370 (0.760, 14.944) |
| | P-value ^{b, c} | | 0.15452 | | 0.10991 |
| | Interaction Test P-value ^d | | | 0.45308 | |
| | Median Time to Onset of the First Event (Days) (95% C.I.) ^e | - (-, -) | - (509.0, -) | - (-, -) | - (-, -) |
| | 25 th , 75 th Percentile | -, - | 509.0, - | -, - | -, - |
| Observed Min, Max ^f | 2, 1327+ | 15, 762+ | 4, 873+ | 12, 839+ | |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (Presence or history of brain metastases: Yes/No and ECOG performance status: 0/1) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.

c. Two-sided p-value calculated from Cox proportional hazards model.

d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and geographic region.

e. Calculated using the complementary log-log transformation method (Collett, 1994). f. '+' means the observed time is from censored subjects.

Snapshot date: 10SEP2020, data cutoff date: 29MAY2020.

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_may2020_dco_1943\v01\outputs\tlfs\pgms\t-ae-km-socpt-subgrp.sas Output:

t02-06-03-ae-km-socpt-sub-2-reg-safs.rtf (14DEC20:17:14) Data: adsl, adae, adttesaf

Seagen Protocol ONT-380-206**Table 2.6.3 Summary of Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Geographic Region - Time-to-Event Analysis Safety Analysis Set**

| System Organ Class/ Preferred Term | Parameters | North America | | Rest of World | |
|---------------------------------------|--|------------------------|------------------------|------------------------|-----------------------|
| | | Tuc+Cap+Tra (N=241) | Pbo+Cap+Tra (N=119) | Tuc+Cap+Tra (N=163) | Pbo+Cap+Tra (N=78) |
| Dysgeusia (PT) | Number of Subjects With at Least One Event, n (%) | 24 (10.0) | 4 (3.4) | 9 (5.5) | 2 (2.6) |
| | Number of Censored Subjects, n (%) | 217 (90.0) | 115 (96.6) | 154 (94.5) | 76 (97.4) |
| | Stratified Hazard Ratio ^{a, b} (95% C.I.) | 2.702 (0.932, 7.834) | | 2.006 (0.427, 9.430) | |
| | P-value ^{b, c} | 0.06728 | | 0.37822 | |
| | Interaction Test P-value ^d | 0.73787 | | | |
| | Median Time to Onset of the First Event (Days) (95% C.I.) ^e | - (-, -) | - (-, -) | - (-, -) | - (-, -) |
| | 25 th , 75 th Percentile | -, - | -, - | -, - | -, - |
| | Observed Min, Max ^f | 1, 1327+ | 12, 762+ | 3, 954+ | 11, 839+ |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (Presence or history of brain metastases: Yes/No and ECOG performance status: 0/1) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.

c. Two-sided p-value calculated from Cox proportional hazards model.

d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and geographic region.

e. Calculated using the complementary log-log transformation method (Collett, 1994). f. '+' means the observed time is from censored subjects.

Snapshot date: 10SEP2020, data cutoff date: 29MAY2020.

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_may2020_dco_1943\v01\outputs\tlfs\pgms\t-ae-km-socpt-subgrp.sas Output: t02-06-03-ae-km-socpt-sub-2-reg-safs.rtf (14DEC20:17:14) Data: adsl, adae, adttesaf

Seagen Protocol ONT-380-206**Table 2.6.3 Summary of Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Geographic Region - Time-to-Event Analysis Safety Analysis Set**

| System Organ Class/ Preferred Term | Parameters | North America | | Rest of World | |
|---------------------------------------|--|------------------------|------------------------|------------------------|-----------------------|
| | | Tuc+Cap+Tra (N=241) | Pbo+Cap+Tra (N=119) | Tuc+Cap+Tra (N=163) | Pbo+Cap+Tra (N=78) |
| Epistaxis (PT) | Number of Subjects With at Least One Event, n (%) | 31 (12.9) | 6 (5.0) | 19 (11.7) | 4 (5.1) |
| | Number of Censored Subjects, n (%) | 210 (87.1) | 113 (95.0) | 144 (88.3) | 74 (94.9) |
| | Stratified Hazard Ratio ^{a, b} (95% C.I.) | 2.339 (0.972, 5.631) | | 2.317 (0.783, 6.853) | |
| | P-value ^{b, c} | 0.05799 | | 0.12886 | |
| | Interaction Test P-value ^d | 0.94764 | | | |
| | Median Time to Onset of the First Event (Days) (95% C.I.) ^e | - (-, -) | - (-, -) | - (-, -) | - (-, -) |
| | 25 th , 75 th Percentile | -, - | -, - | -, - | -, - |
| | Observed Min, Max ^f | 2, 1327+ | 5, 762+ | 1, 873+ | 3, 839+ |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (Presence or history of brain metastases: Yes/No and ECOG performance status: 0/1) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.

c. Two-sided p-value calculated from Cox proportional hazards model.

d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and geographic region.

e. Calculated using the complementary log-log transformation method (Collett, 1994). f. '+' means the observed time is from censored subjects.

Snapshot date: 10SEP2020, data cutoff date: 29MAY2020.

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_may2020_dco_1943\v01\outputs\tlfs\pgms\t-ae-km-socpt-subgrp.sas Output: t02-06-03-ae-km-socpt-sub-2-reg-safs.rtf (14DEC20:17:14) Data: adsl, adae, adttesaf

Seagen Protocol ONT-380-206**Table 2.6.3 Summary of Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Geographic Region - Time-to-Event Analysis Safety Analysis Set**

| System Organ Class/ Preferred Term | Parameters | North America | | Rest of World | |
|---------------------------------------|--|------------------------|------------------------|------------------------|-----------------------|
| | | Tuc+Cap+Tra (N=241) | Pbo+Cap+Tra (N=119) | Tuc+Cap+Tra (N=163) | Pbo+Cap+Tra (N=78) |
| Pleural Effusion (PT) | Number of Subjects With at Least One Event, n (%) | 10 (4.1) | 7 (5.9) | 0 | 4 (5.1) |
| | Number of Censored Subjects, n (%) | 231 (95.9) | 112 (94.1) | 163 (100) | 74 (94.9) |
| | Stratified Hazard Ratio ^{a, b} (95% C.I.) | 0.562 (0.207, 1.529) | | 0.000 (0.000, -) | |
| | P-value ^{b, c} | 0.25932 | | 0.99523 | |
| | Interaction Test P-value ^d | 0.99096 | | | |
| | Median Time to Onset of the First Event (Days) (95% C.I.) ^e | - (-, -) | - (-, -) | - (-, -) | - (-, -) |
| | 25 th , 75 th Percentile | -, - | -, - | -, - | -, - |
| Observed Min, Max ^f | 4+, 1327+ | 13, 762+ | 6+, 954+ | 6, 839+ | |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (Presence or history of brain metastases: Yes/No and ECOG performance status: 0/1) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.

c. Two-sided p-value calculated from Cox proportional hazards model.

d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and geographic region.

e. Calculated using the complementary log-log transformation method (Collett, 1994). f. '+' means the observed time is from censored subjects.

Snapshot date: 10SEP2020, data cutoff date: 29MAY2020.

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_may2020_dco_1943\v01\outputs\tlfs\pgms\t-ae-km-socpt-subgrp.sas Output: t02-06-03-ae-km-socpt-sub-2-reg-safs.rtf (14DEC20:17:14) Data: adsl, adae, adttesaf

Seagen Protocol ONT-380-206**Table 2.6.3 Summary of Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Geographic Region - Time-to-Event Analysis Safety Analysis Set**

| System Organ Class/ Preferred Term | Parameters | North America | | Rest of World | |
|--|---|-------------------------|------------------------|-------------------------|-----------------------|
| | | Tuc+Cap+Tra (N=241) | Pbo+Cap+Tra (N=119) | Tuc+Cap+Tra (N=163) | Pbo+Cap+Tra (N=78) |
| Palmar-Plantar Erythrodysesthesia Syndrome (PT) | Number of Subjects With at Least One Event, n (%) | 162 (67.2) | 65 (54.6) | 100 (61.3) | 40 (51.3) |
| | Number of Censored Subjects, n (%) | 79 (32.8) | 54 (45.4) | 63 (38.7) | 38 (48.7) |
| | Stratified Hazard Ratio ^{a, b} (95% C.I.) | 1.336 (1.000, 1.785) | | 1.190 (0.820, 1.728) | |
| | P-value ^{b, c} | 0.04968 | | 0.35978 | |
| | Interaction Test P-value ^d | 0.76595 | | | |
| | Median Time to Onset of the First Event (Days) (95% C.I.) ^e | 56.0 (43.0, 66.0) | 84.0 (63.0, 141.0) | 84.0 (56.0, 148.0) | 127.0 (65.0, -) |
| | 25 th , 75 th Percentile | 29.0, 324.0 | 33.0, - | 26.0, - | 34.0, - |
| Observed Min, Max ^f | 3, 648 | 1, 407+ | 1, 873+ | 1, 457+ | |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (Presence or history of brain metastases: Yes/No and ECOG performance status: 0/1) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.

c. Two-sided p-value calculated from Cox proportional hazards model.

d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and geographic region.

e. Calculated using the complementary log-log transformation method (Collett, 1994). f. '+' means the observed time is from censored subjects.

Snapshot date: 10SEP2020, data cutoff date: 29MAY2020.

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_may2020_dco_1943\v01\outputs\tlfs\pgms\t-ae-km-socpt-subgrp.sas Output:
t02-06-03-ae-km-socpt-sub-2-reg-safs.rtf (14DEC20:17:14) Data: adsl, adae, adttesaf

Seagen Protocol ONT-380-206**Table 2.6.4 Summary of Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Baseline ECOG Score - Time-to-Event Analysis Safety Analysis Set**

| System Organ Class/ Preferred Term | Parameters | ECOG=0 | | ECOG=1 | |
|---------------------------------------|--|------------------------|-----------------------|------------------------|------------------------|
| | | Tuc+Cap+Tra (N=203) | Pbo+Cap+Tra (N=91) | Tuc+Cap+Tra (N=201) | Pbo+Cap+Tra (N=106) |
| Anaemia (PT) | Number of Subjects With at Least One Event, n (%) | 38 (18.7) | 8 (8.8) | 48 (23.9) | 16 (15.1) |
| | Number of Censored Subjects, n (%) | 165 (81.3) | 83 (91.2) | 153 (76.1) | 90 (84.9) |
| | Stratified Hazard Ratio ^{a, b} (95% C.I.) | 1.976 (0.918, 4.254) | | 1.566 (0.888, 2.762) | |
| | P-value ^{b, c} | 0.08186 | | 0.12166 | |
| | Interaction Test P-value ^d | 0.51116 | | | |
| | Median Time to Onset of the First Event (Days) (95% C.I.) ^e | - (924.0, -) | - (-, -) | - (-, -) | - (-, -) |
| | 25 th , 75 th Percentile | 536.0, - | -, - | 218.0, - | -, - |
| | Observed Min, Max ^f | 1, 1327+ | 12, 839+ | 1, 1154+ | 12, 762+ |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (Presence or history of brain metastases: Yes/No and Region of world: North America /Rest of World) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.

c. Two-sided p-value calculated from Cox proportional hazards model.

d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and baseline ECOG score.

e. Calculated using the complementary log-log transformation method (Collett, 1994). f. '+' means the observed time is from censored subjects.

Snapshot date: 10SEP2020, data cutoff date: 29MAY2020.

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_may2020_dco_1943\v01\outputs\tlfs\pgms\t-ae-km-socpt-subgrp.sas Output: t02-06-04-ae-km-socpt-sub-3-ecog-safs.rtf (14DEC20:17:14) Data: adsl, adae, adttesaf

Seagen Protocol ONT-380-206**Table 2.6.4 Summary of Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Baseline ECOG Score - Time-to-Event Analysis Safety Analysis Set**

| System Organ Class/ Preferred Term | Parameters | ECOG=0 | | ECOG=1 | |
|---------------------------------------|--|------------------------|-----------------------|------------------------|------------------------|
| | | Tuc+Cap+Tra (N=203) | Pbo+Cap+Tra (N=91) | Tuc+Cap+Tra (N=201) | Pbo+Cap+Tra (N=106) |
| Investigations (SOC) | Number of Subjects With at Least One Event, n (%) | 128 (63.1) | 36 (39.6) | 126 (62.7) | 38 (35.8) |
| | Number of Censored Subjects, n (%) | 75 (36.9) | 55 (60.4) | 75 (37.3) | 68 (64.2) |
| | Stratified Hazard Ratio ^{a, b} (95% C.I.) | 1.812 (1.250, 2.625) | | 1.988 (1.380, 2.863) | |
| | P-value ^{b, c} | 0.00170 | | 0.00022 | |
| | Interaction Test P-value ^d | 0.72319 | | | |
| | Median Time to Onset of the First Event (Days) (95% C.I.) ^e | 88.0 (45.0, 167.0) | -(195.0, -) | 82.0 (43.0, 148.0) | 283.0 (231.0, -) |
| | 25 th , 75 th Percentile | 28.0, 757.0 | 51.0, - | 22.0, - | 85.0, 409.0 |
| Observed Min, Max ^f | 4+, 765+ | 1, 598+ | 1, 899+ | 6, 457+ | |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (Presence or history of brain metastases: Yes/No and Region of world: North America /Rest of World) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.

c. Two-sided p-value calculated from Cox proportional hazards model.

d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and baseline ECOG score.

e. Calculated using the complementary log-log transformation method (Collett, 1994). f. '+' means the observed time is from censored subjects.

Snapshot date: 10SEP2020, data cutoff date: 29MAY2020.

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_may2020_dco_1943\v01\outputs\tlfs\pgms\t-ae-km-socpt-subgrp.sas Output: t02-06-04-ae-km-socpt-sub-3-ecog-safs.rtf (14DEC20:17:14) Data: adsl, adae, adttesaf

Seagen Protocol ONT-380-206**Table 2.6.4 Summary of Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Baseline ECOG Score - Time-to-Event Analysis Safety Analysis Set**

| System Organ Class/ Preferred Term | Parameters | ECOG=0 | | ECOG=1 | |
|---|--|------------------------|-----------------------|------------------------|------------------------|
| | | Tuc+Cap+Tra (N=203) | Pbo+Cap+Tra (N=91) | Tuc+Cap+Tra (N=201) | Pbo+Cap+Tra (N=106) |
| Aspartate Aminotransferase Increased (PT) | Number of Subjects With at Least One Event, n (%) | 49 (24.1) | 8 (8.8) | 40 (19.9) | 14 (13.2) |
| | Number of Censored Subjects, n (%) | 154 (75.9) | 83 (91.2) | 161 (80.1) | 92 (86.8) |
| | Stratified Hazard Ratio ^{a, b} (95% C.I.) | 2.748 (1.298, 5.814) | | 1.465 (0.796, 2.698) | |
| | P-value ^{b, c} | 0.00822 | | 0.22022 | |
| | Interaction Test P-value ^d | 0.19571 | | | |
| | Median Time to Onset of the First Event (Days) (95% C.I.) ^e | - (-, -) | - (-, -) | - (-, -) | - (-, -) |
| | 25 th , 75 th Percentile | 337.0, - | -, - | -, - | -, - |
| | Observed Min, Max ^f | 4+, 1156+ | 1, 839+ | 6+, 1154+ | 11, 762+ |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (Presence or history of brain metastases: Yes/No and Region of world: North America /Rest of World) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.

c. Two-sided p-value calculated from Cox proportional hazards model.

d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and baseline ECOG score.

e. Calculated using the complementary log-log transformation method (Collett, 1994). f. '+' means the observed time is from censored subjects.

Snapshot date: 10SEP2020, data cutoff date: 29MAY2020.

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_may2020_dco_1943\v01\outputs\tlfs\pgms\t-ae-km-socpt-subgrp.sas Output:
t02-06-04-ae-km-socpt-sub-3-ecog-safs.rtf (14DEC20:17:14) Data: adsl, adae, adttesaf

Seagen Protocol ONT-380-206**Table 2.6.4 Summary of Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Baseline ECOG Score - Time-to-Event Analysis Safety Analysis Set**

| System Organ Class/ Preferred Term | Parameters | ECOG=0 | | ECOG=1 | |
|---|--|------------------------|-----------------------|------------------------|------------------------|
| | | Tuc+Cap+Tra (N=203) | Pbo+Cap+Tra (N=91) | Tuc+Cap+Tra (N=201) | Pbo+Cap+Tra (N=106) |
| Alanine Aminotransferase Increased (PT) | Number of Subjects With at Least One Event, n (%) | 50 (24.6) | 9 (9.9) | 35 (17.4) | 4 (3.8) |
| | Number of Censored Subjects, n (%) | 153 (75.4) | 82 (90.1) | 166 (82.6) | 102 (96.2) |
| | Stratified Hazard Ratio ^{a, b} (95% C.I.) | 2.533 (1.243, 5.159) | | 4.617 (1.637, 13.019) | |
| | P-value ^{b, c} | 0.01046 | | 0.00383 | |
| | Interaction Test P-value ^d | 0.35078 | | | |
| | Median Time to Onset of the First Event (Days) (95% C.I.) ^e | - (-, -) | - (-, -) | - (-, -) | - (-, -) |
| | 25 th , 75 th Percentile | 302.0, - | -, - | -, - | -, - |
| Observed Min, Max ^f | 4+, 1156+ | 21, 839+ | 6+, 1154+ | 14, 762+ | |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (Presence or history of brain metastases: Yes/No and Region of world: North America /Rest of World) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.

c. Two-sided p-value calculated from Cox proportional hazards model.

d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and baseline ECOG score.

e. Calculated using the complementary log-log transformation method (Collett, 1994). f. '+' means the observed time is from censored subjects.

Snapshot date: 10SEP2020, data cutoff date: 29MAY2020.

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_may2020_dco_1943\v01\outputs\tlfs\pgms\t-ae-km-socpt-subgrp.sas Output:

t02-06-04-ae-km-socpt-sub-3-ecog-safs.rtf (14DEC20:17:14) Data: adsl, adae, adttesaf

Seagen Protocol ONT-380-206**Table 2.6.4 Summary of Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Baseline ECOG Score - Time-to-Event Analysis Safety Analysis Set**

| | | ECOG=0 | | ECOG=1 | |
|---------------------------------------|--|------------------------|-----------------------|------------------------|------------------------|
| System Organ Class/ Preferred Term | Parameters | Tuc+Cap+Tra (N=203) | Pbo+Cap+Tra (N=91) | Tuc+Cap+Tra (N=201) | Pbo+Cap+Tra (N=106) |
| Blood Bilirubin Increased (PT) | Number of Subjects With at Least One Event, n (%) | 42 (20.7) | 8 (8.8) | 38 (18.9) | 13 (12.3) |
| | Number of Censored Subjects, n (%) | 161 (79.3) | 83 (91.2) | 163 (81.1) | 93 (87.7) |
| | Stratified Hazard Ratio ^{a, b} (95% C.I.) | 2.358 (1.106, 5.030) | | 1.466 (0.780, 2.757) | |
| | P-value ^{b, c} | 0.02640 | | 0.23468 | |
| | Interaction Test P-value ^d | 0.29923 | | | |
| | Median Time to Onset of the First Event (Days) (95% C.I.) ^e | - (-, -) | - (-, -) | - (-, -) | - (-, -) |
| | 25 th , 75 th Percentile | 296.0, - | -, - | -, - | -, - |
| Observed Min, Max ^f | 4+, 1156+ | 7, 839+ | 6+, 1154+ | 6, 762+ | |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (Presence or history of brain metastases: Yes/No and Region of world: North America /Rest of World) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.

c. Two-sided p-value calculated from Cox proportional hazards model.

d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and baseline ECOG score.

e. Calculated using the complementary log-log transformation method (Collett, 1994). f. '+' means the observed time is from censored subjects.

Snapshot date: 10SEP2020, data cutoff date: 29MAY2020.

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_may2020_dco_1943\v01\outputs\tlfs\pgms\t-ae-km-socpt-subgrp.sas Output: t02-06-04-ae-km-socpt-sub-3-ecog-safs.rtf (14DEC20:17:14) Data: adsl, adae, adttesaf

Seagen Protocol ONT-380-206**Table 2.6.4 Summary of Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Baseline ECOG Score - Time-to-Event Analysis
Safety Analysis Set**

| System Organ Class/ Preferred Term | Parameters | ECOG=0 | | ECOG=1 | |
|---------------------------------------|--|------------------------|-----------------------|------------------------|------------------------|
| | | Tuc+Cap+Tra (N=203) | Pbo+Cap+Tra (N=91) | Tuc+Cap+Tra (N=201) | Pbo+Cap+Tra (N=106) |
| Blood Creatinine Increased (PT) | Number of Subjects With at Least One Event, n (%) | 40 (19.7) | 2 (2.2) | 22 (10.9) | 1 (0.9) |
| | Number of Censored Subjects, n (%) | 163 (80.3) | 89 (97.8) | 179 (89.1) | 105 (99.1) |
| | Stratified Hazard Ratio ^{a, b} (95% C.I.) | 8.739 (2.107, 36.249) | | 10.374 (1.392, 77.313) | |
| | P-value ^{b, c} | 0.00282 | | 0.02245 | |
| | Interaction Test P-value ^d | | | 0.86596 | |
| | Median Time to Onset of the First Event (Days) (95% C.I.) ^e | - (-, -) | - (-, -) | - (-, -) | - (-, -) |
| | 25 th , 75 th Percentile Observed Min, Max ^f | 610.0, - 4+, 1131+ | -, - 13, 839+ | -, - 6+, 1154+ | -, - 26+, 762+ |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (Presence or history of brain metastases: Yes/No and Region of world: North America /Rest of World) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.

c. Two-sided p-value calculated from Cox proportional hazards model.

d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and baseline ECOG score.

e. Calculated using the complementary log-log transformation method (Collett, 1994). f. '+' means the observed time is from censored subjects.

Snapshot date: 10SEP2020, data cutoff date: 29MAY2020.

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_may2020_dco_1943\v01\outputs\tlfs\pgms\t-ae-km-socpt-subgrp.sas Output: t02-06-04-ae-km-socpt-sub-3-ecog-safs.rtf (14DEC20:17:14) Data: adsl, adae, adttesaf

Seagen Protocol ONT-380-206**Table 2.6.4 Summary of Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Baseline ECOG Score - Time-to-Event Analysis Safety Analysis Set**

| | | ECOG=0 | | ECOG=1 | |
|---------------------------------------|--|------------------------|-----------------------|------------------------|------------------------|
| System Organ Class/ Preferred Term | Parameters | Tuc+Cap+Tra (N=203) | Pbo+Cap+Tra (N=91) | Tuc+Cap+Tra (N=201) | Pbo+Cap+Tra (N=106) |
| Weight Decreased (PT) | Number of Subjects With at Least One Event, n (%) | 23 (11.3) | 3 (3.3) | 39 (19.4) | 9 (8.5) |
| | Number of Censored Subjects, n (%) | 180 (88.7) | 88 (96.7) | 162 (80.6) | 97 (91.5) |
| | Stratified Hazard Ratio ^{a, b} (95% C.I.) | 3.256 (0.971, 10.916) | | 2.095 (1.010, 4.347) | |
| | P-value ^{b, c} | 0.05575 | | 0.04690 | |
| | Interaction Test P-value ^d | | | 0.51734 | |
| | Median Time to Onset of the First Event (Days) (95% C.I.) ^e | - (-, -) | - (-, -) | - (-, -) | - (-, -) |
| | 25 th , 75 th Percentile | -, - | -, - | 375.0, - | -, - |
| | Observed Min, Max ^f | 4+, 1327+ | 9, 839+ | 6, 945+ | 22, 762+ |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (Presence or history of brain metastases: Yes/No and Region of world: North America /Rest of World) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.

c. Two-sided p-value calculated from Cox proportional hazards model.

d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and baseline ECOG score.

e. Calculated using the complementary log-log transformation method (Collett, 1994). f. '+' means the observed time is from censored subjects.

Snapshot date: 10SEP2020, data cutoff date: 29MAY2020.

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_may2020_dco_1943\v01\outputs\tlfs\pgms\t-ae-km-socpt-subgrp.sas Output: t02-06-04-ae-km-socpt-sub-3-ecog-safs.rtf (14DEC20:17:14) Data: adsl, adae, adttesaf

Seagen Protocol ONT-380-206**Table 2.6.4 Summary of Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Baseline ECOG Score - Time-to-Event Analysis Safety Analysis Set**

| System Organ Class/ Preferred Term | Parameters | ECOG=0 | | ECOG=1 | |
|--|--|------------------------|-----------------------|------------------------|------------------------|
| | | Tuc+Cap+Tra (N=203) | Pbo+Cap+Tra (N=91) | Tuc+Cap+Tra (N=201) | Pbo+Cap+Tra (N=106) |
| Metabolism And Nutrition Disorders (SOC) | Number of Subjects With at Least One Event, n (%) | 99 (48.8) | 29 (31.9) | 113 (56.2) | 45 (42.5) |
| | Number of Censored Subjects, n (%) | 104 (51.2) | 62 (68.1) | 88 (43.8) | 61 (57.5) |
| | Stratified Hazard Ratio ^{a, b} (95% C.I.) | 1.680 (1.109, 2.544) | | 1.357 (0.957, 1.924) | |
| | P-value ^{b, c} | 0.01434 | | 0.08690 | |
| | Interaction Test P-value ^d | 0.54818 | | | |
| | Median Time to Onset of the First Event (Days) (95% C.I.) ^e | 211.0 (113.0, -) | 526.0 (333.0, -) | 127.0 (69.0, 266.0) | 281.0 (129.0, -) |
| | 25 th , 75 th Percentile | 35.0, - | 102.0, - | 22.0, 595.0 | 42.0, - |
| Observed Min, Max ^f | 1, 1131+ | 4, 839+ | 1, 718+ | 1, 762+ | |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (Presence or history of brain metastases: Yes/No and Region of world: North America /Rest of World) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.

c. Two-sided p-value calculated from Cox proportional hazards model.

d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and baseline ECOG score.

e. Calculated using the complementary log-log transformation method (Collett, 1994). f. '+' means the observed time is from censored subjects.

Snapshot date: 10SEP2020, data cutoff date: 29MAY2020.

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Seagen Protocol ONT-380-206**Table 2.6.4 Summary of Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Baseline ECOG Score - Time-to-Event Analysis
Safety Analysis Set**

| System Organ Class/ Preferred Term | Parameters | ECOG=0 | | ECOG=1 | |
|---------------------------------------|--|------------------------|-----------------------|------------------------|------------------------|
| | | Tuc+Cap+Tra (N=203) | Pbo+Cap+Tra (N=91) | Tuc+Cap+Tra (N=201) | Pbo+Cap+Tra (N=106) |
| Hyperglycaemia (PT) | Number of Subjects With at Least One Event, n (%) | 8 (3.9) | 1 (1.1) | 15 (7.5) | 2 (1.9) |
| | Number of Censored Subjects, n (%) | 195 (96.1) | 90 (98.9) | 186 (92.5) | 104 (98.1) |
| | Stratified Hazard Ratio ^{a, b} (95% C.I.) | 3.251 (0.402, 26.273) | | 3.691 (0.844, 16.146) | |
| | P-value ^{b, c} | 0.26889 | | 0.08292 | |
| | Interaction Test P-value ^d | 0.93439 | | | |
| | Median Time to Onset of the First Event (Days) (95% C.I.) ^e | - (-, -) | - (-, -) | - (-, -) | - (-, -) |
| | 25 th , 75 th Percentile | -, - | -, - | -, - | -, - |
| Observed Min, Max ^f | 4+, 1327+ | 12, 839+ | 2, 1154+ | 13, 762+ | |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (Presence or history of brain metastases: Yes/No and Region of world: North America /Rest of World) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.

c. Two-sided p-value calculated from Cox proportional hazards model.

d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and baseline ECOG score.

e. Calculated using the complementary log-log transformation method (Collett, 1994). f. '+' means the observed time is from censored subjects.

Snapshot date: 10SEP2020, data cutoff date: 29MAY2020.

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Seagen Protocol ONT-380-206**Table 2.6.4 Summary of Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Baseline ECOG Score - Time-to-Event Analysis
Safety Analysis Set**

| System Organ Class/ Preferred Term | Parameters | ECOG=0 | | ECOG=1 | |
|--|---|-------------------------|-------------------------|-------------------------|-------------------------|
| | | Tuc+Cap+Tra (N=203) | Pbo+Cap+Tra (N=91) | Tuc+Cap+Tra (N=201) | Pbo+Cap+Tra (N=106) |
| Musculoskeletal And Connective Tissue Disorders (SOC) | Number of Subjects With at Least One Event, n (%) | 100 (49.3) | 32 (35.2) | 97 (48.3) | 37 (34.9) |
| | Number of Censored Subjects, n (%) | 103 (50.7) | 59 (64.8) | 104 (51.7) | 69 (65.1) |
| | Stratified Hazard Ratio ^{a, b} (95% C.I.) | | 1.463 (0.978, 2.187) | | 1.297 (0.883, 1.904) |
| | P-value ^{b, c} | | 0.06405 | | 0.18517 |
| | Interaction Test P-value ^d | | | 0.86043 | |
| | Median Time to Onset of the First Event (Days) (95% C.I.) ^e | 253.0 (158.0, 434.0) | 399.0 (286.0, -) | 213.0 (144.0, 354.0) | 275.0 (145.0, -) |
| | 25 th , 75 th Percentile | 49.0, - | 102.0, - | 65.0, - | 104.0, - |
| Observed Min, Max ^f | 1, 1117+ | 1, 839+ | 1, 830+ | 1, 760+ | |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (Presence or history of brain metastases: Yes/No and Region of world: North America /Rest of World) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.

c. Two-sided p-value calculated from Cox proportional hazards model.

d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and baseline ECOG score.

e. Calculated using the complementary log-log transformation method (Collett, 1994). f. '+' means the observed time is from censored subjects.

Snapshot date: 10SEP2020, data cutoff date: 29MAY2020.

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Seagen Protocol ONT-380-206**Table 2.6.4 Summary of Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Baseline ECOG Score - Time-to-Event Analysis Safety Analysis Set**

| System Organ Class/ Preferred Term | Parameters | ECOG=0 | | ECOG=1 | |
|---------------------------------------|--|------------------------|-----------------------|------------------------|------------------------|
| | | Tuc+Cap+Tra (N=203) | Pbo+Cap+Tra (N=91) | Tuc+Cap+Tra (N=201) | Pbo+Cap+Tra (N=106) |
| Arthralgia (PT) | Number of Subjects With at Least One Event, n (%) | 28 (13.8) | 6 (6.6) | 36 (17.9) | 6 (5.7) |
| | Number of Censored Subjects, n (%) | 175 (86.2) | 85 (93.4) | 165 (82.1) | 100 (94.3) |
| | Stratified Hazard Ratio ^{a, b} (95% C.I.) | 1.686 (0.689, 4.127) | | 2.779 (1.163, 6.644) | |
| | P-value ^{b, c} | 0.25295 | | 0.02152 | |
| | Interaction Test P-value ^d | 0.45447 | | | |
| | Median Time to Onset of the First Event (Days) (95% C.I.) ^e | - (959.0, -) | - (-, -) | - (-, -) | - (-, -) |
| | 25 th , 75 th Percentile | 707.0, - | -, - | 449.0, - | -, - |
| Observed Min, Max ^f | 1, 1156+ | 4, 839+ | 1, 1154+ | 7, 762+ | |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (Presence or history of brain metastases: Yes/No and Region of world: North America /Rest of World) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.

c. Two-sided p-value calculated from Cox proportional hazards model.

d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and baseline ECOG score.

e. Calculated using the complementary log-log transformation method (Collett, 1994). f. '+' means the observed time is from censored subjects.

Snapshot date: 10SEP2020, data cutoff date: 29MAY2020.

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Seagen Protocol ONT-380-206**Table 2.6.4 Summary of Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Baseline ECOG Score - Time-to-Event Analysis Safety Analysis Set**

| System Organ Class/ Preferred Term | Parameters | ECOG=0 | | ECOG=1 | |
|---------------------------------------|--|------------------------|-----------------------|------------------------|------------------------|
| | | Tuc+Cap+Tra (N=203) | Pbo+Cap+Tra (N=91) | Tuc+Cap+Tra (N=201) | Pbo+Cap+Tra (N=106) |
| Muscle Spasms (PT) | Number of Subjects With at Least One Event, n (%) | 26 (12.8) | 2 (2.2) | 17 (8.5) | 4 (3.8) |
| | Number of Censored Subjects, n (%) | 177 (87.2) | 89 (97.8) | 184 (91.5) | 102 (96.2) |
| | Stratified Hazard Ratio ^{a, b} (95% C.I.) | 4.785 (1.124, 20.380) | | 1.887 (0.624, 5.714) | |
| | P-value ^{b, c} | 0.03421 | | 0.26098 | |
| | Interaction Test P-value ^d | 0.32616 | | | |
| | Median Time to Onset of the First Event (Days) (95% C.I.) ^e | - (826.0, -) | - (-, -) | - (-, -) | - (-, -) |
| | 25 th , 75 th Percentile | 826.0, - | -, - | -, - | -, - |
| Observed Min, Max ^f | 1, 1327+ | 50+, 839+ | 6+, 830+ | 21, 762+ | |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (Presence or history of brain metastases: Yes/No and Region of world: North America /Rest of World) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.

c. Two-sided p-value calculated from Cox proportional hazards model.

d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and baseline ECOG score.

e. Calculated using the complementary log-log transformation method (Collett, 1994). f. '+' means the observed time is from censored subjects.

Snapshot date: 10SEP2020, data cutoff date: 29MAY2020.

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Seagen Protocol ONT-380-206**Table 2.6.4 Summary of Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Baseline ECOG Score - Time-to-Event Analysis Safety Analysis Set**

| | | ECOG=0 | | ECOG=1 | |
|---------------------------------------|--|------------------------|-----------------------|------------------------|------------------------|
| System Organ Class/ Preferred Term | Parameters | Tuc+Cap+Tra (N=203) | Pbo+Cap+Tra (N=91) | Tuc+Cap+Tra (N=201) | Pbo+Cap+Tra (N=106) |
| Peripheral Sensory Neuropathy (PT) | Number of Subjects With at Least One Event, n (%) | 26 (12.8) | 4 (4.4) | 25 (12.4) | 8 (7.5) |
| | Number of Censored Subjects, n (%) | 177 (87.2) | 87 (95.6) | 176 (87.6) | 98 (92.5) |
| | Stratified Hazard Ratio ^{a, b} (95% C.I.) | | 2.812 (0.978, 8.090) | | 1.521 (0.682, 3.396) |
| | P-value ^{b, c} | | 0.05513 | | 0.30574 |
| | Interaction Test P-value ^d | | | 0.37752 | |
| | Median Time to Onset of the First Event (Days) (95% C.I.) ^e | - (-, -) | - (509.0, -) | - (-, -) | - (-, -) |
| | 25 th , 75 th Percentile | -, - | -, - | -, - | -, - |
| Observed Min, Max ^f | 4, 1327+ | 12, 839+ | 2, 1154+ | 21, 762+ | |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (Presence or history of brain metastases: Yes/No and Region of world: North America /Rest of World) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.

c. Two-sided p-value calculated from Cox proportional hazards model.

d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and baseline ECOG score.

e. Calculated using the complementary log-log transformation method (Collett, 1994). f. '+' means the observed time is from censored subjects.

Snapshot date: 10SEP2020, data cutoff date: 29MAY2020.

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_may2020_dco_1943\v01\outputs\tlfs\pgms\t-ae-km-socpt-subgrp.sas Output:

t02-06-04-ae-km-socpt-sub-3-ecog-safs.rtf (14DEC20:17:14) Data: adsl, adae, adttesaf

Seagen Protocol ONT-380-206**Table 2.6.4 Summary of Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Baseline ECOG Score - Time-to-Event Analysis Safety Analysis Set**

| System Organ Class/ Preferred Term | Parameters | ECOG=0 | | ECOG=1 | |
|---------------------------------------|--|------------------------|-----------------------|------------------------|------------------------|
| | | Tuc+Cap+Tra (N=203) | Pbo+Cap+Tra (N=91) | Tuc+Cap+Tra (N=201) | Pbo+Cap+Tra (N=106) |
| Dysgeusia (PT) | Number of Subjects With at Least One Event, n (%) | 15 (7.4) | 4 (4.4) | 18 (9.0) | 2 (1.9) |
| | Number of Censored Subjects, n (%) | 188 (92.6) | 87 (95.6) | 183 (91.0) | 104 (98.1) |
| | Stratified Hazard Ratio ^{a, b} (95% C.I.) | 1.639 (0.541, 4.966) | | 4.151 (0.955, 18.038) | |
| | P-value ^{b, c} | 0.38219 | | 0.05754 | |
| | Interaction Test P-value ^d | 0.27404 | | | |
| | Median Time to Onset of the First Event (Days) (95% C.I.) ^e | - (-, -) | - (-, -) | - (-, -) | - (-, -) |
| | 25 th , 75 th Percentile | -, - | -, - | -, - | -, - |
| Observed Min, Max ^f | 2, 1327+ | 12, 839+ | 1, 945+ | 11, 762+ | |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (Presence or history of brain metastases: Yes/No and Region of world: North America /Rest of World) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.

c. Two-sided p-value calculated from Cox proportional hazards model.

d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and baseline ECOG score.

e. Calculated using the complementary log-log transformation method (Collett, 1994). f. '+' means the observed time is from censored subjects.

Snapshot date: 10SEP2020, data cutoff date: 29MAY2020.

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_may2020_dco_1943\v01\outputs\tlfs\pgms\t-ae-km-socpt-subgrp.sas Output: t02-06-04-ae-km-socpt-sub-3-ecog-safs.rtf (14DEC20:17:14) Data: adsl, adae, adttesaf

Seagen Protocol ONT-380-206**Table 2.6.4 Summary of Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Baseline ECOG Score - Time-to-Event Analysis Safety Analysis Set**

| System Organ Class/ Preferred Term | Parameters | ECOG=0 | | ECOG=1 | |
|---------------------------------------|--|------------------------|-----------------------|------------------------|------------------------|
| | | Tuc+Cap+Tra (N=203) | Pbo+Cap+Tra (N=91) | Tuc+Cap+Tra (N=201) | Pbo+Cap+Tra (N=106) |
| Epistaxis (PT) | Number of Subjects With at Least One Event, n (%) | 29 (14.3) | 3 (3.3) | 21 (10.4) | 7 (6.6) |
| | Number of Censored Subjects, n (%) | 174 (85.7) | 88 (96.7) | 180 (89.6) | 99 (93.4) |
| | Stratified Hazard Ratio ^{a, b} (95% C.I.) | 4.073 (1.235, 13.440) | | 1.554 (0.659, 3.666) | |
| | P-value ^{b, c} | 0.02111 | | 0.31422 | |
| | Interaction Test P-value ^d | 0.17755 | | | |
| | Median Time to Onset of the First Event (Days) (95% C.I.) ^e | - (-, -) | - (-, -) | - (-, -) | - (-, -) |
| | 25 th , 75 th Percentile | -, - | -, - | -, - | -, - |
| | Observed Min, Max ^f | 1, 1327+ | 3, 839+ | 1, 945+ | 5, 762+ |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (Presence or history of brain metastases: Yes/No and Region of world: North America /Rest of World) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.

c. Two-sided p-value calculated from Cox proportional hazards model.

d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and baseline ECOG score.

e. Calculated using the complementary log-log transformation method (Collett, 1994). f. '+' means the observed time is from censored subjects.

Snapshot date: 10SEP2020, data cutoff date: 29MAY2020.

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_may2020_dco_1943\v01\outputs\tlfs\pgms\t-ae-km-socpt-subgrp.sas Output: t02-06-04-ae-km-socpt-sub-3-ecog-safs.rtf (14DEC20:17:14) Data: adsl, adae, adttesaf

Seagen Protocol ONT-380-206**Table 2.6.4 Summary of Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Baseline ECOG Score - Time-to-Event Analysis
Safety Analysis Set**

| System Organ Class/ Preferred Term | Parameters | ECOG=0 | | ECOG=1 | |
|---------------------------------------|--|------------------------|-----------------------|------------------------|------------------------|
| | | Tuc+Cap+Tra (N=203) | Pbo+Cap+Tra (N=91) | Tuc+Cap+Tra (N=201) | Pbo+Cap+Tra (N=106) |
| Pleural Effusion (PT) | Number of Subjects With at Least One Event, n (%) | 3 (1.5) | 6 (6.6) | 7 (3.5) | 5 (4.7) |
| | Number of Censored Subjects, n (%) | 200 (98.5) | 85 (93.4) | 194 (96.5) | 101 (95.3) |
| | Stratified Hazard Ratio ^{a, b} (95% C.I.) | 0.213 (0.053, 0.855) | | 0.544 (0.162, 1.821) | |
| | P-value ^{b, c} | 0.02924 | | 0.32314 | |
| | Interaction Test P-value ^d | 0.15915 | | | |
| | Median Time to Onset of the First Event (Days) (95% C.I.) ^e | - (-, -) | - (-, -) | 942.0 (942.0, -) | - (-, -) |
| | 25 th , 75 th Percentile | -, - | -, - | 942.0, - | -, - |
| | Observed Min, Max ^f | 4+, 1327+ | 6, 839+ | 6+, 1154+ | 8, 762+ |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (Presence or history of brain metastases: Yes/No and Region of world: North America /Rest of World) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.

c. Two-sided p-value calculated from Cox proportional hazards model.

d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and baseline ECOG score.

e. Calculated using the complementary log-log transformation method (Collett, 1994). f. '+' means the observed time is from censored subjects.

Snapshot date: 10SEP2020, data cutoff date: 29MAY2020.

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_may2020_dco_1943\v01\outputs\tlfs\pgms\t-ae-km-socpt-subgrp.sas Output: t02-06-04-ae-km-socpt-sub-3-ecog-safs.rtf (14DEC20:17:14) Data: adsl, adae, adttesaf

Seagen Protocol ONT-380-206**Table 2.6.4 Summary of Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Baseline ECOG Score - Time-to-Event Analysis
Safety Analysis Set**

| System Organ Class/ Preferred Term | Parameters | ECOG=0 | | ECOG=1 | |
|---|--|------------------------|-----------------------|------------------------|------------------------|
| | | Tuc+Cap+Tra (N=203) | Pbo+Cap+Tra (N=91) | Tuc+Cap+Tra (N=201) | Pbo+Cap+Tra (N=106) |
| Palmar-Plantar Erythrodyssaesthesia Syndrome (PT) | Number of Subjects With at Least One Event, n (%) | 137 (67.5) | 53 (58.2) | 125 (62.2) | 52 (49.1) |
| | Number of Censored Subjects, n (%) | 66 (32.5) | 38 (41.8) | 76 (37.8) | 54 (50.9) |
| | Stratified Hazard Ratio ^{a, b} (95% C.I.) | 1.255 (0.913, 1.726) | | 1.311 (0.944, 1.821) | |
| | P-value ^{b, c} | 0.16138 | | 0.10598 | |
| | Interaction Test P-value ^d | 0.75134 | | | |
| | Median Time to Onset of the First Event (Days) (95% C.I.) ^e | 49.0 (36.0, 64.0) | 65.0 (44.0, 149.0) | 84.0 (61.0, 106.0) | 127.0 (72.0, -) |
| | 25 th , 75 th Percentile | 25.0, 648.0 | 32.0, - | 31.0, 337.0 | 35.0, - |
| Observed Min, Max ^f | 1, 873+ | 1, 450+ | 3, 785+ | 1, 457+ | |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (Presence or history of brain metastases: Yes/No and Region of world: North America /Rest of World) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.

c. Two-sided p-value calculated from Cox proportional hazards model.

d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and baseline ECOG score.

e. Calculated using the complementary log-log transformation method (Collett, 1994). f. '+' means the observed time is from censored subjects.

Snapshot date: 10SEP2020, data cutoff date: 29MAY2020.

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_may2020_dco_1943\v01\outputs\tlfs\pgms\t-ae-km-socpt-subgrp.sas Output: t02-06-04-ae-km-socpt-sub-3-ecog-safs.rtf (14DEC20:17:14) Data: adsl, adae, adttesaf

Seagen Protocol ONT-380-206**Table 2.6.5 Summary of Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Age - Time-to-Event Analysis Safety Analysis Set**

| System Organ Class/ Preferred Term | Parameters | Age < 65 Years | | Age ≥ 65 Years | |
|---------------------------------------|--|------------------------|------------------------|-----------------------|-----------------------|
| | | Tuc+Cap+Tra (N=322) | Pbo+Cap+Tra (N=164) | Tuc+Cap+Tra (N=82) | Pbo+Cap+Tra (N=33) |
| Anaemia (PT) | Number of Subjects With at Least One Event, n (%) | 65 (20.2) | 20 (12.2) | 21 (25.6) | 4 (12.1) |
| | Number of Censored Subjects, n (%) | 257 (79.8) | 144 (87.8) | 61 (74.4) | 29 (87.9) |
| | Stratified Hazard Ratio ^{a, b} (95% C.I.) | 1.519 (0.916, 2.519) | | 2.206 (0.747, 6.518) | |
| | P-value ^{b, c} | 0.10516 | | 0.15231 | |
| | Interaction Test P-value ^d | 0.53328 | | | |
| | Median Time to Onset of the First Event (Days) (95% C.I.) ^e | - (-, -) | - (-, -) | - (472.0, -) | - (-, -) |
| | 25 th , 75 th Percentile | 536.0, - | -, - | 197.0, - | -, - |
| Observed Min, Max ^f | 1, 1327+ | 12, 839+ | 4+, 945+ | 12, 428+ | |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (Presence or history of brain metastases: Yes/No, ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.

c. Two-sided p-value calculated from Cox proportional hazards model.

d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and age.

e. Calculated using the complementary log-log transformation method (Collett, 1994). f. '+' means the observed time is from censored subjects.

Snapshot date: 10SEP2020, data cutoff date: 29MAY2020.

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_may2020_dco_1943\v01\outputs\tlfs\pgms\t-ae-km-socpt-subgrp.sas Output: t02-06-05-ae-km-socpt-sub-4-age-safs.rtf (14DEC20:17:14) Data: adsl, adae, adttesaf

Seagen Protocol ONT-380-206**Table 2.6.5 Summary of Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Age - Time-to-Event Analysis Safety Analysis Set**

| System Organ Class/ Preferred Term | Parameters | Age < 65 Years | | Age ≥ 65 Years | |
|---------------------------------------|--|------------------------|------------------------|-----------------------|-----------------------|
| | | Tuc+Cap+Tra (N=322) | Pbo+Cap+Tra (N=164) | Tuc+Cap+Tra (N=82) | Pbo+Cap+Tra (N=33) |
| Investigations (SOC) | Number of Subjects With at Least One Event, n (%) | 202 (62.7) | 63 (38.4) | 52 (63.4) | 11 (33.3) |
| | Number of Censored Subjects, n (%) | 120 (37.3) | 101 (61.6) | 30 (36.6) | 22 (66.7) |
| | Stratified Hazard Ratio ^{a, b} (95% C.I.) | 1.792 (1.347, 2.384) | | 2.528 (1.268, 5.037) | |
| | P-value ^{b, c} | 0.00006 | | 0.00839 | |
| | Interaction Test P-value ^d | 0.38512 | | | |
| | Median Time to Onset of the First Event (Days) (95% C.I.) ^e | 105.0 (63.0, 152.0) | 409.0 (231.0, -) | 64.0 (42.0, 106.0) | 356.0 (195.0, -) |
| | 25 th , 75 th Percentile | 22.0, 757.0 | 62.0, - | 30.0, - | 127.0, - |
| Observed Min, Max ^f | 1, 899+ | 1, 598+ | 4+, 547+ | 9, 409+ | |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (Presence or history of brain metastases: Yes/No, ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.

c. Two-sided p-value calculated from Cox proportional hazards model.

d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and age.

e. Calculated using the complementary log-log transformation method (Collett, 1994). f. '+' means the observed time is from censored subjects.

Snapshot date: 10SEP2020, data cutoff date: 29MAY2020.

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_may2020_dco_1943\v01\outputs\tlfs\pgms\t-ae-km-socpt-subgrp.sas Output: t02-06-05-ae-km-socpt-sub-4-age-safs.rtf (14DEC20:17:14) Data: adsl, adae, adttesaf

Seagen Protocol ONT-380-206**Table 2.6.5 Summary of Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Age - Time-to-Event Analysis Safety Analysis Set**

| System Organ Class/ Preferred Term | Parameters | Age < 65 Years | | Age ≥ 65 Years | |
|---|--|------------------------|------------------------|-----------------------|-----------------------|
| | | Tuc+Cap+Tra (N=322) | Pbo+Cap+Tra (N=164) | Tuc+Cap+Tra (N=82) | Pbo+Cap+Tra (N=33) |
| Aspartate Aminotransferase Increased (PT) | Number of Subjects With at Least One Event, n (%) | 65 (20.2) | 21 (12.8) | 24 (29.3) | 1 (3.0) |
| | Number of Censored Subjects, n (%) | 257 (79.8) | 143 (87.2) | 58 (70.7) | 32 (97.0) |
| | Stratified Hazard Ratio ^{a, b} (95% C.I.) | 1.558 (0.951, 2.553) | | 9.808 (1.317, 73.050) | |
| | P-value ^{b, c} | 0.07805 | | 0.02584 | |
| | Interaction Test P-value ^d | 0.07755 | | | |
| | Median Time to Onset of the First Event (Days) (95% C.I.) ^e | - (-, -) | - (-, -) | - (-, -) | - (-, -) |
| | 25 th , 75 th Percentile | 677.0, - | -, - | 64.0, - | -, - |
| | Observed Min, Max ^f | 6+, 1156+ | 1, 839+ | 4+, 830+ | 14, 428+ |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (Presence or history of brain metastases: Yes/No, ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.

c. Two-sided p-value calculated from Cox proportional hazards model.

d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and age.

e. Calculated using the complementary log-log transformation method (Collett, 1994). f. '+' means the observed time is from censored subjects.

Snapshot date: 10SEP2020, data cutoff date: 29MAY2020.

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_may2020_dco_1943\v01\outputs\tlfs\pgms\t-ae-km-socpt-subgrp.sas Output: t02-06-05-ae-km-socpt-sub-4-age-safs.rtf (14DEC20:17:14) Data: adsl, adae, adttesaf

Seagen Protocol ONT-380-206**Table 2.6.5 Summary of Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Age - Time-to-Event Analysis Safety Analysis Set**

| System Organ Class/ Preferred Term | Parameters | Age < 65 Years | | Age ≥ 65 Years | |
|---|--|------------------------|------------------------|-----------------------|-------------------------|
| | | Tuc+Cap+Tra (N=322) | Pbo+Cap+Tra (N=164) | Tuc+Cap+Tra (N=82) | Pbo+Cap+Tra (N=33) |
| Alanine Aminotransferase Increased (PT) | Number of Subjects With at Least One Event, n (%) | 62 (19.3) | 13 (7.9) | 23 (28.0) | 0 |
| | Number of Censored Subjects, n (%) | 260 (80.7) | 151 (92.1) | 59 (72.0) | 33 (100) |
| | Stratified Hazard Ratio ^{a, b} (95% C.I.) | | 2.403 (1.318, 4.379) | | 45783272.745 (0.000, -) |
| | P-value ^{b, c} | | 0.00421 | | 0.99341 |
| | Interaction Test P-value ^d | | | | 0.97942 |
| | Median Time to Onset of the First Event (Days) (95% C.I.) ^e | - (-, -) | - (-, -) | - (364.0, -) | - (-, -) |
| | 25 th , 75 th Percentile | -, - | -, - | 92.0, - | -, - |
| Observed Min, Max ^f | 6+, 1156+ | 14, 839+ | 4+, 830+ | 31+, 428+ | |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (Presence or history of brain metastases: Yes/No, ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.

c. Two-sided p-value calculated from Cox proportional hazards model.

d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and age.

e. Calculated using the complementary log-log transformation method (Collett, 1994). f. '+' means the observed time is from censored subjects.

Snapshot date: 10SEP2020, data cutoff date: 29MAY2020.

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_may2020_dco_1943\v01\outputs\tlfs\pgms\t-ae-km-socpt-subgrp.sas Output: t02-06-05-ae-km-socpt-sub-4-age-safs.rtf (14DEC20:17:14) Data: adsl, adae, adttesaf

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Table 2.6.5 Summary of Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Age - Time-to-Event Analysis Safety Analysis Set

| System Organ Class/ Preferred Term | Parameters | Age < 65 Years | | Age >= 65 Years | |
|---------------------------------------|--|------------------------|------------------------|-----------------------|-----------------------|
| | | Tuc+Cap+Tra (N=322) | Pbo+Cap+Tra (N=164) | Tuc+Cap+Tra (N=82) | Pbo+Cap+Tra (N=33) |
| Blood Bilirubin Increased (PT) | Number of Subjects With at Least One Event, n (%) | 61 (18.9) | 17 (10.4) | 19 (23.2) | 4 (12.1) |
| | Number of Censored Subjects, n (%) | 261 (81.1) | 147 (89.6) | 63 (76.8) | 29 (87.9) |
| | Stratified Hazard Ratio ^{a, b} (95% C.I.) | 1.745 (1.017, 2.995) | | 2.266 (0.753, 6.821) | |
| | P-value ^{b, c} | 0.04327 | | 0.14554 | |
| | Interaction Test P-value ^d | 0.86019 | | | |
| | Median Time to Onset of the First Event (Days) (95% C.I.) ^e | - (-, -) | - (-, -) | - (364.0, -) | - (-, -) |
| | 25 th , 75 th Percentile | -, - | -, - | 364.0, - | -, - |
| Observed Min, Max ^f | 6+, 1156+ | 6, 839+ | 4+, 945+ | 14, 428+ | |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (Presence or history of brain metastases: Yes/No, ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.

c. Two-sided p-value calculated from Cox proportional hazards model .

d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and age.

e. Calculated using the complementary log-log transformation method (Collett, 1994). f. '+' means the observed time is from censored subjects.

Snapshot date: 10SEP2020, data cutoff date: 29MAY2020.

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_may2020_dco_1943\v01\outputs\tlfs\pgms\t-ae-km-socpt-subgrp.sas Output: t02-06-05-ae-km-socpt-sub-4-age-safs.rtf (14DEC20:17:14) Data: adsl, adae, adttesaf

Seagen Protocol ONT-380-206**Table 2.6.5 Summary of Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Age - Time-to-Event Analysis Safety Analysis Set**

| System Organ Class/ Preferred Term | Parameters | Age < 65 Years | | Age ≥ 65 Years | |
|---------------------------------------|--|------------------------|-------------------------------|-----------------------|-------------------------|
| | | Tuc+Cap+Tra (N=322) | Pbo+Cap+Tra (N=164) | Tuc+Cap+Tra (N=82) | Pbo+Cap+Tra (N=33) |
| Blood Creatinine Increased (PT) | Number of Subjects With at Least One Event, n (%) | 53 (16.5) | 1 (0.6) | 9 (11.0) | 2 (6.1) |
| | Number of Censored Subjects, n (%) | 269 (83.5) | 163 (99.4) | 73 (89.0) | 31 (93.9) |
| | Stratified Hazard Ratio ^{a, b} (95% C.I.) | | 25.556 (3.530, 185.007) | | 1.465 (0.308, 6.978) |
| | P-value ^{b, c} | | 0.00133 | | 0.63133 |
| | Interaction Test P-value ^d | | | 0.03328 | |
| | Median Time to Onset of the First Event (Days) (95% C.I.) ^e | - (-, -) | - (-, -) | - (-, -) | - (356.0, -) |
| | 25 th , 75 th Percentile | 747.0, - | -, - | -, - | 356.0, - |
| Observed Min, Max ^f | 5, 1154+ | 26+, 839+ | 4+, 945+ | 13, 409+ | |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (Presence or history of brain metastases: Yes/No, ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.

c. Two-sided p-value calculated from Cox proportional hazards model.

d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and age.

e. Calculated using the complementary log-log transformation method (Collett, 1994). f. '+' means the observed time is from censored subjects.

Snapshot date: 10SEP2020, data cutoff date: 29MAY2020.

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_may2020_dco_1943\v01\outputs\tlfs\pgms\t-ae-km-socpt-subgrp.sas Output:

t02-06-05-ae-km-socpt-sub-4-age-safs.rtf (14DEC20:17:14) Data: adsl, adae, adttesaf

Seagen Protocol ONT-380-206**Table 2.6.5 Summary of Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Age - Time-to-Event Analysis Safety Analysis Set**

| System Organ Class/ Preferred Term | Parameters | Age < 65 Years | | Age ≥ 65 Years | |
|---------------------------------------|--|------------------------|------------------------|-----------------------|-----------------------|
| | | Tuc+Cap+Tra (N=322) | Pbo+Cap+Tra (N=164) | Tuc+Cap+Tra (N=82) | Pbo+Cap+Tra (N=33) |
| Weight Decreased (PT) | Number of Subjects With at Least One Event, n (%) | 48 (14.9) | 8 (4.9) | 14 (17.1) | 4 (12.1) |
| | Number of Censored Subjects, n (%) | 274 (85.1) | 156 (95.1) | 68 (82.9) | 29 (87.9) |
| | Stratified Hazard Ratio ^{a, b} (95% C.I.) | 2.805 (1.320, 5.963) | | 1.479 (0.478, 4.571) | |
| | P-value ^{b, c} | 0.00734 | | 0.49716 | |
| | Interaction Test P-value ^d | 0.27582 | | | |
| | Median Time to Onset of the First Event (Days) (95% C.I.) ^e | - (-, -) | - (-, -) | - (-, -) | - (-, -) |
| | 25 th , 75 th Percentile | -, - | -, - | -, - | -, - |
| | Observed Min, Max ^f | 6, 1327+ | 22, 839+ | 4+, 945+ | 9, 428+ |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (Presence or history of brain metastases: Yes/No, ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.

c. Two-sided p-value calculated from Cox proportional hazards model.

d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and age.

e. Calculated using the complementary log-log transformation method (Collett, 1994). f. '+' means the observed time is from censored subjects.

Snapshot date: 10SEP2020, data cutoff date: 29MAY2020.

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_may2020_dco_1943\v01\outputs\tlfs\pgms\t-ae-km-socpt-subgrp.sas Output: t02-06-05-ae-km-socpt-sub-4-age-safs.rtf (14DEC20:17:14) Data: adsl, adae, adttesaf

Seagen Protocol ONT-380-206**Table 2.6.5 Summary of Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Age - Time-to-Event Analysis Safety Analysis Set**

| System Organ Class/ Preferred Term | Parameters | Age < 65 Years | | Age ≥ 65 Years | |
|--|---|-------------------------|-------------------------|-----------------------|-------------------------|
| | | Tuc+Cap+Tra (N=322) | Pbo+Cap+Tra (N=164) | Tuc+Cap+Tra (N=82) | Pbo+Cap+Tra (N=33) |
| Metabolism And Nutrition Disorders (SOC) | Number of Subjects With at Least One Event, n (%) | 162 (50.3) | 58 (35.4) | 50 (61.0) | 16 (48.5) |
| | Number of Censored Subjects, n (%) | 160 (49.7) | 106 (64.6) | 32 (39.0) | 17 (51.5) |
| | Stratified Hazard Ratio ^{a, b} (95% C.I.) | | 1.501 (1.109, 2.031) | | 1.387 (0.752, 2.560) |
| | P-value ^{b, c} | | 0.00856 | | 0.29533 |
| | Interaction Test P-value ^d | | | 0.79776 | |
| | Median Time to Onset of the First Event (Days) (95% C.I.) ^e | 213.0 (131.0, 401.0) | 526.0 (333.0, -) | 64.0 (43.0, 127.0) | 127.0 (51.0, -) |
| | 25 th , 75 th Percentile | 24.0, - | 56.0, - | 22.0, - | 33.0, - |
| Observed Min, Max ^f | 1, 1131+ | 1, 839+ | 1, 436+ | 9, 387+ | |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (Presence or history of brain metastases: Yes/No, ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.

c. Two-sided p-value calculated from Cox proportional hazards model.

d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and age.

e. Calculated using the complementary log-log transformation method (Collett, 1994). f. '+' means the observed time is from censored subjects.

Snapshot date: 10SEP2020, data cutoff date: 29MAY2020.

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_may2020_dco_1943\v01\outputs\tlfs\pgms\t-ae-km-socpt-subgrp.sas Output:
t02-06-05-ae-km-socpt-sub-4-age-safs.rtf (14DEC20:17:14) Data: adsl, adae, adttesaf

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Table 2.6.5 Summary of Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Age - Time-to-Event Analysis Safety Analysis Set

| System Organ Class/ Preferred Term | Parameters | Age < 65 Years | | Age >= 65 Years | |
|---------------------------------------|--|------------------------|------------------------|-----------------------|-----------------------|
| | | Tuc+Cap+Tra (N=322) | Pbo+Cap+Tra (N=164) | Tuc+Cap+Tra (N=82) | Pbo+Cap+Tra (N=33) |
| Hyperglycaemia (PT) | Number of Subjects With at Least One Event, n (%) | 21 (6.5) | 2 (1.2) | 2 (2.4) | 1 (3.0) |
| | Number of Censored Subjects, n (%) | 301 (93.5) | 162 (98.8) | 80 (97.6) | 32 (97.0) |
| | Stratified Hazard Ratio ^{a, b} (95% C.I.) | 5.265 (1.232, 22.504) | | 0.772 (0.069, 8.670) | |
| | P-value ^{b, c} | 0.02501 | | 0.83419 | |
| | Interaction Test P-value ^d | 0.12535 | | | |
| | Median Time to Onset of the First Event (Days) (95% C.I.) ^e | - (-, -) | - (-, -) | - (-, -) | - (-, -) |
| | 25 th , 75 th Percentile | -, - | -, - | -, - | -, - |
| Observed Min, Max ^f | 2, 1327+ | 13, 839+ | 4+, 945+ | 12, 428+ | |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.
 b. Computed using stratification factors (Presence or history of brain metastases: Yes/No, ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.
 c. Two-sided p-value calculated from Cox proportional hazards model.
 d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and age.
 e. Calculated using the complementary log-log transformation method (Collett, 1994). f. '+' means the observed time is from censored subjects.
 Snapshot date: 10SEP2020, data cutoff date: 29MAY2020.
 Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_may2020_dco_1943\v01\outputs\tlfs\pgms\t-ae-km-socpt-subgrp.sas Output:
 t02-06-05-ae-km-socpt-sub-4-age-safs.rtf (14DEC20:17:14) Data: adsl, adae, adttsaf

Seagen Protocol ONT-380-206**Table 2.6.5 Summary of Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Age - Time-to-Event Analysis Safety Analysis Set**

| System Organ Class/ Preferred Term | Parameters | Age < 65 Years | | Age ≥ 65 Years | |
|--|---|-------------------------|-------------------------|-----------------------|-------------------------|
| | | Tuc+Cap+Tra (N=322) | Pbo+Cap+Tra (N=164) | Tuc+Cap+Tra (N=82) | Pbo+Cap+Tra (N=33) |
| Musculoskeletal And Connective Tissue Disorders (SOC) | Number of Subjects With at Least One Event, n (%) | 167 (51.9) | 57 (34.8) | 30 (36.6) | 12 (36.4) |
| | Number of Censored Subjects, n (%) | 155 (48.1) | 107 (65.2) | 52 (63.4) | 21 (63.6) |
| | Stratified Hazard Ratio ^{a, b} (95% C.I.) | | 1.497 (1.103, 2.032) | | 0.939 (0.459, 1.922) |
| | P-value ^{b, c} | | 0.00960 | | 0.86401 |
| | Interaction Test P-value ^d | | | 0.20891 | |
| | Median Time to Onset of the First Event (Days) (95% C.I.) ^e | 211.0 (147.0, 306.0) | 399.0 (275.0, -) | 309.0 (165.0, -) | 304.0 (125.0, -) |
| | 25 th , 75 th Percentile | 43.0, 787.0 | 104.0, - | 113.0, - | 102.0, - |
| Observed Min, Max ^f | 1, 1117+ | 1, 839+ | 1, 830+ | 4, 428+ | |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (Presence or history of brain metastases: Yes/No, ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.

c. Two-sided p-value calculated from Cox proportional hazards model.

d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and age.

e. Calculated using the complementary log-log transformation method (Collett, 1994). f. '+' means the observed time is from censored subjects.

Snapshot date: 10SEP2020, data cutoff date: 29MAY2020.

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_may2020_dco_1943\v01\outputs\tlfs\pgms\t-ae-km-socpt-subgrp.sas Output:

t02-06-05-ae-km-socpt-sub-4-age-safs.rtf (14DEC20:17:14) Data: adsl, adae, adttesaf

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Table 2.6.5 Summary of Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Age - Time-to-Event Analysis Safety Analysis Set

| System Organ Class/ Preferred Term | Parameters | Age < 65 Years | | Age >= 65 Years | |
|---------------------------------------|--|------------------------|------------------------|-----------------------------|-----------------------|
| | | Tuc+Cap+Tra (N=322) | Pbo+Cap+Tra (N=164) | Tuc+Cap+Tra (N=82) | Pbo+Cap+Tra (N=33) |
| Arthralgia (PT) | Number of Subjects With at Least One Event, n (%) | 58 (18.0) | 12 (7.3) | 6 (7.3) | 0 |
| | Number of Censored Subjects, n (%) | 264 (82.0) | 152 (92.7) | 76 (92.7) | 33 (100) |
| | Stratified Hazard Ratio ^{a, b} (95% C.I.) | 2.089 (1.113, 3.922) | | 15778036.73 5 (0.000, -) | |
| | P-value ^{b, c} | 0.02179 | | 0.99540 | |
| | Interaction Test P-value ^d | | | 0.98362 | |
| | Median Time to Onset of the First Event (Days) (95% C.I.) ^e | - (959.0, -) | - (-, -) | - (-, -) | - (-, -) |
| | 25 th , 75 th Percentile | 602.0, - | -, - | -, - | -, - |
| Observed Min, Max ^f | 1, 1156+ | 4, 839+ | 2, 830+ | 31+, 428+ | |

a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.
 b. Computed using stratification factors (Presence or history of brain metastases: Yes/No, ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.
 c. Two-sided p-value calculated from Cox proportional hazards model .
 d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and age.
 e. Calculated using the complementary log-log transformation method (Collett, 1994). f. '+' means the observed time is from censored subjects.
 Snapshot date: 10SEP2020, data cutoff date: 29MAY2020.
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 t02-06-05-ae-km-socpt-sub-4-age-safs.rtf (14DEC20:17:14) Data: adsl, adae, adttesaf

Seagen Protocol ONT-380-206**Table 2.6.5 Summary of Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Age - Time-to-Event Analysis Safety Analysis Set**

| System Organ Class/ Preferred Term | Parameters | Age < 65 Years | | Age ≥ 65 Years | |
|---------------------------------------|--|------------------------|------------------------|-----------------------|-----------------------|
| | | Tuc+Cap+Tra (N=322) | Pbo+Cap+Tra (N=164) | Tuc+Cap+Tra (N=82) | Pbo+Cap+Tra (N=33) |
| Muscle Spasms (PT) | Number of Subjects With at Least One Event, n (%) | 36 (11.2) | 5 (3.0) | 7 (8.5) | 1 (3.0) |
| | Number of Censored Subjects, n (%) | 286 (88.8) | 159 (97.0) | 75 (91.5) | 32 (97.0) |
| | Stratified Hazard Ratio ^{a, b} (95% C.I.) | 2.829 (1.096, 7.303) | | 3.092 (0.378, 25.312) | |
| | P-value ^{b, c} | 0.03162 | | 0.29274 | |
| | Interaction Test P-value ^d | 0.93924 | | | |
| | Median Time to Onset of the First Event (Days) (95% C.I.) ^e | - (826.0, -) | - (-, -) | - (-, -) | - (-, -) |
| | 25 th , 75 th Percentile | 787.0, - | -, - | -, - | -, - |
| Observed Min, Max ^f | 1, 1327+ | 21, 839+ | 2, 830+ | 31+, 428+ | |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (Presence or history of brain metastases: Yes/No, ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.

c. Two-sided p-value calculated from Cox proportional hazards model.

d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and age.

e. Calculated using the complementary log-log transformation method (Collett, 1994). f. '+' means the observed time is from censored subjects.

Snapshot date: 10SEP2020, data cutoff date: 29MAY2020.

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Table 2.6.5 Summary of Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Age - Time-to-Event Analysis Safety Analysis Set

| | | Age < 65 Years | | Age >= 65 Years | | |
|---------------------------------------|--|------------------------|------------------------|-----------------------|-------------------------|----------|
| System Organ Class/ Preferred Term | Parameters | Tuc+Cap+Tra (N=322) | Pbo+Cap+Tra (N=164) | Tuc+Cap+Tra (N=82) | Pbo+Cap+Tra (N=33) | |
| Peripheral Sensory Neuropathy (PT) | Number of Subjects With at Least One Event, n (%) | 41 (12.7) | 12 (7.3) | 10 (12.2) | 0 | |
| | Number of Censored Subjects, n (%) | 281 (87.3) | 152 (92.7) | 72 (87.8) | 33 (100) | |
| | Stratified Hazard Ratio ^{a, b} (95% C.I.) | | 1.640 (0.857, 3.137) | | 48173260.764 (0.000, -) | |
| | P-value ^{b, c} | | 0.13527 | | 0.99565 | |
| | Interaction Test P-value ^d | | | 0.98272 | | |
| | Median Time to Onset of the First Event (Days) (95% C.I.) ^e | | - (-, -) | - (-, -) | - (-, -) | - (-, -) |
| | 25 th , 75 th Percentile | | -, - | -, - | -, - | -, - |
| Observed Min, Max ^f | | 2, 1327+ | 12, 839+ | 4+, 945+ | 31+, 428+ | |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.
 b. Computed using stratification factors (Presence or history of brain metastases: Yes/No, ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.
 c. Two-sided p-value calculated from Cox proportional hazards model.
 d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and age.
 e. Calculated using the complementary log-log transformation method (Collett, 1994). f. '+' means the observed time is from censored subjects.
 Snapshot date: 10SEP2020, data cutoff date: 29MAY2020.
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Seagen Protocol ONT-380-206**Table 2.6.5 Summary of Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Age - Time-to-Event Analysis Safety Analysis Set**

| System Organ Class/ Preferred Term | Parameters | Age < 65 Years | | Age ≥ 65 Years | |
|---------------------------------------|--|------------------------|------------------------|-----------------------|-----------------------|
| | | Tuc+Cap+Tra (N=322) | Pbo+Cap+Tra (N=164) | Tuc+Cap+Tra (N=82) | Pbo+Cap+Tra (N=33) |
| Dysgeusia (PT) | Number of Subjects With at Least One Event, n (%) | 31 (9.6) | 5 (3.0) | 2 (2.4) | 1 (3.0) |
| | Number of Censored Subjects, n (%) | 291 (90.4) | 159 (97.0) | 80 (97.6) | 32 (97.0) |
| | Stratified Hazard Ratio ^{a, b} (95% C.I.) | 2.950 (1.140, 7.632) | | 0.913 (0.075, 11.167) | |
| | P-value ^{b, c} | 0.02573 | | 0.94327 | |
| | Interaction Test P-value ^d | 0.29324 | | | |
| | Median Time to Onset of the First Event (Days) (95% C.I.) ^e | - (-, -) | - (-, -) | - (-, -) | - (-, -) |
| | 25 th , 75 th Percentile | -, - | -, - | -, - | -, - |
| | Observed Min, Max ^f | 1, 1327+ | 12, 839+ | 4+, 945+ | 11, 428+ |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (Presence or history of brain metastases: Yes/No, ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.

c. Two-sided p-value calculated from Cox proportional hazards model.

d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and age.

e. Calculated using the complementary log-log transformation method (Collett, 1994). f. '+' means the observed time is from censored subjects.

Snapshot date: 10SEP2020, data cutoff date: 29MAY2020.

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Table 2.6.5 Summary of Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Age - Time-to-Event Analysis Safety Analysis Set

| System Organ Class/ Preferred Term | Parameters | Age < 65 Years | | Age >= 65 Years | |
|---------------------------------------|--|------------------------|------------------------|-----------------------|-----------------------|
| | | Tuc+Cap+Tra (N=322) | Pbo+Cap+Tra (N=164) | Tuc+Cap+Tra (N=82) | Pbo+Cap+Tra (N=33) |
| Epistaxis (PT) | Number of Subjects With at Least One Event, n (%) | 35 (10.9) | 7 (4.3) | 15 (18.3) | 3 (9.1) |
| | Number of Censored Subjects, n (%) | 287 (89.1) | 157 (95.7) | 67 (81.7) | 30 (90.9) |
| | Stratified Hazard Ratio ^{a, b} (95% C.I.) | 2.424 (1.071, 5.488) | | 1.918 (0.542, 6.791) | |
| | P-value ^{b, c} | 0.03366 | | 0.31260 | |
| | Interaction Test P-value ^d | 0.70403 | | | |
| | Median Time to Onset of the First Event (Days) (95% C.I.) ^e | - (-, -) | - (-, -) | - (-, -) | - (-, -) |
| | 25 th , 75 th Percentile | -, - | -, - | -, - | -, - |
| Observed Min, Max ^f | 1, 1327+ | 5, 839+ | 1, 945+ | 3, 428+ | |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (Presence or history of brain metastases: Yes/No, ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.

c. Two-sided p-value calculated from Cox proportional hazards model.

d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and age.

e. Calculated using the complementary log-log transformation method (Collett, 1994). f. '+' means the observed time is from censored subjects.

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Seagen Protocol ONT-380-206**Table 2.6.5 Summary of Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Age - Time-to-Event Analysis Safety Analysis Set**

| System Organ Class/ Preferred Term | Parameters | Age < 65 Years | | Age ≥ 65 Years | |
|---------------------------------------|--|------------------------|------------------------|-----------------------|-----------------------|
| | | Tuc+Cap+Tra (N=322) | Pbo+Cap+Tra (N=164) | Tuc+Cap+Tra (N=82) | Pbo+Cap+Tra (N=33) |
| Pleural Effusion (PT) | Number of Subjects With at Least One Event, n (%) | 5 (1.6) | 8 (4.9) | 5 (6.1) | 3 (9.1) |
| | Number of Censored Subjects, n (%) | 317 (98.4) | 156 (95.1) | 77 (93.9) | 30 (90.9) |
| | Stratified Hazard Ratio ^{a, b} (95% C.I.) | 0.306 (0.099, 0.942) | | 0.490 (0.105, 2.287) | |
| | P-value ^{b, c} | 0.03910 | | 0.36429 | |
| | Interaction Test P-value ^d | 0.60354 | | | |
| | Median Time to Onset of the First Event (Days) (95% C.I.) ^e | - (-, -) | - (-, -) | 942.0 (-, -) | - (-, -) |
| | 25 th , 75 th Percentile | -, - | -, - | 942.0, 942.0 | -, - |
| Observed Min, Max ^f | 6+, 1327+ | 6, 839+ | 4+, 942 | 14, 428+ | |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (Presence or history of brain metastases: Yes/No, ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.

c. Two-sided p-value calculated from Cox proportional hazards model.

d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and age.

e. Calculated using the complementary log-log transformation method (Collett, 1994). f. '+' means the observed time is from censored subjects.

Snapshot date: 10SEP2020, data cutoff date: 29MAY2020.

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_may2020_dco_1943\v01\outputs\tlfs\pgms\t-ae-km-socpt-subgrp.sas Output:

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Seagen Protocol ONT-380-206**Table 2.6.5 Summary of Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Age - Time-to-Event Analysis Safety Analysis Set**

| System Organ Class/ Preferred Term | Parameters | Age < 65 Years | | Age ≥ 65 Years | |
|--|---|------------------------|-------------------------|-----------------------|-------------------------|
| | | Tuc+Cap+Tra (N=322) | Pbo+Cap+Tra (N=164) | Tuc+Cap+Tra (N=82) | Pbo+Cap+Tra (N=33) |
| Palmar-Plantar Erythrodysesthesia Syndrome (PT) | Number of Subjects With at Least One Event, n (%) | 209 (64.9) | 93 (56.7) | 53 (64.6) | 12 (36.4) |
| | Number of Censored Subjects, n (%) | 113 (35.1) | 71 (43.3) | 29 (35.4) | 21 (63.6) |
| | Stratified Hazard Ratio ^{a, b} (95% C.I.) | | 1.186 (0.926, 1.518) | | 2.104 (1.078, 4.104) |
| | P-value ^{b, c} | | 0.17591 | | 0.02915 |
| | Interaction Test P-value ^d | | | 0.08499 | |
| | Median Time to Onset of the First Event (Days) (95% C.I.) ^e | 64.0 (49.0, 80.0) | 75.0 (63.0, 127.0) | 70.0 (42.0, 106.0) | -(126.0, -) |
| | 25 th , 75 th Percentile | 28.0, 400.0 | 33.0, - | 29.0, 337.0 | 75.0, - |
| Observed Min, Max ^f | 1, 873+ | 1, 457+ | 1, 534+ | 3, 409+ | |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (Presence or history of brain metastases: Yes/No, ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.

c. Two-sided p-value calculated from Cox proportional hazards model.

d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and age.

e. Calculated using the complementary log-log transformation method (Collett, 1994). f. '+' means the observed time is from censored subjects.

Snapshot date: 10SEP2020, data cutoff date: 29MAY2020.

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_may2020_dco_1943\v01\outputs\tlfs\pgms\t-ae-km-socpt-subgrp.sas Output:

t02-06-05-ae-km-socpt-sub-4-age-safs.rtf (14DEC20:17:14) Data: adsl, adae, adttesaf

Seagen Protocol ONT-380-206**Table 2.6.6 Summary of Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Race - Time-to-Event Analysis
Safety Analysis Set**

| System Organ Class/ Preferred Term | Parameters | White | | Non-White | |
|---------------------------------------|--|------------------------|------------------------|------------------------|-----------------------|
| | | Tuc+Cap+Tra (N=283) | Pbo+Cap+Tra (N=153) | Tuc+Cap+Tra (N=121) | Pbo+Cap+Tra (N=44) |
| Anaemia (PT) | Number of Subjects With at Least One Event, n (%) | 62 (21.9) | 21 (13.7) | 24 (19.8) | 3 (6.8) |
| | Number of Censored Subjects, n (%) | 221 (78.1) | 132 (86.3) | 97 (80.2) | 41 (93.2) |
| | Stratified Hazard Ratio ^{a, b} (95% C.I.) | 1.535 (0.932, 2.526) | | 2.588 (0.772, 8.677) | |
| | P-value ^{b, c} | 0.09223 | | 0.12356 | |
| | Interaction Test P-value ^d | 0.43074 | | | |
| | Median Time to Onset of the First Event (Days) (95% C.I.) ^e | - (-, -) | - (-, -) | - (924.0, -) | - (-, -) |
| | 25 th , 75 th Percentile | 390.0, - | -, - | 924.0, - | -, - |
| | Observed Min, Max ^f | 1, 1327+ | 12, 839+ | 4+, 1154+ | 22, 599+ |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (Presence or history of brain metastases: Yes/No, ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.

c. Two-sided p-value calculated from Cox proportional hazards model.

d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and race.

e. Calculated using the complementary log-log transformation method (Collett, 1994). f. '+' means the observed time is from censored subjects.

Snapshot date: 10SEP2020, data cutoff date: 29MAY2020.

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_may2020_dco_1943\v01\outputs\tlfs\pgms\t-ae-km-socpt-subgrp.sas Output: t02-06-06-ae-km-socpt-sub-5-race-safs.rtf (14DEC20:17:14) Data: adsl, adae, adtesaf

Seagen Protocol ONT-380-206**Table 2.6.6 Summary of Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Race - Time-to-Event Analysis
Safety Analysis Set**

| System Organ Class/ Preferred Term | Parameters | White | | Non-White | |
|---------------------------------------|--|------------------------|------------------------|------------------------|-----------------------|
| | | Tuc+Cap+Tra (N=283) | Pbo+Cap+Tra (N=153) | Tuc+Cap+Tra (N=121) | Pbo+Cap+Tra (N=44) |
| Investigations (SOC) | Number of Subjects With at Least One Event, n (%) | 184 (65.0) | 57 (37.3) | 70 (57.9) | 17 (38.6) |
| | Number of Censored Subjects, n (%) | 99 (35.0) | 96 (62.7) | 51 (42.1) | 27 (61.4) |
| | Stratified Hazard Ratio ^{a, b} (95% C.I.) | | 2.089 (1.548, 2.819) | | 1.557 (0.903, 2.685) |
| | P-value ^{b, c} | | <.00001 | | 0.11155 |
| | Interaction Test P-value ^d | | | 0.31832 | |
| | Median Time to Onset of the First Event (Days) (95% C.I.) ^e | 64.0 (43.0, 106.0) | 409.0 (253.0, -) | 168.0 (62.0, 274.0) | 283.0 (103.0, -) |
| | 25 th , 75 th Percentile | 28.0, 757.0 | 64.0, - | 21.5, - | 46.0, - |
| Observed Min, Max ^f | 1, 899+ | 1, 598+ | 4+, 666+ | 13, 443+ | |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (Presence or history of brain metastases: Yes/No, ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.

c. Two-sided p-value calculated from Cox proportional hazards model.

d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and race.

e. Calculated using the complementary log-log transformation method (Collett, 1994). f. '+' means the observed time is from censored subjects.

Snapshot date: 10SEP2020, data cutoff date: 29MAY2020.

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_may2020_dco_1943\v01\outputs\tlfs\pgms\t-ae-km-socpt-subgrp.sas Output: t02-06-06-ae-km-socpt-sub-5-race-safs.rtf (14DEC20:17:14) Data: adsl, adae, adtesaf

Seagen Protocol ONT-380-206

**Table 2.6.6 Summary of Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Race - Time-to-Event Analysis
Safety Analysis Set**

| System Organ Class/ Preferred Term | Parameters | White | | Non-White | |
|---|--|------------------------|------------------------|------------------------|-----------------------|
| | | Tuc+Cap+Tra (N=283) | Pbo+Cap+Tra (N=153) | Tuc+Cap+Tra (N=121) | Pbo+Cap+Tra (N=44) |
| Aspartate Aminotransferase Increased (PT) | Number of Subjects With at Least One Event, n (%) | 64 (22.6) | 16 (10.5) | 25 (20.7) | 6 (13.6) |
| | Number of Censored Subjects, n (%) | 219 (77.4) | 137 (89.5) | 96 (79.3) | 38 (86.4) |
| | Stratified Hazard Ratio ^{a, b} (95% C.I.) | 2.243 (1.296, 3.882) | | 1.476 (0.598, 3.639) | |
| | P-value ^{b, c} | 0.00390 | | 0.39819 | |
| | Interaction Test P-value ^d | 0.41746 | | | |
| | Median Time to Onset of the First Event (Days) (95% C.I.) ^e | - (-, -) | - (-, -) | - (-, -) | - (335.0, -) |
| | 25 th , 75 th Percentile | 358.0, - | -, - | -, - | 335.0, - |
| Observed Min, Max ^f | 6+, 1156+ | 1, 839+ | 4+, 1154+ | 22, 599+ | |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.
 b. Computed using stratification factors (Presence or history of brain metastases: Yes/No, ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.
 c. Two-sided p-value calculated from Cox proportional hazards model.
 d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and race.
 e. Calculated using the complementary log-log transformation method (Collett, 1994). f. '+' means the observed time is from censored subjects.
 Snapshot date: 10SEP2020, data cutoff date: 29MAY2020.
 Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_may2020_dco_1943\v01\outputs\tlfs\pgms\t-ae-km-socpt-subgrp.sas Output:
 t02-06-06-ae-km-socpt-sub-5-race-safs.rtf (14DEC20:17:14) Data: adsl, adae, adtesaf

Seagen Protocol ONT-380-206**Table 2.6.6 Summary of Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Race - Time-to-Event Analysis
Safety Analysis Set**

| System Organ Class/ Preferred Term | Parameters | White | | Non-White | |
|---|--|------------------------|------------------------|------------------------|-----------------------|
| | | Tuc+Cap+Tra (N=283) | Pbo+Cap+Tra (N=153) | Tuc+Cap+Tra (N=121) | Pbo+Cap+Tra (N=44) |
| Alanine Aminotransferase Increased (PT) | Number of Subjects With at Least One Event, n (%) | 64 (22.6) | 9 (5.9) | 21 (17.4) | 4 (9.1) |
| | Number of Censored Subjects, n (%) | 219 (77.4) | 144 (94.1) | 100 (82.6) | 40 (90.9) |
| | Stratified Hazard Ratio ^{a, b} (95% C.I.) | 4.110 (2.042, 8.274) | | 1.814 (0.616, 5.343) | |
| | P-value ^{b, c} | 0.00008 | | 0.27996 | |
| | Interaction Test P-value ^d | | | 0.20575 | |
| | Median Time to Onset of the First Event (Days) (95% C.I.) ^e | - (-, -) | - (-, -) | - (-, -) | - (357.0, -) |
| | 25 th , 75 th Percentile | 356.0, - | -, - | -, - | -, - |
| Observed Min, Max ^f | 6+, 1156+ | 21, 839+ | 4+, 1154+ | 14, 599+ | |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (Presence or history of brain metastases: Yes/No, ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.

c. Two-sided p-value calculated from Cox proportional hazards model.

d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and race.

e. Calculated using the complementary log-log transformation method (Collett, 1994). f. '+' means the observed time is from censored subjects.

Snapshot date: 10SEP2020, data cutoff date: 29MAY2020.

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_may2020_dco_1943\v01\outputs\tlfs\pgms\t-ae-km-socpt-subgrp.sas Output: t02-06-06-ae-km-socpt-sub-5-race-safs.rtf (14DEC20:17:14) Data: adsl, adae, adtesaf

Seagen Protocol ONT-380-206**Table 2.6.6 Summary of Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Race - Time-to-Event Analysis
Safety Analysis Set**

| System Organ Class/ Preferred Term | Parameters | White | | Non-White | |
|---------------------------------------|--|------------------------|------------------------|------------------------|-----------------------|
| | | Tuc+Cap+Tra (N=283) | Pbo+Cap+Tra (N=153) | Tuc+Cap+Tra (N=121) | Pbo+Cap+Tra (N=44) |
| Blood Bilirubin Increased (PT) | Number of Subjects With at Least One Event, n (%) | 57 (20.1) | 14 (9.2) | 23 (19.0) | 7 (15.9) |
| | Number of Censored Subjects, n (%) | 226 (79.9) | 139 (90.8) | 98 (81.0) | 37 (84.1) |
| | Stratified Hazard Ratio ^{a, b} (95% C.I.) | 2.230 (1.241, 4.008) | | 1.043 (0.440, 2.474) | |
| | P-value ^{b, c} | 0.00730 | | 0.92339 | |
| | Interaction Test P-value ^d | 0.17978 | | | |
| | Median Time to Onset of the First Event (Days) (95% C.I.) ^e | - (-, -) | - (-, -) | - (-, -) | - (-, -) |
| | 25 th , 75 th Percentile | 429.0, - | -, - | -, - | -, - |
| | Observed Min, Max ^f | 6+, 1156+ | 6, 839+ | 4+, 1154+ | 15, 599+ |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (Presence or history of brain metastases: Yes/No, ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.

c. Two-sided p-value calculated from Cox proportional hazards model.

d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and race.

e. Calculated using the complementary log-log transformation method (Collett, 1994). f. '+' means the observed time is from censored subjects.

Snapshot date: 10SEP2020, data cutoff date: 29MAY2020.

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_may2020_dco_1943\v01\outputs\tlfs\pgms\t-ae-km-socpt-subgrp.sas Output: t02-06-06-ae-km-socpt-sub-5-race-safs.rtf (14DEC20:17:14) Data: adsl, adae, adtesaf

Seagen Protocol ONT-380-206**Table 2.6.6 Summary of Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Race - Time-to-Event Analysis
Safety Analysis Set**

| System Organ Class/ Preferred Term | Parameters | White | | Non-White | |
|---------------------------------------|--|------------------------|------------------------------|------------------------|--------------------------|
| | | Tuc+Cap+Tra (N=283) | Pbo+Cap+Tra (N=153) | Tuc+Cap+Tra (N=121) | Pbo+Cap+Tra (N=44) |
| Blood Creatinine Increased (PT) | Number of Subjects With at Least One Event, n (%) | 37 (13.1) | 2 (1.3) | 25 (20.7) | 1 (2.3) |
| | Number of Censored Subjects, n (%) | 246 (86.9) | 151 (98.7) | 96 (79.3) | 43 (97.7) |
| | Stratified Hazard Ratio ^{a, b} (95% C.I.) | | 10.118 (2.434, 42.057) | | 7.885 (1.060, 58.662) |
| | P-value ^{b, c} | | 0.00145 | | 0.04371 |
| | Interaction Test P-value ^d | | | 0.85635 | |
| | Median Time to Onset of the First Event (Days) (95% C.I.) ^e | - (-, -) | - (-, -) | - (-, -) | - (-, -) |
| | 25 th , 75 th Percentile | -, - | -, - | 356.0, - | -, - |
| Observed Min, Max ^f | 5, 1131+ | 26+, 839+ | 4+, 1154+ | 13, 599+ | |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (Presence or history of brain metastases: Yes/No, ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.

c. Two-sided p-value calculated from Cox proportional hazards model.

d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and race.

e. Calculated using the complementary log-log transformation method (Collett, 1994). f. '+' means the observed time is from censored subjects.

Snapshot date: 10SEP2020, data cutoff date: 29MAY2020.

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_may2020_dco_1943\v01\outputs\tlfs\pgms\t-ae-km-socpt-subgrp.sas Output:
t02-06-06-ae-km-socpt-sub-5-race-safs.rtf (14DEC20:17:14) Data: adsl, adae, adttesaf

Seagen Protocol ONT-380-206**Table 2.6.6 Summary of Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Race - Time-to-Event Analysis
Safety Analysis Set**

| System Organ Class/ Preferred Term | Parameters | White | | Non-White | |
|---------------------------------------|--|------------------------|------------------------|------------------------|-----------------------|
| | | Tuc+Cap+Tra (N=283) | Pbo+Cap+Tra (N=153) | Tuc+Cap+Tra (N=121) | Pbo+Cap+Tra (N=44) |
| Weight Decreased (PT) | Number of Subjects With at Least One Event, n (%) | 40 (14.1) | 8 (5.2) | 22 (18.2) | 4 (9.1) |
| | Number of Censored Subjects, n (%) | 243 (85.9) | 145 (94.8) | 99 (81.8) | 40 (90.9) |
| | Stratified Hazard Ratio ^{a, b} (95% C.I.) | 2.652 (1.239, 5.679) | | 1.541 (0.516, 4.604) | |
| | P-value ^{b, c} | 0.01202 | | 0.43869 | |
| | Interaction Test P-value ^d | 0.57658 | | | |
| | Median Time to Onset of the First Event (Days) (95% C.I.) ^e | - (-, -) | - (-, -) | - (-, -) | - (-, -) |
| | 25 th , 75 th Percentile | -, - | -, - | 375.0, - | -, - |
| | Observed Min, Max ^f | 6+, 1327+ | 9, 839+ | 4+, 1051+ | 22, 599+ |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (Presence or history of brain metastases: Yes/No, ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.

c. Two-sided p-value calculated from Cox proportional hazards model.

d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and race.

e. Calculated using the complementary log-log transformation method (Collett, 1994). f. '+' means the observed time is from censored subjects.

Snapshot date: 10SEP2020, data cutoff date: 29MAY2020.

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_may2020_dco_1943\v01\outputs\tlfs\pgms\t-ae-km-socpt-subgrp.sas Output: t02-06-06-ae-km-socpt-sub-5-race-safs.rtf (14DEC20:17:14) Data: adsl, adae, adtesaf

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**Table 2.6.6 Summary of Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Race - Time-to-Event Analysis
Safety Analysis Set**

| System Organ Class/ Preferred Term | Parameters | White | | Non-White | |
|--|--|------------------------|------------------------|------------------------|-----------------------|
| | | Tuc+Cap+Tra (N=283) | Pbo+Cap+Tra (N=153) | Tuc+Cap+Tra (N=121) | Pbo+Cap+Tra (N=44) |
| Metabolism And Nutrition Disorders (SOC) | Number of Subjects With at Least One Event, n (%) | 150 (53.0) | 60 (39.2) | 62 (51.2) | 14 (31.8) |
| | Number of Censored Subjects, n (%) | 133 (47.0) | 93 (60.8) | 59 (48.8) | 30 (68.2) |
| | Stratified Hazard Ratio ^{a, b} (95% C.I.) | 1.447 (1.068, 1.960) | | 1.830 (1.019, 3.285) | |
| | P-value ^{b, c} | 0.01712 | | 0.04296 | |
| | Interaction Test P-value ^d | 0.53256 | | | |
| | Median Time to Onset of the First Event (Days) (95% C.I.) ^e | 167.0 (105.0, 364.0) | 526.0 (201.0, -) | 147.0 (83.0, -) | - (335.0, -) |
| | 25 th , 75 th Percentile | 24.0, - | 51.0, - | 22.0, - | 43.5, - |
| Observed Min, Max ^f | 1, 1131+ | 3, 839+ | 2, 666+ | 1, 449+ | |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.
 b. Computed using stratification factors (Presence or history of brain metastases: Yes/No, ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.
 c. Two-sided p-value calculated from Cox proportional hazards model .
 d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and race.
 e. Calculated using the complementary log-log transformation method (Collett, 1994). f. '+' means the observed time is from censored subjects.
 Snapshot date: 10SEP2020, data cutoff date: 29MAY2020.
 Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_may2020_dco_1943\v01\outputs\tlfs\pgms\t-ae-km-socpt-subgrp.sas Output:
 t02-06-06-ae-km-socpt-sub-5-race-safs.rtf (14DEC20:17:14) Data: adsl, adae, adtesaf

Seagen Protocol ONT-380-206**Table 2.6.6 Summary of Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Race - Time-to-Event Analysis
Safety Analysis Set**

| System Organ Class/ Preferred Term | Parameters | White | | Non-White | |
|---------------------------------------|--|------------------------|------------------------|------------------------|-----------------------|
| | | Tuc+Cap+Tra (N=283) | Pbo+Cap+Tra (N=153) | Tuc+Cap+Tra (N=121) | Pbo+Cap+Tra (N=44) |
| Hyperglycaemia (PT) | Number of Subjects With at Least One Event, n (%) | 16 (5.7) | 2 (1.3) | 7 (5.8) | 1 (2.3) |
| | Number of Censored Subjects, n (%) | 267 (94.3) | 151 (98.7) | 114 (94.2) | 43 (97.7) |
| | Stratified Hazard Ratio ^{a, b} (95% C.I.) | 4.237 (0.972, 18.461) | | 2.087 (0.252, 17.289) | |
| | P-value ^{b, c} | 0.05452 | | 0.49535 | |
| | Interaction Test P-value ^d | 0.54415 | | | |
| | Median Time to Onset of the First Event (Days) (95% C.I.) ^e | - (-, -) | - (-, -) | - (-, -) | - (-, -) |
| | 25 th , 75 th Percentile | -, - | -, - | -, - | -, - |
| Observed Min, Max ^f | 6+, 1327+ | 12, 839+ | 2, 1154+ | 13, 599+ | |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (Presence or history of brain metastases: Yes/No, ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.

c. Two-sided p-value calculated from Cox proportional hazards model.

d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and race.

e. Calculated using the complementary log-log transformation method (Collett, 1994). f. '+' means the observed time is from censored subjects.

Snapshot date: 10SEP2020, data cutoff date: 29MAY2020.

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_may2020_dco_1943\v01\outputs\tlfs\pgms\t-ae-km-socpt-subgrp.sas Output: t02-06-06-ae-km-socpt-sub-5-race-safs.rtf (14DEC20:17:14) Data: adsl, adae, adtesaf

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**Table 2.6.6 Summary of Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Race - Time-to-Event Analysis
Safety Analysis Set**

| System Organ Class/ Preferred Term | Parameters | White | | Non-White | |
|--|---|-------------------------|------------------------|-------------------------|-----------------------|
| | | Tuc+Cap+Tra (N=283) | Pbo+Cap+Tra (N=153) | Tuc+Cap+Tra (N=121) | Pbo+Cap+Tra (N=44) |
| Musculoskeletal And Connective Tissue Disorders (SOC) | Number of Subjects With at Least One Event, n (%) | 141 (49.8) | 55 (35.9) | 56 (46.3) | 14 (31.8) |
| | Number of Censored Subjects, n (%) | 142 (50.2) | 98 (64.1) | 65 (53.7) | 30 (68.2) |
| | Stratified Hazard Ratio ^{a, b} (95% C.I.) | 1.395 (1.017, 1.912) | | 1.314 (0.712, 2.424) | |
| | P-value ^{b, c} | 0.03869 | | 0.38285 | |
| | Interaction Test P-value ^d | 0.86759 | | | |
| | Median Time to Onset of the First Event (Days) (95% C.I.) ^e | 201.0 (144.0, 306.0) | 355.0 (215.0, -) | 283.0 (211.0, 538.0) | 275.0 (253.0, -) |
| | 25 th , 75 th Percentile | 61.0, - | 102.0, - | 62.0, 721.0 | 123.0, 399.0 |
| Observed Min, Max ^f | 1, 1117+ | 1, 839+ | 1, 785+ | 1, 443+ | |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.
 b. Computed using stratification factors (Presence or history of brain metastases: Yes/No, ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.
 c. Two-sided p-value calculated from Cox proportional hazards model.
 d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and race.
 e. Calculated using the complementary log-log transformation method (Collett, 1994). f. '+' means the observed time is from censored subjects.
 Snapshot date: 10SEP2020, data cutoff date: 29MAY2020.
 Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_may2020_dco_1943\v01\outputs\tlfs\pgms\t-ae-km-socpt-subgrp.sas Output:
 t02-06-06-ae-km-socpt-sub-5-race-safs.rtf (14DEC20:17:14) Data: adsl, adae, adttesaf

Seagen Protocol ONT-380-206**Table 2.6.6 Summary of Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Race - Time-to-Event Analysis
Safety Analysis Set**

| System Organ Class/ Preferred Term | Parameters | White | | Non-White | |
|---------------------------------------|--|------------------------|------------------------|------------------------|-----------------------|
| | | Tuc+Cap+Tra (N=283) | Pbo+Cap+Tra (N=153) | Tuc+Cap+Tra (N=121) | Pbo+Cap+Tra (N=44) |
| Arthralgia (PT) | Number of Subjects With at Least One Event, n (%) | 42 (14.8) | 10 (6.5) | 22 (18.2) | 2 (4.5) |
| | Number of Censored Subjects, n (%) | 241 (85.2) | 143 (93.5) | 99 (81.8) | 42 (95.5) |
| | Stratified Hazard Ratio ^{a, b} (95% C.I.) | 1.857 (0.922, 3.742) | | 3.519 (0.809, 15.301) | |
| | P-value ^{b, c} | 0.08335 | | 0.09342 | |
| | Interaction Test P-value ^d | 0.52054 | | | |
| | Median Time to Onset of the First Event (Days) (95% C.I.) ^e | - (-, -) | - (-, -) | 959.0 (959.0, -) | - (-, -) |
| | 25 th , 75 th Percentile | 707.0, - | -, - | 455.0, - | -, - |
| Observed Min, Max ^f | 1, 1156+ | 7, 839+ | 1, 1154+ | 4, 599+ | |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (Presence or history of brain metastases: Yes/No, ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.

c. Two-sided p-value calculated from Cox proportional hazards model.

d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and race.

e. Calculated using the complementary log-log transformation method (Collett, 1994). f. '+' means the observed time is from censored subjects.

Snapshot date: 10SEP2020, data cutoff date: 29MAY2020.

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_may2020_dco_1943\v01\outputs\tlfs\pgms\t-ae-km-socpt-subgrp.sas Output: t02-06-06-ae-km-socpt-sub-5-race-safs.rtf (14DEC20:17:14) Data: adsl, adae, adtesaf

Seagen Protocol ONT-380-206**Table 2.6.6 Summary of Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Race - Time-to-Event Analysis
Safety Analysis Set**

| System Organ Class/ Preferred Term | Parameters | White | | Non-White | |
|---------------------------------------|--|------------------------|------------------------|------------------------|-----------------------|
| | | Tuc+Cap+Tra (N=283) | Pbo+Cap+Tra (N=153) | Tuc+Cap+Tra (N=121) | Pbo+Cap+Tra (N=44) |
| Muscle Spasms (PT) | Number of Subjects With at Least One Event, n (%) | 28 (9.9) | 3 (2.0) | 15 (12.4) | 3 (6.8) |
| | Number of Censored Subjects, n (%) | 255 (90.1) | 150 (98.0) | 106 (87.6) | 41 (93.2) |
| | Stratified Hazard Ratio ^{a, b} (95% C.I.) | 4.353 (1.311, 14.451) | | 1.216 (0.328, 4.514) | |
| | P-value ^{b, c} | 0.01630 | | 0.76982 | |
| | Interaction Test P-value ^d | 0.23330 | | | |
| | Median Time to Onset of the First Event (Days) (95% C.I.) ^e | - (841.0, -) | - (-, -) | 966.0 (826.0, -) | - (399.0, -) |
| | 25 th , 75 th Percentile | 841.0, - | -, - | 826.0, - | -, - |
| Observed Min, Max ^f | 2, 1327+ | 21, 839+ | 1, 1051+ | 40+, 599+ | |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (Presence or history of brain metastases: Yes/No, ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.

c. Two-sided p-value calculated from Cox proportional hazards model.

d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and race.

e. Calculated using the complementary log-log transformation method (Collett, 1994). f. '+' means the observed time is from censored subjects.

Snapshot date: 10SEP2020, data cutoff date: 29MAY2020.

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_may2020_dco_1943\v01\outputs\tlfs\pgms\t-ae-km-socpt-subgrp.sas Output: t02-06-06-ae-km-socpt-sub-5-race-safs.rtf (14DEC20:17:14) Data: adsl, adae, adttesaf

Seagen Protocol ONT-380-206**Table 2.6.6 Summary of Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Race - Time-to-Event Analysis
Safety Analysis Set**

| System Organ Class/ Preferred Term | | White | | Non-White | |
|--|---|-------------------------|------------------------|--------------------------|-----------------------|
| | | Tuc+Cap+Tra (N=283) | Pbo+Cap+Tra (N=153) | Tuc+Cap+Tra (N=121) | Pbo+Cap+Tra (N=44) |
| Peripheral Sensory Neuropathy (PT) | Number of Subjects With at Least One Event, n (%) | 34 (12.0) | 10 (6.5) | 17 (14.0) | 2 (4.5) |
| | Number of Censored Subjects, n (%) | 249 (88.0) | 143 (93.5) | 104 (86.0) | 42 (95.5) |
| | Stratified Hazard Ratio ^{a, b} (95% C.I.) | 1.693 (0.833, 3.442) | | 2.923 (0.666, 12.832) | |
| | P-value ^{b, c} | 0.14594 | | 0.15527 | |
| | Interaction Test P-value ^d | 0.57077 | | | |
| | Median Time to Onset of the First Event (Days) (95% C.I.) ^e | - (-, -) | -(509.0, -) | - (-, -) | - (-, -) |
| | 25 th , 75 th Percentile | -, - | -, - | -, - | -, - |
| Observed Min, Max ^f | 2, 1327+ | 12, 839+ | 4, 1154+ | 23, 599+ | |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (Presence or history of brain metastases: Yes/No, ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.

c. Two-sided p-value calculated from Cox proportional hazards model.

d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and race.

e. Calculated using the complementary log-log transformation method (Collett, 1994). f. '+' means the observed time is from censored subjects.

Snapshot date: 10SEP2020, data cutoff date: 29MAY2020.

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_may2020_dco_1943\v01\outputs\tlfs\pgms\t-ae-km-socpt-subgrp.sas Output:

t02-06-06-ae-km-socpt-sub-5-race-safs.rtf (14DEC20:17:14) Data: adsl, adae, adtesaf

Seagen Protocol ONT-380-206**Table 2.6.6 Summary of Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Race - Time-to-Event Analysis
Safety Analysis Set**

| System Organ Class/ Preferred Term | Parameters | White | | Non-White | |
|---------------------------------------|--|------------------------|------------------------|------------------------|-----------------------|
| | | Tuc+Cap+Tra (N=283) | Pbo+Cap+Tra (N=153) | Tuc+Cap+Tra (N=121) | Pbo+Cap+Tra (N=44) |
| Dysgeusia (PT) | Number of Subjects With at Least One Event, n (%) | 15 (5.3) | 5 (3.3) | 18 (14.9) | 1 (2.3) |
| | Number of Censored Subjects, n (%) | 268 (94.7) | 148 (96.7) | 103 (85.1) | 43 (97.7) |
| | Stratified Hazard Ratio ^{a, b} (95% C.I.) | 1.549 (0.557, 4.303) | | 5.328 (0.700, 40.555) | |
| | P-value ^{b, c} | 0.40144 | | 0.10618 | |
| | Interaction Test P-value ^d | 0.20468 | | | |
| | Median Time to Onset of the First Event (Days) (95% C.I.) ^e | - (-, -) | - (-, -) | - (-, -) | - (-, -) |
| | 25 th , 75 th Percentile | -, - | -, - | -, - | -, - |
| Observed Min, Max ^f | 2, 1327+ | 11, 839+ | 1, 1051+ | 40+, 599+ | |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (Presence or history of brain metastases: Yes/No, ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.

c. Two-sided p-value calculated from Cox proportional hazards model.

d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and race.

e. Calculated using the complementary log-log transformation method (Collett, 1994). f. '+' means the observed time is from censored subjects.

Snapshot date: 10SEP2020, data cutoff date: 29MAY2020.

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_may2020_dco_1943\v01\outputs\tlfs\pgms\t-ae-km-socpt-subgrp.sas Output: t02-06-06-ae-km-socpt-sub-5-race-safs.rtf (14DEC20:17:14) Data: adsl, adae, adtesaf

Seagen Protocol ONT-380-206**Table 2.6.6 Summary of Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Race - Time-to-Event Analysis
Safety Analysis Set**

| System Organ Class/ Preferred Term | Parameters | White | | Non-White | |
|---------------------------------------|--|------------------------|------------------------|------------------------|-----------------------|
| | | Tuc+Cap+Tra (N=283) | Pbo+Cap+Tra (N=153) | Tuc+Cap+Tra (N=121) | Pbo+Cap+Tra (N=44) |
| Epistaxis (PT) | Number of Subjects With at Least One Event, n (%) | 38 (13.4) | 8 (5.2) | 12 (9.9) | 2 (4.5) |
| | Number of Censored Subjects, n (%) | 245 (86.6) | 145 (94.8) | 109 (90.1) | 42 (95.5) |
| | Stratified Hazard Ratio ^{a, b} (95% C.I.) | | 2.465 (1.145, 5.308) | | 2.200 (0.485, 9.981) |
| | P-value ^{b, c} | | 0.02113 | | 0.30685 |
| | Interaction Test P-value ^d | | | 0.81307 | |
| | Median Time to Onset of the First Event (Days) (95% C.I.) ^e | - (-, -) | - (-, -) | - (-, -) | - (-, -) |
| | 25 th , 75 th Percentile | -, - | -, - | -, - | -, - |
| Observed Min, Max ^f | 1, 1327+ | 3, 839+ | 4+, 1051+ | 5, 599+ | |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (Presence or history of brain metastases: Yes/No, ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.

c. Two-sided p-value calculated from Cox proportional hazards model.

d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and race.

e. Calculated using the complementary log-log transformation method (Collett, 1994). f. '+' means the observed time is from censored subjects.

Snapshot date: 10SEP2020, data cutoff date: 29MAY2020.

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_may2020_dco_1943\v01\outputs\tlfs\pgms\t-ae-km-socpt-subgrp.sas Output: t02-06-06-ae-km-socpt-sub-5-race-safs.rtf (14DEC20:17:14) Data: adsl, adae, adtesaf

Seagen Protocol ONT-380-206**Table 2.6.6 Summary of Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Race - Time-to-Event Analysis
Safety Analysis Set**

| System Organ Class/ Preferred Term | Parameters | White | | Non-White | |
|---------------------------------------|--|------------------------|------------------------|------------------------|-----------------------|
| | | Tuc+Cap+Tra (N=283) | Pbo+Cap+Tra (N=153) | Tuc+Cap+Tra (N=121) | Pbo+Cap+Tra (N=44) |
| Pleural Effusion (PT) | Number of Subjects With at Least One Event, n (%) | 7 (2.5) | 10 (6.5) | 3 (2.5) | 1 (2.3) |
| | Number of Censored Subjects, n (%) | 276 (97.5) | 143 (93.5) | 118 (97.5) | 43 (97.7) |
| | Stratified Hazard Ratio ^{a, b} (95% C.I.) | | 0.291 (0.105, 0.806) | | 1.147 (0.112, 11.741) |
| | P-value ^{b, c} | | 0.01764 | | 0.90777 |
| | Interaction Test P-value ^d | | | 0.32391 | |
| | Median Time to Onset of the First Event (Days) (95% C.I.) ^e | - (942.0, -) | - (-, -) | - (-, -) | - (-, -) |
| | 25 th , 75 th Percentile | -, - | -, - | -, - | -, - |
| Observed Min, Max ^f | 6+, 1327+ | 6, 839+ | 4+, 1154+ | 40+, 599+ | |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (Presence or history of brain metastases: Yes/No, ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.

c. Two-sided p-value calculated from Cox proportional hazards model.

d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and race.

e. Calculated using the complementary log-log transformation method (Collett, 1994). f. '+' means the observed time is from censored subjects.

Snapshot date: 10SEP2020, data cutoff date: 29MAY2020.

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_may2020_dco_1943\v01\outputs\tlfs\pgms\t-ae-km-socpt-subgrp.sas Output: t02-06-06-ae-km-socpt-sub-5-race-safs.rtf (14DEC20:17:14) Data: adsl, adae, adtesaf

Seagen Protocol ONT-380-206**Table 2.6.6 Summary of Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Race - Time-to-Event Analysis
Safety Analysis Set**

| System Organ Class/ Preferred Term | Parameters | White | | Non-White | |
|--|---|-------------------------|------------------------|-------------------------|-----------------------|
| | | Tuc+Cap+Tra (N=283) | Pbo+Cap+Tra (N=153) | Tuc+Cap+Tra (N=121) | Pbo+Cap+Tra (N=44) |
| Palmar-Plantar Erythrodysesthesia Syndrome (PT) | Number of Subjects With at Least One Event, n (%) | 183 (64.7) | 82 (53.6) | 79 (65.3) | 23 (52.3) |
| | Number of Censored Subjects, n (%) | 100 (35.3) | 71 (46.4) | 42 (34.7) | 21 (47.7) |
| | Stratified Hazard Ratio ^{a, b} (95% C.I.) | 1.296 (0.996, 1.685) | | 1.267 (0.777, 2.066) | |
| | P-value ^{b, c} | 0.05326 | | 0.34200 | |
| | Interaction Test P-value ^d | 0.86926 | | | |
| | Median Time to Onset of the First Event (Days) (95% C.I.) ^e | 63.0 (51.0, 83.0) | 92.0 (64.0, 149.0) | 64.0 (43.0, 109.0) | 91.0 (40.0, -) |
| | 25 th , 75 th Percentile | 29.0, 400.0 | 34.0, - | 23.0, 324.0 | 28.5, - |
| Observed Min, Max ^f | 1, 873+ | 1, 457+ | 4, 785+ | 1, 279+ | |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (Presence or history of brain metastases: Yes/No, ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.

c. Two-sided p-value calculated from Cox proportional hazards model.

d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and race.

e. Calculated using the complementary log-log transformation method (Collett, 1994). f. '+' means the observed time is from censored subjects.

Snapshot date: 10SEP2020, data cutoff date: 29MAY2020.

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_may2020_dco_1943\v01\outputs\tlfs\pgms\t-ae-km-socpt-subgrp.sas Output:
t02-06-06-ae-km-socpt-sub-5-race-safs.rtf (14DEC20:17:14) Data: adsl, adae, adttesaf

Seagen Protocol ONT-380-206**Table 2.6.7 Summary of Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Hormone Receptor Status - Time-to-Event Analysis Safety Analysis Set**

| System Organ Class/ Preferred Term | Parameters | Negative for Both | | Positive for ER or PR or Both | |
|---------------------------------------|--|------------------------|-----------------------|-------------------------------|------------------------|
| | | Tuc+Cap+Tra (N=163) | Pbo+Cap+Tra (N=74) | Tuc+Cap+Tra (N=241) | Pbo+Cap+Tra (N=123) |
| Anaemia (PT) | Number of Subjects With at Least One Event, n (%) | 26 (16.0) | 11 (14.9) | 60 (24.9) | 13 (10.6) |
| | Number of Censored Subjects, n (%) | 137 (84.0) | 63 (85.1) | 181 (75.1) | 110 (89.4) |
| | Stratified Hazard Ratio ^{a, b} (95% C.I.) | 0.981 (0.474, 2.030) | | 2.334 (1.277, 4.263) | |
| | P-value ^{b, c} | 0.95887 | | 0.00585 | |
| | Interaction Test P-value ^d | | | 0.06749 | |
| | Median Time to Onset of the First Event (Days) (95% C.I.) ^e | - (924.0, -) | - (-, -) | - (-, -) | - (-, -) |
| | 25 th , 75 th Percentile | 924.0, - | -, - | 232.0, - | -, - |
| | Observed Min, Max ^f | 1, 1327+ | 22, 580+ | 1, 1131+ | 12, 839+ |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (Presence or history of brain metastases: Yes/No, ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.

c. Two-sided p-value calculated from Cox proportional hazards model.

d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and hormone receptor status.

e. Calculated using the complementary log-log transformation method (Collett, 1994). f. '+' means the observed time is from censored subjects.

Snapshot date: 10SEP2020, data cutoff date: 29MAY2020.

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_may2020_dco_1943\v01\outputs\tlfs\pgms\t-ae-km-socpt-subgrp.sas Output: t02-06-07-ae-km-socpt-sub-6-hr-safs.rtf (14DEC20:17:14) Data: adsl, adae, adttesaf

Seagen Protocol ONT-380-206**Table 2.6.7 Summary of Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Hormone Receptor Status - Time-to-Event Analysis Safety Analysis Set**

| System Organ Class/ Preferred Term | Parameters | Negative for Both | | Positive for ER or PR or Both | |
|---------------------------------------|--|------------------------|-----------------------|-------------------------------|------------------------|
| | | Tuc+Cap+Tra (N=163) | Pbo+Cap+Tra (N=74) | Tuc+Cap+Tra (N=241) | Pbo+Cap+Tra (N=123) |
| Investigations (SOC) | Number of Subjects With at Least One Event, n (%) | 106 (65.0) | 31 (41.9) | 148 (61.4) | 43 (35.0) |
| | Number of Censored Subjects, n (%) | 57 (35.0) | 43 (58.1) | 93 (38.6) | 80 (65.0) |
| | Stratified Hazard Ratio ^{a, b} (95% C.I.) | 1.469 (0.974, 2.215) | | 2.071 (1.470, 2.918) | |
| | P-value ^{b, c} | 0.06648 | | 0.00003 | |
| | Interaction Test P-value ^d | 0.24627 | | | |
| | Median Time to Onset of the First Event (Days) (95% C.I.) ^e | 106.0 (62.0, 176.0) | 231.0 (127.0, -) | 64.0 (43.0, 148.0) | - (283.0, -) |
| | 25 th , 75 th Percentile | 23.0, 520.0 | 50.0, - | 22.0, 757.0 | 65.0, - |
| Observed Min, Max ^f | 1, 765+ | 7, 562+ | 1, 899+ | 1, 598+ | |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (Presence or history of brain metastases: Yes/No, ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.

c. Two-sided p-value calculated from Cox proportional hazards model.

d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and hormone receptor status.

e. Calculated using the complementary log-log transformation method (Collett, 1994). f. '+' means the observed time is from censored subjects.

Snapshot date: 10SEP2020, data cutoff date: 29MAY2020.

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_may2020_dco_1943\v01\outputs\tlfs\pgms\t-ae-km-socpt-subgrp.sas Output: t02-06-07-ae-km-socpt-sub-6-hr-safs.rtf (14DEC20:17:14) Data: adsl, adae, adttesaf

Seagen Protocol ONT-380-206**Table 2.6.7 Summary of Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Hormone Receptor Status - Time-to-Event Analysis Safety Analysis Set**

| System Organ Class/ Preferred Term | Parameters | Negative for Both | | Positive for ER or PR or Both | |
|---|--|------------------------|-----------------------|-------------------------------|------------------------|
| | | Tuc+Cap+Tra (N=163) | Pbo+Cap+Tra (N=74) | Tuc+Cap+Tra (N=241) | Pbo+Cap+Tra (N=123) |
| Aspartate Aminotransferase Increased (PT) | Number of Subjects With at Least One Event, n (%) | 34 (20.9) | 9 (12.2) | 55 (22.8) | 13 (10.6) |
| | Number of Censored Subjects, n (%) | 129 (79.1) | 65 (87.8) | 186 (77.2) | 110 (89.4) |
| | Stratified Hazard Ratio ^{a, b} (95% C.I.) | 1.645 (0.780, 3.468) | | 2.270 (1.237, 4.166) | |
| | P-value ^{b, c} | 0.19073 | | 0.00811 | |
| | Interaction Test P-value ^d | | | 0.44488 | |
| | Median Time to Onset of the First Event (Days) (95% C.I.) ^e | - (-, -) | - (-, -) | - (-, -) | - (-, -) |
| | 25 th , 75 th Percentile | 677.0, - | -, - | 358.0, - | -, - |
| Observed Min, Max ^f | 4+, 1156+ | 11, 562+ | 6+, 899+ | 1, 839+ | |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (Presence or history of brain metastases: Yes/No, ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.

c. Two-sided p-value calculated from Cox proportional hazards model.

d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and hormone receptor status.

e. Calculated using the complementary log-log transformation method (Collett, 1994). f. '+' means the observed time is from censored subjects.

Snapshot date: 10SEP2020, data cutoff date: 29MAY2020.

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_may2020_dco_1943\v01\outputs\tlfs\pgms\t-ae-km-socpt-subgrp.sas Output:

t02-06-07-ae-km-socpt-sub-6-hr-safs.rtf (14DEC20:17:14) Data: adsl, adae, adttesaf

Seagen Protocol ONT-380-206**Table 2.6.7 Summary of Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Hormone Receptor Status - Time-to-Event Analysis Safety Analysis Set**

| System Organ Class/ Preferred Term | Parameters | Negative for Both | | Positive for ER or PR or Both | |
|---|--|------------------------|-----------------------|-------------------------------|------------------------|
| | | Tuc+Cap+Tra (N=163) | Pbo+Cap+Tra (N=74) | Tuc+Cap+Tra (N=241) | Pbo+Cap+Tra (N=123) |
| Alanine Aminotransferase Increased (PT) | Number of Subjects With at Least One Event, n (%) | 30 (18.4) | 4 (5.4) | 55 (22.8) | 9 (7.3) |
| | Number of Censored Subjects, n (%) | 133 (81.6) | 70 (94.6) | 186 (77.2) | 114 (92.7) |
| | Stratified Hazard Ratio ^{a, b} (95% C.I.) | | 3.158 (1.102, 9.055) | | 3.381 (1.668, 6.856) |
| | P-value ^{b, c} | | 0.03236 | | 0.00073 |
| | Interaction Test P-value ^d | | | 0.93562 | |
| | Median Time to Onset of the First Event (Days) (95% C.I.) ^e | - (-, -) | - (-, -) | - (-, -) | - (-, -) |
| | 25 th , 75 th Percentile | -, - | -, - | 337.0, - | -, - |
| Observed Min, Max ^f | 4+, 1156+ | 22, 562+ | 6+, 1131+ | 14, 839+ | |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (Presence or history of brain metastases: Yes/No, ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.

c. Two-sided p-value calculated from Cox proportional hazards model.

d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and hormone receptor status.

e. Calculated using the complementary log-log transformation method (Collett, 1994). f. '+' means the observed time is from censored subjects.

Snapshot date: 10SEP2020, data cutoff date: 29MAY2020.

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_may2020_dco_1943\v01\outputs\tlfs\pgms\t-ae-km-socpt-subgrp.sas Output:

t02-06-07-ae-km-socpt-sub-6-hr-safs.rtf (14DEC20:17:14) Data: adsl, adae, adttesaf

Seagen Protocol ONT-380-206**Table 2.6.7 Summary of Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Hormone Receptor Status - Time-to-Event Analysis Safety Analysis Set**

| System Organ Class/ Preferred Term | Parameters | Negative for Both | | Positive for ER or PR or Both | |
|---------------------------------------|--|------------------------|-----------------------|-------------------------------|------------------------|
| | | Tuc+Cap+Tra (N=163) | Pbo+Cap+Tra (N=74) | Tuc+Cap+Tra (N=241) | Pbo+Cap+Tra (N=123) |
| Blood Bilirubin Increased (PT) | Number of Subjects With at Least One Event, n (%) | 34 (20.9) | 7 (9.5) | 46 (19.1) | 14 (11.4) |
| | Number of Censored Subjects, n (%) | 129 (79.1) | 67 (90.5) | 195 (80.9) | 109 (88.6) |
| | Stratified Hazard Ratio ^{a, b} (95% C.I.) | 2.012 (0.883, 4.586) | | 1.639 (0.898, 2.991) | |
| | P-value ^{b, c} | 0.09623 | | 0.10723 | |
| | Interaction Test P-value ^d | 0.70446 | | | |
| | Median Time to Onset of the First Event (Days) (95% C.I.) ^e | - (-, -) | - (-, -) | - (-, -) | - (-, -) |
| | 25 th , 75 th Percentile | 429.0, - | -, - | -, - | -, - |
| | Observed Min, Max ^f | 4+, 1156+ | 7, 580+ | 6+, 1131+ | 6, 839+ |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (Presence or history of brain metastases: Yes/No, ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.

c. Two-sided p-value calculated from Cox proportional hazards model.

d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and hormone receptor status.

e. Calculated using the complementary log-log transformation method (Collett, 1994). f. '+' means the observed time is from censored subjects.

Snapshot date: 10SEP2020, data cutoff date: 29MAY2020.

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_may2020_dco_1943\v01\outputs\tlfs\pgms\t-ae-km-socpt-subgrp.sas Output: t02-06-07-ae-km-socpt-sub-6-hr-safs.rtf (14DEC20:17:14) Data: adsl, adae, adttesaf

Seagen Protocol ONT-380-206**Table 2.6.7 Summary of Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Hormone Receptor Status - Time-to-Event Analysis Safety Analysis Set**

| System Organ Class/ Preferred Term | Parameters | Negative for Both | | Positive for ER or PR or Both | |
|---------------------------------------|--|------------------------|-----------------------|-------------------------------|------------------------|
| | | Tuc+Cap+Tra (N=163) | Pbo+Cap+Tra (N=74) | Tuc+Cap+Tra (N=241) | Pbo+Cap+Tra (N=123) |
| Blood Creatinine Increased (PT) | Number of Subjects With at Least One Event, n (%) | 18 (11.0) | 1 (1.4) | 44 (18.3) | 2 (1.6) |
| | Number of Censored Subjects, n (%) | 145 (89.0) | 73 (98.6) | 197 (81.7) | 121 (98.4) |
| | Stratified Hazard Ratio ^{a, b} (95% C.I.) | | 6.872 (0.901, 52.395) | | 11.294 (2.729, 46.738) |
| | P-value ^{b, c} | | 0.06291 | | 0.00082 |
| | Interaction Test P-value ^d | | | 0.66345 | |
| | Median Time to Onset of the First Event (Days) (95% C.I.) ^e | - (-, -) | - (356.0, -) | - (-, -) | - (-, -) |
| | 25 th , 75 th Percentile | -, - | -, - | 482.0, - | -, - |
| Observed Min, Max ^f | 4+, 1154+ | 29+, 580+ | 5, 1131+ | 13, 839+ | |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (Presence or history of brain metastases: Yes/No, ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.

c. Two-sided p-value calculated from Cox proportional hazards model.

d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and hormone receptor status.

e. Calculated using the complementary log-log transformation method (Collett, 1994). f. '+' means the observed time is from censored subjects.

Snapshot date: 10SEP2020, data cutoff date: 29MAY2020.

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_may2020_dco_1943\v01\outputs\tlfs\pgms\t-ae-km-socpt-subgrp.sas Output: t02-06-07-ae-km-socpt-sub-6-hr-safs.rtf (14DEC20:17:14) Data: adsl, adae, adttesaf

Seagen Protocol ONT-380-206**Table 2.6.7 Summary of Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Hormone Receptor Status - Time-to-Event Analysis Safety Analysis Set**

| System Organ Class/ Preferred Term | Parameters | Negative for Both | | Positive for ER or PR or Both | |
|---------------------------------------|--|------------------------|-----------------------|-------------------------------|------------------------|
| | | Tuc+Cap+Tra (N=163) | Pbo+Cap+Tra (N=74) | Tuc+Cap+Tra (N=241) | Pbo+Cap+Tra (N=123) |
| Weight Decreased (PT) | Number of Subjects With at Least One Event, n (%) | 24 (14.7) | 7 (9.5) | 38 (15.8) | 5 (4.1) |
| | Number of Censored Subjects, n (%) | 139 (85.3) | 67 (90.5) | 203 (84.2) | 118 (95.9) |
| | Stratified Hazard Ratio ^{a, b} (95% C.I.) | 1.229 (0.518, 2.919) | | 3.778 (1.482, 9.633) | |
| | P-value ^{b, c} | 0.64030 | | 0.00537 | |
| | Interaction Test P-value ^d | | | 0.10957 | |
| | Median Time to Onset of the First Event (Days) (95% C.I.) ^e | - (-, -) | - (-, -) | - (-, -) | - (-, -) |
| | 25 th , 75 th Percentile | -, - | -, - | -, - | -, - |
| | Observed Min, Max ^f | 4+, 1327+ | 25, 580+ | 6, 1131+ | 9, 839+ |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (Presence or history of brain metastases: Yes/No, ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.

c. Two-sided p-value calculated from Cox proportional hazards model.

d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and hormone receptor status.

e. Calculated using the complementary log-log transformation method (Collett, 1994). f. '+' means the observed time is from censored subjects.

Snapshot date: 10SEP2020, data cutoff date: 29MAY2020.

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_may2020_dco_1943\v01\outputs\tlfs\pgms\t-ae-km-socpt-subgrp.sas Output:

t02-06-07-ae-km-socpt-sub-6-hr-safs.rtf (14DEC20:17:14) Data: adsl, adae, adttesaf

Seagen Protocol ONT-380-206**Table 2.6.7 Summary of Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Hormone Receptor Status - Time-to-Event Analysis Safety Analysis Set**

| System Organ Class/ Preferred Term | Parameters | Negative for Both | | Positive for ER or PR or Both | |
|--|--|------------------------|-----------------------|-------------------------------|------------------------|
| | | Tuc+Cap+Tra (N=163) | Pbo+Cap+Tra (N=74) | Tuc+Cap+Tra (N=241) | Pbo+Cap+Tra (N=123) |
| Metabolism And Nutrition Disorders (SOC) | Number of Subjects With at Least One Event, n (%) | 80 (49.1) | 33 (44.6) | 132 (54.8) | 41 (33.3) |
| | Number of Censored Subjects, n (%) | 83 (50.9) | 41 (55.4) | 109 (45.2) | 82 (66.7) |
| | Stratified Hazard Ratio ^{a, b} (95% C.I.) | 0.981 (0.646, 1.488) | | 1.861 (1.307, 2.649) | |
| | P-value ^{b, c} | 0.92668 | | 0.00057 | |
| | Interaction Test P-value ^d | 0.02360 | | | |
| | Median Time to Onset of the First Event (Days) (95% C.I.) ^e | 211.0 (127.0, -) | 333.0 (80.0, -) | 127.0 (84.0, 260.0) | - (526.0, -) |
| | 25 th , 75 th Percentile | 34.0, - | 31.0, - | 22.0, - | 85.0, - |
| Observed Min, Max ^f | 1, 1117+ | 1, 450+ | 1, 1131+ | 3, 839+ | |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (Presence or history of brain metastases: Yes/No, ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.

c. Two-sided p-value calculated from Cox proportional hazards model.

d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and hormone receptor status.

e. Calculated using the complementary log-log transformation method (Collett, 1994). f. '+' means the observed time is from censored subjects.

Snapshot date: 10SEP2020, data cutoff date: 29MAY2020.

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_may2020_dco_1943\v01\outputs\tlfs\pgms\t-ae-km-socpt-subgrp.sas Output:

t02-06-07-ae-km-socpt-sub-6-hr-safs.rtf (14DEC20:17:14) Data: adsl, adae, adttesaf

Seagen Protocol ONT-380-206**Table 2.6.7 Summary of Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Hormone Receptor Status - Time-to-Event Analysis Safety Analysis Set**

| System Organ Class/ Preferred Term | Parameters | Negative for Both | | Positive for ER or PR or Both | |
|---------------------------------------|--|------------------------|-----------------------|-------------------------------|------------------------|
| | | Tuc+Cap+Tra (N=163) | Pbo+Cap+Tra (N=74) | Tuc+Cap+Tra (N=241) | Pbo+Cap+Tra (N=123) |
| Hyperglycaemia (PT) | Number of Subjects With at Least One Event, n (%) | 8 (4.9) | 1 (1.4) | 15 (6.2) | 2 (1.6) |
| | Number of Censored Subjects, n (%) | 155 (95.1) | 73 (98.6) | 226 (93.8) | 121 (98.4) |
| | Stratified Hazard Ratio ^{a, b} (95% C.I.) | 3.484 (0.431, 28.174) | | 3.323 (0.758, 14.571) | |
| | P-value ^{b, c} | 0.24191 | | 0.11125 | |
| | Interaction Test P-value ^d | 0.94370 | | | |
| | Median Time to Onset of the First Event (Days) (95% C.I.) ^e | - (-, -) | - (-, -) | - (-, -) | - (-, -) |
| | 25 th , 75 th Percentile | -, - | -, - | -, - | -, - |
| Observed Min, Max ^f | 4+, 1327+ | 13, 580+ | 2, 1131+ | 12, 839+ | |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (Presence or history of brain metastases: Yes/No, ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.

c. Two-sided p-value calculated from Cox proportional hazards model.

d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and hormone receptor status.

e. Calculated using the complementary log-log transformation method (Collett, 1994). f. '+' means the observed time is from censored subjects.

Snapshot date: 10SEP2020, data cutoff date: 29MAY2020.

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_may2020_dco_1943\v01\outputs\tlfs\pgms\t-ae-km-socpt-subgrp.sas Output: t02-06-07-ae-km-socpt-sub-6-hr-safs.rtf (14DEC20:17:14) Data: adsl, adae, adttesaf

Seagen Protocol ONT-380-206**Table 2.6.7 Summary of Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Hormone Receptor Status - Time-to-Event Analysis Safety Analysis Set**

| System Organ Class/ Preferred Term | Parameters | Negative for Both | | Positive for ER or PR or Both | |
|--|---|-------------------------|-----------------------|-------------------------------|------------------------|
| | | Tuc+Cap+Tra (N=163) | Pbo+Cap+Tra (N=74) | Tuc+Cap+Tra (N=241) | Pbo+Cap+Tra (N=123) |
| Musculoskeletal And Connective Tissue Disorders (SOC) | Number of Subjects With at Least One Event, n (%) | 73 (44.8) | 23 (31.1) | 124 (51.5) | 46 (37.4) |
| | Number of Censored Subjects, n (%) | 90 (55.2) | 51 (68.9) | 117 (48.5) | 77 (62.6) |
| | Stratified Hazard Ratio ^{a, b} (95% C.I.) | 1.341 (0.826, 2.177) | | 1.399 (0.994, 1.971) | |
| | P-value ^{b, c} | 0.23595 | | 0.05433 | |
| | Interaction Test P-value ^d | 0.76923 | | | |
| | Median Time to Onset of the First Event (Days) (95% C.I.) ^e | 309.0 (201.0, 609.0) | -(148.0, -) | 183.0 (133.0, 280.0) | 355.0 (275.0, -) |
| | 25 th , 75 th Percentile | 64.0, - | 123.0, - | 61.0, 787.0 | 99.0, - |
| Observed Min, Max ^f | 1, 1117+ | 1, 557+ | 1, 830+ | 2, 839+ | |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (Presence or history of brain metastases: Yes/No, ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.

c. Two-sided p-value calculated from Cox proportional hazards model.

d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and hormone receptor status.

e. Calculated using the complementary log-log transformation method (Collett, 1994). f. '+' means the observed time is from censored subjects.

Snapshot date: 10SEP2020, data cutoff date: 29MAY2020.

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_may2020_dco_1943\v01\outputs\tlfs\pgms\t-ae-km-socpt-subgrp.sas Output:
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Seagen Protocol ONT-380-206**Table 2.6.7 Summary of Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Hormone Receptor Status - Time-to-Event Analysis Safety Analysis Set**

| System Organ Class/ Preferred Term | Parameters | Negative for Both | | Positive for ER or PR or Both | |
|---------------------------------------|--|------------------------|------------------------------|-------------------------------|-------------------------|
| | | Tuc+Cap+Tra (N=163) | Pbo+Cap+Tra (N=74) | Tuc+Cap+Tra (N=241) | Pbo+Cap+Tra (N=123) |
| Arthralgia (PT) | Number of Subjects With at Least One Event, n (%) | 28 (17.2) | 1 (1.4) | 36 (14.9) | 11 (8.9) |
| | Number of Censored Subjects, n (%) | 135 (82.8) | 73 (98.6) | 205 (85.1) | 112 (91.1) |
| | Stratified Hazard Ratio ^{a, b} (95% C.I.) | | 10.007 (1.344, 74.533) | | 1.511 (0.763, 2.991) |
| | P-value ^{b, c} | | 0.02456 | | 0.23628 |
| | Interaction Test P-value ^d | | | 0.07384 | |
| | Median Time to Onset of the First Event (Days) (95% C.I.) ^e | - (-, -) | - (-, -) | 959.0 (707.0, -) | - (-, -) |
| | 25 th , 75 th Percentile | 449.0, - | -, - | 707.0, - | -, - |
| Observed Min, Max ^f | 1, 1156+ | 29+, 580+ | 1, 1131+ | 4, 839+ | |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (Presence or history of brain metastases: Yes/No, ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.

c. Two-sided p-value calculated from Cox proportional hazards model.

d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and hormone receptor status.

e. Calculated using the complementary log-log transformation method (Collett, 1994). f. '+' means the observed time is from censored subjects.

Snapshot date: 10SEP2020, data cutoff date: 29MAY2020.

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t02-06-07-ae-km-socpt-sub-6-hr-safs.rtf (14DEC20:17:14) Data: adsl, adae, adttesaf

Seagen Protocol ONT-380-206**Table 2.6.7 Summary of Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Hormone Receptor Status - Time-to-Event Analysis Safety Analysis Set**

| System Organ Class/ Preferred Term | Parameters | Negative for Both | | Positive for ER or PR or Both | |
|---------------------------------------|--|-----------------------------|-----------------------|-------------------------------|------------------------|
| | | Tuc+Cap+Tra (N=163) | Pbo+Cap+Tra (N=74) | Tuc+Cap+Tra (N=241) | Pbo+Cap+Tra (N=123) |
| Muscle Spasms (PT) | Number of Subjects With at Least One Event, n (%) | 11 (6.7) | 0 | 32 (13.3) | 6 (4.9) |
| | Number of Censored Subjects, n (%) | 152 (93.3) | 74 (100) | 209 (86.7) | 117 (95.1) |
| | Stratified Hazard Ratio ^{a, b} (95% C.I.) | 15980730.53 8 (0.000, -) | | 2.538 (1.053, 6.117) | |
| | P-value ^{b, c} | 0.99452 | | 0.03793 | |
| | Interaction Test P-value ^d | | | 0.98831 | |
| | Median Time to Onset of the First Event (Days) (95% C.I.) ^e | - (841.0, -) | - (-, -) | - (787.0, -) | - (-, -) |
| | 25 th , 75 th Percentile | 841.0, - | -, - | 534.0, - | -, - |
| Observed Min, Max ^f | 1, 1327+ | 29+, 580+ | 2, 1080+ | 21, 839+ | |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (Presence or history of brain metastases: Yes/No, ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.

c. Two-sided p-value calculated from Cox proportional hazards model.

d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and hormone receptor status.

e. Calculated using the complementary log-log transformation method (Collett, 1994). f. '+' means the observed time is from censored subjects.

Snapshot date: 10SEP2020, data cutoff date: 29MAY2020.

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Seagen Protocol ONT-380-206**Table 2.6.7 Summary of Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Hormone Receptor Status - Time-to-Event Analysis Safety Analysis Set**

| System Organ Class/ Preferred Term | Parameters | Negative for Both | | Positive for ER or PR or Both | |
|---------------------------------------|--|------------------------|-----------------------|-------------------------------|------------------------|
| | | Tuc+Cap+Tra (N=163) | Pbo+Cap+Tra (N=74) | Tuc+Cap+Tra (N=241) | Pbo+Cap+Tra (N=123) |
| Peripheral Sensory Neuropathy (PT) | Number of Subjects With at Least One Event, n (%) | 22 (13.5) | 5 (6.8) | 29 (12.0) | 7 (5.7) |
| | Number of Censored Subjects, n (%) | 141 (86.5) | 69 (93.2) | 212 (88.0) | 116 (94.3) |
| | Stratified Hazard Ratio ^{a, b} (95% C.I.) | | 1.774 (0.659, 4.776) | | 1.895 (0.824, 4.357) |
| | P-value ^{b, c} | | 0.25637 | | 0.13229 |
| | Interaction Test P-value ^d | | | 0.96078 | |
| | Median Time to Onset of the First Event (Days) (95% C.I.) ^e | - (-, -) | - (509.0, -) | - (-, -) | - (-, -) |
| | 25 th , 75 th Percentile | -, - | 509.0, - | -, - | -, - |
| Observed Min, Max ^f | 4, 1327+ | 12, 580+ | 2, 1131+ | 15, 839+ | |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (Presence or history of brain metastases: Yes/No, ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.

c. Two-sided p-value calculated from Cox proportional hazards model.

d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and hormone receptor status.

e. Calculated using the complementary log-log transformation method (Collett, 1994). f. '+' means the observed time is from censored subjects.

Snapshot date: 10SEP2020, data cutoff date: 29MAY2020.

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t02-06-07-ae-km-socpt-sub-6-hr-safs.rtf (14DEC20:17:14) Data: adsl, adae, adttesaf

Seagen Protocol ONT-380-206**Table 2.6.7 Summary of Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Hormone Receptor Status - Time-to-Event Analysis Safety Analysis Set**

| System Organ Class/ Preferred Term | Parameters | Negative for Both | | Positive for ER or PR or Both | |
|---------------------------------------|--|------------------------|-----------------------|-------------------------------|------------------------|
| | | Tuc+Cap+Tra (N=163) | Pbo+Cap+Tra (N=74) | Tuc+Cap+Tra (N=241) | Pbo+Cap+Tra (N=123) |
| Dysgeusia (PT) | Number of Subjects With at Least One Event, n (%) | 15 (9.2) | 3 (4.1) | 18 (7.5) | 3 (2.4) |
| | Number of Censored Subjects, n (%) | 148 (90.8) | 71 (95.9) | 223 (92.5) | 120 (97.6) |
| | Stratified Hazard Ratio ^{a, b} (95% C.I.) | 2.335 (0.670, 8.131) | | 2.550 (0.743, 8.758) | |
| | P-value ^{b, c} | 0.18292 | | 0.13691 | |
| | Interaction Test P-value ^d | 0.77284 | | | |
| | Median Time to Onset of the First Event (Days) (95% C.I.) ^e | - (-, -) | - (-, -) | - (-, -) | - (-, -) |
| | 25 th , 75 th Percentile | -, - | -, - | -, - | -, - |
| Observed Min, Max ^f | 3, 1327+ | 12, 580+ | 1, 1131+ | 11, 839+ | |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (Presence or history of brain metastases: Yes/No, ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.

c. Two-sided p-value calculated from Cox proportional hazards model.

d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and hormone receptor status.

e. Calculated using the complementary log-log transformation method (Collett, 1994). f. '+' means the observed time is from censored subjects.

Snapshot date: 10SEP2020, data cutoff date: 29MAY2020.

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_may2020_dco_1943\v01\outputs\tlfs\pgms\t-ae-km-socpt-subgrp.sas Output: t02-06-07-ae-km-socpt-sub-6-hr-safs.rtf (14DEC20:17:14) Data: adsl, adae, adttesaf

Seagen Protocol ONT-380-206**Table 2.6.7 Summary of Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Hormone Receptor Status - Time-to-Event Analysis Safety Analysis Set**

| System Organ Class/ Preferred Term | Parameters | Negative for Both | | Positive for ER or PR or Both | |
|---------------------------------------|--|------------------------|-----------------------|-------------------------------|------------------------|
| | | Tuc+Cap+Tra (N=163) | Pbo+Cap+Tra (N=74) | Tuc+Cap+Tra (N=241) | Pbo+Cap+Tra (N=123) |
| Epistaxis (PT) | Number of Subjects With at Least One Event, n (%) | 16 (9.8) | 4 (5.4) | 34 (14.1) | 6 (4.9) |
| | Number of Censored Subjects, n (%) | 147 (90.2) | 70 (94.6) | 207 (85.9) | 117 (95.1) |
| | Stratified Hazard Ratio ^{a, b} (95% C.I.) | 1.629 (0.529, 5.015) | | 2.694 (1.127, 6.440) | |
| | P-value ^{b, c} | 0.39510 | | 0.02579 | |
| | Interaction Test P-value ^d | | | 0.49531 | |
| | Median Time to Onset of the First Event (Days) (95% C.I.) ^e | - (-, -) | - (-, -) | - (-, -) | - (-, -) |
| | 25 th , 75 th Percentile | -, - | -, - | -, - | -, - |
| Observed Min, Max ^f | 1, 1327+ | 13, 580+ | 1, 1131+ | 3, 839+ | |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (Presence or history of brain metastases: Yes/No, ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.

c. Two-sided p-value calculated from Cox proportional hazards model.

d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and hormone receptor status.

e. Calculated using the complementary log-log transformation method (Collett, 1994). f. '+' means the observed time is from censored subjects.

Snapshot date: 10SEP2020, data cutoff date: 29MAY2020.

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_may2020_dco_1943\v01\outputs\tlfs\pgms\t-ae-km-socpt-subgrp.sas Output: t02-06-07-ae-km-socpt-sub-6-hr-safs.rtf (14DEC20:17:14) Data: adsl, adae, adttesaf

Seagen Protocol ONT-380-206**Table 2.6.7 Summary of Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Hormone Receptor Status - Time-to-Event Analysis Safety Analysis Set**

| System Organ Class/ Preferred Term | Parameters | Negative for Both | | Positive for ER or PR or Both | |
|--|--|------------------------|-----------------------|-------------------------------|------------------------|
| | | Tuc+Cap+Tra (N=163) | Pbo+Cap+Tra (N=74) | Tuc+Cap+Tra (N=241) | Pbo+Cap+Tra (N=123) |
| Pleural Effusion (PT) | Number of Subjects With at Least One Event, n (%) | 7 (4.3) | 4 (5.4) | 3 (1.2) | 7 (5.7) |
| | Number of Censored Subjects, n (%) | 156 (95.7) | 70 (94.6) | 238 (98.8) | 116 (94.3) |
| | Stratified Hazard Ratio ^{a, b} (95% C.I.) | 0.598 (0.163, 2.200) | | 0.225 (0.058, 0.873) | |
| | P-value ^{b, c} | 0.43934 | | 0.03111 | |
| | Interaction Test P-value ^d | | | 0.22069 | |
| | Median Time to Onset of the First Event (Days) (95% C.I.) ^e | - (-, -) | - (-, -) | - (-, -) | - (-, -) |
| 25 th , 75 th Percentile | -, - | -, - | -, - | -, - | |
| Observed Min, Max ^f | 4+, 1327+ | 6, 580+ | 6+, 1131+ | 8, 839+ | |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (Presence or history of brain metastases: Yes/No, ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.

c. Two-sided p-value calculated from Cox proportional hazards model.

d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and hormone receptor status.

e. Calculated using the complementary log-log transformation method (Collett, 1994). f. '+' means the observed time is from censored subjects.

Snapshot date: 10SEP2020, data cutoff date: 29MAY2020.

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_may2020_dco_1943\v01\outputs\tlfs\pgms\t-ae-km-socpt-subgrp.sas Output: t02-06-07-ae-km-socpt-sub-6-hr-safs.rtf (14DEC20:17:14) Data: adsl, adae, adttesaf

Seagen Protocol ONT-380-206

Table 2.6.7 Summary of Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Hormone Receptor Status - Time-to-Event Analysis Safety Analysis Set

| System Organ Class/ Preferred Term | Parameters | Negative for Both | | Positive for ER or PR or Both | |
|---|--|------------------------|-----------------------|-------------------------------|------------------------|
| | | Tuc+Cap+Tra (N=163) | Pbo+Cap+Tra (N=74) | Tuc+Cap+Tra (N=241) | Pbo+Cap+Tra (N=123) |
| Palmar-Plantar Erythrodysesthesia Syndrome (PT) | Number of Subjects With at Least One Event, n (%) | 106 (65.0) | 34 (45.9) | 156 (64.7) | 71 (57.7) |
| | Number of Censored Subjects, n (%) | 57 (35.0) | 40 (54.1) | 85 (35.3) | 52 (42.3) |
| | Stratified Hazard Ratio ^{a, b} (95% C.I.) | 1.672 (1.127, 2.483) | | 1.137 (0.857, 1.509) | |
| | P-value ^{b, c} | 0.01073 | | 0.37477 | |
| | Interaction Test P-value ^d | 0.19960 | | | |
| | Median Time to Onset of the First Event (Days) (95% C.I.) ^e | 62.0 (43.0, 84.0) | 141.0 (86.0, -) | 64.0 (46.0, 85.0) | 71.0 (57.0, 127.0) |
| | 25 th , 75 th Percentile | 30.0, 384.0 | 36.0, - | 27.0, 337.0 | 32.0, - |
| Observed Min, Max ^f | 1, 873+ | 1, 450+ | 1, 822+ | 1, 457+ | |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.
 b. Computed using stratification factors (Presence or history of brain metastases: Yes/No, ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.
 c. Two-sided p-value calculated from Cox proportional hazards model.
 d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and hormone receptor status.
 e. Calculated using the complementary log-log transformation method (Collett, 1994). f. '+' means the observed time is from censored subjects.
 Snapshot date: 10SEP2020, data cutoff date: 29MAY2020.
 Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_may2020_dco_1943\v01\outputs\tlfs\pgms\t-ae-km-socpt-subgrp.sas Output:
 t02-06-07-ae-km-socpt-sub-6-hr-safs.rtf (14DEC20:17:14) Data: adsl, adae, adttesaf

Seattle Genetics Protocol ONT-380-206

**Table 2.8.2 Summary of Treatment-Emergent Serious Adverse Events by System Organ Class, Preferred Term and History of Brain Metastases at Baseline - Time-to-Event Analysis
Safety Analysis Set**

| System Organ Class/ Preferred Term | Parameters | With Brian Metastases | | Without Brain Metastases | |
|---------------------------------------|------------|------------------------|-----------------------|--------------------------|------------------------|
| | | Tuc+Cap+Tra (N=194) | Pbo+Cap+Tra (N=91) | Tuc+Cap+Tra (N=209) | Pbo+Cap+Tra (N=105) |

NO DATA QUALIFY FOR THIS OUTPUT

- a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.
 - b. Computed using stratification factors (ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.
 - c. Two-sided p-value calculated from Cox proportional hazards model .
 - d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and history of brain metastases at baseline.
 - e. Calculated using the complementary log-log transformation method (Collett, 1994). f. '+' means the observed time is from censored subjects.
- Data Snapshot: 14OCT2019, Data Cutoff Date: 04SEP2019
 Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_1753\v01\outputs\tfs\pgms\t-ae-km-socpt-subgrp.sas Output: t-sae-km-socpt-sub-1-bm-safs.rtf (17JUL20:17:19)
 Data: adsl, adae, adttesaf

Seattle Genetics Protocol ONT-380-206**Table 2.8.3 Summary of Treatment-Emergent Serious Adverse Events by System Organ Class, Preferred Term and Geographic Region - Time-to-Event Analysis Safety Analysis Set**

| System Organ Class/ Preferred Term | Parameters | North America | | Rest of World | |
|---------------------------------------|------------|------------------------|------------------------|------------------------|-----------------------|
| | | Tuc+Cap+Tra (N=241) | Pbo+Cap+Tra (N=119) | Tuc+Cap+Tra (N=163) | Pbo+Cap+Tra (N=78) |

NO DATA QUALIFY FOR THIS OUTPUT

Page 1 of 1

- a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.
- b. Computed using stratification factors (Presence or history of brain metastases: Yes/No and ECOG performance status: 0/1) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.
- c. Two-sided p-value calculated from Cox proportional hazards model .
- d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and geographic region.
- e. Calculated using the complementary log-log transformation method (Collett, 1994). f. '+' means the observed time is from censored subjects.
- Data Snapshot: 14OCT2019, Data Cutoff Date: 04SEP2019
 Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_1753\v01\outputs\tfs\pgms\t-ae-km-socpt-subgrp.sas Output: t-sae-km-socpt-sub-2-reg-safs.rtf (17JUL20:17:19)
 Data: adsl, adae, adttesaf

Seattle Genetics Protocol ONT-380-206

**Table 2.8.4 Summary of Treatment-Emergent Serious Adverse Events by System Organ Class, Preferred Term and Baseline ECOG Score - Time-to-Event Analysis
Safety Analysis Set**

| System Organ Class/ Preferred Term | Parameters | ECOG=0 | | ECOG=1 | |
|---------------------------------------|------------|------------------------|-----------------------|------------------------|------------------------|
| | | Tuc+Cap+Tra (N=203) | Pbo+Cap+Tra (N=91) | Tuc+Cap+Tra (N=201) | Pbo+Cap+Tra (N=106) |

NO DATA QUALIFY FOR THIS OUTPUT

- a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.
- b. Computed using stratification factors (Presence or history of brain metastases: Yes/No and Region of world: North America /Rest of World) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.
- c. Two-sided p-value calculated from Cox proportional hazards model .
- d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and baseline ECOG score.
- e. Calculated using the complementary log-log transformation method (Collett, 1994). f. '+' means the observed time is from censored subjects.

Data Snapshot: 14OCT2019, Data Cutoff Date: 04SEP2019

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_1753\v01\outputs\tlfs\pgms\t-ae-km-socpt-subgrp.sas Output: t-sae-km-socpt-sub-3-ecog-safs.rtf (17JUL20:17:19) Data: adsl, adae, adttesaf

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**Table 2.8.5 Summary of Treatment-Emergent Serious Adverse Events by System Organ Class, Preferred Term and Age - Time-to-Event Analysis
Safety Analysis Set**

| System Organ Class/ Preferred Term | Parameters | Age < 65 Years | | Age >= 65 Years | |
|---------------------------------------|------------|------------------------|------------------------|-----------------------|-----------------------|
| | | Tuc+Cap+Tra (N=322) | Pbo+Cap+Tra (N=164) | Tuc+Cap+Tra (N=82) | Pbo+Cap+Tra (N=33) |

NO DATA QUALIFY FOR THIS OUTPUT

a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.
 b. Computed using stratification factors (Presence or history of brain metastases: Yes/No, ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.
 c. Two-sided p-value calculated from Cox proportional hazards model .
 d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and age.
 e. Calculated using the complementary log-log transformation method (Collett, 1994). f. '+' means the observed time is from censored subjects.
 Data Snapshot: 14OCT2019, Data Cutoff Date: 04SEP2019
 Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_1753\v01\outputs\tlfs\pgms\t-ae-km-socpt-subgrp.sas Output: t-sae-km-socpt-sub-4-age-safs.rtf (17JUL20:17:19)
 Data: adsl, adae, adttesaf

Seattle Genetics Protocol ONT-380-206

**Table 2.8.6 Summary of Treatment-Emergent Serious Adverse Events by System Organ Class, Preferred Term and Race - Time-to-Event Analysis
Safety Analysis Set**

| System Organ Class/ Preferred Term | Parameters | White | | Non-White | |
|---------------------------------------|------------|------------------------|------------------------|------------------------|-----------------------|
| | | Tuc+Cap+Tra (N=283) | Pbo+Cap+Tra (N=153) | Tuc+Cap+Tra (N=121) | Pbo+Cap+Tra (N=44) |

NO DATA QUALIFY FOR THIS OUTPUT

- a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.
- b. Computed using stratification factors (Presence or history of brain metastases: Yes/No, ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.
- c. Two-sided p-value calculated from Cox proportional hazards model .
- d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and race.
- e. Calculated using the complementary log-log transformation method (Collett, 1994). f. '+' means the observed time is from censored subjects.

Data Snapshot: 14OCT2019, Data Cutoff Date: 04SEP2019

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_1753\v01\outputs\tlfs\pgms\t-ae-km-socpt-subgrp.sas Output: t-sae-km-socpt-sub-5-race-safs.rtf (17JUL20:17:19) Data: adsl, adae, adttesaf

Seattle Genetics Protocol ONT-380-206

**Table 2.8.7 Summary of Treatment-Emergent Serious Adverse Events by System Organ Class, Preferred Term and Hormone Receptor Status - Time-to-Event Analysis
Safety Analysis Set**

| System Organ Class/ Preferred Term | Parameters | Negative for Both | | Positive for ER or PR or Both | |
|---------------------------------------|------------|------------------------|-----------------------|-------------------------------|------------------------|
| | | Tuc+Cap+Tra (N=163) | Pbo+Cap+Tra (N=74) | Tuc+Cap+Tra (N=241) | Pbo+Cap+Tra (N=123) |

NO DATA QUALIFY FOR THIS OUTPUT

Page 1 of 1

- a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.
 - b. Computed using stratification factors (Presence or history of brain metastases: Yes/No, ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.
 - c. Two-sided p-value calculated from Cox proportional hazards model .
 - d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and hormone receptor status.
 - e. Calculated using the complementary log-log transformation method (Collett, 1994). f. '+' means the observed time is from censored subjects.
- Data Snapshot: 14OCT2019, Data Cutoff Date: 04SEP2019
 Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_1753\v01\outputs\tfs\pgms\t-ae-km-socpt-subgrp.sas Output: t-sae-km-socpt-sub-6-hr-safs.rtf (17JUL20:17:19)
 Data: adsl, adae, adttesaf

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**Table 2.8.2 Summary of Treatment-Emergent Serious Adverse Events by System Organ Class, Preferred Term and History of Brain Metastases at Baseline - Time-to-Event Analysis
Safety Analysis Set**

| System Organ Class/ Preferred Term | Parameters | With Brian Metastases | | Without Brain Metastases | |
|--|--|------------------------|----------------------------|--------------------------|----------------------------|
| | | Tuc+Cap+Tra (N=194) | Pbo+Cap+Tra (N=91) | Tuc+Cap+Tra (N=209) | Pbo+Cap+Tra (N=105) |
| Serious Respiratory, Thoracic And Mediastinal Disorders (SOC) | Number of Subjects With at Least One Event, n (%) | 9 (4.6) | 5 (5.5) | 9 (4.3) | 10 (9.5) |
| | Number of Censored Subjects, n (%) | 185 (95.4) | 86 (94.5) | 200 (95.7) | 95 (90.5) |
| | Stratified Hazard Ratio ^{a, b} (95% C.I.) | | 0.774 (0.258, 2.323) | | 0.360 (0.142, 0.914) |
| | P-value ^{b, c} | | 0.64812 | | 0.03166 |
| | Interaction Test P-value ^d | | | 0.43012 | |

Page 1 of 2

a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.

c. Two-sided p-value calculated from Cox proportional hazards model .

d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and history of brain metastases at baseline.

e. Calculated using the complementary log-log transformation method (Collett, 1994). f. '+' means the observed time is from censored subjects.

Snapshot date: 10SEP2020, data cutoff date: 29MAY2020.

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_may2020_dco_1943\v01\outputs\tlfs\pgms\t-sae-km-socpt-subgrp.sas Output:

t02-08-02-sae-km-socpt-sub-1-bm-safs.rtf (14DEC20:17:16) Data: adsl, adae, adttesaf

Seagen Protocol ONT-380-206**Table 2.8.2 Summary of Treatment-Emergent Serious Adverse Events by System Organ Class, Preferred Term and History of Brain Metastases at Baseline - Time-to-Event Analysis
Safety Analysis Set**

| System Organ Class/ Preferred Term | Parameters | With Brian Metastases | | Without Brain Metastases | |
|---------------------------------------|---|------------------------|-----------------------|--------------------------|------------------------|
| | | Tuc+Cap+Tra (N=194) | Pbo+Cap+Tra (N=91) | Tuc+Cap+Tra (N=209) | Pbo+Cap+Tra (N=105) |
| | Median Time to Onset of the First Event (Days) (95% C.I.) ^e | - (-, -) | - (-, -) | - (942.0, -) | - (-, -) |
| | 25 th , 75 th Percentile | -, - | -, - | -, - | -, - |
| | Observed Min, Max ^f | 1, 1156+ | 21, 599+ | 18, 1327+ | 8, 839+ |

Page 2 of 2

a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.

c. Two-sided p-value calculated from Cox proportional hazards model .

d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and history of brain metastases at baseline.

e. Calculated using the complementary log-log transformation method (Collett, 1994). f. '+' means the observed time is from censored subjects.

Snapshot date: 10SEP2020, data cutoff date: 29MAY2020.

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_may2020_dco_1943\v01\outputs\tlfs\pgms\t-sae-km-socpt-subgrp.sas Output:
t02-08-02-sae-km-socpt-sub-1-bm-safs.rtf (14DEC20:17:16) Data: adsl, adae, adttesaf

Seagen Protocol ONT-380-206**Table 2.8.3 Summary of Treatment-Emergent Serious Adverse Events by System Organ Class, Preferred Term and Geographic Region - Time-to-Event Analysis Safety Analysis Set**

| System Organ Class/ Preferred Term | Parameters | North America | | Rest of World | |
|--|--|------------------------|----------------------------|------------------------|----------------------------|
| | | Tuc+Cap+Tra (N=241) | Pbo+Cap+Tra (N=119) | Tuc+Cap+Tra (N=163) | Pbo+Cap+Tra (N=78) |
| Serious Respiratory, Thoracic And Mediastinal Disorders (SOC) | Number of Subjects With at Least One Event, n (%) | 9 (3.7) | 10 (8.4) | 9 (5.5) | 5 (6.4) |
| | Number of Censored Subjects, n (%) | 232 (96.3) | 109 (91.6) | 154 (94.5) | 73 (93.6) |
| | Stratified Hazard Ratio ^{a, b} (95% C.I.) | | 0.362 (0.143, 0.920) | | 0.761 (0.253, 2.285) |
| | P-value ^{b, c} | | 0.03275 | | 0.62610 |
| | Interaction Test P-value ^d | | | 0.28421 | |

Page 1 of 2

a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (Presence or history of brain metastases: Yes/No and ECOG performance status: 0/1) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.

c. Two-sided p-value calculated from Cox proportional hazards model.

d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and geographic region.

e. Calculated using the complementary log-log transformation method (Collett, 1994). f. '+' means the observed time is from censored subjects.

Snapshot date: 10SEP2020, data cutoff date: 29MAY2020.

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_may2020_dco_1943\v01\outputs\tlfs\pgms\t-sae-km-socpt-subgrp.sas Output: t02-08-03-sae-km-socpt-sub-2-reg-safs.rtf (14DEC20:17:16) Data: adsl, adae, adttesaf

Seagen Protocol ONT-380-206**Table 2.8.3 Summary of Treatment-Emergent Serious Adverse Events by System Organ Class, Preferred Term and Geographic Region - Time-to-Event Analysis Safety Analysis Set**

| System Organ Class/ Preferred Term | Parameters | North America | | Rest of World | |
|---------------------------------------|--|------------------------|------------------------|------------------------|-----------------------|
| | | Tuc+Cap+Tra (N=241) | Pbo+Cap+Tra (N=119) | Tuc+Cap+Tra (N=163) | Pbo+Cap+Tra (N=78) |
| | Median Time to Onset of the First Event (Days) (95% C.I.) ^e | - (-, -) | - (-, -) | - (-, -) | - (-, -) |
| | 25 th , 75 th Percentile | -, - | -, - | -, - | -, - |
| | Observed Min, Max ^f | 4+, 1327+ | 21, 762+ | 1, 954+ | 8, 839+ |

Page 2 of 2

a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (Presence or history of brain metastases: Yes/No and ECOG performance status: 0/1) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.

c. Two-sided p-value calculated from Cox proportional hazards model.

d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and geographic region.

e. Calculated using the complementary log-log transformation method (Collett, 1994). f. '+' means the observed time is from censored subjects.

Snapshot date: 10SEP2020, data cutoff date: 29MAY2020.

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_may2020_dco_1943\v01\outputs\tlfs\pgms\t-sae-km-socpt-subgrp.sas Output: t02-08-03-sae-km-socpt-sub-2-reg-safs.rtf (14DEC20:17:16) Data: adsl, adae, adttesaf

Seagen Protocol ONT-380-206**Table 2.8.4 Summary of Treatment-Emergent Serious Adverse Events by System Organ Class, Preferred Term and Baseline ECOG Score - Time-to-Event Analysis
Safety Analysis Set**

| System Organ Class/ Preferred Term | Parameters | ECOG=0 | | ECOG=1 | |
|--|--|------------------------|----------------------------|------------------------|----------------------------|
| | | Tuc+Cap+Tra (N=203) | Pbo+Cap+Tra (N=91) | Tuc+Cap+Tra (N=201) | Pbo+Cap+Tra (N=106) |
| Serious Respiratory, Thoracic And Mediastinal Disorders (SOC) | Number of Subjects With at Least One Event, n (%) | 2 (1.0) | 6 (6.6) | 16 (8.0) | 9 (8.5) |
| | Number of Censored Subjects, n (%) | 201 (99.0) | 85 (93.4) | 185 (92.0) | 97 (91.5) |
| | Stratified Hazard Ratio ^{a, b} (95% C.I.) | | 0.132 (0.027, 0.657) | | 0.792 (0.345, 1.817) |
| | P-value ^{b, c} | | 0.01340 | | 0.58269 |
| | Interaction Test P-value ^d | | | 0.03867 | |

Page 1 of 2

a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.
b. Computed using stratification factors (Presence or history of brain metastases: Yes/No and Region of world: North America /Rest of World) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.
c. Two-sided p-value calculated from Cox proportional hazards model .
d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and baseline ECOG score.
e. Calculated using the complementary log-log transformation method (Collett, 1994). f. '+' means the observed time is from censored subjects.
Snapshot date: 10SEP2020, data cutoff date: 29MAY2020.
Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_may2020_dco_1943\v01\outputs\tlfs\pgms\t-sae-km-socpt-subgrp.sas Output:
t02-08-04-sae-km-socpt-sub-3-ecog-safs.rtf (14DEC20:17:16) Data: adsl, adae, adttesaf

Seagen Protocol ONT-380-206**Table 2.8.4 Summary of Treatment-Emergent Serious Adverse Events by System Organ Class, Preferred Term and Baseline ECOG Score - Time-to-Event Analysis
Safety Analysis Set**

| System Organ Class/ Preferred Term | Parameters | ECOG=0 | | ECOG=1 | |
|---------------------------------------|---|------------------------|-----------------------|------------------------|------------------------|
| | | Tuc+Cap+Tra (N=203) | Pbo+Cap+Tra (N=91) | Tuc+Cap+Tra (N=201) | Pbo+Cap+Tra (N=106) |
| | Median Time to Onset of the First Event (Days) (95% C.I.) ^e | - (-, -) | - (-, -) | 942.0 (942.0, -) | - (-, -) |
| | 25 th , 75 th Percentile | -, - | -, - | 942.0, - | -, - |
| | Observed Min, Max ^f | 4+, 1327+ | 37, 839+ | 1, 1154+ | 8, 762+ |

Page 2 of 2

a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (Presence or history of brain metastases: Yes/No and Region of world: North America /Rest of World) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.

c. Two-sided p-value calculated from Cox proportional hazards model .

d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and baseline ECOG score.

e. Calculated using the complementary log-log transformation method (Collett, 1994). f. '+' means the observed time is from censored subjects.

Snapshot date: 10SEP2020, data cutoff date: 29MAY2020.

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_may2020_dco_1943\v01\outputs\tlfs\pgms\t-sae-km-socpt-subgrp.sas Output:

t02-08-04-sae-km-socpt-sub-3-ecog-safs.rtf (14DEC20:17:16) Data: adsl, adae, adttesaf

Seagen Protocol ONT-380-206**Table 2.8.5 Summary of Treatment-Emergent Serious Adverse Events by System Organ Class, Preferred Term and Age - Time-to-Event Analysis
Safety Analysis Set**

| System Organ Class/ Preferred Term | Parameters | Age < 65 Years | | Age ≥ 65 Years | |
|--|--|------------------------|----------------------------|-----------------------|----------------------------|
| | | Tuc+Cap+Tra (N=322) | Pbo+Cap+Tra (N=164) | Tuc+Cap+Tra (N=82) | Pbo+Cap+Tra (N=33) |
| Serious Respiratory, Thoracic And Mediastinal Disorders (SOC) | Number of Subjects With at Least One Event, n (%) | 11 (3.4) | 12 (7.3) | 7 (8.5) | 3 (9.1) |
| | Number of Censored Subjects, n (%) | 311 (96.6) | 152 (92.7) | 75 (91.5) | 30 (90.9) |
| | Stratified Hazard Ratio ^{a, b} (95% C.I.) | | 0.420 (0.185, 0.957) | | 0.804 (0.195, 3.323) |
| | P-value ^{b, c} | | 0.03890 | | 0.76325 |
| | Interaction Test P-value ^d | | | 0.48632 | |

Page 1 of 2

a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (Presence or history of brain metastases: Yes/No, ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.

c. Two-sided p-value calculated from Cox proportional hazards model.

d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and age.

e. Calculated using the complementary log-log transformation method (Collett, 1994). f. '+' means the observed time is from censored subjects. Snapshot date: 10SEP2020, data cutoff date: 29MAY2020.

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_may2020_dco_1943\v01\outputs\tlfs\pgms\t-sae-km-socpt-subgrp.sas Output: t02-08-05-sae-km-socpt-sub-4-age-safs.rtf (14DEC20:17:16) Data: adsl, adae, adttesaf

Seagen Protocol ONT-380-206**Table 2.8.5 Summary of Treatment-Emergent Serious Adverse Events by System Organ Class, Preferred Term and Age - Time-to-Event Analysis
Safety Analysis Set**

| System Organ Class/ Preferred Term | Parameters | Age < 65 Years | | Age ≥ 65 Years | |
|---------------------------------------|--|------------------------|------------------------|-----------------------|-----------------------|
| | | Tuc+Cap+Tra (N=322) | Pbo+Cap+Tra (N=164) | Tuc+Cap+Tra (N=82) | Pbo+Cap+Tra (N=33) |
| | Median Time to Onset of the First Event (Days) (95% C.I.) ^e | - (-, -) | - (-, -) | 942.0 (-, -) | - (-, -) |
| | 25 th , 75 th Percentile | -, - | -, - | 942.0, 942.0 | -, - |
| | Observed Min, Max ^f | 1, 1327+ | 8, 839+ | 4+, 942 | 14, 428+ |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (Presence or history of brain metastases: Yes/No, ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.

c. Two-sided p-value calculated from Cox proportional hazards model.

d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and age.

e. Calculated using the complementary log-log transformation method (Collett, 1994). f. '+' means the observed time is from censored subjects.

Snapshot date: 10SEP2020, data cutoff date: 29MAY2020.

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_may2020_dco_1943\v01\outputs\tlfs\pgms\t-sae-km-socpt-subgrp.sas Output:

t02-08-05-sae-km-socpt-sub-4-age-safs.rtf (14DEC20:17:16) Data: adsl, adae, adttesaf

Seagen Protocol ONT-380-206**Table 2.8.6 Summary of Treatment-Emergent Serious Adverse Events by System Organ Class, Preferred Term and Race - Time-to-Event Analysis
Safety Analysis Set**

| System Organ Class/ Preferred Term | Parameters | White | | Non-White | |
|--|--|------------------------|----------------------------|------------------------|-----------------------------|
| | | Tuc+Cap+Tra (N=283) | Pbo+Cap+Tra (N=153) | Tuc+Cap+Tra (N=121) | Pbo+Cap+Tra (N=44) |
| Serious Respiratory, Thoracic And Mediastinal Disorders (SOC) | Number of Subjects With at Least One Event, n (%) | 12 (4.2) | 14 (9.2) | 6 (5.0) | 1 (2.3) |
| | Number of Censored Subjects, n (%) | 271 (95.8) | 139 (90.8) | 115 (95.0) | 43 (97.7) |
| | Stratified Hazard Ratio ^{a, b} (95% C.I.) | | 0.396 (0.179, 0.875) | | 1.588 (0.189, 13.372) |
| | P-value ^{b, c} | | 0.02192 | | 0.67058 |
| | Interaction Test P-value ^d | | | 0.16315 | |

Page 1 of 2

a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (Presence or history of brain metastases: Yes/No, ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.

c. Two-sided p-value calculated from Cox proportional hazards model.

d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and race.

e. Calculated using the complementary log-log transformation method (Collett, 1994). f. '+' means the observed time is from censored subjects.

Snapshot date: 10SEP2020, data cutoff date: 29MAY2020.

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_may2020_dco_1943\v01\outputs\tlfs\pgms\t-sae-km-socpt-subgrp.sas Output:

t02-08-06-sae-km-socpt-sub-5-race-safs.rtf (14DEC20:17:16) Data: adsl, adae, adttesaf

Seagen Protocol ONT-380-206

**Table 2.8.6 Summary of Treatment-Emergent Serious Adverse Events by System Organ Class, Preferred Term and Race - Time-to-Event Analysis
Safety Analysis Set**

| System Organ Class/ Preferred Term | Parameters | White | | Non-White | |
|---------------------------------------|--|------------------------|------------------------|------------------------|-----------------------|
| | | Tuc+Cap+Tra (N=283) | Pbo+Cap+Tra (N=153) | Tuc+Cap+Tra (N=121) | Pbo+Cap+Tra (N=44) |
| | Median Time to Onset of the First Event (Days) (95% C.I.) ^e | - (942.0, -) | - (-, -) | - (-, -) | - (-, -) |
| | 25 th , 75 th Percentile | -, - | -, - | -, - | -, - |
| | Observed Min, Max ^f | 1, 1327+ | 8, 839+ | 4+, 1154+ | 40+, 599+ |

Page 2 of 2

- a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.
- b. Computed using stratification factors (Presence or history of brain metastases: Yes/No, ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.
- c. Two-sided p-value calculated from Cox proportional hazards model .
- d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and race.
- e. Calculated using the complementary log-log transformation method (Collett, 1994). f. '+' means the observed time is from censored subjects.

Snapshot date: 10SEP2020, data cutoff date: 29MAY2020.

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_may2020_dco_1943\v01\outputs\tlfs\pgms\t-sae-km-socpt-subgrp.sas Output: t02-08-06-sae-km-socpt-sub-5-race-safs.rtf (14DEC20:17:16) Data: adsl, adae, adttesaf

Seagen Protocol ONT-380-206**Table 2.8.7 Summary of Treatment-Emergent Serious Adverse Events by System Organ Class, Preferred Term and Hormone Receptor Status - Time-to-Event Analysis
Safety Analysis Set**

| System Organ Class/ Preferred Term | Parameters | Negative for Both | | Positive for ER or PR or Both | |
|--|--|------------------------|----------------------------|-------------------------------|----------------------------|
| | | Tuc+Cap+Tra (N=163) | Pbo+Cap+Tra (N=74) | Tuc+Cap+Tra (N=241) | Pbo+Cap+Tra (N=123) |
| Serious Respiratory, Thoracic And Mediastinal Disorders (SOC) | Number of Subjects With at Least One Event, n (%) | 12 (7.4) | 6 (8.1) | 6 (2.5) | 9 (7.3) |
| | Number of Censored Subjects, n (%) | 151 (92.6) | 68 (91.9) | 235 (97.5) | 114 (92.7) |
| | Stratified Hazard Ratio ^{a, b} (95% C.I.) | | 0.738 (0.266, 2.048) | | 0.322 (0.114, 0.909) |
| | P-value ^{b, c} | | 0.55954 | | 0.03229 |
| | Interaction Test P-value ^d | | | 0.26207 | |

Page 1 of 2

a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (Presence or history of brain metastases: Yes/No, ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.

c. Two-sided p-value calculated from Cox proportional hazards model.

d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and hormone receptor status.

e. Calculated using the complementary log-log transformation method (Collett, 1994). f. '+' means the observed time is from censored subjects.

Snapshot date: 10SEP2020, data cutoff date: 29MAY2020.

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_may2020_dco_1943\v01\outputs\tlfs\pgms\t-sae-km-socpt-subgrp.sas Output:

t02-08-07-sae-km-socpt-sub-6-hr-safs.rtf (14DEC20:17:16) Data: adsl, adae, adttesaf

Seagen Protocol ONT-380-206**Table 2.8.7 Summary of Treatment-Emergent Serious Adverse Events by System Organ Class, Preferred Term and Hormone Receptor Status - Time-to-Event Analysis
Safety Analysis Set**

| System Organ Class/ Preferred Term | Parameters | Negative for Both | | Positive for ER or PR or Both | |
|---------------------------------------|---|------------------------|-----------------------|-------------------------------|------------------------|
| | | Tuc+Cap+Tra (N=163) | Pbo+Cap+Tra (N=74) | Tuc+Cap+Tra (N=241) | Pbo+Cap+Tra (N=123) |
| | Median Time to Onset of the First Event (Days) (95% C.I.) ^e | - (-, -) | - (-, -) | - (-, -) | - (-, -) |
| | 25 th , 75 th Percentile | -, - | -, - | -, - | -, - |
| | Observed Min, Max ^f | 4+, 1327+ | 14, 580+ | 1, 1131+ | 8, 839+ |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (Presence or history of brain metastases: Yes/No, ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.

c. Two-sided p-value calculated from Cox proportional hazards model .

d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and hormone receptor status.

e. Calculated using the complementary log-log transformation method (Collett, 1994). f. '+' means the observed time is from censored subjects.

Snapshot date: 10SEP2020, data cutoff date: 29MAY2020.

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_may2020_dco_1943\v01\outputs\tlfs\pgms\t-sae-km-socpt-subgrp.sas Output:

t02-08-07-sae-km-socpt-sub-6-hr-safs.rtf (14DEC20:17:16) Data: adsl, adae, adttesaf

Seattle Genetics Protocol ONT-380-206**Table 2.10.2 Summary of Treatment-Emergent Severe (\geq Grade 3) Adverse Events by System Organ Class, Preferred Term and History of Brain Metastases at Baseline - Time-to-Event Analysis
Safety Analysis Set**

| System Organ Class/ Preferred Term | Parameters | With Brain Metastases | | Without Brain Metastases | |
|---------------------------------------|---|------------------------|----------------------------|--------------------------|-----------------------------|
| | | Tuc+Cap+Tra (N=194) | Pbo+Cap+Tra (N=91) | Tuc+Cap+Tra (N=209) | Pbo+Cap+Tra (N=105) |
| Severe Investigations (SOC) | Number of Subjects With at Least One Event, n (%) | 22 (11.3) | 5 (5.5) | 24 (11.5) | 3 (2.9) |
| | Number of Censored Subjects, n (%) | 172 (88.7) | 86 (94.5) | 185 (88.5) | 102 (97.1) |
| | Stratified Hazard Ratio ^{a, b} (95% C.I.) | | 1.836 (0.689, 4.895) | | 3.950 (1.187, 13.139) |
| | P-value ^{b, c} | | 0.22450 | | 0.02509 |
| | Interaction Test P-value ^d | | | 0.29966 | |
| | Median Time to Onset of the First Event (Days) (95% C.I.) ^e | - (-, -) | - (-, -) | - (-, -) | - (-, -) |
| | 25 th , 75 th Percentile | -, - | -, - | -, - | -, - |
| Observed Min, Max ^f | 4+, 1070+ | 26+, 580+ | 13, 945+ | 6, 762+ | |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.

c. Two-sided p-value calculated from Cox proportional hazards model.

d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and history of brain metastases at baseline.

e. Calculated using the complementary log-log transformation method (Collett, 1994). f. '+' means the observed time is from censored subjects.

Data Snapshot: 14OCT2019, Data Cutoff Date: 04SEP2019

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_1753\v01\outputs\tlfs\pgms\t-ae-km-socpt-subgrp.sas Output: t-g3ae-km-socpt-sub-1-bm-safs.rtf (17JUL20:17:19) Data: adsl, adae, adttesaf

Seattle Genetics Protocol ONT-380-206**Table 2.10.2 Summary of Treatment-Emergent Severe (\geq Grade 3) Adverse Events by System Organ Class, Preferred Term and History of Brain Metastases at Baseline - Time-to-Event Analysis
Safety Analysis Set**

| System Organ Class/ Preferred Term | Parameters | With Brain Metastases | | Without Brain Metastases | |
|--|---|------------------------|-----------------------------|--------------------------|--------------------------------|
| | | Tuc+Cap+Tra (N=194) | Pbo+Cap+Tra (N=91) | Tuc+Cap+Tra (N=209) | Pbo+Cap+Tra (N=105) |
| Severe Alanine Aminotransferase Increased (PT) | Number of Subjects With at Least One Event, n (%) | 11 (5.7) | 1 (1.1) | 11 (5.3) | 0 |
| | Number of Censored Subjects, n (%) | 183 (94.3) | 90 (98.9) | 198 (94.7) | 105 (100) |
| | Stratified Hazard Ratio ^{a, b} (95% C.I.) | | 4.788 (0.615, 37.302) | | 17427206.9 13 (0.000, -) |
| | P-value ^{b, c} | | 0.13488 | | 0.99252 |
| | Interaction Test P-value ^d | | | 0.99256 | |
| | Median Time to Onset of the First Event (Days) (95% C.I.) ^e | - (-, -) | - (-, -) | - (-, -) | - (-, -) |
| | 25 th , 75 th Percentile | -, - | -, - | -, - | -, - |
| Observed Min, Max ^f | 4+, 1070+ | 26+, 580+ | 22, 945+ | 29+, 762+ | |

Page 2 of 5

a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.

c. Two-sided p-value calculated from Cox proportional hazards model.

d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and history of brain metastases at baseline.

e. Calculated using the complementary log-log transformation method (Collett, 1994). f. '+' means the observed time is from censored subjects.

Data Snapshot: 14OCT2019, Data Cutoff Date: 04SEP2019

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_1753\v01\outputs\tlfs\pgms\t-ae-km-socpt-subgrp.sas Output: t-g3ae-km-socpt-sub-1-bm-safs.rtf (17JUL20:17:19) Data: adsl, adae, adttesaf

Seattle Genetics Protocol ONT-380-206**Table 2.10.2 Summary of Treatment-Emergent Severe (\geq Grade 3) Adverse Events by System Organ Class, Preferred Term and History of Brain Metastases at Baseline - Time-to-Event Analysis
Safety Analysis Set**

| System Organ Class/ Preferred Term | Parameters | With Brain Metastases | | Without Brain Metastases | |
|--|---|------------------------|--------------------------------|--------------------------|-----------------------------|
| | | Tuc+Cap+Tra (N=194) | Pbo+Cap+Tra (N=91) | Tuc+Cap+Tra (N=209) | Pbo+Cap+Tra (N=105) |
| Severe Aspartate Aminotransferase Increased (PT) | Number of Subjects With at Least One Event, n (%) | 7 (3.6) | 0 | 11 (5.3) | 1 (1.0) |
| | Number of Censored Subjects, n (%) | 187 (96.4) | 91 (100) | 198 (94.7) | 104 (99.0) |
| | Stratified Hazard Ratio ^{a, b} (95% C.I.) | | 16315771.7 64 (0.000, -) | | 5.785 (0.746, 44.846) |
| | P-value ^{b, c} | | 0.99424 | | 0.09299 |
| | Interaction Test P-value ^d | | | 0.99114 | |
| | Median Time to Onset of the First Event (Days) (95% C.I.) ^e | - (-, -) | - (-, -) | - (-, -) | - (-, -) |
| | 25 th , 75 th Percentile | -, - | -, - | -, - | -, - |
| Observed Min, Max ^f | 4+, 1070+ | 26+, 583+ | 14, 945+ | 14, 762+ | |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.

c. Two-sided p-value calculated from Cox proportional hazards model.

d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and history of brain metastases at baseline.

e. Calculated using the complementary log-log transformation method (Collett, 1994). f. '+' means the observed time is from censored subjects.

Data Snapshot: 14OCT2019, Data Cutoff Date: 04SEP2019

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_1753\v01\outputs\tlfs\pgms\t-ae-km-socpt-subgrp.sas Output: t-g3ae-km-socpt-sub-1-bm-safs.rtf (17JUL20:17:19) Data: adsl, adae, adttesaf

Seattle Genetics Protocol ONT-380-206**Table 2.10.2 Summary of Treatment-Emergent Severe (≥ Grade 3) Adverse Events by System Organ Class, Preferred Term and History of Brain Metastases at Baseline - Time-to-Event Analysis
Safety Analysis Set**

| System Organ Class/ Preferred Term | Parameters | With Brain Metastases | | Without Brain Metastases | |
|---|---|------------------------|----------------------------|--------------------------|----------------------------|
| | | Tuc+Cap+Tra (N=194) | Pbo+Cap+Tra (N=91) | Tuc+Cap+Tra (N=209) | Pbo+Cap+Tra (N=105) |
| Severe Musculoskeletal And Connective Tissue Disorders (SOC) | Number of Subjects With at Least One Event, n (%) | 7 (3.6) | 5 (5.5) | 9 (4.3) | 8 (7.6) |
| | Number of Censored Subjects, n (%) | 187 (96.4) | 86 (94.5) | 200 (95.7) | 97 (92.4) |
| | Stratified Hazard Ratio ^{a, b} (95% C.I.) | | 0.303 (0.084, 1.088) | | 0.369 (0.132, 1.031) |
| | P-value ^{b, c} | | 0.06725 | | 0.05722 |
| | Interaction Test P-value ^d | | | 0.83068 | |
| | Median Time to Onset of the First Event (Days) (95% C.I.) ^e | - (626.0, -) | - (-, -) | 932.0 (932.0, -) | - (-, -) |
| | 25 th , 75 th Percentile | -, - | -, - | 932.0, - | -, - |
| Observed Min, Max ^f | 4+, 1070+ | 7, 583+ | 15, 1059+ | 29+, 762+ | |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.

c. Two-sided p-value calculated from Cox proportional hazards model.

d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and history of brain metastases at baseline.

e. Calculated using the complementary log-log transformation method (Collett, 1994). f. '+' means the observed time is from censored subjects.

Data Snapshot: 14OCT2019, Data Cutoff Date: 04SEP2019

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_1753\v01\outputs\tlfs\pgms\t-ae-km-socpt-subgrp.sas Output: t-g3ae-km-socpt-sub-1-bm-safs.rtf (17JUL20:17:19) Data: adsl, adae, adttesaf

Seattle Genetics Protocol ONT-380-206**Table 2.10.2 Summary of Treatment-Emergent Severe (\geq Grade 3) Adverse Events by System Organ Class, Preferred Term and History of Brain Metastases at Baseline - Time-to-Event Analysis
Safety Analysis Set**

| System Organ Class/ Preferred Term | Parameters | With Brain Metastases | | Without Brain Metastases | |
|---------------------------------------|---|------------------------|----------------------------|--------------------------|----------------------------|
| | | Tuc+Cap+Tra (N=194) | Pbo+Cap+Tra (N=91) | Tuc+Cap+Tra (N=209) | Pbo+Cap+Tra (N=105) |
| Severe Dyspnoea (PT) | Number of Subjects With at Least One Event, n (%) | 4 (2.1) | 3 (3.3) | 3 (1.4) | 7 (6.7) |
| | Number of Censored Subjects, n (%) | 190 (97.9) | 88 (96.7) | 206 (98.6) | 98 (93.3) |
| | Stratified Hazard Ratio ^{a, b} (95% C.I.) | | 0.598 (0.133, 2.697) | | 0.196 (0.051, 0.759) |
| | P-value ^{b, c} | | 0.50343 | | 0.01832 |
| | Interaction Test P-value ^d | | | 0.28966 | |
| | Median Time to Onset of the First Event (Days) (95% C.I.) ^e | - (-, -) | - (-, -) | - (-, -) | - (-, -) |
| | 25 th , 75 th Percentile | -, - | -, - | -, - | -, - |
| Observed Min, Max ^f | 4+, 1070+ | 21, 583+ | 18, 1059+ | 27, 762+ | |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.

c. Two-sided p-value calculated from Cox proportional hazards model.

d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and history of brain metastases at baseline.

e. Calculated using the complementary log-log transformation method (Collett, 1994). f. '+' means the observed time is from censored subjects.

Data Snapshot: 14OCT2019, Data Cutoff Date: 04SEP2019

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_1753\v01\outputs\tlfs\pgms\t-ae-km-socpt-subgrp.sas Output: t-g3ae-km-socpt-sub-1-bm-safs.rtf (17JUL20:17:19) Data: adsl, adae, adttesaf

Seattle Genetics Protocol ONT-380-206**Table 2.10.3 Summary of Treatment-Emergent Severe (≥ Grade 3) Adverse Events by System Organ Class, Preferred Term and Geographic Region - Time-to-Event Analysis
Safety Analysis Set**

| System Organ Class/ Preferred Term | Parameters | North America | | Rest of World | |
|---------------------------------------|---|------------------------|----------------------------|------------------------|-----------------------------|
| | | Tuc+Cap+Tra (N=241) | Pbo+Cap+Tra (N=119) | Tuc+Cap+Tra (N=163) | Pbo+Cap+Tra (N=78) |
| Severe Investigations (SOC) | Number of Subjects With at Least One Event, n (%) | 24 (10.0) | 6 (5.0) | 22 (13.5) | 2 (2.6) |
| | Number of Censored Subjects, n (%) | 217 (90.0) | 113 (95.0) | 141 (86.5) | 76 (97.4) |
| | Stratified Hazard Ratio ^{a, b} (95% C.I.) | | 1.887 (0.767, 4.640) | | 4.889 (1.146, 20.851) |
| | P-value ^{b, c} | | 0.16689 | | 0.03201 |
| | Interaction Test P-value ^d | | | 0.23183 | |
| | Median Time to Onset of the First Event (Days) (95% C.I.) ^e | - (-, -) | - (-, -) | - (-, -) | - (-, -) |
| | 25 th , 75 th Percentile | -, - | -, - | -, - | -, - |
| Observed Min, Max ^f | 4+, 1070+ | 26+, 762+ | 6+, 720+ | 6, 588+ | |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (Presence or history of brain metastases: Yes/No and ECOG performance status: 0/1) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.

c. Two-sided p-value calculated from Cox proportional hazards model.

d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and geographic region.

e. Calculated using the complementary log-log transformation method (Collett, 1994). f. '+' means the observed time is from censored subjects.

Data Snapshot: 14OCT2019, Data Cutoff Date: 04SEP2019

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_1753\v01\outputs\tlfs\pgms\t-ae-km-socpt-subgrp.sas Output: t-g3ae-km-socpt-sub-2-reg-safs.rtf (17JUL20:17:19) Data: adsl, adae, adttesaf

Seattle Genetics Protocol ONT-380-206**Table 2.10.3 Summary of Treatment-Emergent Severe (≥ Grade 3) Adverse Events by System Organ Class, Preferred Term and Geographic Region - Time-to-Event Analysis
Safety Analysis Set**

| System Organ Class/ Preferred Term | Parameters | North America | | Rest of World | |
|--|--|------------------------|-----------------------------|------------------------|--------------------------------|
| | | Tuc+Cap+Tra (N=241) | Pbo+Cap+Tra (N=119) | Tuc+Cap+Tra (N=163) | Pbo+Cap+Tra (N=78) |
| Severe Alanine Aminotransferase Increased (PT) | Number of Subjects With at Least One Event, n (%) | 11 (4.6) | 1 (0.8) | 11 (6.7) | 0 |
| | Number of Censored Subjects, n (%) | 230 (95.4) | 118 (99.2) | 152 (93.3) | 78 (100) |
| | Stratified Hazard Ratio ^{a, b} (95% C.I.) | | 5.527 (0.713, 42.847) | | 16691716.1 54 (0.000, -) |
| | P-value ^{b, c} | | 0.10181 | | 0.99281 |
| | Interaction Test P-value ^d | | | 0.99025 | |
| | Median Time to Onset of the First Event (Days) (95% C.I.) ^e | - (-, -) | - (-, -) | - (-, -) | - (-, -) |
| | 25 th , 75 th Percentile Observed Min, Max ^f | - , - 4+, 1070+ | - , - 26+, 762+ | - , - 6+, 720+ | - , - 34+, 588+ |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (Presence or history of brain metastases: Yes/No and ECOG performance status: 0/1) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.

c. Two-sided p-value calculated from Cox proportional hazards model.

d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and geographic region.

e. Calculated using the complementary log-log transformation method (Collett, 1994). f. '+' means the observed time is from censored subjects.

Data Snapshot: 14OCT2019, Data Cutoff Date: 04SEP2019

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_1753\v01\outputs\tlfs\pgms\t-ae-km-socpt-subgrp.sas Output: t-g3ae-km-socpt-sub-2-reg-safs.rtf (17JUL20:17:19) Data: adsl, adae, adttesaf

Seattle Genetics Protocol ONT-380-206**Table 2.10.3 Summary of Treatment-Emergent Severe (≥ Grade 3) Adverse Events by System Organ Class, Preferred Term and Geographic Region - Time-to-Event Analysis
Safety Analysis Set**

| System Organ Class/ Preferred Term | Parameters | North America | | Rest of World | |
|--|---|------------------------|--------------------------------|------------------------|-----------------------------|
| | | Tuc+Cap+Tra (N=241) | Pbo+Cap+Tra (N=119) | Tuc+Cap+Tra (N=163) | Pbo+Cap+Tra (N=78) |
| Severe Aspartate Aminotransferase Increased (PT) | Number of Subjects With at Least One Event, n (%) | 11 (4.6) | 0 | 7 (4.3) | 1 (1.3) |
| | Number of Censored Subjects, n (%) | 230 (95.4) | 119 (100) | 156 (95.7) | 77 (98.7) |
| | Stratified Hazard Ratio ^{a, b} (95% C.I.) | | 17127828.4 72 (0.000, -) | | 3.331 (0.408, 27.189) |
| | P-value ^{b, c} | | 0.99257 | | 0.26127 |
| | Interaction Test P-value ^d | | | 0.99288 | |
| | Median Time to Onset of the First Event (Days) (95% C.I.) ^e | - (-, -) | - (-, -) | - (-, -) | - (-, -) |
| | 25 th , 75 th Percentile | -, - | -, - | -, - | -, - |
| Observed Min, Max ^f | 4+, 1070+ | 26+, 762+ | 6+, 720+ | 14, 588+ | |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (Presence or history of brain metastases: Yes/No and ECOG performance status: 0/1) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.

c. Two-sided p-value calculated from Cox proportional hazards model.

d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and geographic region.

e. Calculated using the complementary log-log transformation method (Collett, 1994). f. '+' means the observed time is from censored subjects.

Data Snapshot: 14OCT2019, Data Cutoff Date: 04SEP2019

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_1753\v01\outputs\tlfs\pgms\t-ae-km-socpt-subgrp.sas Output: t-g3ae-km-socpt-sub-2-reg-safs.rtf (17JUL20:17:19) Data: adsl, adae, adttesaf

Seattle Genetics Protocol ONT-380-206**Table 2.10.3 Summary of Treatment-Emergent Severe (≥ Grade 3) Adverse Events by System Organ Class, Preferred Term and Geographic Region - Time-to-Event Analysis
Safety Analysis Set**

| System Organ Class/ Preferred Term | Parameters | North America | | Rest of World | |
|---|---|------------------------|----------------------------|------------------------|----------------------------|
| | | Tuc+Cap+Tra (N=241) | Pbo+Cap+Tra (N=119) | Tuc+Cap+Tra (N=163) | Pbo+Cap+Tra (N=78) |
| Severe Musculoskeletal And Connective Tissue Disorders (SOC) | Number of Subjects With at Least One Event, n (%) | 10 (4.1) | 6 (5.0) | 6 (3.7) | 7 (9.0) |
| | Number of Censored Subjects, n (%) | 231 (95.9) | 113 (95.0) | 157 (96.3) | 71 (91.0) |
| | Stratified Hazard Ratio ^{a, b} (95% C.I.) | | 0.309 (0.091, 1.047) | | 0.334 (0.110, 1.012) |
| | P-value ^{b, c} | | 0.05934 | | 0.05251 |
| | Interaction Test P-value ^d | | | 0.84748 | |
| | Median Time to Onset of the First Event (Days) (95% C.I.) ^e | - (932.0, -) | - (-, -) | - (-, -) | - (-, -) |
| | 25 th , 75 th Percentile | 932.0, - | -, - | -, - | -, - |
| Observed Min, Max ^f | 4+, 1070+ | 20, 762+ | 6+, 720+ | 7, 588+ | |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (Presence or history of brain metastases: Yes/No and ECOG performance status: 0/1) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.

c. Two-sided p-value calculated from Cox proportional hazards model.

d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and geographic region.

e. Calculated using the complementary log-log transformation method (Collett, 1994). f. '+' means the observed time is from censored subjects.

Data Snapshot: 14OCT2019, Data Cutoff Date: 04SEP2019

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_1753\v01\outputs\tlfs\pgms\t-ae-km-socpt-subgrp.sas Output: t-g3ae-km-socpt-sub-2-reg-safs.rtf (17JUL20:17:19) Data: adsl, adae, adttesaf

Seattle Genetics Protocol ONT-380-206**Table 2.10.3 Summary of Treatment-Emergent Severe (≥ Grade 3) Adverse Events by System Organ Class, Preferred Term and Geographic Region - Time-to-Event Analysis
Safety Analysis Set**

| System Organ Class/ Preferred Term | Parameters | North America | | Rest of World | |
|---------------------------------------|---|------------------------|----------------------------|------------------------|-----------------------------|
| | | Tuc+Cap+Tra (N=241) | Pbo+Cap+Tra (N=119) | Tuc+Cap+Tra (N=163) | Pbo+Cap+Tra (N=78) |
| Severe Dyspnoea (PT) | Number of Subjects With at Least One Event, n (%) | 3 (1.2) | 9 (7.6) | 4 (2.5) | 1 (1.3) |
| | Number of Censored Subjects, n (%) | 238 (98.8) | 110 (92.4) | 159 (97.5) | 77 (98.7) |
| | Stratified Hazard Ratio ^{a, b} (95% C.I.) | | 0.153 (0.041, 0.567) | | 1.708 (0.190, 15.339) |
| | P-value ^{b, c} | | 0.00499 | | 0.63268 |
| | Interaction Test P-value ^d | | | 0.06120 | |
| | Median Time to Onset of the First Event (Days) (95% C.I.) ^e | - (-, -) | - (-, -) | - (-, -) | - (-, -) |
| | 25 th , 75 th Percentile | -, - | -, - | -, - | -, - |
| Observed Min, Max ^f | 4+, 1070+ | 21, 762+ | 6+, 720+ | 34+, 588+ | |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (Presence or history of brain metastases: Yes/No and ECOG performance status: 0/1) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.

c. Two-sided p-value calculated from Cox proportional hazards model.

d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and geographic region.

e. Calculated using the complementary log-log transformation method (Collett, 1994). f. '+' means the observed time is from censored subjects.

Data Snapshot: 14OCT2019, Data Cutoff Date: 04SEP2019

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_1753\v01\outputs\tlfs\pgms\t-ae-km-socpt-subgrp.sas Output: t-g3ae-km-socpt-sub-2-reg-safs.rtf (17JUL20:17:19) Data: adsl, adae, adttesaf

Seattle Genetics Protocol ONT-380-206**Table 2.10.4 Summary of Treatment-Emergent Severe (\geq Grade 3) Adverse Events by System Organ Class, Preferred Term and Baseline ECOG Score - Time-to-Event Analysis
Safety Analysis Set**

| System Organ Class/ Preferred Term | Parameters | ECOG=0 | | ECOG=1 | |
|---------------------------------------|---|------------------------|-----------------------------|------------------------|----------------------------|
| | | Tuc+Cap+Tra (N=203) | Pbo+Cap+Tra (N=91) | Tuc+Cap+Tra (N=201) | Pbo+Cap+Tra (N=106) |
| Severe Investigations (SOC) | Number of Subjects With at Least One Event, n (%) | 23 (11.3) | 3 (3.3) | 23 (11.4) | 5 (4.7) |
| | Number of Censored Subjects, n (%) | 180 (88.7) | 88 (96.7) | 178 (88.6) | 101 (95.3) |
| | Stratified Hazard Ratio ^{a, b} (95% C.I.) | | 3.215 (0.960, 10.767) | | 2.368 (0.898, 6.242) |
| | P-value ^{b, c} | | 0.05823 | | 0.08135 |
| | Interaction Test P-value ^d | | | 0.57502 | |
| | Median Time to Onset of the First Event (Days) (95% C.I.) ^e | - (-, -) | - (-, -) | - (-, -) | - (-, -) |
| | 25 th , 75 th Percentile | -, - | -, - | -, - | -, - |
| Observed Min, Max ^f | 4+, 944+ | 50+, 588+ | 6+, 1070+ | 6, 762+ | |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (Presence or history of brain metastases: Yes/No and Region of world: North America /Rest of World) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.

c. Two-sided p-value calculated from Cox proportional hazards model.

d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and baseline ECOG score.

e. Calculated using the complementary log-log transformation method (Collett, 1994). f. '+' means the observed time is from censored subjects.

Data Snapshot: 14OCT2019, Data Cutoff Date: 04SEP2019

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_1753\v01\outputs\tlfs\pgms\t-ae-km-socpt-subgrp.sas Output: t-g3ae-km-socpt-sub-3-ecog-safs.rtf (17JUL20:17:19) Data: adsl, adae, adttesaf

Seattle Genetics Protocol ONT-380-206**Table 2.10.4 Summary of Treatment-Emergent Severe (\geq Grade 3) Adverse Events by System Organ Class, Preferred Term and Baseline ECOG Score - Time-to-Event Analysis
Safety Analysis Set**

| System Organ Class/ Preferred Term | Parameters | ECOG=0 | | ECOG=1 | |
|--|--|------------------------|-----------------------------|------------------------|--------------------------------|
| | | Tuc+Cap+Tra (N=203) | Pbo+Cap+Tra (N=91) | Tuc+Cap+Tra (N=201) | Pbo+Cap+Tra (N=106) |
| Severe Alanine Aminotransferase Increased (PT) | Number of Subjects With at Least One Event, n (%) | 14 (6.9) | 1 (1.1) | 8 (4.0) | 0 |
| | Number of Censored Subjects, n (%) | 189 (93.1) | 90 (98.9) | 193 (96.0) | 106 (100) |
| | Stratified Hazard Ratio ^{a, b} (95% C.I.) | | 6.157 (0.807, 46.949) | | 18434709.2 20 (0.000, -) |
| | P-value ^{b, c} | | 0.07952 | | 0.99348 |
| | Interaction Test P-value ^d | | | 0.98984 | |
| | Median Time to Onset of the First Event (Days) (95% C.I.) ^e | - (-, -) | - (-, -) | - (-, -) | - (-, -) |
| | 25 th , 75 th Percentile Observed Min, Max ^f | - , - 4+, 988+ | - , - 50+, 588+ | - , - 6+, 1070+ | - , - 26+, 762+ |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (Presence or history of brain metastases: Yes/No and Region of world: North America /Rest of World) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.

c. Two-sided p-value calculated from Cox proportional hazards model.

d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and baseline ECOG score.

e. Calculated using the complementary log-log transformation method (Collett, 1994). f. '+' means the observed time is from censored subjects.

Data Snapshot: 14OCT2019, Data Cutoff Date: 04SEP2019

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_1753\v01\outputs\tlfs\pgms\t-ae-km-socpt-subgrp.sas Output: t-g3ae-km-socpt-sub-3-ecog-safs.rtf (17JUL20:17:19) Data: adsl, adae, adttesaf

Seattle Genetics Protocol ONT-380-206**Table 2.10.4 Summary of Treatment-Emergent Severe (\geq Grade 3) Adverse Events by System Organ Class, Preferred Term and Baseline ECOG Score - Time-to-Event Analysis
Safety Analysis Set**

| System Organ Class/ Preferred Term | Parameters | ECOG=0 | | ECOG=1 | |
|--|--|------------------------|--------------------------------|------------------------|-----------------------------|
| | | Tuc+Cap+Tra (N=203) | Pbo+Cap+Tra (N=91) | Tuc+Cap+Tra (N=201) | Pbo+Cap+Tra (N=106) |
| Severe Aspartate Aminotransferase Increased (PT) | Number of Subjects With at Least One Event, n (%) | 10 (4.9) | 0 | 8 (4.0) | 1 (0.9) |
| | Number of Censored Subjects, n (%) | 193 (95.1) | 91 (100) | 193 (96.0) | 105 (99.1) |
| | Stratified Hazard Ratio ^{a, b} (95% C.I.) | | 16462649.1 05 (0.000, -) | | 4.077 (0.508, 32.735) |
| | P-value ^{b, c} | | 0.99304 | | 0.18613 |
| | Interaction Test P-value ^d | | | 0.99014 | |
| | Median Time to Onset of the First Event (Days) (95% C.I.) ^e | - (-, -) | - (-, -) | - (-, -) | - (-, -) |
| | 25 th , 75 th Percentile Observed Min, Max ^f | - , - 4+, 988+ | - , - 50+, 588+ | - , - 6+, 1070+ | - , - 14, 762+ |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (Presence or history of brain metastases: Yes/No and Region of world: North America /Rest of World) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.

c. Two-sided p-value calculated from Cox proportional hazards model.

d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and baseline ECOG score.

e. Calculated using the complementary log-log transformation method (Collett, 1994). f. '+' means the observed time is from censored subjects.

Data Snapshot: 14OCT2019, Data Cutoff Date: 04SEP2019

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_1753\v01\outputs\tlfs\pgms\t-ae-km-socpt-subgrp.sas Output: t-g3ae-km-socpt-sub-3-ecog-safs.rtf (17JUL20:17:19) Data: adsl, adae, adttesaf

Seattle Genetics Protocol ONT-380-206**Table 2.10.4 Summary of Treatment-Emergent Severe (≥ Grade 3) Adverse Events by System Organ Class, Preferred Term and Baseline ECOG Score - Time-to-Event Analysis
Safety Analysis Set**

| System Organ Class/ Preferred Term | Parameters | ECOG=0 | | ECOG=1 | |
|---|---|------------------------|----------------------------|------------------------|----------------------------|
| | | Tuc+Cap+Tra (N=203) | Pbo+Cap+Tra (N=91) | Tuc+Cap+Tra (N=201) | Pbo+Cap+Tra (N=106) |
| Severe Musculoskeletal And Connective Tissue Disorders (SOC) | Number of Subjects With at Least One Event, n (%) | 7 (3.4) | 3 (3.3) | 9 (4.5) | 10 (9.4) |
| | Number of Censored Subjects, n (%) | 196 (96.6) | 88 (96.7) | 192 (95.5) | 96 (90.6) |
| | Stratified Hazard Ratio ^{a, b} (95% C.I.) | | 0.756 (0.187, 3.057) | | 0.310 (0.117, 0.823) |
| | P-value ^{b, c} | | 0.69520 | | 0.01869 |
| | Interaction Test P-value ^d | | | 0.29003 | |
| | Median Time to Onset of the First Event (Days) (95% C.I.) ^e | - (707.0, -) | - (-, -) | 932.0 (932.0, -) | - (-, -) |
| | 25 th , 75 th Percentile | -, - | -, - | 932.0, - | -, - |
| Observed Min, Max ^f | 4+, 1059+ | 50+, 588+ | 6+, 1070+ | 7, 762+ | |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (Presence or history of brain metastases: Yes/No and Region of world: North America /Rest of World) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.

c. Two-sided p-value calculated from Cox proportional hazards model.

d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and baseline ECOG score.

e. Calculated using the complementary log-log transformation method (Collett, 1994). f. '+' means the observed time is from censored subjects.

Data Snapshot: 14OCT2019, Data Cutoff Date: 04SEP2019

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_1753\v01\outputs\tlfs\pgms\t-ae-km-socpt-subgrp.sas Output: t-g3ae-km-socpt-sub-3-ecog-safs.rtf (17JUL20:17:19) Data: adsl, adae, adttesaf

Seattle Genetics Protocol ONT-380-206**Table 2.10.4 Summary of Treatment-Emergent Severe (\geq Grade 3) Adverse Events by System Organ Class, Preferred Term and Baseline ECOG Score - Time-to-Event Analysis
Safety Analysis Set**

| System Organ Class/ Preferred Term | Parameters | ECOG=0 | | ECOG=1 | |
|---------------------------------------|---|------------------------|----------------------------|------------------------|----------------------------|
| | | Tuc+Cap+Tra (N=203) | Pbo+Cap+Tra (N=91) | Tuc+Cap+Tra (N=201) | Pbo+Cap+Tra (N=106) |
| Severe Dyspnoea (PT) | Number of Subjects With at Least One Event, n (%) | 1 (0.5) | 3 (3.3) | 6 (3.0) | 7 (6.6) |
| | Number of Censored Subjects, n (%) | 202 (99.5) | 88 (96.7) | 195 (97.0) | 99 (93.4) |
| | Stratified Hazard Ratio ^{a, b} (95% C.I.) | | 0.125 (0.013, 1.206) | | 0.436 (0.146, 1.299) |
| | P-value ^{b, c} | | 0.07216 | | 0.13613 |
| | Interaction Test P-value ^d | | | 0.42791 | |
| | Median Time to Onset of the First Event (Days) (95% C.I.) ^e | - (-, -) | - (-, -) | - (-, -) | - (-, -) |
| | 25 th , 75 th Percentile | -, - | -, - | -, - | -, - |
| Observed Min, Max ^f | 4+, 1059+ | 43, 588+ | 6+, 1070+ | 21, 762+ | |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (Presence or history of brain metastases: Yes/No and Region of world: North America /Rest of World) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.

c. Two-sided p-value calculated from Cox proportional hazards model.

d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and baseline ECOG score.

e. Calculated using the complementary log-log transformation method (Collett, 1994). f. '+' means the observed time is from censored subjects.

Data Snapshot: 14OCT2019, Data Cutoff Date: 04SEP2019

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_1753\v01\outputs\tlfs\pgms\t-ae-km-socpt-subgrp.sas Output: t-g3ae-km-socpt-sub-3-ecog-safs.rtf (17JUL20:17:19) Data: adsl, adae, adttesaf

Seattle Genetics Protocol ONT-380-206**Table 2.10.5 Summary of Treatment-Emergent Severe (≥ Grade 3) Adverse Events by System Organ Class, Preferred Term and Age - Time-to-Event Analysis
Safety Analysis Set**

| System Organ Class/ Preferred Term | Parameters | Age < 65 Years | | Age ≥ 65 Years | |
|---------------------------------------|---|------------------------|----------------------------|-----------------------|----------------------------|
| | | Tuc+Cap+Tra (N=322) | Pbo+Cap+Tra (N=164) | Tuc+Cap+Tra (N=82) | Pbo+Cap+Tra (N=33) |
| Severe Investigations (SOC) | Number of Subjects With at Least One Event, n (%) | 37 (11.5) | 6 (3.7) | 9 (11.0) | 2 (6.1) |
| | Number of Censored Subjects, n (%) | 285 (88.5) | 158 (96.3) | 73 (89.0) | 31 (93.9) |
| | Stratified Hazard Ratio ^{a, b} (95% C.I.) | | 2.932 (1.232, 6.976) | | 1.466 (0.313, 6.866) |
| | P-value ^{b, c} | | 0.01503 | | 0.62751 |
| | Interaction Test P-value ^d | | | 0.53554 | |
| | Median Time to Onset of the First Event (Days) (95% C.I.) ^e | - (-, -) | - (-, -) | - (-, -) | - (-, -) |
| | 25 th , 75 th Percentile | -, - | -, - | -, - | -, - |
| Observed Min, Max ^f | 6+, 1070+ | 6, 762+ | 4+, 945+ | 14, 409+ | |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (Presence or history of brain metastases: Yes/No, ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.

c. Two-sided p-value calculated from Cox proportional hazards model.

d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and age.

e. Calculated using the complementary log-log transformation method (Collett, 1994). f. '+' means the observed time is from censored subjects.

Data Snapshot: 14OCT2019, Data Cutoff Date: 04SEP2019

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_1753\v01\outputs\tlfs\pgms\t-ae-km-socpt-subgrp.sas Output: t-g3ae-km-socpt-sub-4-age-safs.rtf (17JUL20:17:19) Data: adsl, adae, adttesaf

Seattle Genetics Protocol ONT-380-206**Table 2.10.5 Summary of Treatment-Emergent Severe (\geq Grade 3) Adverse Events by System Organ Class, Preferred Term and Age - Time-to-Event Analysis Safety Analysis Set**

| System Organ Class/ Preferred Term | Parameters | Age < 65 Years | | Age \geq 65 Years | |
|--|---|------------------------|-----------------------------|-----------------------|--------------------------------|
| | | Tuc+Cap+Tra (N=322) | Pbo+Cap+Tra (N=164) | Tuc+Cap+Tra (N=82) | Pbo+Cap+Tra (N=33) |
| Severe Alanine Aminotransferase Increased (PT) | Number of Subjects With at Least One Event, n (%) | 17 (5.3) | 1 (0.6) | 5 (6.1) | 0 |
| | Number of Censored Subjects, n (%) | 305 (94.7) | 163 (99.4) | 77 (93.9) | 33 (100) |
| | Stratified Hazard Ratio ^{a, b} (95% C.I.) | | 8.478 (1.125, 63.857) | | 14287422.5 30 (0.000, -) |
| | P-value ^{b, c} | | 0.03802 | | 0.99565 |
| | Interaction Test P-value ^d | | | 0.99163 | |
| | Median Time to Onset of the First Event (Days) (95% C.I.) ^e | - (-, -) | - (-, -) | - (-, -) | - (-, -) |
| | 25 th , 75 th Percentile | -, - | -, - | -, - | -, - |
| Observed Min, Max ^f | 6+, 1070+ | 26+, 762+ | 4+, 945+ | 31+, 409+ | |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (Presence or history of brain metastases: Yes/No, ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.

c. Two-sided p-value calculated from Cox proportional hazards model.

d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and age.

e. Calculated using the complementary log-log transformation method (Collett, 1994). f. '+' means the observed time is from censored subjects.

Data Snapshot: 14OCT2019, Data Cutoff Date: 04SEP2019

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_1753\v01\outputs\tlfs\pgms\t-ae-km-socpt-subgrp.sas Output: t-g3ae-km-socpt-sub-4-age-safs.rtf (17JUL20:17:19) Data: adsl, adae, adttesaf

Seattle Genetics Protocol ONT-380-206**Table 2.10.5 Summary of Treatment-Emergent Severe (\geq Grade 3) Adverse Events by System Organ Class, Preferred Term and Age - Time-to-Event Analysis Safety Analysis Set**

| System Organ Class/ Preferred Term | Parameters | Age < 65 Years | | Age \geq 65 Years | |
|--|--|------------------------|--------------------------------|-----------------------|-----------------------------|
| | | Tuc+Cap+Tra (N=322) | Pbo+Cap+Tra (N=164) | Tuc+Cap+Tra (N=82) | Pbo+Cap+Tra (N=33) |
| Severe Aspartate Aminotransferase Increased (PT) | Number of Subjects With at Least One Event, n (%) | 14 (4.3) | 0 | 4 (4.9) | 1 (3.0) |
| | Number of Censored Subjects, n (%) | 308 (95.7) | 164 (100) | 78 (95.1) | 32 (97.0) |
| | Stratified Hazard Ratio ^{a, b} (95% C.I.) | | 17178232.1 27 (0.000, -) | | 1.586 (0.175, 14.382) |
| | P-value ^{b, c} | | 0.99166 | | 0.68172 |
| | Interaction Test P-value ^d | | | 0.99120 | |
| | Median Time to Onset of the First Event (Days) (95% C.I.) ^e | - (-, -) | - (-, -) | - (-, -) | - (-, -) |
| | 25 th , 75 th Percentile Observed Min, Max ^f | - , - 6+, 1070+ | - , - 26+, 762+ | - , - 4+, 945+ | - , - 14, 409+ |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (Presence or history of brain metastases: Yes/No, ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.

c. Two-sided p-value calculated from Cox proportional hazards model.

d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and age.

e. Calculated using the complementary log-log transformation method (Collett, 1994). f. '+' means the observed time is from censored subjects.

Data Snapshot: 14OCT2019, Data Cutoff Date: 04SEP2019

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_1753\v01\outputs\tlfs\pgms\t-ae-km-socpt-subgrp.sas Output: t-g3ae-km-socpt-sub-4-age-safs.rtf (17JUL20:17:19) Data: adsl, adae, adttesaf

Seattle Genetics Protocol ONT-380-206**Table 2.10.5 Summary of Treatment-Emergent Severe (≥ Grade 3) Adverse Events by System Organ Class, Preferred Term and Age - Time-to-Event Analysis
Safety Analysis Set**

| System Organ Class/ Preferred Term | Parameters | Age < 65 Years | | Age ≥ 65 Years | |
|---|---|------------------------|----------------------------|-----------------------|----------------------------|
| | | Tuc+Cap+Tra (N=322) | Pbo+Cap+Tra (N=164) | Tuc+Cap+Tra (N=82) | Pbo+Cap+Tra (N=33) |
| Severe Musculoskeletal And Connective Tissue Disorders (SOC) | Number of Subjects With at Least One Event, n (%) | 12 (3.7) | 8 (4.9) | 4 (4.9) | 5 (15.2) |
| | Number of Censored Subjects, n (%) | 310 (96.3) | 156 (95.1) | 78 (95.1) | 28 (84.8) |
| | Stratified Hazard Ratio ^{a, b} (95% C.I.) | | 0.447 (0.168, 1.186) | | 0.107 (0.012, 0.930) |
| | P-value ^{b, c} | | 0.10565 | | 0.04279 |
| | Interaction Test P-value ^d | | | 0.28942 | |
| | Median Time to Onset of the First Event (Days) (95% C.I.) ^e | - (-, -) | - (-, -) | 932.0 (-, -) | - (215.0, -) |
| | 25 th , 75 th Percentile | -, - | -, - | 932.0, 932.0 | 215.0, - |
| Observed Min, Max ^f | 6+, 1070+ | 7, 762+ | 4+, 932 | 31+, 409+ | |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (Presence or history of brain metastases: Yes/No, ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.

c. Two-sided p-value calculated from Cox proportional hazards model.

d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and age.

e. Calculated using the complementary log-log transformation method (Collett, 1994). f. '+' means the observed time is from censored subjects.

Data Snapshot: 14OCT2019, Data Cutoff Date: 04SEP2019

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_1753\v01\outputs\tlfs\pgms\t-ae-km-socpt-subgrp.sas Output: t-g3ae-km-socpt-sub-4-age-safs.rtf (17JUL20:17:19) Data: adsl, adae, adttesaf

Seattle Genetics Protocol ONT-380-206**Table 2.10.5 Summary of Treatment-Emergent Severe (≥ Grade 3) Adverse Events by System Organ Class, Preferred Term and Age - Time-to-Event Analysis
Safety Analysis Set**

| System Organ Class/ Preferred Term | Parameters | Age < 65 Years | | Age ≥ 65 Years | |
|---------------------------------------|---|------------------------|----------------------------|-----------------------|----------------------------|
| | | Tuc+Cap+Tra (N=322) | Pbo+Cap+Tra (N=164) | Tuc+Cap+Tra (N=82) | Pbo+Cap+Tra (N=33) |
| Severe Dyspnoea (PT) | Number of Subjects With at Least One Event, n (%) | 6 (1.9) | 8 (4.9) | 1 (1.2) | 2 (6.1) |
| | Number of Censored Subjects, n (%) | 316 (98.1) | 156 (95.1) | 81 (98.8) | 31 (93.9) |
| | Stratified Hazard Ratio ^{a, b} (95% C.I.) | | 0.382 (0.132, 1.105) | | 0.141 (0.012, 1.674) |
| | P-value ^{b, c} | | 0.07569 | | 0.12077 |
| | Interaction Test P-value ^d | | | 0.53804 | |
| | Median Time to Onset of the First Event (Days) (95% C.I.) ^e | - (-, -) | - (-, -) | - (-, -) | - (318.0, -) |
| | 25 th , 75 th Percentile | -, - | -, - | -, - | -, - |
| Observed Min, Max ^f | 6+, 1070+ | 21, 762+ | 4+, 945+ | 31+, 409+ | |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (Presence or history of brain metastases: Yes/No, ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.

c. Two-sided p-value calculated from Cox proportional hazards model.

d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and age.

e. Calculated using the complementary log-log transformation method (Collett, 1994). f. '+' means the observed time is from censored subjects.

Data Snapshot: 14OCT2019, Data Cutoff Date: 04SEP2019

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_1753\v01\outputs\tlfs\pgms\t-ae-km-socpt-subgrp.sas Output: t-g3ae-km-socpt-sub-4-age-safs.rtf (17JUL20:17:19) Data: adsl, adae, adttesaf

Seattle Genetics Protocol ONT-380-206**Table 2.10.6 Summary of Treatment-Emergent Severe (≥ Grade 3) Adverse Events by System Organ Class, Preferred Term and Race - Time-to-Event Analysis
Safety Analysis Set**

| System Organ Class/ Preferred Term | Parameters | White | | Non-White | |
|---------------------------------------|---|------------------------|----------------------------|------------------------|-----------------------------|
| | | Tuc+Cap+Tra (N=283) | Pbo+Cap+Tra (N=153) | Tuc+Cap+Tra (N=121) | Pbo+Cap+Tra (N=44) |
| Severe Investigations (SOC) | Number of Subjects With at Least One Event, n (%) | 37 (13.1) | 7 (4.6) | 9 (7.4) | 1 (2.3) |
| | Number of Censored Subjects, n (%) | 246 (86.9) | 146 (95.4) | 112 (92.6) | 43 (97.7) |
| | Stratified Hazard Ratio ^{a, b} (95% C.I.) | | 2.762 (1.228, 6.215) | | 2.601 (0.322, 21.014) |
| | P-value ^{b, c} | | 0.01404 | | 0.36990 |
| | Interaction Test P-value ^d | | | 0.95797 | |
| | Median Time to Onset of the First Event (Days) (95% C.I.) ^e | - (-, -) | - (-, -) | - (567.0, -) | - (-, -) |
| | 25 th , 75 th Percentile | -, - | -, - | -, - | -, - |
| Observed Min, Max ^f | 6+, 945+ | 6, 762+ | 4+, 1070+ | 40+, 580+ | |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (Presence or history of brain metastases: Yes/No, ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.

c. Two-sided p-value calculated from Cox proportional hazards model.

d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and race.

e. Calculated using the complementary log-log transformation method (Collett, 1994). f. '+' means the observed time is from censored subjects.

Data Snapshot: 14OCT2019, Data Cutoff Date: 04SEP2019

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_1753\v01\outputs\tlfs\pgms\t-ae-km-socpt-subgrp.sas Output: t-g3ae-km-socpt-sub-5-race-safs.rtf (17JUL20:17:19) Data: adsl, adae, adttesaf

Seattle Genetics Protocol ONT-380-206

Table 2.10.6 Summary of Treatment-Emergent Severe (≥ Grade 3) Adverse Events by System Organ Class, Preferred Term and Race - Time-to-Event Analysis Safety Analysis Set

| System Organ Class/ Preferred Term | Parameters | White | | Non-White | |
|--|--|------------------------|--------------------------------|------------------------|----------------------------|
| | | Tuc+Cap+Tra (N=283) | Pbo+Cap+Tra (N=153) | Tuc+Cap+Tra (N=121) | Pbo+Cap+Tra (N=44) |
| Severe Alanine Aminotransferase Increased (PT) | Number of Subjects With at Least One Event, n (%) | 21 (7.4) | 0 | 1 (0.8) | 1 (2.3) |
| | Number of Censored Subjects, n (%) | 262 (92.6) | 153 (100) | 120 (99.2) | 43 (97.7) |
| | Stratified Hazard Ratio ^{a, b} (95% C.I.) | | 18651894.9 12 (0.000, -) | | 0.343 (0.020, 5.761) |
| | P-value ^{b, c} | | 0.98964 | | 0.45725 |
| | Interaction Test P-value ^d | | | 0.99059 | |
| | Median Time to Onset of the First Event (Days) (95% C.I.) ^e | - (-, -) | - (-, -) | - (-, -) | - (-, -) |
| | 25 th , 75 th Percentile Observed Min, Max ^f | - , - 6+, 945+ | - , - 26+, 762+ | - , - 4+, 1070+ | - , - 40+, 580+ |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.
 b. Computed using stratification factors (Presence or history of brain metastases: Yes/No, ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.
 c. Two-sided p-value calculated from Cox proportional hazards model .
 d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and race.
 e. Calculated using the complementary log-log transformation method (Collett, 1994). f. '+' means the observed time is from censored subjects.
 Data Snapshot: 14OCT2019, Data Cutoff Date: 04SEP2019
 Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_1753\v01\outputs\tlfs\pgms\t-ae-km-socpt-subgrp.sas Output: t-g3ae-km-socpt-sub-5-race-safs.rtf
 (17JUL20:17:19) Data: adsl, adae, adttesaf

Seattle Genetics Protocol ONT-380-206**Table 2.10.6 Summary of Treatment-Emergent Severe (≥ Grade 3) Adverse Events by System Organ Class, Preferred Term and Race - Time-to-Event Analysis
Safety Analysis Set**

| System Organ Class/ Preferred Term | Parameters | White | | Non-White | |
|--|--|------------------------|-----------------------------|------------------------|--------------------------------|
| | | Tuc+Cap+Tra (N=283) | Pbo+Cap+Tra (N=153) | Tuc+Cap+Tra (N=121) | Pbo+Cap+Tra (N=44) |
| Severe Aspartate Aminotransferase Increased (PT) | Number of Subjects With at Least One Event, n (%) | 16 (5.7) | 1 (0.7) | 2 (1.7) | 0 |
| | Number of Censored Subjects, n (%) | 267 (94.3) | 152 (99.3) | 119 (98.3) | 44 (100) |
| | Stratified Hazard Ratio ^{a, b} (95% C.I.) | | 8.723 (1.156, 65.825) | | 13672121.5 11 (0.000, -) |
| | P-value ^{b, c} | | 0.03568 | | 0.99727 |
| | Interaction Test P-value ^d | | | 0.99468 | |
| | Median Time to Onset of the First Event (Days) (95% C.I.) ^e | - (-, -) | - (-, -) | - (-, -) | - (-, -) |
| | 25 th , 75 th Percentile Observed Min, Max ^f | - , - 6+, 945+ | - , - 14, 762+ | - , - 4+, 1070+ | - , - 40+, 583+ |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (Presence or history of brain metastases: Yes/No, ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.

c. Two-sided p-value calculated from Cox proportional hazards model.

d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and race.

e. Calculated using the complementary log-log transformation method (Collett, 1994). f. '+' means the observed time is from censored subjects.

Data Snapshot: 14OCT2019, Data Cutoff Date: 04SEP2019

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_1753\v01\outputs\tlfs\pgms\t-ae-km-socpt-subgrp.sas Output: t-g3ae-km-socpt-sub-5-race-safs.rtf (17JUL20:17:19) Data: adsl, adae, adttesaf

Seattle Genetics Protocol ONT-380-206

**Table 2.10.6 Summary of Treatment-Emergent Severe (≥ Grade 3) Adverse Events by System Organ Class, Preferred Term and Race - Time-to-Event Analysis
Safety Analysis Set**

| System Organ Class/ Preferred Term | Parameters | White | | Non-White | |
|---|---|------------------------|----------------------------|------------------------|----------------------------|
| | | Tuc+Cap+Tra (N=283) | Pbo+Cap+Tra (N=153) | Tuc+Cap+Tra (N=121) | Pbo+Cap+Tra (N=44) |
| Severe Musculoskeletal And Connective Tissue Disorders (SOC) | Number of Subjects With at Least One Event, n (%) | 14 (4.9) | 11 (7.2) | 2 (1.7) | 2 (4.5) |
| | Number of Censored Subjects, n (%) | 269 (95.1) | 142 (92.8) | 119 (98.3) | 42 (95.5) |
| | Stratified Hazard Ratio ^{a, b} (95% C.I.) | | 0.328 (0.132, 0.815) | | 0.309 (0.043, 2.221) |
| | P-value ^{b, c} | | 0.01633 | | 0.24303 |
| | Interaction Test P-value ^d | | | 0.58759 | |
| | Median Time to Onset of the First Event (Days) (95% C.I.) ^e | 932.0 (932.0, -) | - (-, -) | - (-, -) | - (-, -) |
| | 25 th , 75 th Percentile | 932.0, - | -, - | -, - | -, - |
| Observed Min, Max ^f | 6+, 1059+ | 7, 762+ | 4+, 1070+ | 40+, 583+ | |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.
 b. Computed using stratification factors (Presence or history of brain metastases: Yes/No, ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.
 c. Two-sided p-value calculated from Cox proportional hazards model .
 d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and race.
 e. Calculated using the complementary log-log transformation method (Collett, 1994). f. '+' means the observed time is from censored subjects.
 Data Snapshot: 14OCT2019, Data Cutoff Date: 04SEP2019
 Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_1753\v01\outputs\tlfs\pgms\t-ae-km-socpt-subgrp.sas Output: t-g3ae-km-socpt-sub-5-race-safs.rtf
 (17JUL20:17:19) Data: adsl, adae, adttesaf

Seattle Genetics Protocol ONT-380-206**Table 2.10.6 Summary of Treatment-Emergent Severe (≥ Grade 3) Adverse Events by System Organ Class, Preferred Term and Race - Time-to-Event Analysis
Safety Analysis Set**

| System Organ Class/ Preferred Term | Parameters | White | | Non-White | |
|---------------------------------------|---|------------------------|----------------------------|------------------------|----------------------------|
| | | Tuc+Cap+Tra (N=283) | Pbo+Cap+Tra (N=153) | Tuc+Cap+Tra (N=121) | Pbo+Cap+Tra (N=44) |
| Severe Dyspnoea (PT) | Number of Subjects With at Least One Event, n (%) | 6 (2.1) | 9 (5.9) | 1 (0.8) | 1 (2.3) |
| | Number of Censored Subjects, n (%) | 277 (97.9) | 144 (94.1) | 120 (99.2) | 43 (97.7) |
| | Stratified Hazard Ratio ^{a, b} (95% C.I.) | | 0.345 (0.123, 0.971) | | 0.279 (0.017, 4.464) |
| | P-value ^{b, c} | | 0.04382 | | 0.36694 |
| | Interaction Test P-value ^d | | | 0.92832 | |
| | Median Time to Onset of the First Event (Days) (95% C.I.) ^e | - (-, -) | - (-, -) | - (-, -) | - (-, -) |
| | 25 th , 75 th Percentile | -, - | -, - | -, - | -, - |
| Observed Min, Max ^f | 6+, 1059+ | 21, 762+ | 4+, 1070+ | 40+, 583+ | |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (Presence or history of brain metastases: Yes/No, ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.

c. Two-sided p-value calculated from Cox proportional hazards model.

d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and race.

e. Calculated using the complementary log-log transformation method (Collett, 1994). f. '+' means the observed time is from censored subjects.

Data Snapshot: 14OCT2019, Data Cutoff Date: 04SEP2019

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_1753\v01\outputs\tlfs\pgms\t-ae-km-socpt-subgrp.sas Output: t-g3ae-km-socpt-sub-5-race-safs.rtf (17JUL20:17:19) Data: adsl, adae, adttesaf

Seattle Genetics Protocol ONT-380-206**Table 2.10.7 Summary of Treatment-Emergent Severe (\geq Grade 3) Adverse Events by System Organ Class, Preferred Term and Hormone Receptor Status - Time-to-Event Analysis
Safety Analysis Set**

| System Organ Class/ Preferred Term | Parameters | Negative for Both | | Positive for ER or PR or Both | |
|---------------------------------------|---|------------------------|----------------------------|-------------------------------|----------------------------|
| | | Tuc+Cap+Tra (N=163) | Pbo+Cap+Tra (N=74) | Tuc+Cap+Tra (N=241) | Pbo+Cap+Tra (N=123) |
| Severe Investigations (SOC) | Number of Subjects With at Least One Event, n (%) | 25 (15.3) | 4 (5.4) | 21 (8.7) | 4 (3.3) |
| | Number of Censored Subjects, n (%) | 138 (84.7) | 70 (94.6) | 220 (91.3) | 119 (96.7) |
| | Stratified Hazard Ratio ^{a, b} (95% C.I.) | | 2.072 (0.708, 6.061) | | 2.689 (0.921, 7.853) |
| | P-value ^{b, c} | | 0.18343 | | 0.07042 |
| | Interaction Test P-value ^d | | | 0.82206 | |
| | Median Time to Onset of the First Event (Days) (95% C.I.) ^e | - (-, -) | - (-, -) | - (-, -) | - (-, -) |
| | 25 th , 75 th Percentile | -, - | -, - | -, - | -, - |
| Observed Min, Max ^f | 4+, 1070+ | 14, 580+ | 6+, 891+ | 6, 762+ | |

Page 1 of 4

a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (Presence or history of brain metastases: Yes/No, ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.

c. Two-sided p-value calculated from Cox proportional hazards model.

d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and hormone receptor status.

e. Calculated using the complementary log-log transformation method (Collett, 1994). f. '+' means the observed time is from censored subjects.

Data Snapshot: 14OCT2019, Data Cutoff Date: 04SEP2019

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_1753\v01\outputs\tlfs\pgms\t-ae-km-socpt-subgrp.sas Output: t-g3ae-km-socpt-sub-6-hr-safs.rtf (17JUL20:17:19)

Data: adsl, adae, addtesaf

Seattle Genetics Protocol ONT-380-206

**Table 2.10.7 Summary of Treatment-Emergent Severe (≥ Grade 3) Adverse Events by System Organ Class, Preferred Term and Hormone Receptor Status - Time-to-Event Analysis
Safety Analysis Set**

| System Organ Class/ Preferred Term | Parameters | Negative for Both | | Positive for ER or PR or Both | |
|--|--|------------------------|--------------------------------|-------------------------------|-----------------------------|
| | | Tuc+Cap+Tra (N=163) | Pbo+Cap+Tra (N=74) | Tuc+Cap+Tra (N=241) | Pbo+Cap+Tra (N=123) |
| Severe Alanine Aminotransferase Increased (PT) | Number of Subjects With at Least One Event, n (%) | 12 (7.4) | 0 | 10 (4.1) | 1 (0.8) |
| | Number of Censored Subjects, n (%) | 151 (92.6) | 74 (100) | 231 (95.9) | 122 (99.2) |
| | Stratified Hazard Ratio ^{a, b} (95% C.I.) | | 15104009.9 86 (0.000, -) | | 5.357 (0.684, 41.968) |
| | P-value ^{b, c} | | 0.99308 | | 0.11005 |
| | Interaction Test P-value ^d | | | 0.99118 | |
| | Median Time to Onset of the First Event (Days) (95% C.I.) ^e | - (-, -) | - (-, -) | - (-, -) | - (-, -) |
| | 25 th , 75 th Percentile Observed Min, Max ^f | - , - 4+, 1070+ | - , - 29+, 580+ | - , - 6+, 891+ | - , - 26+, 762+ |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.
 b. Computed using stratification factors (Presence or history of brain metastases: Yes/No, ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.
 c. Two-sided p-value calculated from Cox proportional hazards model .
 d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and hormone receptor status.
 e. Calculated using the complementary log-log transformation method (Collett, 1994). f. '+' means the observed time is from censored subjects.
 Data Snapshot: 14OCT2019, Data Cutoff Date: 04SEP2019
 Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_1753\v01\outputs\tlfs\pgms\t-ae-km-socpt-subgrp.sas Output: t-g3ae-km-socpt-sub-6-hr-safs.rtf (17JUL20:17:19)
 Data: adsl, adae, adttesaf

Seattle Genetics Protocol ONT-380-206**Table 2.10.7 Summary of Treatment-Emergent Severe (\geq Grade 3) Adverse Events by System Organ Class, Preferred Term and Hormone Receptor Status - Time-to-Event Analysis
Safety Analysis Set**

| System Organ Class/ Preferred Term | Parameters | Negative for Both | | Positive for ER or PR or Both | |
|--|--|------------------------|-----------------------------|-------------------------------|--------------------------------|
| | | Tuc+Cap+Tra (N=163) | Pbo+Cap+Tra (N=74) | Tuc+Cap+Tra (N=241) | Pbo+Cap+Tra (N=123) |
| Severe Aspartate Aminotransferase Increased (PT) | Number of Subjects With at Least One Event, n (%) | 11 (6.7) | 1 (1.4) | 7 (2.9) | 0 |
| | Number of Censored Subjects, n (%) | 152 (93.3) | 73 (98.6) | 234 (97.1) | 123 (100) |
| | Stratified Hazard Ratio ^{a, b} (95% C.I.) | | 4.628 (0.590, 36.301) | | 18004960.5 71 (0.000, -) |
| | P-value ^{b, c} | | 0.14481 | | 0.99394 |
| | Interaction Test P-value ^d | | | 0.99343 | |
| | Median Time to Onset of the First Event (Days) (95% C.I.) ^e | - (-, -) | - (-, -) | - (-, -) | - (-, -) |
| | 25 th , 75 th Percentile Observed Min, Max ^f | - , - 4+, 1070+ | - , - 14, 580+ | - , - 6+, 891+ | - , - 26+, 762+ |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (Presence or history of brain metastases: Yes/No, ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.

c. Two-sided p-value calculated from Cox proportional hazards model.

d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and hormone receptor status.

e. Calculated using the complementary log-log transformation method (Collett, 1994). f. '+' means the observed time is from censored subjects.

Data Snapshot: 14OCT2019, Data Cutoff Date: 04SEP2019

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_1753\v01\outputs\tlfs\pgms\t-ae-km-socpt-subgrp.sas Output: t-g3ae-km-socpt-sub-6-hr-safs.rtf (17JUL20:17:19)

Data: adsl, adae, adttesaf

Seattle Genetics Protocol ONT-380-206**Table 2.10.7 Summary of Treatment-Emergent Severe (≥ Grade 3) Adverse Events by System Organ Class, Preferred Term and Hormone Receptor Status - Time-to-Event Analysis
Safety Analysis Set**

| System Organ Class/ Preferred Term | Parameters | Negative for Both | | Positive for ER or PR or Both | |
|---|---|------------------------|----------------------------|-------------------------------|----------------------------|
| | | Tuc+Cap+Tra (N=163) | Pbo+Cap+Tra (N=74) | Tuc+Cap+Tra (N=241) | Pbo+Cap+Tra (N=123) |
| Severe Musculoskeletal And Connective Tissue Disorders (SOC) | Number of Subjects With at Least One Event, n (%) | 9 (5.5) | 5 (6.8) | 7 (2.9) | 8 (6.5) |
| | Number of Censored Subjects, n (%) | 154 (94.5) | 69 (93.2) | 234 (97.1) | 115 (93.5) |
| | Stratified Hazard Ratio ^{a, b} (95% C.I.) | | 0.277 (0.070, 1.102) | | 0.264 (0.085, 0.815) |
| | P-value ^{b, c} | | 0.06840 | | 0.02059 |
| | Interaction Test P-value ^d | | | 0.84705 | |
| | Median Time to Onset of the First Event (Days) (95% C.I.) ^e | - (932.0, -) | - (-, -) | - (707.0, -) | - (-, -) |
| | 25 th , 75 th Percentile | 932.0, - | -, - | -, - | -, - |
| Observed Min, Max ^f | 4+, 1070+ | 29+, 580+ | 6+, 891+ | 7, 762+ | |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (Presence or history of brain metastases: Yes/No, ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.

c. Two-sided p-value calculated from Cox proportional hazards model.

d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and hormone receptor status.

e. Calculated using the complementary log-log transformation method (Collett, 1994). f. '+' means the observed time is from censored subjects.

Data Snapshot: 14OCT2019, Data Cutoff Date: 04SEP2019

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_1753\v01\outputs\tlfs\pgms\t-ae-km-socpt-subgrp.sas Output: t-g3ae-km-socpt-sub-6-hr-safs.rtf (17JUL20:17:19)

Data: adsl, adae, adttesaf

Seagen Protocol ONT-380-206**Table 2.10.2 Summary of Treatment-Emergent Severe (\geq Grade 3) Adverse Events by System Organ Class, Preferred Term and History of Brain Metastases at Baseline - Time-to-Event Analysis
Safety Analysis Set**

| System Organ Class/ Preferred Term | Parameters | With Brain Metastases | | Without Brain Metastases | |
|---------------------------------------|---|------------------------|----------------------------|-----------------------------|------------------------|
| | | Tuc+Cap+Tra (N=194) | Pbo+Cap+Tra (N=91) | Tuc+Cap+Tra (N=209) | Pbo+Cap+Tra (N=105) |
| Severe Investigations (SOC) | Number of Subjects With at Least One Event, n (%) | 25 (12.9) | 5 (5.5) | 28 (13.4) | 3 (2.9) |
| | Number of Censored Subjects, n (%) | 169 (87.1) | 86 (94.5) | 181 (86.6) | 102 (97.1) |
| | Stratified Hazard Ratio ^{a, b} (95% C.I.) | | 2.015 (0.764, 5.312) | 4.368 (1.323, 14.422) | |
| | P-value ^{b, c} | | 0.15658 | 0.01557 | |
| | Interaction Test P-value ^d | | | 0.29371 | |
| | Median Time to Onset of the First Event (Days) (95% C.I.) ^e | - (-, -) | - (-, -) | - (-, -) | - (-, -) |
| | 25 th , 75 th Percentile | -, - | -, - | -, - | -, - |
| Observed Min, Max ^f | 4+, 1156+ | 26+, 599+ | 13, 1131+ | 6, 839+ | |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.

c. Two-sided p-value calculated from Cox proportional hazards model.

d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and history of brain metastases at baseline.

e. Calculated using the complementary log-log transformation method (Collett, 1994). f. '+' means the observed time is from censored subjects.

Snapshot date: 10SEP2020, data cutoff date: 29MAY2020.

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_may2020_dco_1943\v01\outputs\tlfs\pgms\t-g3ae-km-socpt-subgrp.sas Output:
t02-10-02-g3ae-km-socpt-sub-1-bm-safs.rtf (14DEC20:17:16) Data: adsl, adae, adttesaf

Seagen Protocol ONT-380-206**Table 2.10.2 Summary of Treatment-Emergent Severe (\geq Grade 3) Adverse Events by System Organ Class, Preferred Term and History of Brain Metastases at Baseline - Time-to-Event Analysis
Safety Analysis Set**

| System Organ Class/ Preferred Term | Parameters | With Brain Metastases | | Without Brain Metastases | |
|--|--|------------------------|-----------------------------|--------------------------|--------------------------------|
| | | Tuc+Cap+Tra (N=194) | Pbo+Cap+Tra (N=91) | Tuc+Cap+Tra (N=209) | Pbo+Cap+Tra (N=105) |
| Severe Alanine Aminotransferase Increased (PT) | Number of Subjects With at Least One Event, n (%) | 11 (5.7) | 1 (1.1) | 12 (5.7) | 0 |
| | Number of Censored Subjects, n (%) | 183 (94.3) | 90 (98.9) | 197 (94.3) | 105 (100) |
| | Stratified Hazard Ratio ^{a, b} (95% C.I.) | | 4.796 (0.616, 37.361) | | 17160737.2 09 (0.000, -) |
| | P-value ^{b, c} | | 0.13439 | | 0.99226 |
| | Interaction Test P-value ^d | | | 0.99234 | |
| | Median Time to Onset of the First Event (Days) (95% C.I.) ^e | - (-, -) | - (-, -) | - (-, -) | - (-, -) |
| | 25 th , 75 th Percentile Observed Min, Max ^f | - , - 4+, 1156+ | - , - 26+, 599+ | - , - 22, 1131+ | - , - 29+, 839+ |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.

c. Two-sided p-value calculated from Cox proportional hazards model.

d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and history of brain metastases at baseline.

e. Calculated using the complementary log-log transformation method (Collett, 1994). f. '+' means the observed time is from censored subjects.

Snapshot date: 10SEP2020, data cutoff date: 29MAY2020.

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_may2020_dco_1943\v01\outputs\tlfs\pgms\t-g3ae-km-socpt-subgrp.sas Output:
t02-10-02-g3ae-km-socpt-sub-1-bm-safs.rtf (14DEC20:17:16) Data: adsl, adae, adttesaf

Seagen Protocol ONT-380-206**Table 2.10.2 Summary of Treatment-Emergent Severe (\geq Grade 3) Adverse Events by System Organ Class, Preferred Term and History of Brain Metastases at Baseline - Time-to-Event Analysis
Safety Analysis Set**

| System Organ Class/ Preferred Term | Parameters | With Brain Metastases | | Without Brain Metastases | |
|--|--|------------------------|--------------------------------|--------------------------|-----------------------------|
| | | Tuc+Cap+Tra (N=194) | Pbo+Cap+Tra (N=91) | Tuc+Cap+Tra (N=209) | Pbo+Cap+Tra (N=105) |
| Severe Aspartate Aminotransferase Increased (PT) | Number of Subjects With at Least One Event, n (%) | 7 (3.6) | 0 | 12 (5.7) | 1 (1.0) |
| | Number of Censored Subjects, n (%) | 187 (96.4) | 91 (100) | 197 (94.3) | 104 (99.0) |
| | Stratified Hazard Ratio ^{a, b} (95% C.I.) | | 16315771.7 65 (0.000, -) | | 6.128 (0.796, 47.203) |
| | P-value ^{b, c} | | 0.99424 | | 0.08177 |
| | Interaction Test P-value ^d | | | 0.99124 | |
| | Median Time to Onset of the First Event (Days) (95% C.I.) ^e | - (-, -) | - (-, -) | - (-, -) | - (-, -) |
| | 25 th , 75 th Percentile Observed Min, Max ^f | - , - 4+, 1156+ | - , - 26+, 599+ | - , - 14, 1131+ | - , - 14, 839+ |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.

c. Two-sided p-value calculated from Cox proportional hazards model.

d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and history of brain metastases at baseline.

e. Calculated using the complementary log-log transformation method (Collett, 1994). f. '+' means the observed time is from censored subjects.

Snapshot date: 10SEP2020, data cutoff date: 29MAY2020.

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_may2020_dco_1943\v01\outputs\tlfs\pgms\t-g3ae-km-socpt-subgrp.sas Output:
t02-10-02-g3ae-km-socpt-sub-1-bm-safs.rtf (14DEC20:17:16) Data: adsl, adae, adttesaf

Seagen Protocol ONT-380-206**Table 2.10.2 Summary of Treatment-Emergent Severe (\geq Grade 3) Adverse Events by System Organ Class, Preferred Term and History of Brain Metastases at Baseline - Time-to-Event Analysis
Safety Analysis Set**

| System Organ Class/ Preferred Term | Parameters | With Brian Metastases | | Without Brain Metastases | |
|---|---|------------------------|----------------------------|--------------------------|----------------------------|
| | | Tuc+Cap+Tra (N=194) | Pbo+Cap+Tra (N=91) | Tuc+Cap+Tra (N=209) | Pbo+Cap+Tra (N=105) |
| Severe Musculoskeletal And Connective Tissue Disorders (SOC) | Number of Subjects With at Least One Event, n (%) | 8 (4.1) | 5 (5.5) | 10 (4.8) | 8 (7.6) |
| | Number of Censored Subjects, n (%) | 186 (95.9) | 86 (94.5) | 199 (95.2) | 97 (92.4) |
| | Stratified Hazard Ratio ^{a, b} (95% C.I.) | | 0.345 (0.104, 1.137) | | 0.396 (0.146, 1.074) |
| | P-value ^{b, c} | | 0.08023 | | 0.06888 |
| | Interaction Test P-value ^d | | | 0.86702 | |
| | Median Time to Onset of the First Event (Days) (95% C.I.) ^e | - (-, -) | - (-, -) | - (932.0, -) | - (-, -) |
| | 25 th , 75 th Percentile | -, - | -, - | -, - | -, - |
| Observed Min, Max ^f | 4+, 1154+ | 7, 599+ | 15, 1327+ | 29+, 839+ | |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.

c. Two-sided p-value calculated from Cox proportional hazards model.

d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and history of brain metastases at baseline.

e. Calculated using the complementary log-log transformation method (Collett, 1994). f. '+' means the observed time is from censored subjects.

Snapshot date: 10SEP2020, data cutoff date: 29MAY2020.

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_may2020_dco_1943\v01\outputs\tlfs\pgms\t-g3ae-km-socpt-subgrp.sas Output:
t02-10-02-g3ae-km-socpt-sub-1-bm-safs.rtf (14DEC20:17:16) Data: adsl, adae, adttesaf

Seagen Protocol ONT-380-206**Table 2.10.2 Summary of Treatment-Emergent Severe (\geq Grade 3) Adverse Events by System Organ Class, Preferred Term and History of Brain Metastases at Baseline - Time-to-Event Analysis
Safety Analysis Set**

| System Organ Class/ Preferred Term | Parameters | With Brain Metastases | | Without Brain Metastases | |
|---------------------------------------|--|------------------------|----------------------------|--------------------------|----------------------------|
| | | Tuc+Cap+Tra (N=194) | Pbo+Cap+Tra (N=91) | Tuc+Cap+Tra (N=209) | Pbo+Cap+Tra (N=105) |
| Severe Dyspnoea (PT) | Number of Subjects With at Least One Event, n (%) | 4 (2.1) | 3 (3.3) | 3 (1.4) | 7 (6.7) |
| | Number of Censored Subjects, n (%) | 190 (97.9) | 88 (96.7) | 206 (98.6) | 98 (93.3) |
| | Stratified Hazard Ratio ^{a, b} (95% C.I.) | | 0.579 (0.128, 2.624) | | 0.192 (0.050, 0.744) |
| | P-value ^{b, c} | | 0.47875 | | 0.01694 |
| | Interaction Test P-value ^d | | | 0.28145 | |
| | Median Time to Onset of the First Event (Days) (95% C.I.) ^e | - (-, -) | - (-, -) | - (-, -) | - (-, -) |
| | 25 th , 75 th Percentile | -, - | -, - | -, - | -, - |
| Observed Min, Max ^f | 4+, 1156+ | 21, 599+ | 18, 1327+ | 27, 839+ | |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.

c. Two-sided p-value calculated from Cox proportional hazards model.

d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and history of brain metastases at baseline.

e. Calculated using the complementary log-log transformation method (Collett, 1994). f. '+' means the observed time is from censored subjects.

Snapshot date: 10SEP2020, data cutoff date: 29MAY2020.

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_may2020_dco_1943\v01\outputs\tlfs\pgms\t-g3ae-km-socpt-subgrp.sas Output: t02-10-02-g3ae-km-socpt-sub-1-bm-safs.rtf (14DEC20:17:16) Data: adsl, adae, adttesaf

Seagen Protocol ONT-380-206**Table 2.10.3 Summary of Treatment-Emergent Severe (≥ Grade 3) Adverse Events by System Organ Class, Preferred Term and Geographic Region - Time-to-Event Analysis
Safety Analysis Set**

| System Organ Class/ Preferred Term | Parameters | North America | | Rest of World | |
|---------------------------------------|---|------------------------|----------------------------|------------------------|-----------------------------|
| | | Tuc+Cap+Tra (N=241) | Pbo+Cap+Tra (N=119) | Tuc+Cap+Tra (N=163) | Pbo+Cap+Tra (N=78) |
| Severe Investigations (SOC) | Number of Subjects With at Least One Event, n (%) | 27 (11.2) | 6 (5.0) | 26 (16.0) | 2 (2.6) |
| | Number of Censored Subjects, n (%) | 214 (88.8) | 113 (95.0) | 137 (84.0) | 76 (97.4) |
| | Stratified Hazard Ratio ^{a, b} (95% C.I.) | | 2.084 (0.856, 5.072) | | 5.299 (1.251, 22.451) |
| | P-value ^{b, c} | | 0.10577 | | 0.02360 |
| | Interaction Test P-value ^d | | | 0.20378 | |
| | Median Time to Onset of the First Event (Days) (95% C.I.) ^e | - (-, -) | - (-, -) | - (-, -) | - (-, -) |
| | 25 th , 75 th Percentile | -, - | -, - | -, - | -, - |
| Observed Min, Max ^f | 4+, 1156+ | 26+, 762+ | 6+, 954+ | 6, 839+ | |

Page 1 of 5

a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (Presence or history of brain metastases: Yes/No and ECOG performance status: 0/1) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.

c. Two-sided p-value calculated from Cox proportional hazards model.

d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and geographic region.

e. Calculated using the complementary log-log transformation method (Collett, 1994). f. '+' means the observed time is from censored subjects.

Snapshot date: 10SEP2020, data cutoff date: 29MAY2020.

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_may2020_dco_1943\v01\outputs\tlfs\pgms\t-g3ae-km-socpt-subgrp.sas Output:
t02-10-03-g3ae-km-socpt-sub-2-reg-safs.rtf (14DEC20:17:16) Data: adsl, adae, adttesaf

Seagen Protocol ONT-380-206**Table 2.10.3 Summary of Treatment-Emergent Severe (≥ Grade 3) Adverse Events by System Organ Class, Preferred Term and Geographic Region - Time-to-Event Analysis
Safety Analysis Set**

| System Organ Class/ Preferred Term | Parameters | North America | | Rest of World | |
|--|--|------------------------|-----------------------------|------------------------|--------------------------------|
| | | Tuc+Cap+Tra (N=241) | Pbo+Cap+Tra (N=119) | Tuc+Cap+Tra (N=163) | Pbo+Cap+Tra (N=78) |
| Severe Alanine Aminotransferase Increased (PT) | Number of Subjects With at Least One Event, n (%) | 12 (5.0) | 1 (0.8) | 11 (6.7) | 0 |
| | Number of Censored Subjects, n (%) | 229 (95.0) | 118 (99.2) | 152 (93.3) | 78 (100) |
| | Stratified Hazard Ratio ^{a, b} (95% C.I.) | | 5.869 (0.762, 45.205) | | 16646808.6 26 (0.000, -) |
| | P-value ^{b, c} | | 0.08929 | | 0.99281 |
| | Interaction Test P-value ^d | | | 0.99017 | |
| | Median Time to Onset of the First Event (Days) (95% C.I.) ^e | - (-, -) | - (-, -) | - (-, -) | - (-, -) |
| | 25 th , 75 th Percentile Observed Min, Max ^f | - , - 4+, 1156+ | - , - 26+, 762+ | - , - 6+, 954+ | - , - 34+, 839+ |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (Presence or history of brain metastases: Yes/No and ECOG performance status: 0/1) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.

c. Two-sided p-value calculated from Cox proportional hazards model.

d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and geographic region.

e. Calculated using the complementary log-log transformation method (Collett, 1994). f. '+' means the observed time is from censored subjects.

Snapshot date: 10SEP2020, data cutoff date: 29MAY2020.

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_may2020_dco_1943\v01\outputs\tlfs\pgms\t-g3ae-km-socpt-subgrp.sas Output:
t02-10-03-g3ae-km-socpt-sub-2-reg-safs.rtf (14DEC20:17:16) Data: adsl, adae, adttesaf

Seagen Protocol ONT-380-206

**Table 2.10.3 Summary of Treatment-Emergent Severe (≥ Grade 3) Adverse Events by System Organ Class, Preferred Term and Geographic Region - Time-to-Event Analysis
Safety Analysis Set**

| System Organ Class/ Preferred Term | Parameters | North America | | Rest of World | |
|--|---|------------------------|--------------------------------|------------------------|-----------------------------|
| | | Tuc+Cap+Tra (N=241) | Pbo+Cap+Tra (N=119) | Tuc+Cap+Tra (N=163) | Pbo+Cap+Tra (N=78) |
| Severe Aspartate Aminotransferase Increased (PT) | Number of Subjects With at Least One Event, n (%) | 12 (5.0) | 0 | 7 (4.3) | 1 (1.3) |
| | Number of Censored Subjects, n (%) | 229 (95.0) | 119 (100) | 156 (95.7) | 77 (98.7) |
| | Stratified Hazard Ratio ^{a, b} (95% C.I.) | | 16913768.2 46 (0.000, -) | | 3.331 (0.408, 27.189) |
| | P-value ^{b, c} | | 0.99230 | | 0.26127 |
| | Interaction Test P-value ^d | | | 0.99274 | |
| | Median Time to Onset of the First Event (Days) (95% C.I.) ^e | - (-, -) | - (-, -) | - (-, -) | - (-, -) |
| | 25 th , 75 th Percentile | -, - | -, - | -, - | -, - |
| Observed Min, Max ^f | 4+, 1156+ | 26+, 762+ | 6+, 954+ | 14, 839+ | |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (Presence or history of brain metastases: Yes/No and ECOG performance status: 0/1) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.

c. Two-sided p-value calculated from Cox proportional hazards model.

d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and geographic region.

e. Calculated using the complementary log-log transformation method (Collett, 1994). f. '+' means the observed time is from censored subjects.

Snapshot date: 10SEP2020, data cutoff date: 29MAY2020.

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_may2020_dco_1943\v01\outputs\tlfs\pgms\t-g3ae-km-socpt-subgrp.sas Output: t02-10-03-g3ae-km-socpt-sub-2-reg-safs.rtf (14DEC20:17:16) Data: adsl, adae, adttesaf

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**Table 2.10.3 Summary of Treatment-Emergent Severe (≥ Grade 3) Adverse Events by System Organ Class, Preferred Term and Geographic Region - Time-to-Event Analysis
Safety Analysis Set**

| System Organ Class/ Preferred Term | Parameters | North America | | Rest of World | |
|---|---|------------------------|----------------------------|------------------------|----------------------------|
| | | Tuc+Cap+Tra (N=241) | Pbo+Cap+Tra (N=119) | Tuc+Cap+Tra (N=163) | Pbo+Cap+Tra (N=78) |
| Severe Musculoskeletal And Connective Tissue Disorders (SOC) | Number of Subjects With at Least One Event, n (%) | 11 (4.6) | 6 (5.0) | 7 (4.3) | 7 (9.0) |
| | Number of Censored Subjects, n (%) | 230 (95.4) | 113 (95.0) | 156 (95.7) | 71 (91.0) |
| | Stratified Hazard Ratio ^{a, b} (95% C.I.) | | 0.409 (0.137, 1.227) | | 0.339 (0.115, 0.999) |
| | P-value ^{b, c} | | 0.11089 | | 0.04981 |
| | Interaction Test P-value ^d | | | 0.60831 | |
| | Median Time to Onset of the First Event (Days) (95% C.I.) ^e | - (932.0, -) | - (-, -) | - (-, -) | - (-, -) |
| | 25 th , 75 th Percentile | 932.0, - | -, - | -, - | -, - |
| Observed Min, Max ^f | 4+, 1327+ | 20, 762+ | 6+, 954+ | 7, 839+ | |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (Presence or history of brain metastases: Yes/No and ECOG performance status: 0/1) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.

c. Two-sided p-value calculated from Cox proportional hazards model.

d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and geographic region.

e. Calculated using the complementary log-log transformation method (Collett, 1994). f. '+' means the observed time is from censored subjects.

Snapshot date: 10SEP2020, data cutoff date: 29MAY2020.

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_may2020_dco_1943\v01\outputs\tlfs\pgms\t-g3ae-km-socpt-subgrp.sas Output:
t02-10-03-g3ae-km-socpt-sub-2-reg-safs.rtf (14DEC20:17:16) Data: adsl, adae, adttesaf

Seagen Protocol ONT-380-206**Table 2.10.3 Summary of Treatment-Emergent Severe (≥ Grade 3) Adverse Events by System Organ Class, Preferred Term and Geographic Region - Time-to-Event Analysis
Safety Analysis Set**

| System Organ Class/ Preferred Term | Parameters | North America | | Rest of World | |
|---------------------------------------|---|------------------------|----------------------------|------------------------|-----------------------------|
| | | Tuc+Cap+Tra (N=241) | Pbo+Cap+Tra (N=119) | Tuc+Cap+Tra (N=163) | Pbo+Cap+Tra (N=78) |
| Severe Dyspnoea (PT) | Number of Subjects With at Least One Event, n (%) | 3 (1.2) | 9 (7.6) | 4 (2.5) | 1 (1.3) |
| | Number of Censored Subjects, n (%) | 238 (98.8) | 110 (92.4) | 159 (97.5) | 77 (98.7) |
| | Stratified Hazard Ratio ^{a, b} (95% C.I.) | | 0.148 (0.040, 0.549) | | 1.691 (0.188, 15.184) |
| | P-value ^{b, c} | | 0.00427 | | 0.63890 |
| | Interaction Test P-value ^d | | | 0.05995 | |
| | Median Time to Onset of the First Event (Days) (95% C.I.) ^e | - (-, -) | - (-, -) | - (-, -) | - (-, -) |
| | 25 th , 75 th Percentile | -, - | -, - | -, - | -, - |
| Observed Min, Max ^f | 4+, 1327+ | 21, 762+ | 6+, 954+ | 34+, 839+ | |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (Presence or history of brain metastases: Yes/No and ECOG performance status: 0/1) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.

c. Two-sided p-value calculated from Cox proportional hazards model.

d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and geographic region.

e. Calculated using the complementary log-log transformation method (Collett, 1994). f. '+' means the observed time is from censored subjects.

Snapshot date: 10SEP2020, data cutoff date: 29MAY2020.

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_may2020_dco_1943\v01\outputs\tlfs\pgms\t-g3ae-km-socpt-subgrp.sas Output:
t02-10-03-g3ae-km-socpt-sub-2-reg-safs.rtf (14DEC20:17:16) Data: adsl, adae, adttesaf

Seagen Protocol ONT-380-206**Table 2.10.4 Summary of Treatment-Emergent Severe (\geq Grade 3) Adverse Events by System Organ Class, Preferred Term and Baseline ECOG Score - Time-to-Event Analysis
Safety Analysis Set**

| System Organ Class/ Preferred Term | Parameters | ECOG=0 | | ECOG=1 | |
|---------------------------------------|---|------------------------|-----------------------------|------------------------|----------------------------|
| | | Tuc+Cap+Tra (N=203) | Pbo+Cap+Tra (N=91) | Tuc+Cap+Tra (N=201) | Pbo+Cap+Tra (N=106) |
| Severe Investigations (SOC) | Number of Subjects With at Least One Event, n (%) | 26 (12.8) | 3 (3.3) | 27 (13.4) | 5 (4.7) |
| | Number of Censored Subjects, n (%) | 177 (87.2) | 88 (96.7) | 174 (86.6) | 101 (95.3) |
| | Stratified Hazard Ratio ^{a, b} (95% C.I.) | | 3.445 (1.036, 11.462) | | 2.558 (0.979, 6.679) |
| | P-value ^{b, c} | | 0.04368 | | 0.05519 |
| | Interaction Test P-value ^d | | | 0.65409 | |
| | Median Time to Onset of the First Event (Days) (95% C.I.) ^e | - (-, -) | - (-, -) | - (-, -) | - (-, -) |
| | 25 th , 75 th Percentile | -, - | -, - | -, - | -, - |
| Observed Min, Max ^f | 4+, 1156+ | 50+, 839+ | 6+, 1154+ | 6, 762+ | |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (Presence or history of brain metastases: Yes/No and Region of world: North America /Rest of World) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.

c. Two-sided p-value calculated from Cox proportional hazards model.

d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and baseline ECOG score.

e. Calculated using the complementary log-log transformation method (Collett, 1994). f. '+' means the observed time is from censored subjects.

Snapshot date: 10SEP2020, data cutoff date: 29MAY2020.

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_may2020_dco_1943\v01\outputs\tlfs\pgms\t-g3ae-km-socpt-subgrp.sas Output:
t02-10-04-g3ae-km-socpt-sub-3-ecog-safs.rtf (14DEC20:17:16) Data: adsl, adae, adttesaf

Seagen Protocol ONT-380-206**Table 2.10.4 Summary of Treatment-Emergent Severe (\geq Grade 3) Adverse Events by System Organ Class, Preferred Term and Baseline ECOG Score - Time-to-Event Analysis
Safety Analysis Set**

| System Organ Class/ Preferred Term | Parameters | ECOG=0 | | ECOG=1 | |
|--|--|------------------------|-----------------------------|------------------------|--------------------------------|
| | | Tuc+Cap+Tra (N=203) | Pbo+Cap+Tra (N=91) | Tuc+Cap+Tra (N=201) | Pbo+Cap+Tra (N=106) |
| Severe Alanine Aminotransferase Increased (PT) | Number of Subjects With at Least One Event, n (%) | 15 (7.4) | 1 (1.1) | 8 (4.0) | 0 |
| | Number of Censored Subjects, n (%) | 188 (92.6) | 90 (98.9) | 193 (96.0) | 106 (100) |
| | Stratified Hazard Ratio ^{a, b} (95% C.I.) | | 6.229 (0.818, 47.456) | | 18370082.6 75 (0.000, -) |
| | P-value ^{b, c} | | 0.07746 | | 0.99349 |
| | Interaction Test P-value ^d | | | 0.98962 | |
| | Median Time to Onset of the First Event (Days) (95% C.I.) ^e | - (-, -) | - (-, -) | - (-, -) | - (-, -) |
| | 25 th , 75 th Percentile Observed Min, Max ^f | - , - 4+, 1156+ | - , - 50+, 839+ | - , - 6+, 1154+ | - , - 26+, 762+ |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (Presence or history of brain metastases: Yes/No and Region of world: North America /Rest of World) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.

c. Two-sided p-value calculated from Cox proportional hazards model.

d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and baseline ECOG score.

e. Calculated using the complementary log-log transformation method (Collett, 1994). f. '+' means the observed time is from censored subjects.

Snapshot date: 10SEP2020, data cutoff date: 29MAY2020.

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_may2020_dco_1943\v01\outputs\tlfs\pgms\t-g3ae-km-socpt-subgrp.sas Output:
t02-10-04-g3ae-km-socpt-sub-3-ecog-safs.rtf (14DEC20:17:16) Data: adsl, adae, adttsaf

Seagen Protocol ONT-380-206**Table 2.10.4 Summary of Treatment-Emergent Severe (\geq Grade 3) Adverse Events by System Organ Class, Preferred Term and Baseline ECOG Score - Time-to-Event Analysis
Safety Analysis Set**

| System Organ Class/ Preferred Term | Parameters | ECOG=0 | | ECOG=1 | |
|--|--|------------------------|--------------------------------|------------------------|-----------------------------|
| | | Tuc+Cap+Tra (N=203) | Pbo+Cap+Tra (N=91) | Tuc+Cap+Tra (N=201) | Pbo+Cap+Tra (N=106) |
| Severe Aspartate Aminotransferase Increased (PT) | Number of Subjects With at Least One Event, n (%) | 11 (5.4) | 0 | 8 (4.0) | 1 (0.9) |
| | Number of Censored Subjects, n (%) | 192 (94.6) | 91 (100) | 193 (96.0) | 105 (99.1) |
| | Stratified Hazard Ratio ^{a, b} (95% C.I.) | | 16462649.1 14 (0.000, -) | | 4.077 (0.508, 32.735) |
| | P-value ^{b, c} | | 0.99304 | | 0.18613 |
| | Interaction Test P-value ^d | | | 0.99016 | |
| | Median Time to Onset of the First Event (Days) (95% C.I.) ^e | - (-, -) | - (-, -) | - (-, -) | - (-, -) |
| | 25 th , 75 th Percentile Observed Min, Max ^f | - , - 4+, 1156+ | - , - 50+, 839+ | - , - 6+, 1154+ | - , - 14, 762+ |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (Presence or history of brain metastases: Yes/No and Region of world: North America /Rest of World) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.

c. Two-sided p-value calculated from Cox proportional hazards model.

d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and baseline ECOG score.

e. Calculated using the complementary log-log transformation method (Collett, 1994). f. '+' means the observed time is from censored subjects.

Snapshot date: 10SEP2020, data cutoff date: 29MAY2020.

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_may2020_dco_1943\v01\outputs\tlfs\pgms\t-g3ae-km-socpt-subgrp.sas Output:
t02-10-04-g3ae-km-socpt-sub-3-ecog-safs.rtf (14DEC20:17:16) Data: adsl, adae, adttesaf

Seagen Protocol ONT-380-206**Table 2.10.4 Summary of Treatment-Emergent Severe (≥ Grade 3) Adverse Events by System Organ Class, Preferred Term and Baseline ECOG Score - Time-to-Event Analysis
Safety Analysis Set**

| System Organ Class/ Preferred Term | Parameters | ECOG=0 | | ECOG=1 | |
|---|---|------------------------|----------------------------|------------------------|----------------------------|
| | | Tuc+Cap+Tra (N=203) | Pbo+Cap+Tra (N=91) | Tuc+Cap+Tra (N=201) | Pbo+Cap+Tra (N=106) |
| Severe Musculoskeletal And Connective Tissue Disorders (SOC) | Number of Subjects With at Least One Event, n (%) | 8 (3.9) | 3 (3.3) | 10 (5.0) | 10 (9.4) |
| | Number of Censored Subjects, n (%) | 195 (96.1) | 88 (96.7) | 191 (95.0) | 96 (90.6) |
| | Stratified Hazard Ratio ^{a, b} (95% C.I.) | | 0.810 (0.206, 3.178) | | 0.309 (0.119, 0.802) |
| | P-value ^{b, c} | | 0.76226 | | 0.01577 |
| | Interaction Test P-value ^d | | | | 0.34248 |
| | Median Time to Onset of the First Event (Days) (95% C.I.) ^e | - (-, -) | - (-, -) | 932.0 (932.0, -) | - (-, -) |
| | 25 th , 75 th Percentile | -, - | -, - | 932.0, - | -, - |
| Observed Min, Max ^f | 4+, 1327+ | 50+, 839+ | 6+, 1154+ | 7, 762+ | |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (Presence or history of brain metastases: Yes/No and Region of world: North America /Rest of World) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.

c. Two-sided p-value calculated from Cox proportional hazards model.

d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and baseline ECOG score.

e. Calculated using the complementary log-log transformation method (Collett, 1994). f. '+' means the observed time is from censored subjects.

Snapshot date: 10SEP2020, data cutoff date: 29MAY2020.

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_may2020_dco_1943\v01\outputs\tlfs\pgms\t-g3ae-km-socpt-subgrp.sas Output:
t02-10-04-g3ae-km-socpt-sub-3-ecog-safs.rtf (14DEC20:17:16) Data: adsl, adae, adttesaf

Seagen Protocol ONT-380-206**Table 2.10.4 Summary of Treatment-Emergent Severe (\geq Grade 3) Adverse Events by System Organ Class, Preferred Term and Baseline ECOG Score - Time-to-Event Analysis
Safety Analysis Set**

| System Organ Class/ Preferred Term | Parameters | ECOG=0 | | ECOG=1 | |
|---------------------------------------|---|------------------------|----------------------------|------------------------|----------------------------|
| | | Tuc+Cap+Tra (N=203) | Pbo+Cap+Tra (N=91) | Tuc+Cap+Tra (N=201) | Pbo+Cap+Tra (N=106) |
| Severe Dyspnoea (PT) | Number of Subjects With at Least One Event, n (%) | 1 (0.5) | 3 (3.3) | 6 (3.0) | 7 (6.6) |
| | Number of Censored Subjects, n (%) | 202 (99.5) | 88 (96.7) | 195 (97.0) | 99 (93.4) |
| | Stratified Hazard Ratio ^{a, b} (95% C.I.) | | 0.115 (0.012, 1.110) | | 0.434 (0.146, 1.295) |
| | P-value ^{b, c} | | 0.06152 | | 0.13465 |
| | Interaction Test P-value ^d | | | 0.41632 | |
| | Median Time to Onset of the First Event (Days) (95% C.I.) ^e | - (-, -) | - (-, -) | - (-, -) | - (-, -) |
| | 25 th , 75 th Percentile | -, - | -, - | -, - | -, - |
| Observed Min, Max ^f | 4+, 1327+ | 43, 839+ | 6+, 1154+ | 21, 762+ | |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (Presence or history of brain metastases: Yes/No and Region of world: North America /Rest of World) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.

c. Two-sided p-value calculated from Cox proportional hazards model.

d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and baseline ECOG score.

e. Calculated using the complementary log-log transformation method (Collett, 1994). f. '+' means the observed time is from censored subjects.

Snapshot date: 10SEP2020, data cutoff date: 29MAY2020.

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_may2020_dco_1943\v01\outputs\tlfs\pgms\t-g3ae-km-socpt-subgrp.sas Output:
t02-10-04-g3ae-km-socpt-sub-3-ecog-safs.rtf (14DEC20:17:16) Data: adsl, adae, adttesaf

Seagen Protocol ONT-380-206**Table 2.10.5 Summary of Treatment-Emergent Severe (≥ Grade 3) Adverse Events by System Organ Class, Preferred Term and Age - Time-to-Event Analysis Safety Analysis Set**

| System Organ Class/ Preferred Term | Parameters | Age < 65 Years | | Age ≥ 65 Years | |
|---------------------------------------|---|------------------------|----------------------------|-----------------------|----------------------------|
| | | Tuc+Cap+Tra (N=322) | Pbo+Cap+Tra (N=164) | Tuc+Cap+Tra (N=82) | Pbo+Cap+Tra (N=33) |
| Severe Investigations (SOC) | Number of Subjects With at Least One Event, n (%) | 44 (13.7) | 6 (3.7) | 9 (11.0) | 2 (6.1) |
| | Number of Censored Subjects, n (%) | 278 (86.3) | 158 (96.3) | 73 (89.0) | 31 (93.9) |
| | Stratified Hazard Ratio ^{a, b} (95% C.I.) | | 3.273 (1.387, 7.722) | | 1.426 (0.303, 6.703) |
| | P-value ^{b, c} | | 0.00680 | | 0.65294 |
| | Interaction Test P-value ^d | | | 0.44557 | |
| | Median Time to Onset of the First Event (Days) (95% C.I.) ^e | - (-, -) | - (-, -) | - (-, -) | - (-, -) |
| | 25 th , 75 th Percentile | -, - | -, - | -, - | -, - |
| Observed Min, Max ^f | 6+, 1156+ | 6, 839+ | 4+, 945+ | 14, 428+ | |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (Presence or history of brain metastases: Yes/No, ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.

c. Two-sided p-value calculated from Cox proportional hazards model.

d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and age.

e. Calculated using the complementary log-log transformation method (Collett, 1994). f. '+' means the observed time is from censored subjects.

Snapshot date: 10SEP2020, data cutoff date: 29MAY2020.

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_may2020_dco_1943\v01\outputs\tlfs\pgms\t-g3ae-km-socpt-subgrp.sas Output: t02-10-05-g3ae-km-socpt-sub-4-age-safs.rtf (14DEC20:17:16) Data: adsl, adae, addtesaf

Seagen Protocol ONT-380-206**Table 2.10.5 Summary of Treatment-Emergent Severe (\geq Grade 3) Adverse Events by System Organ Class, Preferred Term and Age - Time-to-Event Analysis Safety Analysis Set**

| System Organ Class/ Preferred Term | Parameters | Age < 65 Years | | Age \geq 65 Years | |
|--|---|------------------------|-----------------------------|-----------------------|--------------------------------|
| | | Tuc+Cap+Tra (N=322) | Pbo+Cap+Tra (N=164) | Tuc+Cap+Tra (N=82) | Pbo+Cap+Tra (N=33) |
| Severe Alanine Aminotransferase Increased (PT) | Number of Subjects With at Least One Event, n (%) | 18 (5.6) | 1 (0.6) | 5 (6.1) | 0 |
| | Number of Censored Subjects, n (%) | 304 (94.4) | 163 (99.4) | 77 (93.9) | 33 (100) |
| | Stratified Hazard Ratio ^{a, b} (95% C.I.) | | 8.817 (1.174, 66.207) | | 14287422.5 29 (0.000, -) |
| | P-value ^{b, c} | | 0.03434 | | 0.99565 |
| | Interaction Test P-value ^d | | | 0.99167 | |
| | Median Time to Onset of the First Event (Days) (95% C.I.) ^e | - (-, -) | - (-, -) | - (-, -) | - (-, -) |
| | 25 th , 75 th Percentile | -, - | -, - | -, - | -, - |
| Observed Min, Max ^f | 6+, 1156+ | 26+, 839+ | 4+, 945+ | 31+, 428+ | |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (Presence or history of brain metastases: Yes/No, ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.

c. Two-sided p-value calculated from Cox proportional hazards model.

d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and age.

e. Calculated using the complementary log-log transformation method (Collett, 1994). f. '+' means the observed time is from censored subjects.

Snapshot date: 10SEP2020, data cutoff date: 29MAY2020.

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_may2020_dco_1943\v01\outputs\tlfs\pgms\t-g3ae-km-socpt-subgrp.sas Output: t02-10-05-g3ae-km-socpt-sub-4-age-safs.rtf (14DEC20:17:16) Data: adsl, adae, adttesaf

Seagen Protocol ONT-380-206**Table 2.10.5 Summary of Treatment-Emergent Severe (\geq Grade 3) Adverse Events by System Organ Class, Preferred Term and Age - Time-to-Event Analysis Safety Analysis Set**

| System Organ Class/ Preferred Term | Parameters | Age < 65 Years | | Age \geq 65 Years | |
|--|--|------------------------|--------------------------------|-----------------------|-----------------------------|
| | | Tuc+Cap+Tra (N=322) | Pbo+Cap+Tra (N=164) | Tuc+Cap+Tra (N=82) | Pbo+Cap+Tra (N=33) |
| Severe Aspartate Aminotransferase Increased (PT) | Number of Subjects With at Least One Event, n (%) | 15 (4.7) | 0 | 4 (4.9) | 1 (3.0) |
| | Number of Censored Subjects, n (%) | 307 (95.3) | 164 (100) | 78 (95.1) | 32 (97.0) |
| | Stratified Hazard Ratio ^{a, b} (95% C.I.) | | 17002700.2 84 (0.000, -) | | 1.586 (0.175, 14.382) |
| | P-value ^{b, c} | | 0.99142 | | 0.68172 |
| | Interaction Test P-value ^d | | | 0.99099 | |
| | Median Time to Onset of the First Event (Days) (95% C.I.) ^e | - (-, -) | - (-, -) | - (-, -) | - (-, -) |
| | 25 th , 75 th Percentile Observed Min, Max ^f | - , - 6+, 1156+ | - , - 26+, 839+ | - , - 4+, 945+ | - , - 14, 428+ |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (Presence or history of brain metastases: Yes/No, ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.

c. Two-sided p-value calculated from Cox proportional hazards model.

d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and age.

e. Calculated using the complementary log-log transformation method (Collett, 1994). f. '+' means the observed time is from censored subjects.

Snapshot date: 10SEP2020, data cutoff date: 29MAY2020.

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_may2020_dco_1943\v01\outputs\tlfs\pgms\t-g3ae-km-socpt-subgrp.sas Output: t02-10-05-g3ae-km-socpt-sub-4-age-safs.rtf (14DEC20:17:16) Data: adsl, adae, adttesaf

Seagen Protocol ONT-380-206**Table 2.10.5 Summary of Treatment-Emergent Severe (\geq Grade 3) Adverse Events by System Organ Class, Preferred Term and Age - Time-to-Event Analysis
Safety Analysis Set**

| System Organ Class/ Preferred Term | Parameters | Age < 65 Years | | Age \geq 65 Years | |
|---|---|------------------------|----------------------------|-----------------------|----------------------------|
| | | Tuc+Cap+Tra (N=322) | Pbo+Cap+Tra (N=164) | Tuc+Cap+Tra (N=82) | Pbo+Cap+Tra (N=33) |
| Severe Musculoskeletal And Connective Tissue Disorders (SOC) | Number of Subjects With at Least One Event, n (%) | 14 (4.3) | 8 (4.9) | 4 (4.9) | 5 (15.2) |
| | Number of Censored Subjects, n (%) | 308 (95.7) | 156 (95.1) | 78 (95.1) | 28 (84.8) |
| | Stratified Hazard Ratio ^{a, b} (95% C.I.) | | 0.518 (0.205, 1.309) | | 0.224 (0.049, 1.019) |
| | P-value ^{b, c} | | 0.16428 | | 0.05294 |
| | Interaction Test P-value ^d | | | 0.19179 | |
| | Median Time to Onset of the First Event (Days) (95% C.I.) ^e | - (-, -) | - (-, -) | 932.0 (-, -) | - (215.0, -) |
| | 25 th , 75 th Percentile | -, - | -, - | 932.0, 932.0 | 304.0, - |
| Observed Min, Max ^f | 6+, 1327+ | 7, 839+ | 4+, 932 | 31+, 428+ | |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (Presence or history of brain metastases: Yes/No, ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.

c. Two-sided p-value calculated from Cox proportional hazards model.

d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and age.

e. Calculated using the complementary log-log transformation method (Collett, 1994). f. '+' means the observed time is from censored subjects.

Snapshot date: 10SEP2020, data cutoff date: 29MAY2020.

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_may2020_dco_1943\v01\outputs\tlfs\pgms\t-g3ae-km-socpt-subgrp.sas Output:
t02-10-05-g3ae-km-socpt-sub-4-age-safs.rtf (14DEC20:17:16) Data: adsl, adae, adttesaf

Seagen Protocol ONT-380-206**Table 2.10.5 Summary of Treatment-Emergent Severe (≥ Grade 3) Adverse Events by System Organ Class, Preferred Term and Age - Time-to-Event Analysis
Safety Analysis Set**

| System Organ Class/ Preferred Term | Parameters | Age < 65 Years | | Age ≥ 65 Years | |
|---------------------------------------|---|------------------------|----------------------------|-----------------------|----------------------------|
| | | Tuc+Cap+Tra (N=322) | Pbo+Cap+Tra (N=164) | Tuc+Cap+Tra (N=82) | Pbo+Cap+Tra (N=33) |
| Severe Dyspnoea (PT) | Number of Subjects With at Least One Event, n (%) | 6 (1.9) | 8 (4.9) | 1 (1.2) | 2 (6.1) |
| | Number of Censored Subjects, n (%) | 316 (98.1) | 156 (95.1) | 81 (98.8) | 31 (93.9) |
| | Stratified Hazard Ratio ^{a, b} (95% C.I.) | | 0.379 (0.131, 1.096) | | 0.165 (0.014, 1.915) |
| | P-value ^{b, c} | | 0.07328 | | 0.14960 |
| | Interaction Test P-value ^d | | | 0.54836 | |
| | Median Time to Onset of the First Event (Days) (95% C.I.) ^e | - (-, -) | - (-, -) | - (-, -) | - (318.0, -) |
| | 25 th , 75 th Percentile | -, - | -, - | -, - | -, - |
| Observed Min, Max ^f | 6+, 1327+ | 21, 839+ | 4+, 945+ | 31+, 428+ | |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (Presence or history of brain metastases: Yes/No, ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.

c. Two-sided p-value calculated from Cox proportional hazards model.

d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and age.

e. Calculated using the complementary log-log transformation method (Collett, 1994). f. '+' means the observed time is from censored subjects.

Snapshot date: 10SEP2020, data cutoff date: 29MAY2020.

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_may2020_dco_1943\v01\outputs\tlfs\pgms\t-g3ae-km-socpt-subgrp.sas Output:
t02-10-05-g3ae-km-socpt-sub-4-age-safs.rtf (14DEC20:17:16) Data: adsl, adae, adttesaf

Seagen Protocol ONT-380-206**Table 2.10.6 Summary of Treatment-Emergent Severe (≥ Grade 3) Adverse Events by System Organ Class, Preferred Term and Race - Time-to-Event Analysis Safety Analysis Set**

| System Organ Class/ Preferred Term | Parameters | White | | Non-White | |
|---------------------------------------|---|------------------------|----------------------------|------------------------|-----------------------------|
| | | Tuc+Cap+Tra (N=283) | Pbo+Cap+Tra (N=153) | Tuc+Cap+Tra (N=121) | Pbo+Cap+Tra (N=44) |
| Severe Investigations (SOC) | Number of Subjects With at Least One Event, n (%) | 43 (15.2) | 7 (4.6) | 10 (8.3) | 1 (2.3) |
| | Number of Censored Subjects, n (%) | 240 (84.8) | 146 (95.4) | 111 (91.7) | 43 (97.7) |
| | Stratified Hazard Ratio ^{a, b} (95% C.I.) | | 3.029 (1.356, 6.768) | | 2.647 (0.328, 21.371) |
| | P-value ^{b, c} | | 0.00690 | | 0.36089 |
| | Interaction Test P-value ^d | | | 0.99373 | |
| | Median Time to Onset of the First Event (Days) (95% C.I.) ^e | - (-, -) | - (-, -) | - (-, -) | - (-, -) |
| | 25 th , 75 th Percentile | -, - | -, - | -, - | -, - |
| Observed Min, Max ^f | 6+, 1156+ | 6, 839+ | 4+, 1154+ | 40+, 599+ | |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (Presence or history of brain metastases: Yes/No, ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.

c. Two-sided p-value calculated from Cox proportional hazards model.

d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and race.

e. Calculated using the complementary log-log transformation method (Collett, 1994). f. '+' means the observed time is from censored subjects.

Snapshot date: 10SEP2020, data cutoff date: 29MAY2020.

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_may2020_dco_1943\v01\outputs\tlfs\pgms\t-g3ae-km-socpt-subgrp.sas Output:
t02-10-06-g3ae-km-socpt-sub-5-race-safs.rtf (14DEC20:17:16) Data: adsl, adae, adtesaf

Seagen Protocol ONT-380-206**Table 2.10.6 Summary of Treatment-Emergent Severe (≥ Grade 3) Adverse Events by System Organ Class, Preferred Term and Race - Time-to-Event Analysis Safety Analysis Set**

| System Organ Class/ Preferred Term | Parameters | White | | Non-White | |
|--|--|------------------------|--------------------------------|------------------------|----------------------------|
| | | Tuc+Cap+Tra (N=283) | Pbo+Cap+Tra (N=153) | Tuc+Cap+Tra (N=121) | Pbo+Cap+Tra (N=44) |
| Severe Alanine Aminotransferase Increased (PT) | Number of Subjects With at Least One Event, n (%) | 22 (7.8) | 0 | 1 (0.8) | 1 (2.3) |
| | Number of Censored Subjects, n (%) | 261 (92.2) | 153 (100) | 120 (99.2) | 43 (97.7) |
| | Stratified Hazard Ratio ^{a, b} (95% C.I.) | | 18482509.6 22 (0.000, -) | | 0.343 (0.020, 5.761) |
| | P-value ^{b, c} | | 0.98943 | | 0.45725 |
| | Interaction Test P-value ^d | | | 0.99038 | |
| | Median Time to Onset of the First Event (Days) (95% C.I.) ^e | - (-, -) | - (-, -) | - (-, -) | - (-, -) |
| | 25 th , 75 th Percentile Observed Min, Max ^f | - , - 6+, 1156+ | - , - 26+, 839+ | - , - 4+, 1154+ | - , - 40+, 599+ |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (Presence or history of brain metastases: Yes/No, ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.

c. Two-sided p-value calculated from Cox proportional hazards model.

d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and race.

e. Calculated using the complementary log-log transformation method (Collett, 1994). f. '+' means the observed time is from censored subjects.

Snapshot date: 10SEP2020, data cutoff date: 29MAY2020.

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_may2020_dco_1943\v01\outputs\tlfs\pgms\t-g3ae-km-socpt-subgrp.sas Output:
t02-10-06-g3ae-km-socpt-sub-5-race-safs.rtf (14DEC20:17:16) Data: adsl, adae, adtesaf

Seagen Protocol ONT-380-206

**Table 2.10.6 Summary of Treatment-Emergent Severe (≥ Grade 3) Adverse Events by System Organ Class, Preferred Term and Race - Time-to-Event Analysis
Safety Analysis Set**

| System Organ Class/ Preferred Term | Parameters | White | | Non-White | |
|--|--|------------------------|-----------------------------|------------------------|--------------------------------|
| | | Tuc+Cap+Tra (N=283) | Pbo+Cap+Tra (N=153) | Tuc+Cap+Tra (N=121) | Pbo+Cap+Tra (N=44) |
| Severe Aspartate Aminotransferase Increased (PT) | Number of Subjects With at Least One Event, n (%) | 17 (6.0) | 1 (0.7) | 2 (1.7) | 0 |
| | Number of Censored Subjects, n (%) | 266 (94.0) | 152 (99.3) | 119 (98.3) | 44 (100) |
| | Stratified Hazard Ratio ^{a, b} (95% C.I.) | | 9.129 (1.214, 68.647) | | 13672121.5 15 (0.000, -) |
| | P-value ^{b, c} | | 0.03169 | | 0.99727 |
| | Interaction Test P-value ^d | | | 0.99200 | |
| | Median Time to Onset of the First Event (Days) (95% C.I.) ^e | - (-, -) | - (-, -) | - (-, -) | - (-, -) |
| | 25 th , 75 th Percentile Observed Min, Max ^f | -, - 6+, 1156+ | -, - 14, 839+ | -, - 4+, 1154+ | -, - 40+, 599+ |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.
 b. Computed using stratification factors (Presence or history of brain metastases: Yes/No, ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.
 c. Two-sided p-value calculated from Cox proportional hazards model.
 d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and race.
 e. Calculated using the complementary log-log transformation method (Collett, 1994). f. '+' means the observed time is from censored subjects.
 Snapshot date: 10SEP2020, data cutoff date: 29MAY2020.
 Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_may2020_dco_1943\v01\outputs\tlfs\pgms\t-g3ae-km-socpt-subgrp.sas Output:
 t02-10-06-g3ae-km-socpt-sub-5-race-safs.rtf (14DEC20:17:16) Data: adsl, adae, adtesaf

Seagen Protocol ONT-380-206**Table 2.10.6 Summary of Treatment-Emergent Severe (≥ Grade 3) Adverse Events by System Organ Class, Preferred Term and Race - Time-to-Event Analysis
Safety Analysis Set**

| System Organ Class/ Preferred Term | Parameters | White | | Non-White | |
|---|---|------------------------|----------------------------|------------------------|----------------------------|
| | | Tuc+Cap+Tra (N=283) | Pbo+Cap+Tra (N=153) | Tuc+Cap+Tra (N=121) | Pbo+Cap+Tra (N=44) |
| Severe Musculoskeletal And Connective Tissue Disorders (SOC) | Number of Subjects With at Least One Event, n (%) | 16 (5.7) | 11 (7.2) | 2 (1.7) | 2 (4.5) |
| | Number of Censored Subjects, n (%) | 267 (94.3) | 142 (92.8) | 119 (98.3) | 42 (95.5) |
| | Stratified Hazard Ratio ^{a, b} (95% C.I.) | | 0.419 (0.182, 0.963) | | 0.271 (0.037, 1.967) |
| | P-value ^{b, c} | | 0.04050 | | 0.19676 |
| | Interaction Test P-value ^d | | | 0.45063 | |
| | Median Time to Onset of the First Event (Days) (95% C.I.) ^e | - (932.0, -) | - (-, -) | - (-, -) | - (-, -) |
| | 25 th , 75 th Percentile | 932.0, - | -, - | -, - | -, - |
| Observed Min, Max ^f | 6+, 1327+ | 7, 839+ | 4+, 1154+ | 40+, 599+ | |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (Presence or history of brain metastases: Yes/No, ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.

c. Two-sided p-value calculated from Cox proportional hazards model.

d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and race.

e. Calculated using the complementary log-log transformation method (Collett, 1994). f. '+' means the observed time is from censored subjects.

Snapshot date: 10SEP2020, data cutoff date: 29MAY2020.

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_may2020_dco_1943\v01\outputs\tlfs\pgms\t-g3ae-km-socpt-subgrp.sas Output: t02-10-06-g3ae-km-socpt-sub-5-race-safs.rtf (14DEC20:17:16) Data: adsl, adae, adttesaf

Seagen Protocol ONT-380-206**Table 2.10.6 Summary of Treatment-Emergent Severe (≥ Grade 3) Adverse Events by System Organ Class, Preferred Term and Race - Time-to-Event Analysis Safety Analysis Set**

| System Organ Class/ Preferred Term | Parameters | White | | Non-White | |
|---------------------------------------|---|------------------------|----------------------------|------------------------|----------------------------|
| | | Tuc+Cap+Tra (N=283) | Pbo+Cap+Tra (N=153) | Tuc+Cap+Tra (N=121) | Pbo+Cap+Tra (N=44) |
| Severe Dyspnoea (PT) | Number of Subjects With at Least One Event, n (%) | 6 (2.1) | 9 (5.9) | 1 (0.8) | 1 (2.3) |
| | Number of Censored Subjects, n (%) | 277 (97.9) | 144 (94.1) | 120 (99.2) | 43 (97.7) |
| | Stratified Hazard Ratio ^{a, b} (95% C.I.) | | 0.334 (0.119, 0.941) | | 0.279 (0.017, 4.464) |
| | P-value ^{b, c} | | 0.03793 | | 0.36694 |
| | Interaction Test P-value ^d | | | 0.93172 | |
| | Median Time to Onset of the First Event (Days) (95% C.I.) ^e | - (-, -) | - (-, -) | - (-, -) | - (-, -) |
| | 25 th , 75 th Percentile | -, - | -, - | -, - | -, - |
| Observed Min, Max ^f | 6+, 1327+ | 21, 839+ | 4+, 1154+ | 40+, 599+ | |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (Presence or history of brain metastases: Yes/No, ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.

c. Two-sided p-value calculated from Cox proportional hazards model.

d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and race.

e. Calculated using the complementary log-log transformation method (Collett, 1994). f. '+' means the observed time is from censored subjects.

Snapshot date: 10SEP2020, data cutoff date: 29MAY2020.

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_may2020_dco_1943\v01\outputs\tlfs\pgms\t-g3ae-km-socpt-subgrp.sas Output: t02-10-06-g3ae-km-socpt-sub-5-race-safs.rtf (14DEC20:17:16) Data: adsl, adae, adtesaf

Seagen Protocol ONT-380-206**Table 2.10.7 Summary of Treatment-Emergent Severe (\geq Grade 3) Adverse Events by System Organ Class, Preferred Term and Hormone Receptor Status - Time-to-Event Analysis
Safety Analysis Set**

| System Organ Class/ Preferred Term | Parameters | Negative for Both | | Positive for ER or PR or Both | |
|---------------------------------------|---|------------------------|----------------------------|-------------------------------|----------------------------|
| | | Tuc+Cap+Tra (N=163) | Pbo+Cap+Tra (N=74) | Tuc+Cap+Tra (N=241) | Pbo+Cap+Tra (N=123) |
| Severe Investigations (SOC) | Number of Subjects With at Least One Event, n (%) | 27 (16.6) | 4 (5.4) | 26 (10.8) | 4 (3.3) |
| | Number of Censored Subjects, n (%) | 136 (83.4) | 70 (94.6) | 215 (89.2) | 119 (96.7) |
| | Stratified Hazard Ratio ^{a, b} (95% C.I.) | | 2.052 (0.701, 6.009) | | 3.111 (1.080, 8.964) |
| | P-value ^{b, c} | | 0.18980 | | 0.03556 |
| | Interaction Test P-value ^d | | | 0.63621 | |
| | Median Time to Onset of the First Event (Days) (95% C.I.) ^e | - (-, -) | - (-, -) | - (-, -) | - (-, -) |
| | 25 th , 75 th Percentile | 697.0, - | -, - | -, - | -, - |
| Observed Min, Max ^f | 4+, 1156+ | 14, 580+ | 6+, 1131+ | 6, 839+ | |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (Presence or history of brain metastases: Yes/No, ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.

c. Two-sided p-value calculated from Cox proportional hazards model.

d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and hormone receptor status.

e. Calculated using the complementary log-log transformation method (Collett, 1994). f. '+' means the observed time is from censored subjects.

Snapshot date: 10SEP2020, data cutoff date: 29MAY2020.

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_may2020_dco_1943\v01\outputs\tlfs\pgms\t-g3ae-km-socpt-subgrp.sas Output:
t02-10-07-g3ae-km-socpt-sub-6-hr-safs.rtf (14DEC20:17:16) Data: adsl, adae, adtesaf

Seagen Protocol ONT-380-206

**Table 2.10.7 Summary of Treatment-Emergent Severe (≥ Grade 3) Adverse Events by System Organ Class, Preferred Term and Hormone Receptor Status - Time-to-Event Analysis
Safety Analysis Set**

| System Organ Class/ Preferred Term | Parameters | Negative for Both | | Positive for ER or PR or Both | |
|--|--|------------------------|--------------------------------|-------------------------------|-----------------------------|
| | | Tuc+Cap+Tra (N=163) | Pbo+Cap+Tra (N=74) | Tuc+Cap+Tra (N=241) | Pbo+Cap+Tra (N=123) |
| Severe Alanine Aminotransferase Increased (PT) | Number of Subjects With at Least One Event, n (%) | 13 (8.0) | 0 | 10 (4.1) | 1 (0.8) |
| | Number of Censored Subjects, n (%) | 150 (92.0) | 74 (100) | 231 (95.9) | 122 (99.2) |
| | Stratified Hazard Ratio ^{a, b} (95% C.I.) | | 15101482.7 94 (0.000, -) | | 5.322 (0.679, 41.697) |
| | P-value ^{b, c} | | 0.99313 | | 0.11142 |
| | Interaction Test P-value ^d | | | 0.99135 | |
| | Median Time to Onset of the First Event (Days) (95% C.I.) ^e | - (-, -) | - (-, -) | - (-, -) | - (-, -) |
| | 25 th , 75 th Percentile Observed Min, Max ^f | -, - 4+, 1156+ | -, - 29+, 580+ | -, - 6+, 1131+ | -, - 26+, 839+ |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (Presence or history of brain metastases: Yes/No, ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.

c. Two-sided p-value calculated from Cox proportional hazards model.

d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and hormone receptor status.

e. Calculated using the complementary log-log transformation method (Collett, 1994). f. '+' means the observed time is from censored subjects.

Snapshot date: 10SEP2020, data cutoff date: 29MAY2020.

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_may2020_dco_1943\v01\outputs\tlfs\pgms\t-g3ae-km-socpt-subgrp.sas Output:
t02-10-07-g3ae-km-socpt-sub-6-hr-safs.rtf (14DEC20:17:16) Data: adsl, adae, adttesaf

Seagen Protocol ONT-380-206**Table 2.10.7 Summary of Treatment-Emergent Severe (≥ Grade 3) Adverse Events by System Organ Class, Preferred Term and Hormone Receptor Status - Time-to-Event Analysis
Safety Analysis Set**

| System Organ Class/ Preferred Term | Parameters | Negative for Both | | Positive for ER or PR or Both | |
|--|---|------------------------|-----------------------------|-------------------------------|--------------------------------|
| | | Tuc+Cap+Tra (N=163) | Pbo+Cap+Tra (N=74) | Tuc+Cap+Tra (N=241) | Pbo+Cap+Tra (N=123) |
| Severe Aspartate Aminotransferase Increased (PT) | Number of Subjects With at Least One Event, n (%) | 12 (7.4) | 1 (1.4) | 7 (2.9) | 0 |
| | Number of Censored Subjects, n (%) | 151 (92.6) | 73 (98.6) | 234 (97.1) | 123 (100) |
| | Stratified Hazard Ratio ^{a, b} (95% C.I.) | | 4.628 (0.590, 36.301) | | 18004960.5 73 (0.000, -) |
| | P-value ^{b, c} | | 0.14481 | | 0.99394 |
| | Interaction Test P-value ^d | | | 0.99333 | |
| | Median Time to Onset of the First Event (Days) (95% C.I.) ^e | - (-, -) | - (-, -) | - (-, -) | - (-, -) |
| | 25 th , 75 th Percentile | -, - | -, - | -, - | -, - |
| Observed Min, Max ^f | 4+, 1156+ | 14, 580+ | 6+, 1131+ | 26+, 839+ | |

Page 3 of 4

a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (Presence or history of brain metastases: Yes/No, ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.

c. Two-sided p-value calculated from Cox proportional hazards model.

d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and hormone receptor status.

e. Calculated using the complementary log-log transformation method (Collett, 1994). f. '+' means the observed time is from censored subjects.

Snapshot date: 10SEP2020, data cutoff date: 29MAY2020.

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_may2020_dco_1943\v01\outputs\tlfs\pgms\t-g3ae-km-socpt-subgrp.sas Output:
t02-10-07-g3ae-km-socpt-sub-6-hr-safs.rtf (14DEC20:17:16) Data: adsl, adae, adttesaf

Seagen Protocol ONT-380-206**Table 2.10.7 Summary of Treatment-Emergent Severe (≥ Grade 3) Adverse Events by System Organ Class, Preferred Term and Hormone Receptor Status - Time-to-Event Analysis
Safety Analysis Set**

| System Organ Class/ Preferred Term | Parameters | Negative for Both | | Positive for ER or PR or Both | |
|---|---|------------------------|----------------------------|-------------------------------|----------------------------|
| | | Tuc+Cap+Tra (N=163) | Pbo+Cap+Tra (N=74) | Tuc+Cap+Tra (N=241) | Pbo+Cap+Tra (N=123) |
| Severe Musculoskeletal And Connective Tissue Disorders (SOC) | Number of Subjects With at Least One Event, n (%) | 10 (6.1) | 5 (6.8) | 8 (3.3) | 8 (6.5) |
| | Number of Censored Subjects, n (%) | 153 (93.9) | 69 (93.2) | 233 (96.7) | 115 (93.5) |
| | Stratified Hazard Ratio ^{a, b} (95% C.I.) | | 0.339 (0.095, 1.209) | | 0.289 (0.102, 0.822) |
| | P-value ^{b, c} | | 0.09540 | | 0.01991 |
| | Interaction Test P-value ^d | | | 0.66304 | |
| | Median Time to Onset of the First Event (Days) (95% C.I.) ^e | - (932.0, -) | - (-, -) | - (-, -) | - (-, -) |
| | 25 th , 75 th Percentile | -, - | -, - | -, - | -, - |
| Observed Min, Max ^f | 4+, 1327+ | 29+, 580+ | 6+, 1131+ | 7, 839+ | |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

b. Computed using stratification factors (Presence or history of brain metastases: Yes/No, ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.

c. Two-sided p-value calculated from Cox proportional hazards model.

d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and hormone receptor status.

e. Calculated using the complementary log-log transformation method (Collett, 1994). f. '+' means the observed time is from censored subjects.

Snapshot date: 10SEP2020, data cutoff date: 29MAY2020.

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_may2020_dco_1943\v01\outputs\tlfs\pgms\t-g3ae-km-socpt-subgrp.sas Output:
t02-10-07-g3ae-km-socpt-sub-6-hr-safs.rtf (14DEC20:17:16) Data: adsl, adae, adttesaf

Seattle Genetics Protocol ONT-380-206**Table 2.13.2 Summary of Treatment-Emergent Adverse Events of Special Interest (AESI) by History of Brain Metastases at Baseline - Time-to-Event Analysis
Safety Analysis Set**

| Parameters | With Brian Metastases | | Without Brain Metastases | |
|------------|------------------------|-----------------------|--------------------------|------------------------|
| | Tuc+Cap+Tra (N=194) | Pbo+Cap+Tra (N=91) | Tuc+Cap+Tra (N=209) | Pbo+Cap+Tra (N=105) |

NO DATA QUALIFY FOR THIS OUTPUT

Page 1 of 1

- a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.
- b. Computed using stratification factors (ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.
- c. Two-sided p-value calculated from Cox proportional hazards model .
- d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and history of brain metastases at baseline.
- e. Calculated using the complementary log-log transformation method (Collett, 1994).
- f. '+' means the observed time is from censored subjects.
- Data Snapshot: 14OCT2019, Data Cutoff Date: 04SEP2019
- Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_1753\v01\outputs\tlfs\pgms\t-ae-km-aesi-subgrp.sas Output: t-ae-km-aesi-sub-1-bm-safs.rtf (17JUL20:17:17)
- Data: adsl, adae, adttesaf

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Table 2.13.3 Summary of Treatment-Emergent Adverse Events of Special Interest (AESI) by Geographic Region - Time-to-Event Analysis Safety Analysis Set

| Parameters | North America | | Rest of World | |
|------------|------------------------|------------------------|------------------------|-----------------------|
| | Tuc+Cap+Tra (N=241) | Pbo+Cap+Tra (N=119) | Tuc+Cap+Tra (N=163) | Pbo+Cap+Tra (N=78) |

NO DATA QUALIFY FOR THIS OUTPUT

Page 1 of 1

- a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.
 - b. Computed using stratification factors (Presence or history of brain metastases: Yes/No and ECOG performance status: 0/1) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.
 - c. Two-sided p-value calculated from Cox proportional hazards model .
 - d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and geographic region.
 - e. Calculated using the complementary log-log transformation method (Collett, 1994).
 - f. '+' means the observed time is from censored subjects.
- Data Snapshot: 14OCT2019, Data Cutoff Date: 04SEP2019
 Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_1753\v01\outputs\tlfs\pgms\t-ae-km-aesi-subgrp.sas Output: t-ae-km-aesi-sub-2-reg-safs.rtf (17JUL20:17:17)
 Data: adsl, adae, adttesaf

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**Table 2.13.4 Summary of Treatment-Emergent Adverse Events of Special Interest (AESI) by Baseline ECOG Score - Time-to-Event Analysis
Safety Analysis Set**

| Parameters | ECOG=0 | | ECOG=1 | |
|------------|------------------------|-----------------------|------------------------|------------------------|
| | Tuc+Cap+Tra (N=203) | Pbo+Cap+Tra (N=91) | Tuc+Cap+Tra (N=201) | Pbo+Cap+Tra (N=106) |

NO DATA QUALIFY FOR THIS OUTPUT

- a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.
- b. Computed using stratification factors (Presence or history of brain metastases: Yes/No and Region of world: North America /Rest of World) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.
- c. Two-sided p-value calculated from Cox proportional hazards model .
- d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and baseline ECOG score.
- e. Calculated using the complementary log-log transformation method (Collett, 1994).
- f. '+' means the observed time is from censored subjects.

Data Snapshot: 14OCT2019, Data Cutoff Date: 04SEP2019

Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_1753\v01\outputs\tlfs\pgms\t-ae-km-aesi-subgrp.sas Output: t-ae-km-aesi-sub-3-ecog-safs.rtf (17JUL20:17:17)

Data: adsl, adae, adttesaf

Seattle Genetics Protocol ONT-380-206**Table 2.13.5 Summary of Treatment-Emergent Adverse Events of Special Interest (AESI) by Age - Time-to-Event Analysis
Safety Analysis Set**

| Parameters | Age < 65 Years | | Age >= 65 Years | |
|------------|------------------------|------------------------|-----------------------|-----------------------|
| | Tuc+Cap+Tra (N=322) | Pbo+Cap+Tra (N=164) | Tuc+Cap+Tra (N=82) | Pbo+Cap+Tra (N=33) |

NO DATA QUALIFY FOR THIS OUTPUT

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- a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.
- b. Computed using stratification factors (Presence or history of brain metastases: Yes/No, ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.
- c. Two-sided p-value calculated from Cox proportional hazards model .
- d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and age.
- e. Calculated using the complementary log-log transformation method (Collett, 1994).
- f. '+' means the observed time is from censored subjects.
- Data Snapshot: 14OCT2019, Data Cutoff Date: 04SEP2019
 Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_1753\v01\outputs\tlfs\pgms\t-ae-km-aesi-subgrp.sas Output: t-ae-km-aesi-sub-4-age-safs.rtf (17JUL20:17:17)
 Data: adsl, adae, adttesaf

Seattle Genetics Protocol ONT-380-206

**Table 2.13.6 Summary of Treatment-Emergent Adverse Events of Special Interest (AESI) by Race - Time-to-Event Analysis
Safety Analysis Set**

| Parameters | White | | Non-White | | |
|-------------------------------------|--|------------------------|------------------------|-----------------------------|-----------|
| | Tuc+Cap+Tra (N=283) | Pbo+Cap+Tra (N=153) | Tuc+Cap+Tra (N=121) | Pbo+Cap+Tra (N=44) | |
| Potential Drug-induced Liver Injury | Number of Subjects With at Least One Event, n (%) | 8 (2.8) | 2 (1.3) | 1 (0.8) | 0 |
| | Number of Censored Subjects, n (%) | 275 (97.2) | 151 (98.7) | 120 (99.2) | 44 (100) |
| | Stratified Hazard Ratio ^{a, b} (95% C.I.) | 2.112 (0.447, 9.984) | | 38549597.69 3 (0.000, -) | |
| | P-value ^{b, c} | 0.34567 | | 0.99870 | |
| | Interaction Test P-value ^d | 0.99492 | | | |
| | Median Time to Onset of the First Event (Days) (95% C.I.) ^e | - (-, -) | - (-, -) | - (-, -) | - (-, -) |
| | 25 th , 75 th Percentile | -, - | -, - | -, - | -, - |
| | Observed Min, Max ^f | 6+, 1059+ | 6, 762+ | 4+, 1070+ | 40+, 583+ |

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a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.
 b. Computed using stratification factors (Presence or history of brain metastases: Yes/No, ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.
 c. Two-sided p-value calculated from Cox proportional hazards model.
 d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and race.
 e. Calculated using the complementary log-log transformation method (Collett, 1994).
 f. '+' means the observed time is from censored subjects.
 Data Snapshot: 14OCT2019, Data Cutoff Date: 04SEP2019
 Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_1753\v01\outputs\tlfs\pgms\t-ae-km-aesi-subgrp.sas Output: t-ae-km-aesi-sub-5-race-safs.rtf (17JUL20:17:17)
 Data: adsl, adae, adttesaf

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Table 2.13.7 Summary of Treatment-Emergent Adverse Events of Special Interest (AESI) by Hormone Receptor Status - Time-to-Event Analysis
Safety Analysis Set

| Parameters | Negative for Both | | Positive for ER or PR or Both | |
|------------|------------------------|-----------------------|-------------------------------|------------------------|
| | Tuc+Cap+Tra (N=163) | Pbo+Cap+Tra (N=74) | Tuc+Cap+Tra (N=241) | Pbo+Cap+Tra (N=123) |

NO DATA QUALIFY FOR THIS OUTPUT

Page 1 of 1

- a. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.
- b. Computed using stratification factors (Presence or history of brain metastases: Yes/No, ECOG performance status: 0/1 and Region of world: North America /Rest of World) at randomization. For any subgroup with subjects less than 10% of the total population, an unstratified Cox model was run.
- c. Two-sided p-value calculated from Cox proportional hazards model .
- d. Interaction test p-value calculated from stratified Cox proportional hazards model for the interaction term of treatment and hormone receptor status.
- e. Calculated using the complementary log-log transformation method (Collett, 1994).
- f. '+' means the observed time is from censored subjects.
- Data Snapshot: 14OCT2019, Data Cutoff Date: 04SEP2019
- Source: O:\Projects\Tucatinib\ONT380-206\germanreimburse_1753\v01\outputs\tlfs\pgms\t-ae-km-aesi-subgrp.sas Output: t-ae-km-aesi-sub-6-hr-safs.rtf (17JUL20:17:17)
- Data: adsl, adae, adttesaf