

Dossier zur Nutzenbewertung gemäß § 35a SGB V

Nivolumab (OPDIVO®)

Bristol-Myers Squibb GmbH & Co. KGaA

Modul 4 R – Anhang 4-G

*Zur adjuvanten Behandlung des muskelinvasiven
Urothelkarzinoms (MIUC) mit Tumorzell-PD-L1-Expression
 ≥ 1 % bei Erwachsenen mit hohem Rezidivrisiko nach
radikaler Resektion des MIUC*

Ergänzende Informationen zu
Modul 4 Medizinischer Nutzen und
medizinischer Zusatznutzen,
Patientengruppen mit therapeutisch
bedeutsamem Zusatznutzen

Stand: 12.12.2025

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1 Hintergrund

Auf den nachfolgenden Seiten finden sich alle im Dossier angeführten ergänzenden Analysen und Zusatzanalysen sowie alle Subgruppenanalysen für die Hauptanalysen. Für die Verträglichkeit auf Ebene nach SOC und PT wurden darüber hinaus Subgruppenanalysen für schwere UE sowie SUE durchgeführt.

Alle Analysen werden, sofern als sinnvoll erachtet, als Ausgabe der Statistik-Software dargestellt und beruhen auf dem Datenschnitt 06.01.2025 der Studie CA209-274.

2 Mortalität:

2.1 Endpunkt Gesamtüberleben (OS)

Für die Auswertungen wurde ITT-Population herangezogen.

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

2.1.1 Zensierungsgründe (deskriptive Darstellung)

Table 5.2
Overall Survival Incidence by OS Component
FAS

	Placebo N = 142	Nivolumab N = 140
NUMBER OF DEATHS (%)	72 (50.7)	52 (37.1)
NUMBER OF SUBJECTS CENSORED (%)	70 (49.3)	88 (62.9)
CENSORED AT DATE OF RANDOMIZATION		
NEVER TREATED	2 (1.4)	0
OTHER	2 (1.4)	0
CENSORED ON LAST KNOWN DATE ALIVE		
ON-STUDY	68 (47.9)	88 (62.9)
OFF-STUDY	46 (32.4)	64 (45.7)
LOST TO FOLLOW-UP	22 (15.5)	24 (17.1)
SUBJECT WITHDREW CONSENT	7 (4.9)	5 (3.6)
OTHER	12 (8.5)	16 (11.4)
	3 (2.1)	3 (2.1)

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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

2.1.2 Subgruppenanalysen

Table 6.2
Subgroup Analyses of Overall Survival
FAS

Subgroups	Placebo			Nivolumab			Nivolumab vs. Placebo	
	N	Subjects with Event n (%)	KME [95%CI] (mon) (1)	N	Subjects with Event n (%)	KME [95%CI] (mon) (1)	HR [95%CI] P-value (2) (3)	Test for Interaction P-value (4) (5)
OVERALL	142	72 (50.7)	59.43 (29.14, N.A.)	140	52 (37.1)	N.A. (70.01, N.A.)	0.630 (0.441, 0.900) 0.0105	
PRIOR NEO-ADJUVANT CISPLATIN THERAPY								0.2875
YES	61	34 (55.7)	37.55 (28.22, N.A.)	57	20 (35.1)	N.A. (59.40, N.A.)	0.485 (0.279, 0.843) 0.0088	
NO	81	38 (46.9)	72.08 (26.22, N.A.)	83	32 (38.6)	N.A. (64.76, N.A.)	0.756 (0.472, 1.210) 0.2427	

FEB2025 DBL. HR = hazard ratio; KME = Kaplan-Meier estimate; N.M.E. = Not meaningful estimate; N.A. = Not reached.

(1) KME of median time to event. (2) Unstratified Cox proportional hazard model. HR is Nivolumab over Placebo.

(3) Unstratified Log-rank test. (4) Unstratified Cox proportional hazard model with treatment, subgroup and treatment*subgroup.

p-value is from the treatment*subgroup interaction.

(5) A p-value of <0.05 is indicated by 1 asterisk.

IUC = invasive urothelial carcinoma.

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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

Table 6.2
Subgroup Analyses of Overall Survival
FAS

Subgroups	Placebo			Nivolumab			Nivolumab vs. Placebo	
	N	Subjects with Event n (%)	KME [95%CI] (mon) (1)	N	Subjects with Event n (%)	KME [95%CI] (mon) (1)	HR [95%CI] P-value (2) (3)	Test for Interaction P-value (4) (5)
PRIOR CISPLATIN STATUS								
RECEIVED NEO-ADJUVANT	61	34 (55.7)	37.55 (28.22, N.A.)	57	20 (35.1)	N.A. (59.40, N.A.)	0.485 (0.279, 0.843) 0.0088	0.4792
UNWILLING TO RECEIVE NEO-ADJUVANT	46	20 (43.5)	80.69 (26.22, N.A.)	51	19 (37.3)	N.A. (56.71, N.A.)	0.842 (0.450, 1.579) 0.5922	
NOT ELIGIBLE TO RECEIVE NEO-ADJUVANT	34	18 (52.9)	38.21 (10.55, N.A.)	27	10 (37.0)	N.A. (59.47, N.A.)	0.581 (0.268, 1.260) 0.1638	
USE OF ANY PRIOR NEO-ADJUVANT SYSTEMIC THERAPY								0.1379
YES	62	35 (56.5)	36.53 (27.76, 92.12)	61	20 (32.8)	N.A. (60.45, N.A.)	0.447 (0.258, 0.774) 0.0032	
NO	80	37 (46.3)	72.08 (26.22, N.A.)	79	32 (40.5)	N.A. (61.21, N.A.)	0.812 (0.506, 1.303) 0.3874	

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(1) KME of median time to event. (2) Unstratified Cox proportional hazard model. HR is Nivolumab over Placebo.

(3) Unstratified Log-rank test. (4) Unstratified Cox proportional hazard model with treatment, subgroup and treatment*subgroup.

p-value is from the treatment*subgroup interaction.

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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

Table 6.2
Subgroup Analyses of Overall Survival
FAS

Subgroups	Placebo			Nivolumab			Nivolumab vs. Placebo	
	N	Subjects with Event n (%)	KME [95%CI] (mon) (1)	N	Subjects with Event n (%)	KME [95%CI] (mon) (1)	HR [95%CI] P-value (2) (3)	Test for Interaction P-value (4) (5)
PATHOLOGICAL LYMPH NODE STATUS								0.1087
N+	66	43 (65.2)	27.76 (21.59, 38.21)	60	28 (46.7)	79.24 (41.82, N.A.)	0.515 (0.319, 0.832) 0.0057	
N0/X WITH <10 NODES REMOVED	38	13 (34.2)	N.A. (59.43, N.A.)	38	14 (36.8)	N.A. (54.08, N.A.)	1.246 (0.585, 2.654) 0.5675	
N0 WITH >= 10 NODES REMOVED	38	16 (42.1)	92.12 (28.98, N.A.)	42	10 (23.8)	N.A. (75.01, N.A.)	0.479 (0.217, 1.056) 0.0621	

FEB2025 DBL. HR = hazard ratio; KME = Kaplan-Meier estimate; N.M.E. = Not meaningful estimate; N.A. = Not reached.

(1) KME of median time to event. (2) Unstratified Cox proportional hazard model. HR is Nivolumab over Placebo.

(3) Unstratified Log-rank test. (4) Unstratified Cox proportional hazard model with treatment, subgroup and treatment*subgroup. p-value is from the treatment*subgroup interaction.

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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

Table 6.2
Subgroup Analyses of Overall Survival
FAS

Subgroups	Placebo			Nivolumab			Nivolumab vs. Placebo	
	N	Subjects with Event n (%)	KME [95%CI] (mon) (1)	N	Subjects with Event n (%)	KME [95%CI] (mon) (1)	HR [95%CI] P-value (2) (3)	Test for Interaction P-value (4) (5)
PATHOLOGICAL STATUS								
PT0-2	31	18 (58.1)	37.55 (22.67, N.A.)	26	11 (42.3)	N.A. (46.00, N.A.)	0.582 (0.274, 1.234) 0.1529	0.9399
PT3	83	38 (45.8)	72.08 (29.04, N.A.)	87	32 (36.8)	N.A. (66.50, N.A.)	0.706 (0.441, 1.130) 0.1447	
PT4A	27	15 (55.6)	36.11 (18.69, N.A.)	23	9 (39.1)	N.A. (33.94, N.A.)	0.635 (0.275, 1.464) 0.2825	
AGE CATEGORY I								
< 65	61	25 (41.0)	N.A. (29.04, N.A.)	67	18 (26.9)	N.A. (N.A., N.A.)	0.585 (0.319, 1.073) 0.0794	0.6425
>= 65	81	47 (58.0)	40.74 (25.89, 80.69)	73	34 (46.6)	75.01 (55.49, N.A.)	0.687 (0.441, 1.068) 0.0938	

FEB2025 DBL. HR = hazard ratio; KME = Kaplan-Meier estimate; N.M.E. = Not meaningful estimate; N.A. = Not reached.

(1) KME of median time to event. (2) Unstratified Cox proportional hazard model. HR is Nivolumab over Placebo.

(3) Unstratified Log-rank test. (4) Unstratified Cox proportional hazard model with treatment, subgroup and treatment*subgroup.

p-value is from the treatment*subgroup interaction.

(5) A p-value of <0.05 is indicated by 1 asterisk.

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Table 6.2

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen
 Subgroup Analyses of Overall Survival
 FAS

Subgroups	Placebo			Nivolumab			Nivolumab vs. Placebo	
	N	Subjects with Event n (%)	KME [95%CI] (mon) (1)	N	Subjects with Event n (%)	KME [95%CI] (mon) (1)	HR [95%CI] P-value (2) (3)	Test for Interaction P-value (4) (5)
AGE CATEGORY II								0.5944
< 65	61	25 (41.0)	N.A. (29.04, N.A.)	67	18 (26.9)	N.A. (N.A., N.A.)	0.585 (0.319, 1.073) 0.0794	
>= 65 AND < 75	59	33 (55.9)	40.74 (21.59, N.A.)	49	20 (40.8)	N.A. (59.40, N.A.)	0.585 (0.335, 1.021) 0.0562	
>= 75	22	14 (63.6)	38.21 (5.06, N.A.)	24	14 (58.3)	39.49 (11.24, N.A.)	0.919 (0.438, 1.932) 0.8248	

FEB2025 DBL. HR = hazard ratio; KME = Kaplan-Meier estimate; N.M.E. = Not meaningful estimate; N.A. = Not reached.

(1) KME of median time to event. (2) Unstratified Cox proportional hazard model. HR is Nivolumab over Placebo.

(3) Unstratified Log-rank test. (4) Unstratified Cox proportional hazard model with treatment, subgroup and treatment*subgroup.

p-value is from the treatment*subgroup interaction.

(5) A p-value of <0.05 is indicated by 1 asterisk.

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Table 6.2
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Subgroups	Placebo			Nivolumab			Nivolumab vs. Placebo	
	N	Subjects with Event n (%)	KME [95%CI] (mon) (1)	N	Subjects with Event n (%)	KME [95%CI] (mon) (1)	HR [95%CI] P-value (2) (3)	Test for Interaction P-value (4) (5)
REGION								
US	24	12 (50.0)	38.21 (13.67, N.A.)	17	4 (23.5)	N.A. (54.08, N.A.)	0.343 (0.110, 1.066) 0.0526	0.0918
EUROPE	70	42 (60.0)	36.53 (25.89, 80.69)	73	30 (41.1)	N.A. (59.47, N.A.)	0.543 (0.339, 0.868) 0.0096	
ASIA	28	7 (25.0)	N.A. (72.08, N.A.)	33	12 (36.4)	79.24 (27.56, N.A.)	1.808 (0.710, 4.602) 0.2078	
REST OF WORLD	20	11 (55.0)	64.49 (9.69, N.A.)	17	6 (35.3)	N.A. (28.88, N.A.)	0.502 (0.185, 1.362) 0.1677	
GENDER								
MALE	112	63 (56.3)	40.74 (27.47, 80.69)	101	38 (37.6)	N.A. (70.01, N.A.)	0.552 (0.369, 0.826) 0.0033	0.1114
FEMALE	30	9 (30.0)	N.A. (28.98, N.A.)	39	14 (35.9)	N.A. (36.40, N.A.)	1.150 (0.498, 2.659) 0.7431	

FEB2025 DBL. HR = hazard ratio; KME = Kaplan-Meier estimate; N.M.E. = Not meaningful estimate; N.A. = Not reached.

(1) KME of median time to event. (2) Unstratified Cox proportional hazard model. HR is Nivolumab over Placebo.

(3) Unstratified Log-rank test. (4) Unstratified Cox proportional hazard model with treatment, subgroup and treatment*subgroup.

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Table 6.2
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Subgroups	Placebo			Nivolumab			Nivolumab vs. Placebo	
	N	Subjects with Event n (%)	KME [95%CI] (mon) (1)	N	Subjects with Event n (%)	KME [95%CI] (mon) (1)	HR [95%CI] P-value (2) (3)	Test for Interaction P-value (4) (5)
RACE								0.0156*
WHITE	109	61 (56.0)	37.55 (27.47, 80.69)	104	38 (36.5)	N.A. (75.01, N.A.)	0.507 (0.338, 0.761) 0.0008	
ASIAN	28	7 (25.0)	N.A. (72.08, N.A.)	33	12 (36.4)	79.24 (27.56, N.A.)	1.808 (0.710, 4.602) 0.2078	
BASELINE ECOG STATUS								0.4928
0	85	39 (45.9)	64.49 (29.57, N.A.)	86	28 (32.6)	N.A. (79.24, N.A.)	0.609 (0.375, 0.991) 0.0438	
1	53	29 (54.7)	69.88 (22.31, N.A.)	51	24 (47.1)	59.47 (33.94, N.A.)	0.805 (0.468, 1.385) 0.4330	

FEB2025 DBL. HR = hazard ratio; KME = Kaplan-Meier estimate; N.M.E. = Not meaningful estimate; N.A. = Not reached.

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(3) Unstratified Log-rank test. (4) Unstratified Cox proportional hazard model with treatment, subgroup and treatment*subgroup.

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Subgroups	Placebo			Nivolumab			Nivolumab vs. Placebo	
	N	Subjects with Event n (%)	KME [95%CI] (mon) (1)	N	Subjects with Event n (%)	KME [95%CI] (mon) (1)	HR [95%CI] P-value (2) (3)	Test for Interaction P-value (4) (5)
SMOKING STATUS								
NEVER SMOKED	40	17 (42.5)	N.A. (26.91, N.A.)	42	15 (35.7)	N.A. (43.99, N.A.)	0.792 (0.395, 1.586) 0.5090	0.4338
CURRENT/FORMER	101	55 (54.5)	54.44 (27.76, 92.12)	96	36 (37.5)	N.A. (75.01, N.A.)	0.567 (0.372, 0.863) 0.0074	
BASELINE HEMOGLOBIN								
<10 G/DL	14	7 (50.0)	43.43 (8.41, N.A.)	7	4 (57.1)	66.50 (2.37, N.A.)	1.050 (0.306, 3.599) 0.9383	0.4565
>=10 G/DL	125	64 (51.2)	64.49 (29.27, N.A.)	132	47 (35.6)	N.A. (75.01, N.A.)	0.608 (0.417, 0.886) 0.0089	

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(1) KME of median time to event. (2) Unstratified Cox proportional hazard model. HR is Nivolumab over Placebo.

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Table 6.2
Subgroup Analyses of Overall Survival
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Subgroups	Placebo			Nivolumab			Nivolumab vs. Placebo	
	N	Subjects with Event n (%)	KME [95%CI] (mon) (1)	N	Subjects with Event n (%)	KME [95%CI] (mon) (1)	HR [95%CI] P-value (2) (3)	Test for Interaction P-value (4) (5)
BASELINE CREATININE CLEARANCE								
<60 ML/MIN	60	29 (48.3)	80.69 (29.04, N.A.)	54	27 (50.0)	64.76 (28.88, N.A.)	1.054 (0.624, 1.782) 0.8431	0.0103*
>=60 ML/MIN	79	42 (53.2)	37.55 (25.89, N.A.)	84	23 (27.4)	N.A. (N.A., N.A.)	0.399 (0.240, 0.664) 0.0003	
TIME FROM IUC SURGERY TO RANDOMIZATION (DAYS)								
>30-60	28	12 (42.9)	N.A. (26.22, N.A.)	35	17 (48.6)	59.47 (27.56, N.A.)	1.194 (0.570, 2.501) 0.6381	0.1319
>60-90	66	33 (50.0)	71.72 (22.90, N.A.)	57	19 (33.3)	N.A. (79.24, N.A.)	0.574 (0.326, 1.009) 0.0507	
>90-120	41	24 (58.5)	38.21 (28.22, 80.69)	46	15 (32.6)	N.A. (66.50, N.A.)	0.412 (0.215, 0.789) 0.0058	

FEB2025 DBL. HR = hazard ratio; KME = Kaplan-Meier estimate; N.M.E. = Not meaningful estimate; N.A. = Not reached.

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Program Name: rt-ef-sursub-ebr45.sas

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Table 6.2
Subgroup Analyses of Overall Survival
FAS

Subgroups	Placebo			Nivolumab			Nivolumab vs. Placebo	
	N	Subjects with Event n (%)	KME [95%CI] (mon) (1)	N	Subjects with Event n (%)	KME [95%CI] (mon) (1)	HR [95%CI] P-value (2) (3)	Test for Interaction P-value (4) (5)
INITIAL TUMOR ORIGIN								
URINARY BLADDER	117	66 (56.4)	38.21 (27.76, 72.08)	113	41 (36.3)	N.A. (75.01, N.A.)	0.512 (0.346, 0.756) 0.0006	0.0349*
RENAL PELVIS	14	2 (14.3)	N.A. (21.19, N.A.)	19	9 (47.4)	66.50 (11.24, N.A.)	4.018 (0.862, 18.719) 0.0557	
URETER	11	4 (36.4)	N.A. (4.76, N.A.)	8	2 (25.0)	N.A. (9.82, N.A.)	0.778 (0.142, 4.262) 0.7716	
MINOR HISTOLOGICAL VARIANTS								
PRESENCE	62	29 (46.8)	80.69 (29.27, N.A.)	62	27 (43.5)	70.01 (46.00, N.A.)	0.870 (0.515, 1.470) 0.6026	0.1026
ABSENCE	80	43 (53.8)	37.55 (24.15, N.A.)	78	25 (32.1)	N.A. (79.24, N.A.)	0.486 (0.297, 0.797) 0.0035	

FEB2025 DBL. HR = hazard ratio; KME = Kaplan-Meier estimate; N.M.E. = Not meaningful estimate; N.A. = Not reached.

(1) KME of median time to event. (2) Unstratified Cox proportional hazard model. HR is Nivolumab over Placebo.

(3) Unstratified Log-rank test. (4) Unstratified Cox proportional hazard model with treatment, subgroup and treatment*subgroup.
p-value is from the treatment*subgroup interaction.

(5) A p-value of <0.05 is indicated by 1 asterisk.

IUC = invasive urothelial carcinoma.

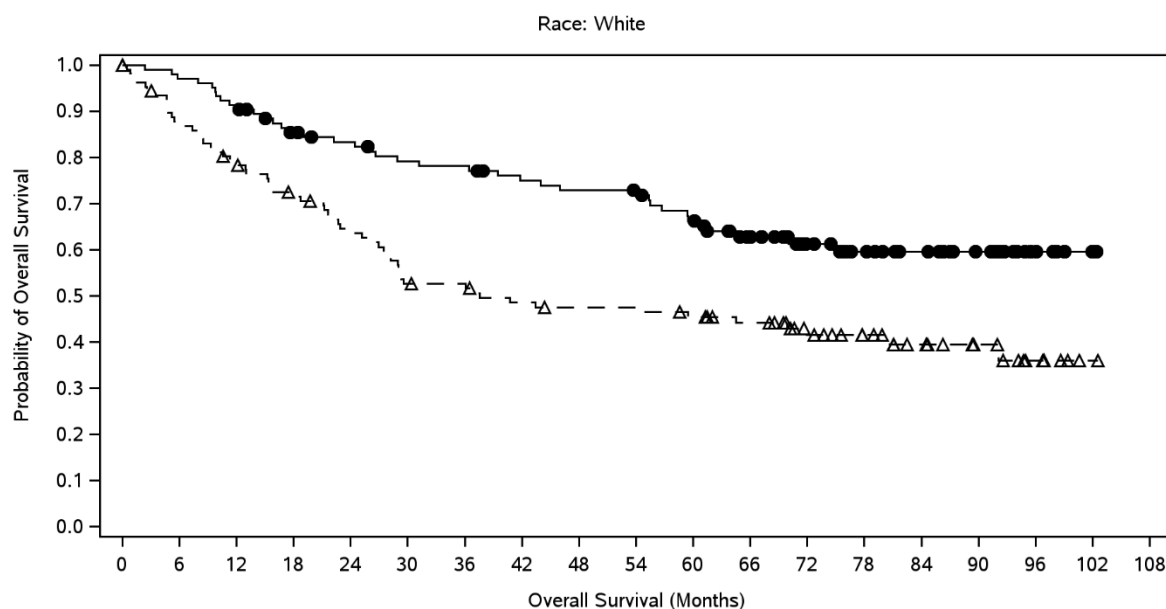
Program Path: /projects/bms214671/stats/market/ma274_202502/prog/tables

Program Name: rt-ef-sursub-ebr45.sas

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2.1.3 Kaplan-Meier Kurven für Subgruppen mit statistisch signifikantem Interaktionsterm

Figure 6.1.2
Kaplan-Meier Plot of Overall Survival - by Significant Subgroups - FAS



FEB2025 DBL.

Unstratified Cox proportional hazard.

Symbols represent censored observations.

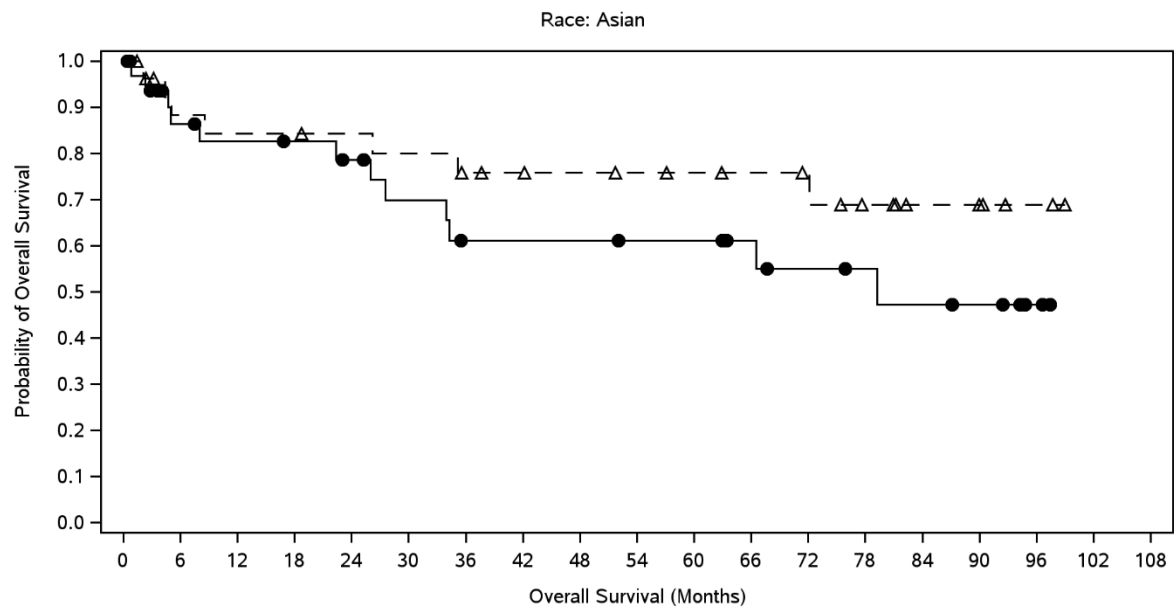
Program Path: /projects/bms214671/stats/market/ma274_202502/prog/figures

Program Name: rg-ef-subpdllrc-ebr45.sas

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Figure 6.1.2

Kaplan-Meier Plot of Overall Survival - by Significant Subgroups - FAS



Number of Subjects at Risk

Placebo

28 22 21 21 20 19 17 16 15 14 13 12 11 8 5 4 2 0 0

Nivolumab

33 24 22 21 19 16 13 13 13 12 12 10 8 7 6 5 2 0 0

—△— Placebo (events: 7/28), median and 95% CI: N.A. (72.08, N.A.)

—●— Nivolumab (events: 12/33), median and 95% CI: 79.24 (27.56, N.A.)

Hazard Ratio (Nivolumab vs. Placebo) and 95% CI: 1.808 (0.710, 4.602).

FEB2025 DBL.

Unstratified Cox proportional hazard.

Symbols represent censored observations.

Program Path: /projects/bms214671/stats/market/ma274_202502/prog/figures

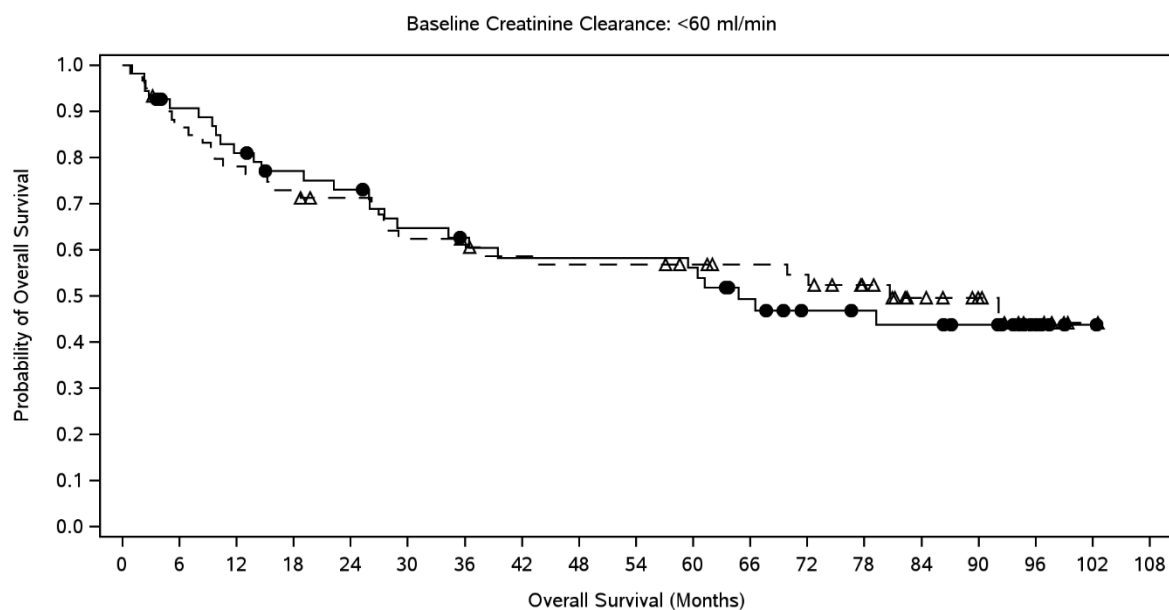
Program Name: rg-ef-subpdllrc-ebr45.sas

24JUL2025:04:02:15

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

Figure 6.1.2

Kaplan-Meier Plot of Overall Survival - by Significant Subgroups - FAS



Number of Subjects at Risk

Placebo

60 51 46 43 40 35 34 31 30 30 28 26 25 20 14 10 5 1 0

Nivolumab

54 47 42 38 36 31 29 27 27 27 26 20 16 15 14 12 5 1 0

—△— Placebo (events: 29/60), median and 95% CI: 80.69 (29.04, N.A.)

—●— Nivolumab (events: 27/54), median and 95% CI: 64.76 (28.88, N.A.)

Hazard Ratio (Nivolumab vs. Placebo) and 95% CI: 1.054 (0.624, 1.782).

FEB2025 DBL.

Unstratified Cox proportional hazard.

Symbols represent censored observations.

Program Path: /projects/bms214671/stats/market/ma274_202502/prog/figures

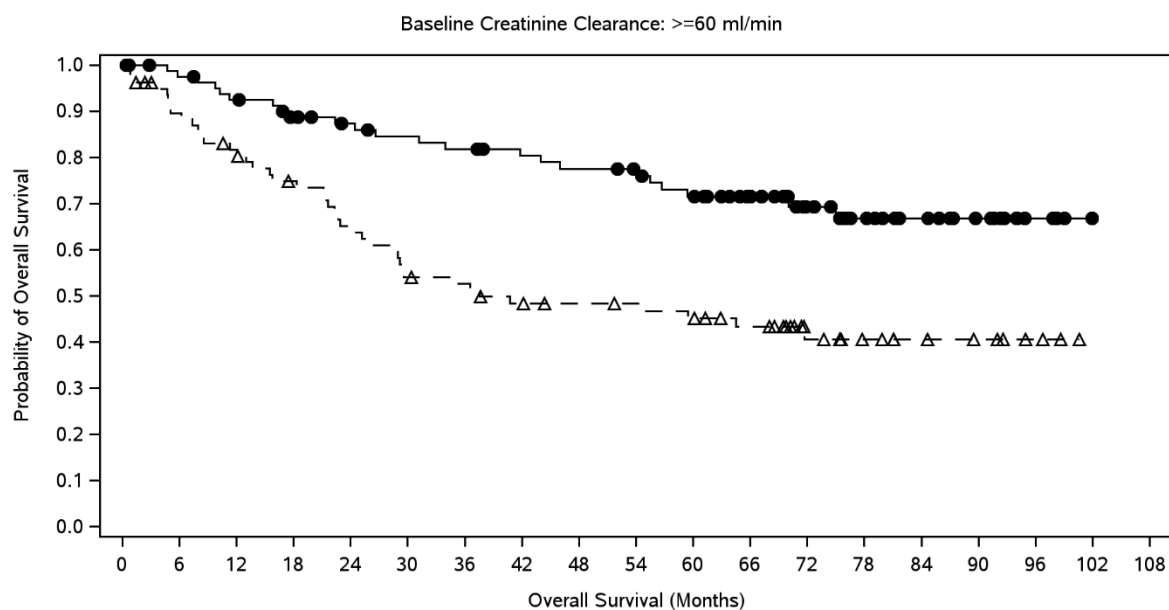
Program Name: rg-ef-subpdllrc-eb45.sas

24JUL2025:04:02:15

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

Figure 6.1.2

Kaplan-Meier Plot of Overall Survival - by Significant Subgroups - FAS



Number of Subjects at Risk

Placebo

79 68 61 54 47 39 37 33 31 30 28 24 15 11 8 6 3 0 0

Nivolumab

84 79 74 68 64 61 59 56 54 52 47 40 29 21 16 11 4 0 0

—△— Placebo (events: 42/79), median and 95% CI: 37.55 (25.89, N.A.)

—●— Nivolumab (events: 23/84), median and 95% CI: N.A.

Hazard Ratio (Nivolumab vs. Placebo) and 95% CI: 0.399 (0.240, 0.664).

FEB2025 DBL.

Unstratified Cox proportional hazard.

Symbols represent censored observations.

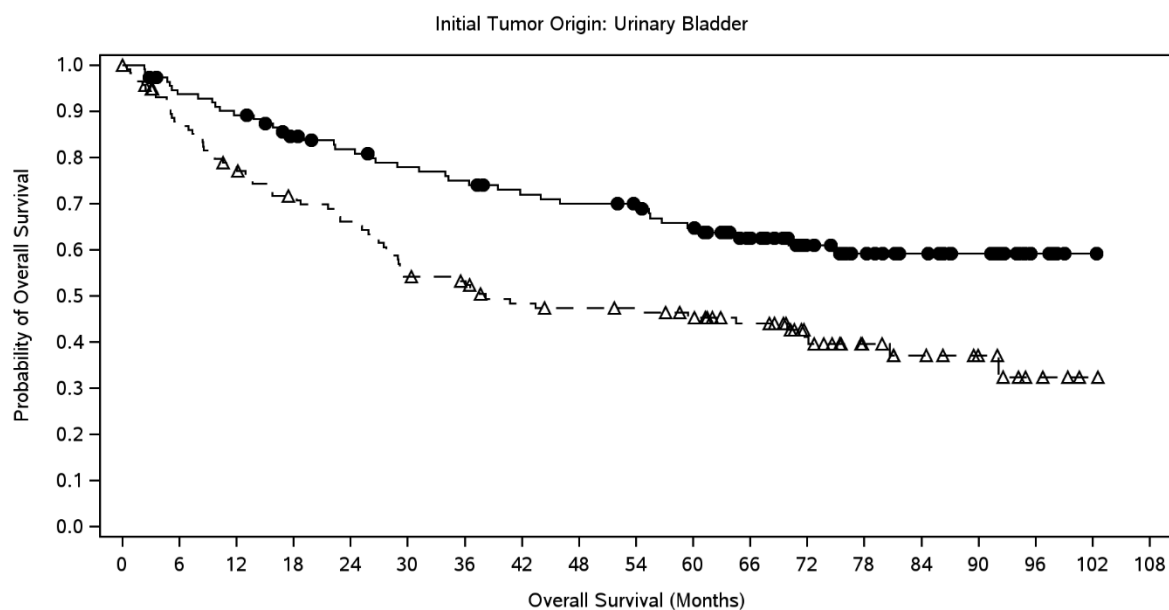
Program Path: /projects/bms214671/stats/market/ma274_202502/prog/figures

Program Name: rg-ef-subpdllrc-ebr45.sas

24JUL2025:04:02:15

Figure 6.1.2

Kaplan-Meier Plot of Overall Survival - by Significant Subgroups - FAS



Number of Subjects at Risk

Placebo

117 99 87 78 72 59 56 49 47 46 42 36 26 17 13 9 4 1 0

Nivolumab

113 104 99 90 85 80 77 72 70 68 62 50 36 27 22 17 5 1 0

— Δ — Placebo (events: 66/117), median and 95% CI: 38.21 (27.76, 72.08)

— ● — Nivolumab (events: 41/113), median and 95% CI: N.A. (75.01, N.A.)

Hazard Ratio (Nivolumab vs. Placebo) and 95% CI: 0.512 (0.346, 0.756).

FEB2025 DBL.

Unstratified Cox proportional hazard.

Symbols represent censored observations.

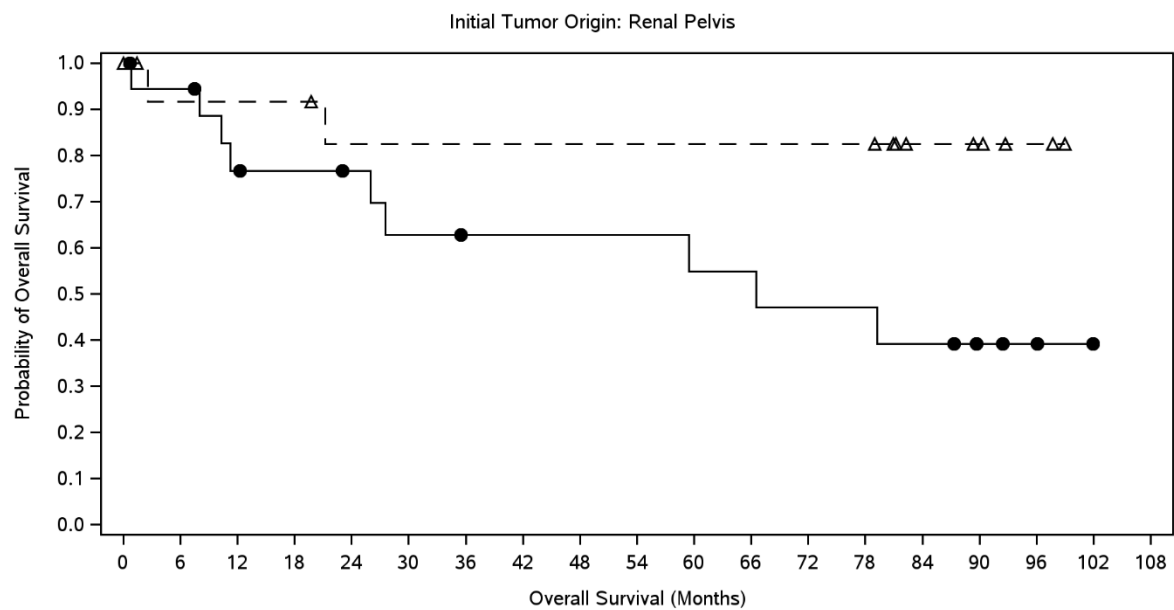
Program Path: /projects/bms214671/stats/market/ma274_202502/prog/figures

Program Name: rg-ef-subpdllrc-ebr45.sas

24JUL2025:04:02:15

Figure 6.1.2

Kaplan-Meier Plot of Overall Survival - by Significant Subgroups - FAS



FEB2025 DBL.

Unstratified Cox proportional hazard.

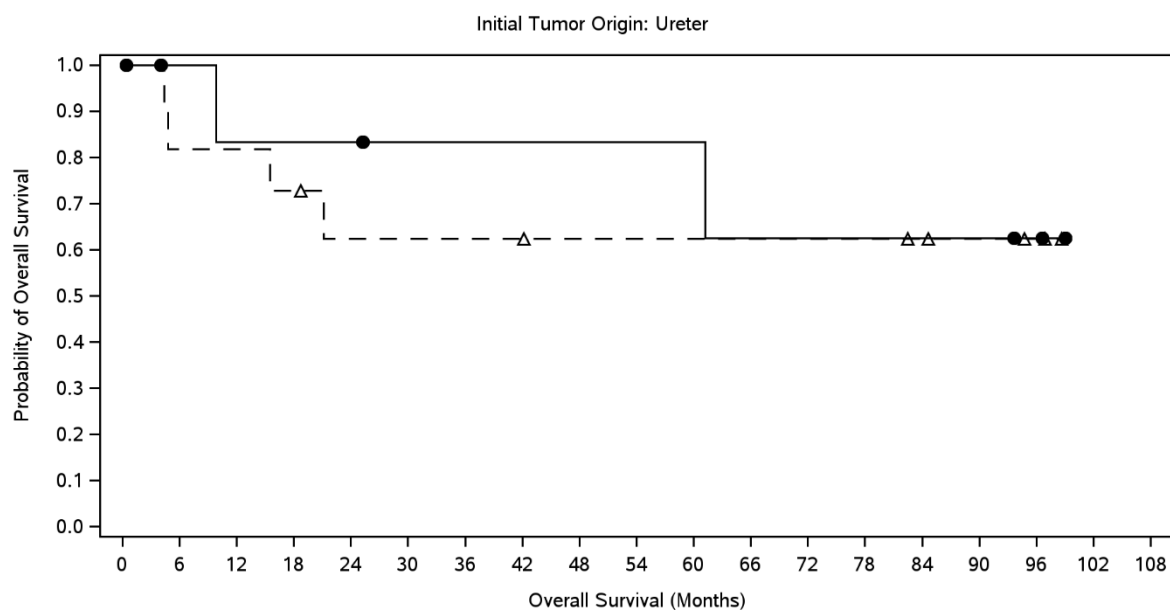
Symbols represent censored observations.

Program Path: /projects/bms214671/stats/market/ma274_202502/prog/figures

Program Name: rg-ef-subpdllrc-eb45.sas

24JUL2025:04:02:15

Figure 6.1.2
Kaplan-Meier Plot of Overall Survival - by Significant Subgroups - FAS



Number of Subjects at Risk

Placebo

11 9 9 8 6 6 6 6 5 5 5 5 5 5 4 3 2 0 0

Nivolumab

8 6 5 5 5 4 4 4 4 4 4 3 3 3 3 3 2 0 0

— Δ — Placebo (events: 4/11), median and 95% CI: N.A. (4.76, N.A.)

— ● — Nivolumab (events: 2/8), median and 95% CI: N.A. (9.82, N.A.)

Hazard Ratio (Nivolumab vs. Placebo) and 95% CI: 0.778 (0.142, 4.262).

FEB2025 DBL.

Unstratified Cox proportional hazard.

Symbols represent censored observations.

Program Path: /projects/bms214671/stats/market/ma274_202502/prog/figures

Program Name: rg-ef-subpdllrc-ebr45.sas

24JUL2025:04:02:15

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

2.1.4 Deskriptive Darstellung der ersten systemischen Folgetherapie

CA209-274 Wirkstoff(kombination)	Nivolumab (N = 140)	Placebo (N = 142)
Patient:innen mit Rezidiv ^{a,b} , n (%)	57 (40,7)	80 (56,3)
Patient:innen mit mind. einer systemischen Folgetherapie, n (% ^c)	39 (68,4)	56 (70,0)
Immuncheckpoint-Inhibitor	2 (3,5)	29 (36,3)
Atezolizumab	0	10 (12,5)
Nivolumab	1 (1,8)	2 (2,5)
Nivolumab + Ipilimumab	0	1 (1,3)
Pembrolizumab	0	15 (18,8)
Pembrolizumab + Carboplatin + Paclitaxel	1 (1,8)	0
Pembrolizumab + Cisplatin	0	1 (1,3)
Chemotherapie	36 (63,2)	25 (31,3)
Bevacizumab + Gemcitabin	0	1 (1,3)
Carboplatin + Enfortumab Vedotin	0	1 (1,3)
Carboplatin + Gemcitabin	11 (19,3)	8 (10,0)
Carboplatin + Gemcitabin + Paclitaxel	0	1 (1,3)
Carboplatin + Paclitaxel	2 (3,5)	0
Cisplatin + Docetaxel + Cetuximab	1 (1,8)	0
Cisplatin + Gemcitabin	11 (19,3)	8 (10,0)
Cisplatin + Gemcitabin + Guadecitabin	0	1 (1,3)
Cisplatin + Gemcitabin + Paclitaxel	0	1 (1,3)
Docetaxel	2 (3,5)	0
Gemcitabin	2 (3,5)	0
Methotrexat + Vinblastin + Doxorubicin + Cisplatin	2 (3,5)	2 (2,5)
Mitomycin	1 (1,8)	0
Mitomycin + Fluorouracil	1 (1,8)	0
Paclitaxel	2 (3,5)	1 (1,3)
Vinflunin	1 (1,8)	1 (1,3)
Andere	1 (1,8)	2 (2,5)
BCG (intravesikal)	0	1 (1,3)
Cabozantinib	1 (1,8)	0
Chinesische Heilkräuter	0	1 (1,3)

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

CA209-274 Wirkstoff(kombination)	Nivolumab (N = 140)	Placebo (N = 142)
ITT-Population; Datenschnitt 06.01.2025 a. gemäß DFS-Auswertung (<i>cf.</i> Modul 4, Tabelle 4-27). b. Bei 94,2 % dieser Patient:innen ist das Rezidiv schon vor dem Zeitpunkt der ersten prä-spezifizierten Interimsanalyse für das OS aufgetreten (Datum des zugehörigen Datenschnitts am 01.02.2021 mit DBL 19.05.2021, <i>cf.</i> Tabelle 4-15 in Modul 4 R). c. bezogen auf Patient:innen mit Rezidiv BCG: Bacillus Calmette-Guérin; DBL: <i>Data Base Lock</i> ; DFS: Krankheitsfreies Überleben (<i>Disease-free survival</i>); OS: Gesamtüberleben (<i>Overall survival</i>)		

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

2.1.5 Deskriptive Darstellung jeglicher Folgetherapien

Table 2.1
Subsequent Cancer Therapy Summary
FAS

	Number of Subjects (%)	
	Placebo N = 142	Nivolumab N = 140
SUBJECTS WITH ANY SUBSEQUENT THERAPY (%) (1)	63 (44.4)	50 (35.7)
SUBJECTS WHO RECEIVED SUBSEQUENT RADIOTHERAPY (%)	16 (11.3)	10 (7.1)
CURATIVE	6 (4.2)	6 (4.3)
PALLIATIVE	11 (7.7)	5 (3.6)
OTHER	1 (0.7)	1 (0.7)
SUBJECTS WHO RECEIVED SUBSEQUENT SURGERY (%)	5 (3.5)	5 (3.6)
TUMOR RESECTION, CURATIVE	2 (1.4)	3 (2.1)
TUMOR RESECTION, PALLIATIVE	3 (2.1)	1 (0.7)
OTHER	0	1 (0.7)
SUBJECTS WHO RECEIVED SUBSEQUENT SYSTEMIC THERAPY (%)	56 (39.4)	45 (32.1)
SUBJECTS WHO RECEIVED SUBSEQUENT IMMUNOTHERAPY (%)	38 (26.8)	15 (10.7)
SUBJECTS WHO RECEIVED MORE THAN ONE SINGLE DOSE OF SUBSEQUENT INTRAVESICAL CHEMOTHERAPY (%)	1 (0.7)	2 (1.4)
SUBJECTS WHO RECEIVED ONE SINGLE DOSE OF SUBSEQUENT INTRAVESICAL CHEMOTHERAPY (%)	0	0
ANTI-PD1	26 (18.3)	9 (6.4)
NIVOLUMAB	5 (3.5)	1 (0.7)
PEMBROLIZUMAB	21 (14.8)	8 (5.7)
ANTI-PDL1	12 (8.5)	7 (5.0)
ATEZOLIZUMAB	12 (8.5)	5 (3.6)
AVELUMAB	0	2 (1.4)
ANTI-CTLA4	2 (1.4)	1 (0.7)
IPILIMUMAB	2 (1.4)	1 (0.7)

FEB2025 DBL

(1) Subject may have received more than one type of subsequent therapy. Subsequent therapy was defined as therapy started on or after first dosing date (randomization date if subject never treated).

Program Path: /projects/bms214671/stats/market/ma274_202502/prog/tables

Program Name: rt-ct-futherapy-ebr45.sas

29MAY2025:14:49:05

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

Table 2.1
Subsequent Cancer Therapy Summary
FAS

	Number of Subjects (%)	
	Placebo N = 142	Nivolumab N = 140
OTHER IMMUNOTHERAPY	1 (0.7)	0
BCG VACCINE LIVE INTRAVESICAL	1 (0.7)	0
PLATINUM-BASED CHEMOTHERAPY	27 (19.0)	34 (24.3)
CARBOPLATIN	12 (8.5)	19 (13.6)
CARPLA/TAXOL	0	1 (0.7)
CISPLATIN	15 (10.6)	14 (10.0)
CISPLT/DOXRUB/METREX/VINBLA	0	2 (1.4)
OXALIPLATIN	0	2 (1.4)
VEGFR INHIBITORS	1 (0.7)	0
BEVACIZUMAB	1 (0.7)	0
UNASSIGNED	37 (26.1)	42 (30.0)
5 FLOUROCELE	0	1 (0.7)
5-FLUOROURACIL	0	1 (0.7)
5-FU	0	1 (0.7)
ALBUMIN PACLITAXEL	0	1 (0.7)
ALPELISIB	1 (0.7)	0
ANTICANCER CHINESE MEDICINE	1 (0.7)	0
AZD4547	0	1 (0.7)
CAPECITABINE AT 1500MG/1000MG	0	1 (0.7)
CAPECITABINE AT 850MG/M2 BID	0	1 (0.7)
CARBOZANTINIB	0	1 (0.7)
DOCETAXEL	0	1 (0.7)
DABRAFENIB	0	1 (0.7)
DOCETAXEL	1 (0.7)	3 (2.1)
DOXIRIBUCIN	0	1 (0.7)
DOXORUBICIN	1 (0.7)	1 (0.7)
DOXORUBICIN HCL	1 (0.7)	1 (0.7)
ENFORTUMAB	0	1 (0.7)

FEB2025 DBL

(1) Subject may have received more than one type of subsequent therapy. Subsequent therapy was defined as therapy started on or after first dosing date (randomization date if subject never treated).

Program Path: /projects/bms214671/stats/market/ma274_202502/prog/tables

Program Name: rt-ct-futherapy-ebr45.sas

29MAY2025:14:49:05

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

Table 2.1
Subsequent Cancer Therapy Summary
FAS

	Number of Subjects (%)	
	Placebo N = 142	Nivolumab N = 140
ENFORTUMAB VEDOTIN	2 (1.4)	3 (2.1)
ENFORTUMAB-VEDOTIN	0	1 (0.7)
ERBITUX	0	1 (0.7)
ERDAFITINIB	1 (0.7)	0
FLURORURACIL	0	1 (0.7)
GEMBITABINE	1 (0.7)	0
GEMCITABIN	1 (0.7)	4 (2.9)
GEMCITABINE	15 (10.6)	15 (10.7)
GEMCITABINE 1200 MG+SODIUM CHLORIDE 250ML IVD	1 (0.7)	0
GEMCITABINE 1200MG+SODIUM CHLORIDE 250 ML IVD	1 (0.7)	0
GEMCITABINE 1200MG+SODIUM CHLORIDE 250ML IVD	1 (0.7)	0
GEMCITABINE 1550MG + SODIUM CHLORIDE 250ML IVD	1 (0.7)	0
GEMCITABINE 1550MG+SODIUM CHLORIDE 250ML IVD	1 (0.7)	0
GEMCITABINE HYDROCHLORIDE	3 (2.1)	3 (2.1)
GEMCITABINE IV	1 (0.7)	0
GEMCITACIBINE	0	1 (0.7)
GEMCITIBINE	1 (0.7)	0
GEMZAR	2 (1.4)	4 (2.9)
GENCITABINE	1 (0.7)	0
IFOSFAMIDE	1 (0.7)	0
LEUCOVORIN	0	1 (0.7)
METHOTREXATE	2 (1.4)	2 (1.4)
MITOMYCIN	0	1 (0.7)
MITOMYCINC	0	1 (0.7)
PACLITAXEL	9 (6.3)	4 (2.9)
PADCEV	0	1 (0.7)
SACITUZUMAB GOVITECAN	0	1 (0.7)
SGI 110	1 (0.7)	0
TAXOL	0	1 (0.7)
TRAMETINIB	0	1 (0.7)
VINBLASTINE	1 (0.7)	1 (0.7)

FEB2025 DBL

(1) Subject may have received more than one type of subsequent therapy. Subsequent therapy was defined as therapy started on or after first dosing date (randomization date if subject never treated).

Program Path: /projects/bms214671/stats/market/ma274_202502/prog/tables

Program Name: rt-ct-futherapy-ebr45.sas

29MAY2025:14:49:05

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

Table 2.1
Subsequent Cancer Therapy Summary
FAS

	Number of Subjects (%)	
	Placebo N = 142	Nivolumab N = 140
VINBLASTINE SULFATE	1 (0.7)	1 (0.7)
VINFLUNIN	0	1 (0.7)
VINFLUNINA	1 (0.7)	0
VINFLUNINE	1 (0.7)	3 (2.1)
VINFLUNINUM	1 (0.7)	0
VOFATAMAB	1 (0.7)	0

FEB2025 DBL

(1) Subject may have received more than one type of subsequent therapy. Subsequent therapy was defined as therapy started on or after first dosing date (randomization date if subject never treated).

Program Path: /projects/bms214671/stats/market/ma274_202502/prog/tables

Program Name: rt-ct-futherapy-ebr45.sas

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3 Morbidität

3.1 Rezidive: Endpunkt Krankheitsfreies Überleben (DFS)

Für die Auswertungen wurde ITT-Population herangezogen.

3.1.1 Zensierungsgründe (deskriptive Darstellung)

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

Table 5.1
Disease Free Survival (AMNOG Primary Definition) Incidence by DFS Component
FAS

	Number of Subjects (%)	
	Placebo N = 142	Nivolumab N = 140
NUMBER OF EVENTS (%)	92 (64.8)	68 (48.6)
TYPE OF EVENTS (%)		
DISEASE AT BASELINE	1 (0.7)	0
RECURRENCE	80 (56.3)	57 (40.7)
DISTANT RECURRENCE	55 (38.7)	46 (32.9)
LOCAL NON-UROTHELIAL TRACT	20 (14.1)	7 (5.0)
LOCAL UROTHELIAL TRACT INVASIVE	3 (2.1)	1 (0.7)
LOCAL UROTHELIAL TRACT NON-INVASIVE	2 (1.4)	3 (2.1)
DEATH	11 (7.7)	11 (7.9)
NUMBER OF SUBJECTS CENSORED (%)	50 (35.2)	72 (51.4)
CENSORED ON DATE OF RANDOMIZATION	5 (3.5)	4 (2.9)
NO BASELINE DISEASE ASSESSMENT	0	0
NEVER TREATED	0	0
OTHER	0	0
NO ON-STUDY DISEASE ASSESSMENT AND NO DEATH	5 (3.5)	4 (2.9)
NEVER TREATED	2 (1.4)	0
NEW NON-UROTHELIAL CARCINOMA PRIMARY CANCER	0	1 (0.7)
RECEIVED SUBSEQUENT ANTI CANCER THERAPY	0	0
OFF STUDY	3 (2.1)	3 (2.1)
OTHER	0	0

FEB2025 DBL. If there are no subjects with or without events in treatment groups, presentation of effect measures as N.M.E.

(1) Odds Ratio (OR) and Relative Risk (RR) of Nivolumab over Placebo. Risk difference (RD) is Nivolumab minus Placebo.

Estimates are based on Mantel-Haenszel method adjusted by prior neo-adjuvant cisplatin, pathological nodal status, as entered in IRT. 95% CIs are based on normal approximation.

p-value are based on normal approximation,

DFS (AMNOG Primary Definition) accounts for disease assessments occurring on or after initiation of subsequent anticancer therapy.

Program Path: /projects/bms214671/stats/market/ma274_202502/prog/tables

Program Name: rt-ef-dfscomp-ebr45.sas

16JUL2025:11:02:04

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

Table 5.1
Disease Free Survival (AMNOG Primary Definition) Incidence by DFS Component
FAS

	Number of Subjects (%)	
	Placebo N = 142	Nivolumab N = 140
CENSORED ON DATE OF LAST DISEASE ASSESSMENT ON-STUDY	45 (31.7)	68 (48.6)
NEW NON-UROTHELIAL CARCINOMA PRIMARY CANCER	3 (2.1)	5 (3.6)
STILL ON-TREATMENT	0	0
IN FOLLOW-UP	31 (21.8)	52 (37.1)
OFF STUDY	11 (7.7)	11 (7.9)
LOST TO FOLLOW-UP	5 (3.5)	4 (2.9)
SUBJECT WITHDREW CONSENT	3 (2.1)	5 (3.6)
OTHER	3 (2.1)	2 (1.4)
ODDS RATIO (1) (95% CI)	0.51 (0.32, 0.83)	
RELATIVE RISK (1) (95% CI) P-VALUE	0.75 (0.61, 0.92) 0.0068	
RISK DIFFERENCE (1) (95% CI)	-16.27 (-27.66, -4.87)	

FEB2025 DBL. If there are no subjects with or without events in treatment groups, presentation of effect measures as N.M.E.

(1) Odds Ratio (OR) and Relative Risk (RR) of Nivolumab over Placebo. Risk difference (RD) is Nivolumab minus Placebo.

Estimates are based on Mantel-Haenszel method adjusted by prior neo-adjuvant cisplatin, pathological nodal status,

as entered in IRT. 95% CIs are based on normal approximation.

p-value are based on normal approximation,

DFS (AMNOG Primary Definition) accounts for disease assessments occurring on or after initiation of subsequent anticancer therapy.

Program Path: /projects/bms214671/stats/market/ma274_202502/prog/tables

Program Name: rt-ef-dfscomp-ebr45.sas

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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

3.1.2 Subgruppenanalysen

Table 6.1
Subgroup Analyses of Disease Free Survival (AMNOG Primary Definition)
FAS

Subgroups	Placebo			Nivolumab			Nivolumab vs. Placebo	
	N	Subjects with Event n (%)	KME [95%CI] (mon) (1)	N	Subjects with Event n (%)	KME [95%CI] (mon) (1)	HR [95%CI] P-value (2) (3)	Test for Interaction P-value (4) (5)
OVERALL	142	92 (64.8)	8.41 (5.59, 20.04)	140	68 (48.6)	55.49 (25.79, 66.50)	0.579 (0.422, 0.793) 0.0006	
PRIOR NEO-ADJUVANT CISPLATIN THERAPY								0.1404
YES	61	44 (72.1)	7.59 (3.02, 16.59)	57	26 (45.6)	59.40 (25.79, N.A.)	0.438 (0.268, 0.714) 0.0007	
NO	81	48 (59.3)	11.37 (5.59, 37.75)	83	42 (50.6)	39.49 (19.45, N.A.)	0.715 (0.471, 1.085) 0.1142	

FEB2025 DBL. HR = hazard ratio; KME = Kaplan-Meier estimate; N.M.E. = Not meaningful estimate; N.A. = Not reached.

(1) KME of median time to event. (2) Unstratified Cox proportional hazard model. HR is Nivolumab over Placebo.

(3) Unstratified Log-rank test. (4) Unstratified Cox proportional hazard model with treatment, subgroup and treatment*subgroup.

p-value is from the treatment*subgroup interaction.

(5) A p-value of <0.05 is indicated by 1 asterisk.

IUC = invasive urothelial carcinoma.

DFS (AMNOG Primary Definition) accounts for disease assessments occurring on or after initiation of subsequent anticancer therapy.

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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

Table 6.1
Subgroup Analyses of Disease Free Survival (AMNOG Primary Definition)
FAS

Subgroups	Placebo			Nivolumab			Nivolumab vs. Placebo	
	N	Subjects with Event n (%)	KME [95%CI] (mon) (1)	N	Subjects with Event n (%)	KME [95%CI] (mon) (1)	HR [95%CI] P-value (2) (3)	Test for Interaction P-value (4) (5)
PRIOR CISPLATIN STATUS								
RECEIVED NEO-ADJUVANT	61	44 (72.1)	7.59 (3.02, 16.59)	57	26 (45.6)	59.40 (25.79, N.A.)	0.438 (0.268, 0.714) 0.0007	0.1540
UNWILLING TO RECEIVE NEO-ADJUVANT	46	27 (58.7)	21.59 (5.55, N.A.)	51	27 (52.9)	29.67 (19.42, N.A.)	0.870 (0.505, 1.502) 0.6203	
NOT ELIGIBLE TO RECEIVE NEO-ADJUVANT	34	21 (61.8)	7.66 (2.83, 21.19)	27	11 (40.7)	N.A. (8.34, N.A.)	0.453 (0.218, 0.944) 0.0298	
USE OF ANY PRIOR NEO-ADJUVANT SYSTEMIC THERAPY								
YES	62	45 (72.6)	6.77 (3.02, 15.21)	61	28 (45.9)	59.40 (25.79, N.A.)	0.437 (0.271, 0.703) 0.0005	0.1180
NO	80	47 (58.8)	16.72 (5.59, 37.75)	79	40 (50.6)	39.49 (19.45, N.A.)	0.728 (0.476, 1.113) 0.1430	

FEB2025 DBL. HR = hazard ratio; KME = Kaplan-Meier estimate; N.M.E. = Not meaningful estimate; N.A. = Not reached.

(1) KME of median time to event. (2) Unstratified Cox proportional hazard model. HR is Nivolumab over Placebo.

(3) Unstratified Log-rank test. (4) Unstratified Cox proportional hazard model with treatment, subgroup and treatment*subgroup.

p-value is from the treatment*subgroup interaction.

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PATHOLOGICAL LYMPH NODE STATUS								0.2111
N+	66	52 (78.8)	5.49 (2.79, 8.41)	60	34 (56.7)	47.11 (8.31, N.A.)	0.474 (0.306, 0.736) 0.0007	
N0/X WITH <10 NODES REMOVED	38	19 (50.0)	25.95 (5.62, N.A.)	38	19 (50.0)	39.49 (10.78, N.A.)	0.901 (0.473, 1.718) 0.7543	
N0 WITH >= 10 NODES REMOVED	38	21 (55.3)	28.98 (5.59, N.A.)	42	15 (35.7)	N.A. (42.55, N.A.)	0.508 (0.261, 0.986) 0.0416	

FEB2025 DBL. HR = hazard ratio; KME = Kaplan-Meier estimate; N.M.E. = Not meaningful estimate; N.A. = Not reached.

(1) KME of median time to event. (2) Unstratified Cox proportional hazard model. HR is Nivolumab over Placebo.

(3) Unstratified Log-rank test. (4) Unstratified Cox proportional hazard model with treatment, subgroup and treatment*subgroup. p-value is from the treatment*subgroup interaction.

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	N	Subjects with Event n (%)	KME [95%CI] (mon) (1)	N	Subjects with Event n (%)	KME [95%CI] (mon) (1)	HR [95%CI] P-value (2) (3)	Test for Interaction P-value (4) (5)
PATHOLOGICAL STATUS								
PT0-2	31	19 (61.3)	15.21 (6.77, N.A.)	26	13 (50.0)	59.40 (14.75, N.A.)	0.698 (0.341, 1.429) 0.3264	0.8360
PT3	83	52 (62.7)	5.75 (3.25, 21.19)	87	43 (49.4)	52.53 (19.42, N.A.)	0.567 (0.378, 0.850) 0.0054	
PT4A	27	20 (74.1)	8.25 (2.83, 28.98)	23	12 (52.2)	29.67 (4.99, N.A.)	0.589 (0.287, 1.208) 0.1446	
AGE CATEGORY I								
< 65	61	35 (57.4)	10.84 (3.25, N.A.)	67	28 (41.8)	62.69 (47.11, N.A.)	0.549 (0.333, 0.904) 0.0169	0.5732
>= 65	81	57 (70.4)	8.25 (5.49, 22.14)	73	40 (54.8)	29.67 (14.75, N.A.)	0.627 (0.417, 0.942) 0.0234	

FEB2025 DBL. HR = hazard ratio; KME = Kaplan-Meier estimate; N.M.E. = Not meaningful estimate; N.A. = Not reached.

(1) KME of median time to event. (2) Unstratified Cox proportional hazard model. HR is Nivolumab over Placebo.

(3) Unstratified Log-rank test. (4) Unstratified Cox proportional hazard model with treatment, subgroup and treatment*subgroup.

p-value is from the treatment*subgroup interaction.

(5) A p-value of <0.05 is indicated by 1 asterisk.

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FAS

Subgroups	Placebo			Nivolumab			Nivolumab vs. Placebo	
	N	Subjects with Event n (%)	KME [95%CI] (mon) (1)	N	Subjects with Event n (%)	KME [95%CI] (mon) (1)	HR [95%CI] P-value (2) (3)	Test for Interaction P-value (4) (5)
AGE CATEGORY II								0.8185
< 65	61	35 (57.4)	10.84 (3.25, N.A.)	67	28 (41.8)	62.69 (47.11, N.A.)	0.549 (0.333, 0.904) 0.0169	
>= 65 AND < 75	59	40 (67.8)	10.87 (5.55, 25.95)	49	25 (51.0)	54.08 (14.75, N.A.)	0.583 (0.352, 0.965) 0.0339	
>= 75	22	17 (77.3)	5.52 (2.63, 22.14)	24	15 (62.5)	21.75 (2.86, N.A.)	0.730 (0.360, 1.479) 0.3792	

FEB2025 DBL. HR = hazard ratio; KME = Kaplan-Meier estimate; N.M.E. = Not meaningful estimate; N.A. = Not reached.

(1) KME of median time to event. (2) Unstratified Cox proportional hazard model. HR is Nivolumab over Placebo.

(3) Unstratified Log-rank test. (4) Unstratified Cox proportional hazard model with treatment, subgroup and treatment*subgroup. p-value is from the treatment*subgroup interaction.

(5) A p-value of <0.05 is indicated by 1 asterisk.

IUC = invasive urothelial carcinoma.

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	N	Subjects with Event n (%)	KME [95%CI] (mon) (1)	N	Subjects with Event n (%)	KME [95%CI] (mon) (1)	HR [95%CI] P-value (2) (3)	Test for Interaction P-value (4) (5)
REGION								0.1828
US	24	16 (66.7)	10.84 (2.37, 37.75)	17	6 (35.3)	N.A. (8.31, N.A.)	0.382 (0.149, 0.979) 0.0374	
EUROPE	70	46 (65.7)	13.57 (4.70, 24.38)	73	38 (52.1)	55.49 (21.75, N.A.)	0.607 (0.393, 0.936) 0.0230	
ASIA	28	14 (50.0)	25.95 (5.45, N.A.)	33	16 (48.5)	29.67 (5.59, N.A.)	0.911 (0.440, 1.889) 0.8071	
REST OF WORLD	20	16 (80.0)	5.55 (2.63, 8.21)	17	8 (47.1)	N.A. (5.16, N.A.)	0.308 (0.128, 0.743) 0.0057	
GENDER								0.1183
MALE	112	78 (69.6)	8.25 (5.19, 17.94)	101	47 (46.5)	55.49 (25.79, N.A.)	0.498 (0.346, 0.717) 0.0001	
FEMALE	30	14 (46.7)	28.98 (2.79, N.A.)	39	21 (53.8)	42.55 (5.72, N.A.)	0.908 (0.458, 1.800) 0.7868	

FEB2025 DBL. HR = hazard ratio; KME = Kaplan-Meier estimate; N.M.E. = Not meaningful estimate; N.A. = Not reached.

(1) KME of median time to event. (2) Unstratified Cox proportional hazard model. HR is Nivolumab over Placebo.

(3) Unstratified Log-rank test. (4) Unstratified Cox proportional hazard model with treatment, subgroup and treatment*subgroup.

p-value is from the treatment*subgroup interaction.

(5) A p-value of <0.05 is indicated by 1 asterisk.

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FAS

Subgroups	Placebo			Nivolumab			Nivolumab vs. Placebo	
	N	Subjects with Event n (%)	KME [95%CI] (mon) (1)	N	Subjects with Event n (%)	KME [95%CI] (mon) (1)	HR [95%CI] P-value (2) (3)	Test for Interaction P-value (4) (5)
RACE								0.1234
WHITE	109	74 (67.9)	8.41 (5.19, 17.94)	104	50 (48.1)	59.40 (25.79, N.A.)	0.499 (0.347, 0.716) 0.0001	
ASIAN	28	14 (50.0)	25.95 (5.45, N.A.)	33	16 (48.5)	29.67 (5.59, N.A.)	0.911 (0.440, 1.889) 0.8071	
BASELINE ECOG STATUS								0.2041
0	85	54 (63.5)	10.87 (5.59, 22.14)	86	37 (43.0)	62.69 (39.49, N.A.)	0.510 (0.335, 0.776) 0.0014	
1	53	34 (64.2)	8.41 (2.92, 33.25)	51	31 (60.8)	25.79 (11.86, 59.40)	0.787 (0.481, 1.288) 0.3430	

FEB2025 DBL. HR = hazard ratio; KME = Kaplan-Meier estimate; N.M.E. = Not meaningful estimate; N.A. = Not reached.

(1) KME of median time to event. (2) Unstratified Cox proportional hazard model. HR is Nivolumab over Placebo.

(3) Unstratified Log-rank test. (4) Unstratified Cox proportional hazard model with treatment, subgroup and treatment*subgroup.

p-value is from the treatment*subgroup interaction.

(5) A p-value of <0.05 is indicated by 1 asterisk.

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	N	Subjects with Event n (%)	KME [95%CI] (mon) (1)	N	Subjects with Event n (%)	KME [95%CI] (mon) (1)	HR [95%CI] P-value (2) (3)	Test for Interaction P-value (4) (5)
SMOKING STATUS								
NEVER SMOKED	40	24 (60.0)	8.21 (2.79, N.A.)	42	22 (52.4)	19.45 (5.62, N.A.)	0.686 (0.382, 1.233) 0.2091	0.3615
CURRENT/FORMER	101	68 (67.3)	8.41 (5.59, 20.70)	96	44 (45.8)	59.40 (25.79, N.A.)	0.503 (0.343, 0.737) 0.0003	
BASELINE HEMOGLOBIN								
<10 G/DL	14	7 (50.0)	15.21 (2.04, N.A.)	7	4 (57.1)	66.50 (1.97, N.A.)	0.813 (0.210, 3.147) 0.7708	0.3621
>=10 G/DL	125	84 (67.2)	8.41 (5.59, 20.04)	132	63 (47.7)	55.49 (25.79, N.A.)	0.544 (0.392, 0.756) 0.0002	

FEB2025 DBL. HR = hazard ratio; KME = Kaplan-Meier estimate; N.M.E. = Not meaningful estimate; N.A. = Not reached.

(1) KME of median time to event. (2) Unstratified Cox proportional hazard model. HR is Nivolumab over Placebo.

(3) Unstratified Log-rank test. (4) Unstratified Cox proportional hazard model with treatment, subgroup and treatment*subgroup.

p-value is from the treatment*subgroup interaction.

(5) A p-value of <0.05 is indicated by 1 asterisk.

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	N	Subjects with Event n (%)	KME [95%CI] (mon) (1)	N	Subjects with Event n (%)	KME [95%CI] (mon) (1)	HR [95%CI] P-value (2) (3)	Test for Interaction P-value (4) (5)
BASELINE CREATININE CLEARANCE								0.0203*
<60 ML/MIN	60	37 (61.7)	8.21 (4.63, N.A.)	54	32 (59.3)	20.80 (5.72, N.A.)	0.898 (0.555, 1.451)	
>=60 ML/MIN	79	54 (68.4)	10.84 (5.19, 20.70)	84	34 (40.5)	N.A. (51.48, N.A.)	0.6626 0.406 (0.263, 0.625) <0.0001	
TIME FROM IUC SURGERY TO RANDOMIZATION (DAYS)								0.2153
>30-60	28	16 (57.1)	7.08 (2.73, N.A.)	35	22 (62.9)	9.89 (5.16, 47.11)	0.964 (0.506, 1.837)	
>60-90	66	41 (62.1)	11.86 (4.63, 24.38)	57	23 (40.4)	N.A. (25.79, N.A.)	0.9217 0.490 (0.293, 0.818)	
>90-120	41	31 (75.6)	8.41 (4.63, 20.04)	46	22 (47.8)	55.49 (42.55, N.A.)	0.0052 0.492 (0.281, 0.862) 0.0120	

FEB2025 DBL. HR = hazard ratio; KME = Kaplan-Meier estimate; N.M.E. = Not meaningful estimate; N.A. = Not reached.

(1) KME of median time to event. (2) Unstratified Cox proportional hazard model. HR is Nivolumab over Placebo.

(3) Unstratified Log-rank test. (4) Unstratified Cox proportional hazard model with treatment, subgroup and treatment*subgroup.

p-value is from the treatment*subgroup interaction.

(5) A p-value of <0.05 is indicated by 1 asterisk.

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	N	Subjects with Event n (%)	KME [95%CI] (mon) (1)	N	Subjects with Event n (%)	KME [95%CI] (mon) (1)	HR [95%CI] P-value (2) (3)	Test for Interaction P-value (4) (5)
INITIAL TUMOR ORIGIN								
URINARY BLADDER	117	79 (67.5)	8.25 (4.70, 16.59)	113	53 (46.9)	59.40 (39.49, N.A.)	0.502 (0.353, 0.713) <0.0001	0.0393*
RENAL PELVIS	14	5 (35.7)	N.A. (2.76, N.A.)	19	12 (63.2)	11.24 (5.06, N.A.)	2.091 (0.718, 6.087)	
URETER	11	8 (72.7)	5.75 (2.37, N.A.)	8	3 (37.5)	N.A. (2.79, N.A.)	0.1670 0.479 (0.126, 1.819) 0.2692	
MINOR HISTOLOGICAL VARIANTS								
PRESENCE	62	39 (62.9)	11.37 (5.65, 69.88)	62	35 (56.5)	42.55 (19.45, 62.69)	0.754 (0.476, 1.195) 0.2288	0.0974
ABSENCE	80	53 (66.3)	5.75 (3.25, 20.70)	78	33 (42.3)	66.50 (25.79, N.A.)	0.449 (0.289, 0.697) 0.0003	

FEB2025 DBL. HR = hazard ratio; KME = Kaplan-Meier estimate; N.M.E. = Not meaningful estimate; N.A. = Not reached.

(1) KME of median time to event. (2) Unstratified Cox proportional hazard model. HR is Nivolumab over Placebo.

(3) Unstratified Log-rank test. (4) Unstratified Cox proportional hazard model with treatment, subgroup and treatment*subgroup.
p-value is from the treatment*subgroup interaction.

(5) A p-value of <0.05 is indicated by 1 asterisk.

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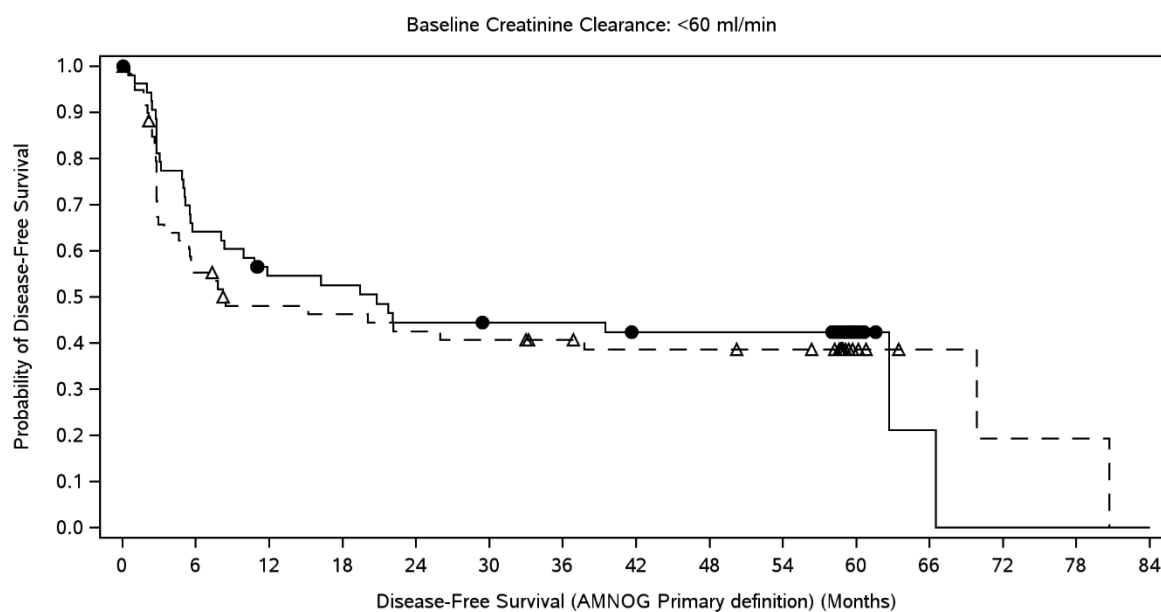
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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

3.1.3 Kaplan-Meier Kurven für Subgruppen mit statistisch signifikantem Interaktionsterm

Figure 6.1.1

Kaplan-Meier Plot of Disease Free Survival (AMNOG Primary Definition) - by Significant Subgroups - FAS



Number of Subjects at Risk

Placebo

60	32	26	25	23	22	20	18	18	17	5	2	1	1	0

Nivolumab

54	34	27	26	22	21	21	19	19	19	5	1	0	0	0

— Δ — Placebo (events: 37/60), median and 95% CI: 8.21 (4.63, N.A.)

— ● — Nivolumab (events: 32/54), median and 95% CI: 20.80 (5.72, N.A.)

Hazard Ratio (Nivolumab vs. Placebo) and 95% CI: 0.898 (0.555, 1.451).

FEB2025 DBL.

Unstratified Cox proportional hazard.

Symbols represent censored observations.

DFS (AMNOG Primary Definition) accounts for disease assessments occurring on or after initiation of subsequent anticancer therapy.

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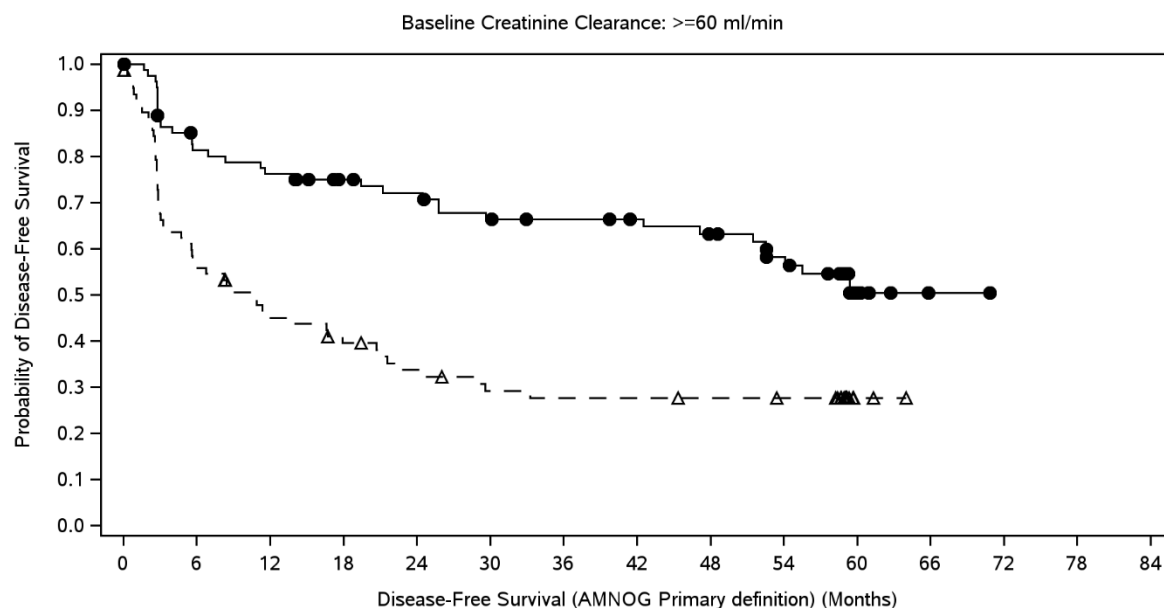
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Figure 6.1.1

Kaplan-Meier Plot of Disease Free Survival (AMNOG Primary Definition) - by Significant Subgroups - FAS



Number of Subjects at Risk

Placebo

79 43 33 28 23 19 18 18 17 16 2 0 0 0 0

Nivolumab

84 64 60 54 51 46 44 42 39 33 7 1 0 0 0

— △ — Placebo (events: 54/79), median and 95% CI: 10.84 (5.19, 20.70)

— ● — Nivolumab (events: 34/84), median and 95% CI: N.A. (51.48, N.A.)

Hazard Ratio (Nivolumab vs. Placebo) and 95% CI: 0.406 (0.263, 0.625).

FEB2025 DBL.

Unstratified Cox proportional hazard.

Symbols represent censored observations.

DFS (AMNOG Primary Definition) accounts for disease assessments occurring on or after initiation of subsequent anticancer therapy.

Program Path: /projects/bms214671/stats/market/ma274_202502/prog/figures

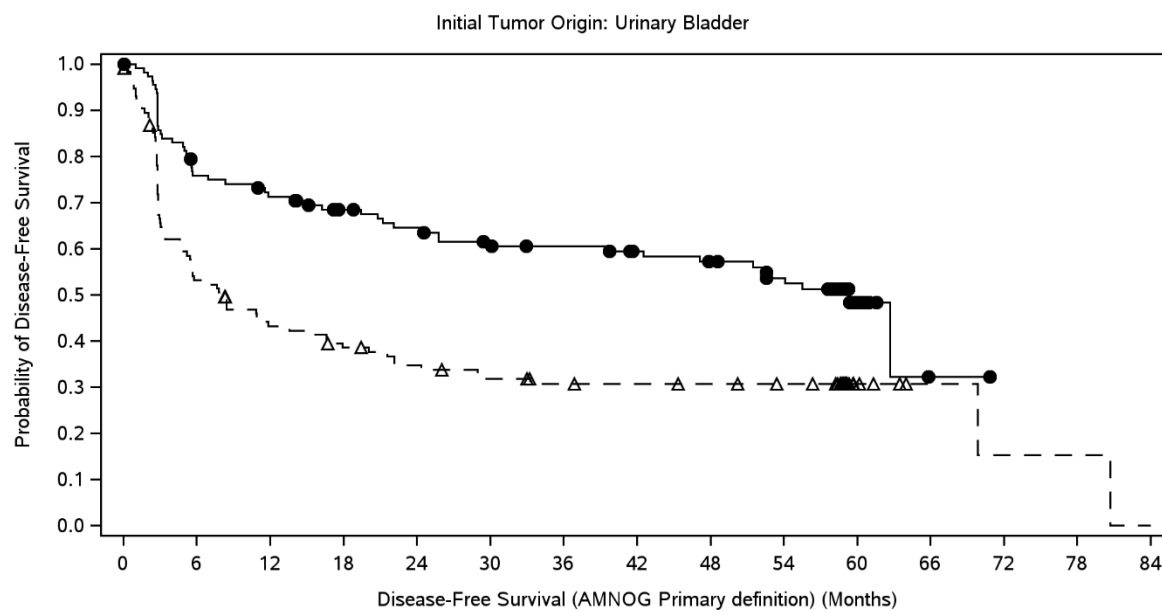
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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

Figure 6.1.1

Kaplan-Meier Plot of Disease Free Survival (AMNOG Primary Definition) - by Significant Subgroups - FAS



Number of Subjects at Risk

Placebo

117 60 47 41 36 32 29 28 27 25 6 2 1 1 0

Nivolumab

113 84 78 70 65 59 57 53 50 44 10 1 0 0 0

— Δ — Placebo (events: 79/117), median and 95% CI: 8.25 (4.70, 16.59)

—●— Nivolumab (events: 53/113), median and 95% CI: 59.40 (39.49, N.A.)

Hazard Ratio (Nivolumab vs. Placebo) and 95% CI: 0.502 (0.353, 0.713).

FEB2025 DBL.

Unstratified Cox proportional hazard.

Symbols represent censored observations.

DFS (AMNOG Primary Definition) accounts for disease assessments occurring on or after initiation of subsequent anticancer therapy.

Program Path: /projects/bms214671/stats/market/ma274_202502/prog/figures

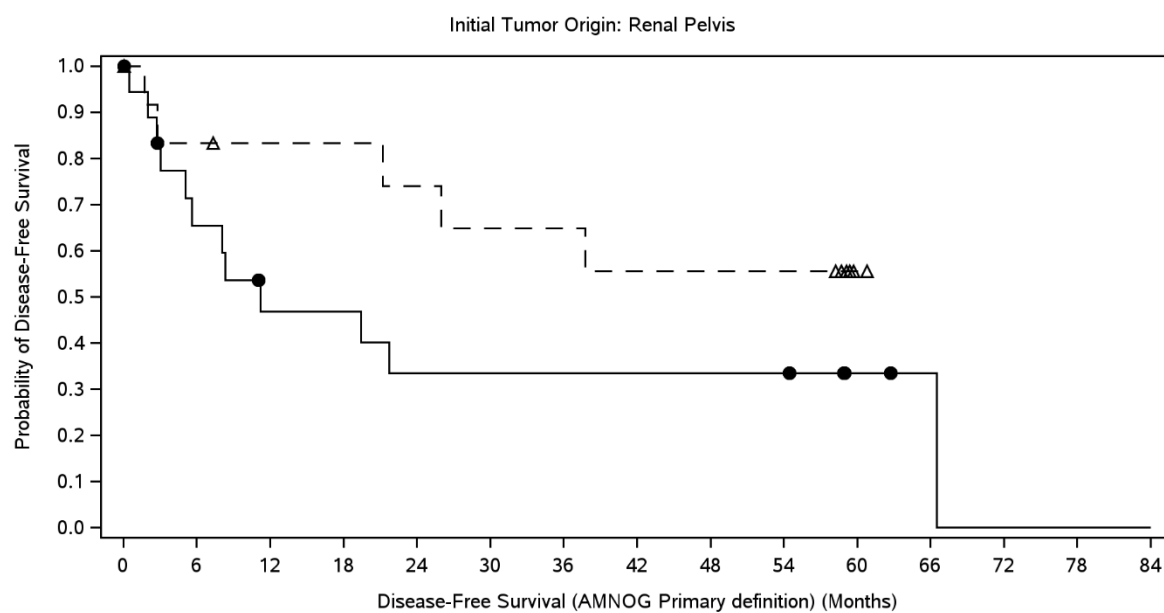
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24JUL2025:04:02:43

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

Figure 6.1.1

Kaplan-Meier Plot of Disease Free Survival (AMNOG Primary Definition) - by Significant Subgroups - FAS



Number of Subjects at Risk

Placebo

14 10 9 9 8 7 7 6 6 6 1 0 0 0 0

Nivolumab

19 11 7 7 5 5 5 5 5 5 2 1 0 0 0

— △ — Placebo (events: 5/14), median and 95% CI: N.A. (2.76, N.A.)

— ● — Nivolumab (events: 12/19), median and 95% CI: 11.24 (5.06, N.A.)

Hazard Ratio (Nivolumab vs. Placebo) and 95% CI: 2.091 (0.718, 6.087).

FEB2025 DBL.

Unstratified Cox proportional hazard.

Symbols represent censored observations.

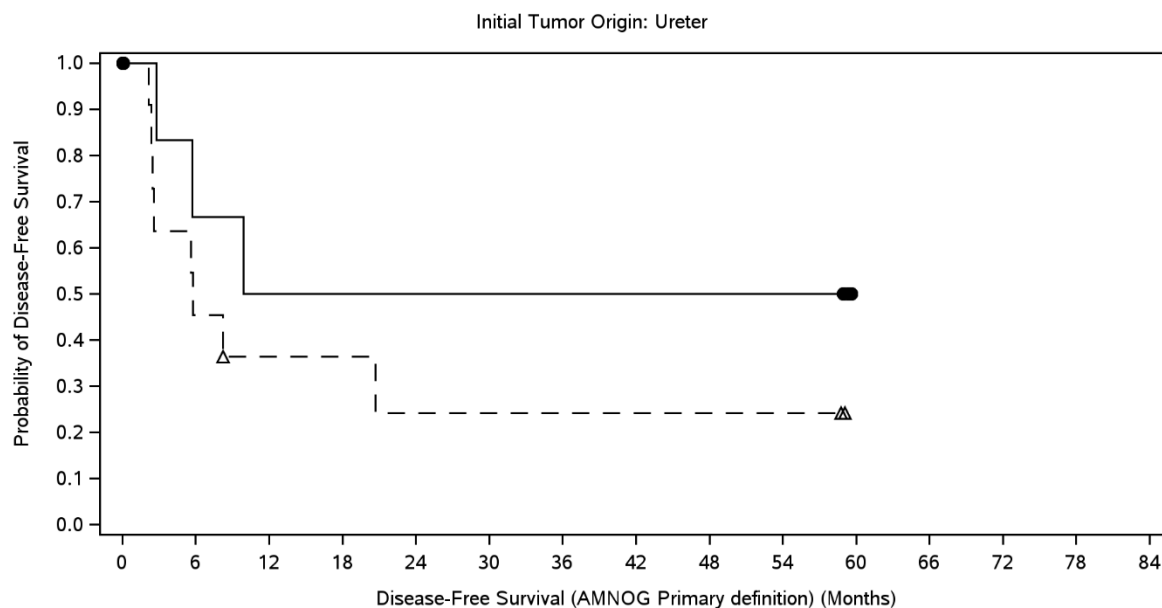
DFS (AMNOG Primary Definition) accounts for disease assessments occurring on or after initiation of subsequent anticancer therapy.

Program Path: /projects/bms214671/stats/market/ma274_202502/prog/figures

Program Name: rg-ef-subpdllrc-ebr45.sas

24JUL2025:04:02:43

Figure 6.1.1
Kaplan-Meier Plot of Disease Free Survival (AMNOG Primary Definition) - by Significant Subgroups - FAS



Number of Subjects at Risk

Placebo

11 5 3 3 2 2 2 2 2 2 0 0 0 0 0

Nivolumab

8 4 3 3 3 3 3 3 3 3 0 0 0 0 0

— Δ — Placebo (events: 8/11), median and 95% CI: 5.75 (2.37, N.A.)

— $\bullet$ — Nivolumab (events: 3/8), median and 95% CI: N.A. (2.79, N.A.)

Hazard Ratio (Nivolumab vs. Placebo) and 95% CI: 0.479 (0.126, 1.819).

FEB2025 DBL.

Unstratified Cox proportional hazard.

Symbols represent censored observations.

DFS (AMNOG Primary Definition) accounts for disease assessments occurring on or after initiation of subsequent anticancer therapy.

Program Path: /projects/bms214671/stats/market/ma274_202502/prog/figures

Program Name: rg-ef-subpdllrc-ebr45.sas

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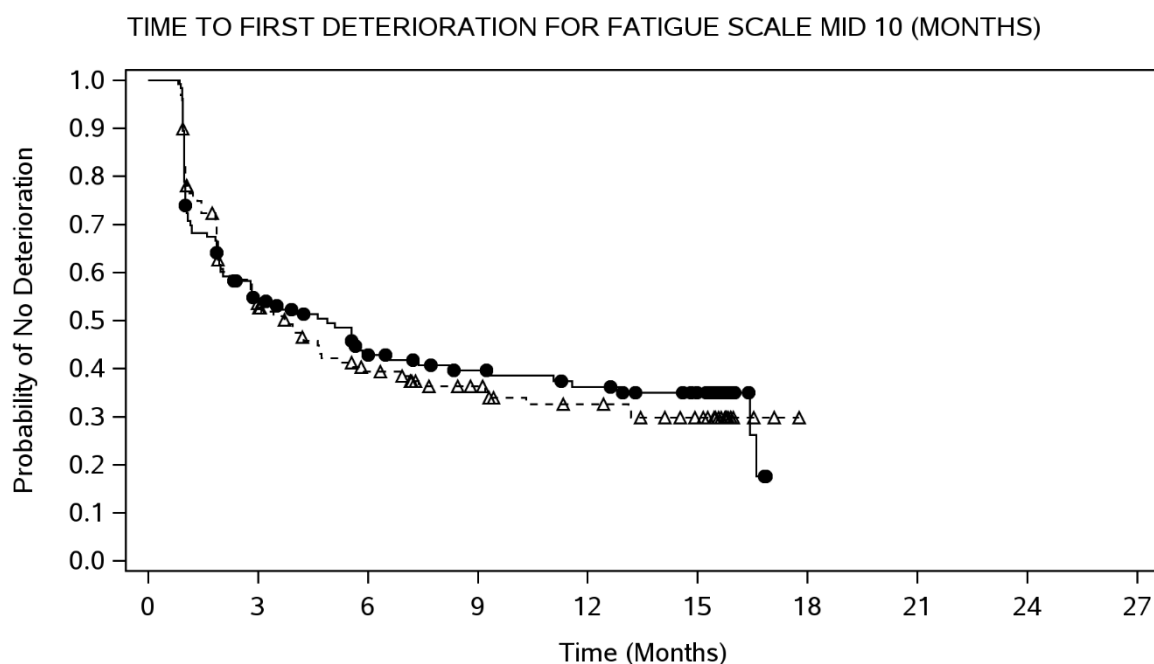
3.2 Symptomatik: Endpunkt Zeit bis zur ersten Verschlechterung der krankheitsbedingten Symptomatik gemäß den Domänen des EORTC QLQ-C30

Für die Auswertungen wurde PRO-Population herangezogen. Eine Verschlechterung wurde als klinisch relevante Verschlechterung der jeweiligen Domäne des EORTC-QLQ-C30 um ≥ 10 Punkte gegenüber Baseline definiert.

3.2.1 Kaplan-Meier-Kurven

Figure 1.1

Kaplan-Meier Plot of EORTC QLQ-C30 Time to First Deterioration - PROS



Number of Subjects at Risk

(Number of Censored Subjects)

Placebo

128	64	42	31	24	17	0	0	0	0
(0)	(6)	(12)	(20)	(24)	(29)	(46)	(46)	(46)	(46)

Nivolumab

123	62	44	36	31	24	0	0	0	0
(0)	(5)	(11)	(16)	(18)	(24)	(46)	(46)	(46)	(46)

--△-- Placebo (events: 82/128), median and 95% CI: 3.78 (2.50, 5.19)

—●— Nivolumab (events: 77/123), median and 95% CI: 4.90 (2.04, 7.39)

Hazard Ratio (Nivolumab vs Placebo) and 95% CI: 0.972 (0.708, 1.334)

FEB2025 DBL

Symbols represent censored observations.

Stratified Cox proportional hazard model

with baseline PRO score as a covariate.

Program Path: /projects/bms214671/stats/market/ma274_202502/prog/figures

Program Name: rg-sy-tdd-ebr45.sas

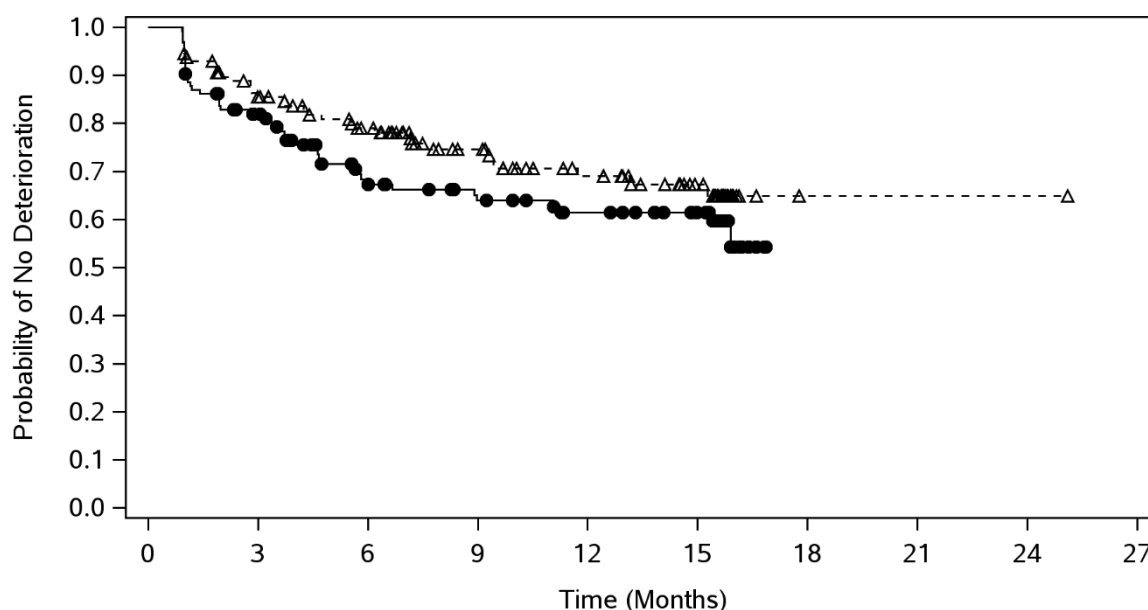
21NOV2025:14:45:48

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

Figure 1.1

Kaplan-Meier Plot of EORTC QLQ-C30 Time to First Deterioration - PROS

TIME TO FIRST DETERIORATION FOR NAUSEA AND VOMITING SCALE MID 10 (MONTHS)



Number of Subjects at Risk

(Number of Censored Subjects)

Placebo

128	100	81	59	44	30	1	1	1	0
(0)	(10)	(22)	(40)	(51)	(64)	(92)	(92)	(92)	(93)

Nivolumab

123	92	65	55	47	39	0	0	0	0
(0)	(9)	(22)	(28)	(34)	(42)	(79)	(79)	(79)	(79)

--△-- Placebo (events: 35/128), median and 95% CI: N.A.

—●— Nivolumab (events: 44/123), median and 95% CI: N.A. (15.41, N.A.)

Hazard Ratio (Nivolumab vs Placebo) and 95% CI: 1.347 (0.862, 2.104)

FEB2025 DBL

Symbols represent censored observations.

Stratified Cox proportional hazard model

with baseline PRO score as a covariate.

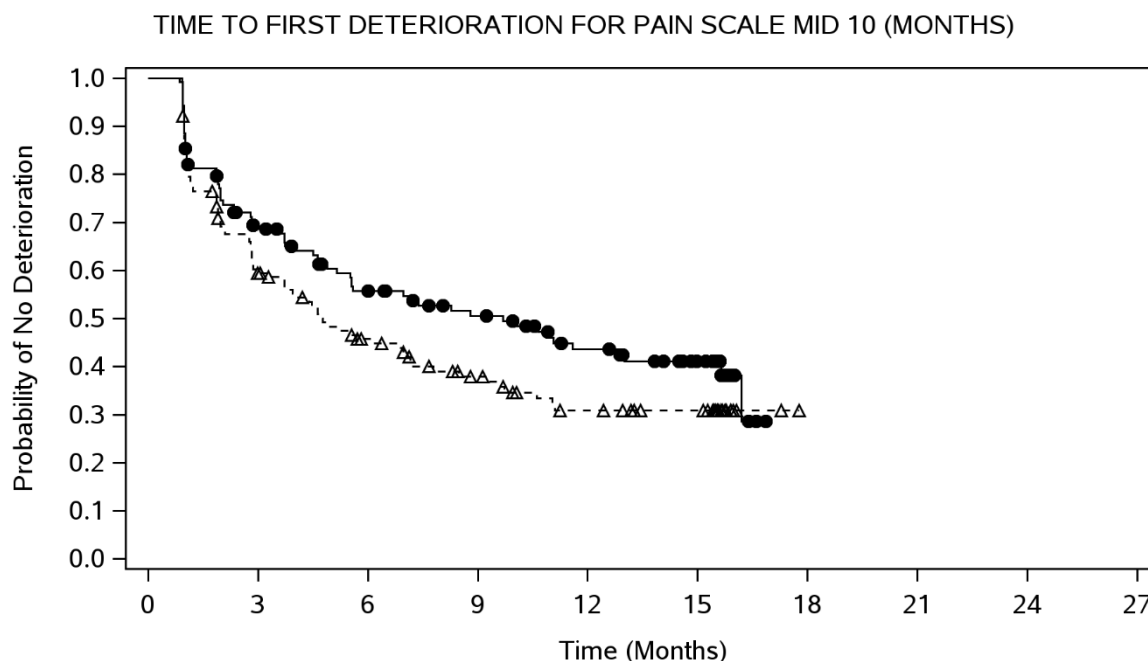
Program Path: /projects/bms214671/stats/market/ma274_202502/prog/figures

Program Name: rg-sy-tdd-ebr45.sas

21NOV2025:14:45:48

Figure 1.1

Kaplan-Meier Plot of EORTC QLQ-C30 Time to First Deterioration - PROS



FEB2025 DBL

Symbols represent censored observations.

Stratified Cox proportional hazard model

with baseline PRO score as a covariate.

Program Path: /projects/bms214671/stats/market/ma274_202502/prog/figures

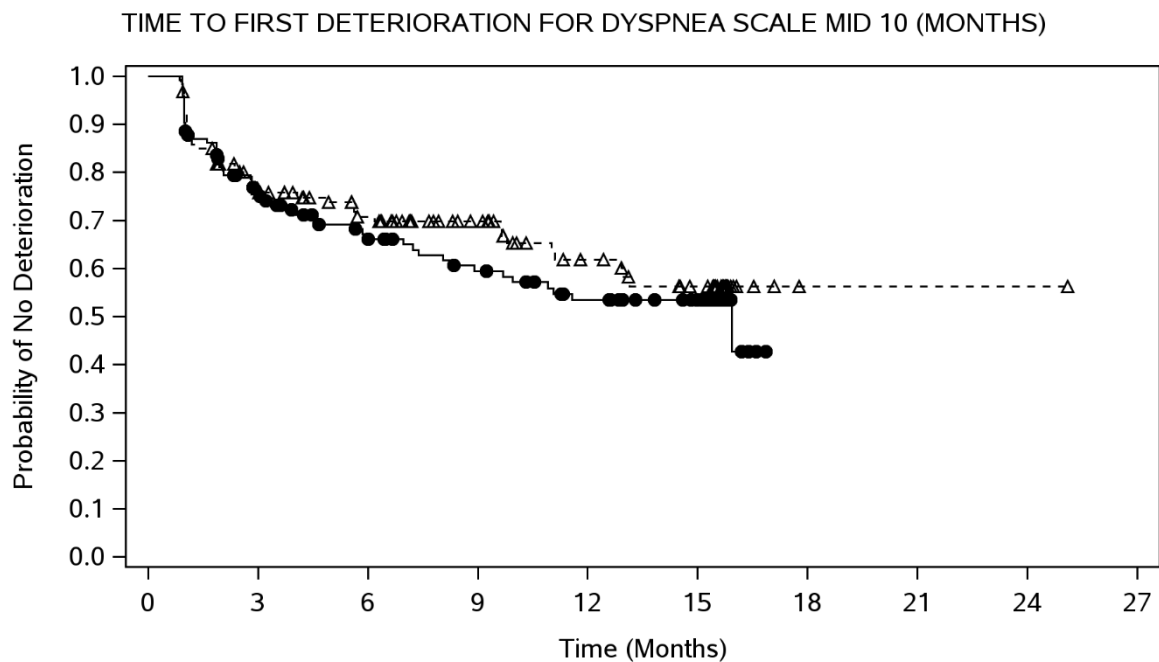
Program Name: rg-sy-tdd-ebr45.sas

21NOV2025:14:45:48

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

Figure 1.1

Kaplan-Meier Plot of EORTC QLQ-C30 Time to First Deterioration - PROS



Number of Subjects at Risk

(Number of Censored Subjects)

Placebo

127	88	69	51	35	26	1	1	1	0
(0)	(10)	(23)	(40)	(51)	(57)	(82)	(82)	(82)	(83)

Nivolumab

123	82	65	53	42	33	0	0	0	0
(0)	(11)	(20)	(25)	(31)	(40)	(72)	(72)	(72)	(72)

--△-- Placebo (events: 44/127), median and 95% CI: N.A. (12.91, N.A.)

—●— Nivolumab (events: 51/123), median and 95% CI: 15.93 (8.90, N.A.)

Hazard Ratio (Nivolumab vs Placebo) and 95% CI: 1.166 (0.776, 1.751)

FEB2025 DBL

Symbols represent censored observations.

Stratified Cox proportional hazard model

with baseline PRO score as a covariate.

Program Path: /projects/bms214671/stats/market/ma274_202502/prog/figures

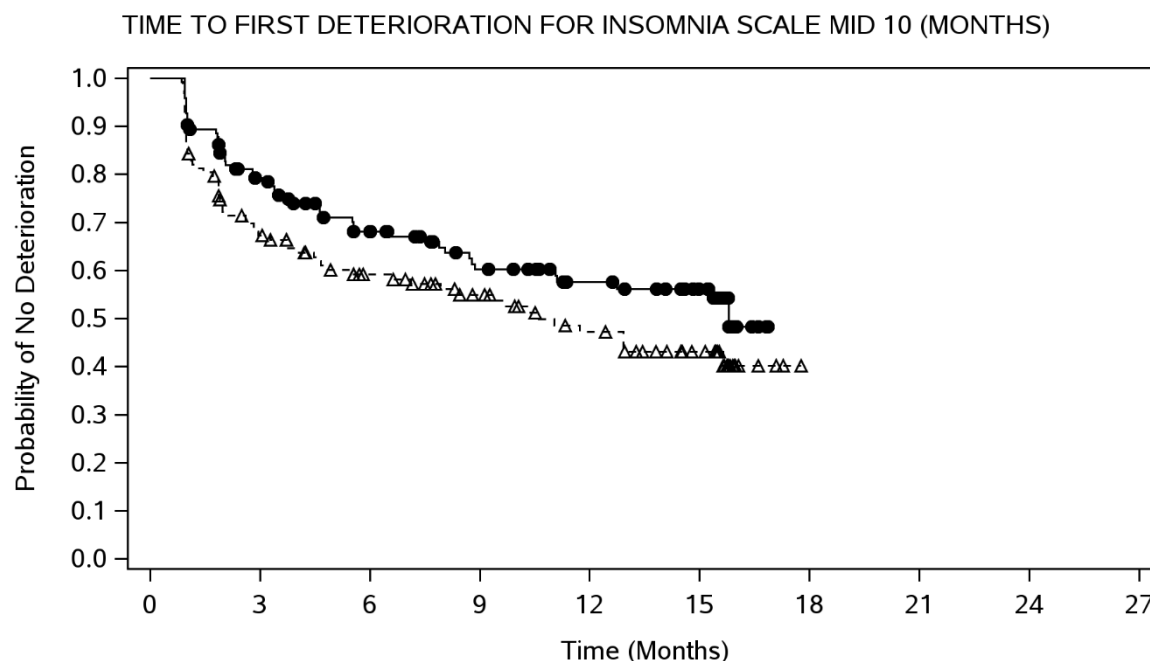
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21NOV2025:14:45:48

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

Figure 1.1

Kaplan-Meier Plot of EORTC QLQ-C30 Time to First Deterioration - PROS



Number of Subjects at Risk

(Number of Censored Subjects)

Placebo

128	80	60	47	35	22	0	0	0	0
(0)	(7)	(18)	(27)	(33)	(43)	(64)	(64)	(64)	(64)

Nivolumab

123	89	69	52	41	32	0	0	0	0
(0)	(9)	(17)	(27)	(36)	(44)	(74)	(74)	(74)	(74)

--△-- Placebo (events: 64/128), median and 95% CI: 10.61 (5.49, N.A.)

—●— Nivolumab (events: 49/123), median and 95% CI: 15.80 (11.07, N.A.)

Hazard Ratio (Nivolumab vs Placebo) and 95% CI: 0.723 (0.494, 1.058)

FEB2025 DBL

Symbols represent censored observations.

Stratified Cox proportional hazard model

with baseline PRO score as a covariate.

Program Path: /projects/bms214671/stats/market/ma274_202502/prog/figures

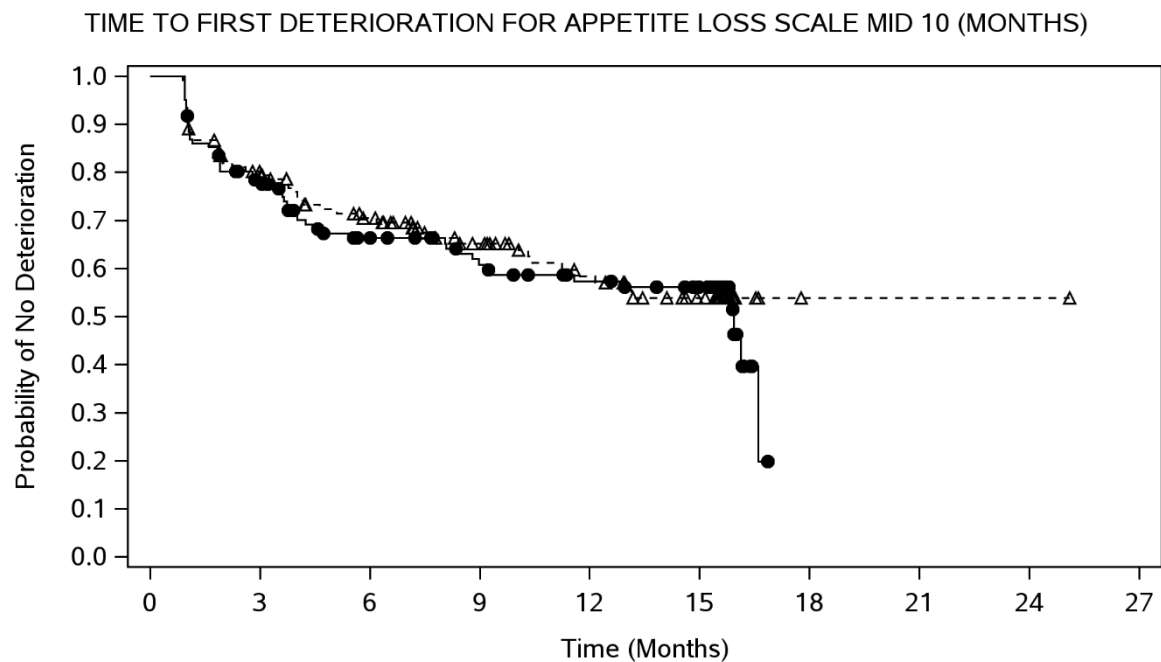
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21NOV2025:14:45:48

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

Figure 1.1

Kaplan-Meier Plot of EORTC QLQ-C30 Time to First Deterioration - PROS



Number of Subjects at Risk

(Number of Censored Subjects)

Placebo

128	96	75	55	42	29	1	1	1	0
(0)	(7)	(17)	(32)	(40)	(50)	(78)	(78)	(78)	(79)

Nivolumab

122	87	66	55	47	39	0	0	0	0
(0)	(8)	(17)	(23)	(28)	(35)	(70)	(70)	(70)	(70)

--△-- Placebo (events: 49/128), median and 95% CI: N.A. (11.24, N.A.)

—●— Nivolumab (events: 52/122), median and 95% CI: 15.93 (9.23, N.A.)

Hazard Ratio (Nivolumab vs Placebo) and 95% CI: 1.144 (0.767, 1.707)

FEB2025 DBL

Symbols represent censored observations.

Stratified Cox proportional hazard model

with baseline PRO score as a covariate.

Program Path: /projects/bms214671/stats/market/ma274_202502/prog/figures

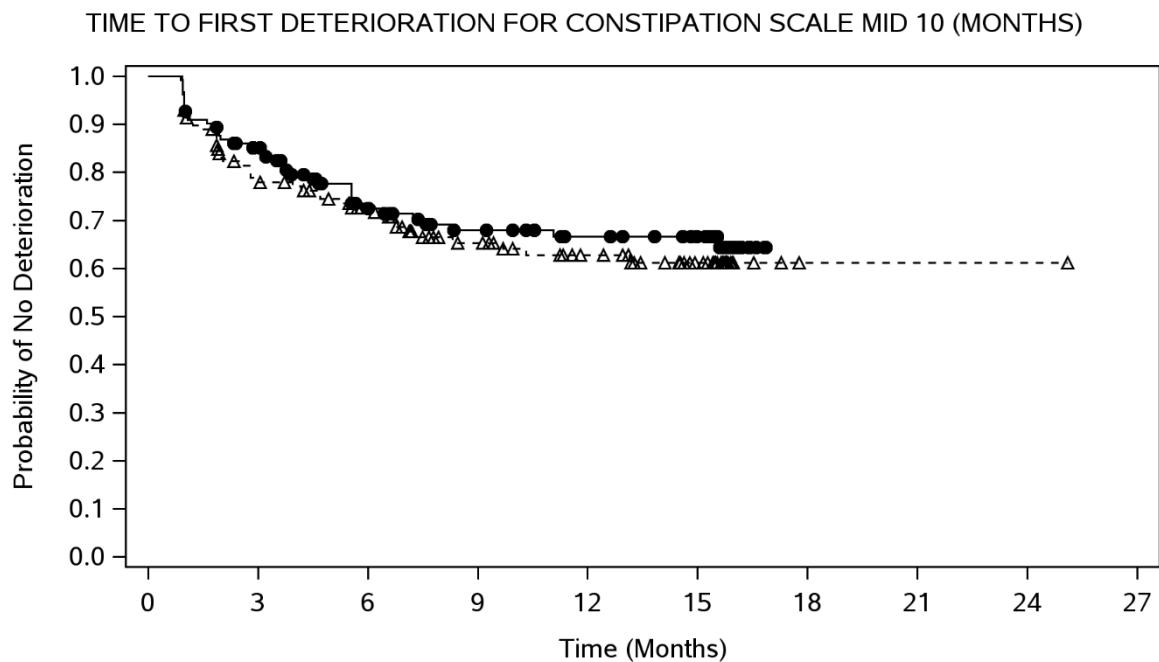
Program Name: rg-sy-tdd-ebr45.sas

21NOV2025:14:45:48

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

Figure 1.1

Kaplan-Meier Plot of EORTC QLQ-C30 Time to First Deterioration - PROS



Number of Subjects at Risk

(Number of Censored Subjects)

Placebo

127	91	75	54	43	29	1	1	1	0
(0)	(9)	(18)	(33)	(42)	(55)	(83)	(83)	(83)	(84)

Nivolumab

122	95	70	56	48	42	0	0	0	0
(0)	(9)	(22)	(31)	(38)	(44)	(85)	(85)	(85)	(85)

--△-- Placebo (events: 43/127), median and 95% CI: N.A.

—●— Nivolumab (events: 37/122), median and 95% CI: N.A.

Hazard Ratio (Nivolumab vs Placebo) and 95% CI: 0.877 (0.564, 1.363)

FEB2025 DBL

Symbols represent censored observations.

Stratified Cox proportional hazard model

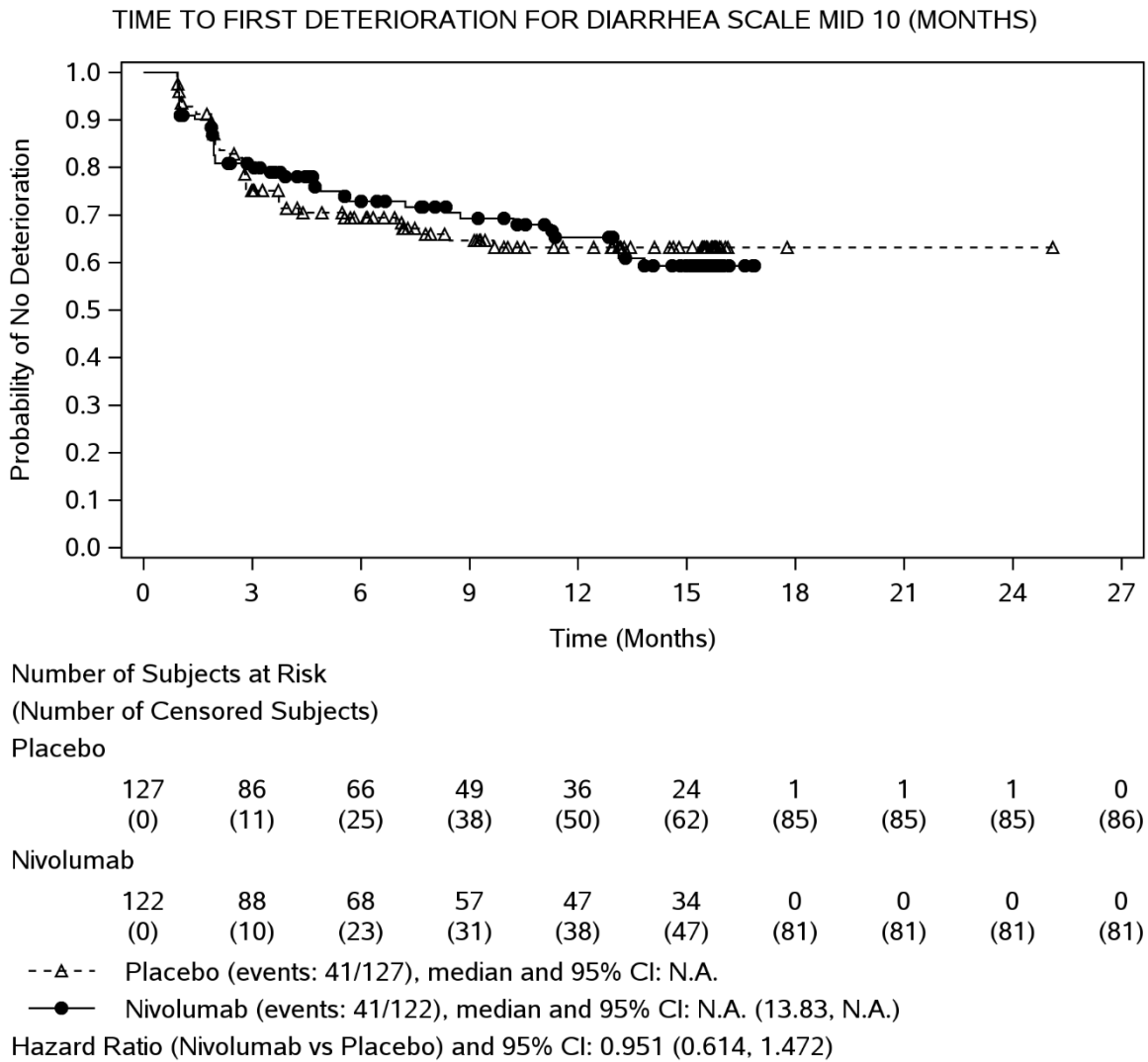
with baseline PRO score as a covariate.

Program Path: /projects/bms214671/stats/market/ma274_202502/prog/figures

Program Name: rg-sy-tdd-ebr45.sas

21NOV2025:14:45:48

Figure 1.1
Kaplan-Meier Plot of EORTC QLQ-C30 Time to First Deterioration - PROS

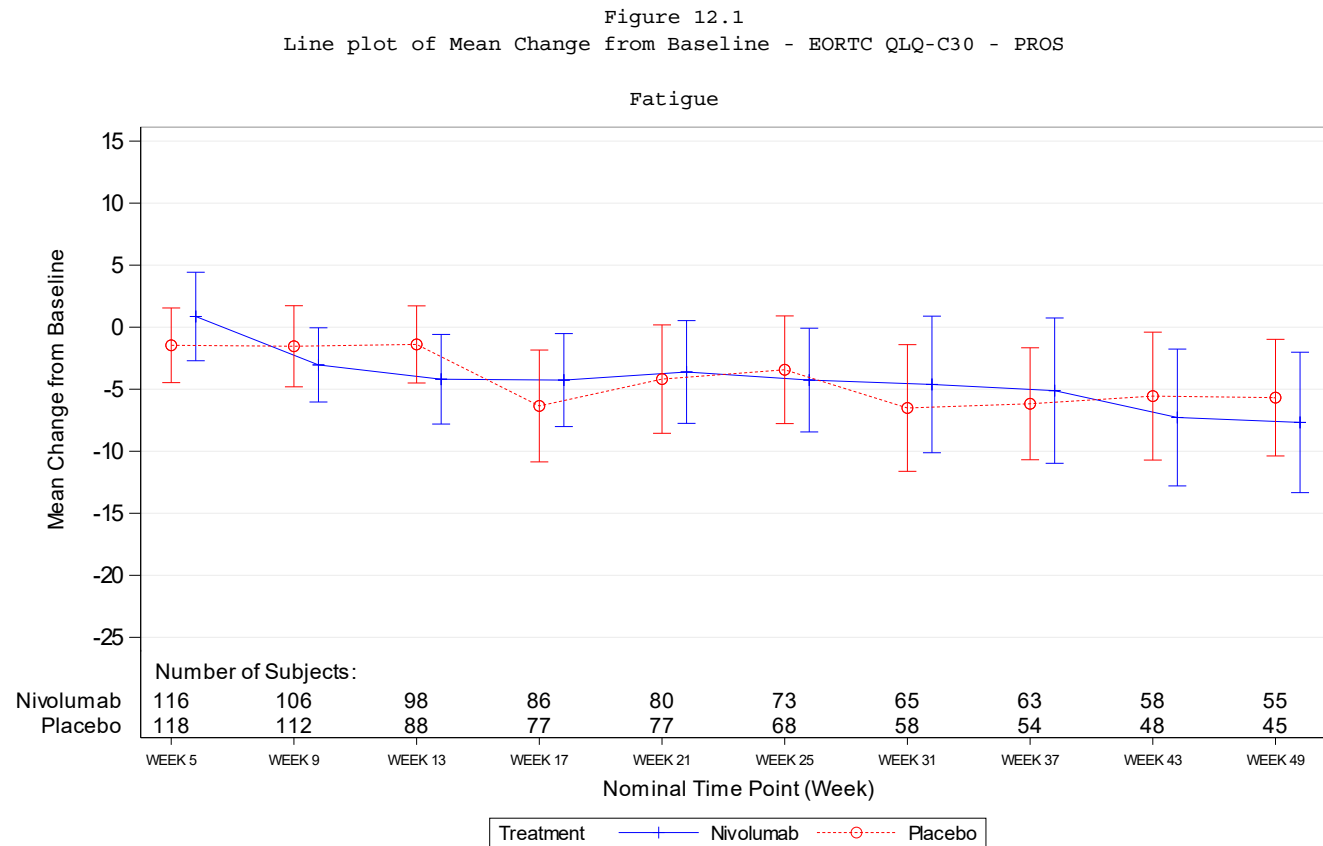


FEB2025 DBL
 Symbols represent censored observations.
 Stratified Cox proportional hazard model
 with baseline PRO score as a covariate.
 Program Path: /projects/bms214671/stats/market/ma274_202502/prog/figures
 Program Name: rg-sy-tdd-ebr45.sas

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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

3.2.2 Grafische Darstellung der mittleren Veränderung gegenüber Baseline im zeitlichen Verlauf



Error bars represent 95% CI for the mean change.

Only on-treatment visits with data for at least 10 patients across both treatment groups are plotted.

FEB2025 DBL

Program Path: /projects/bms214671/stats/market/ma274_202502/prog/figures

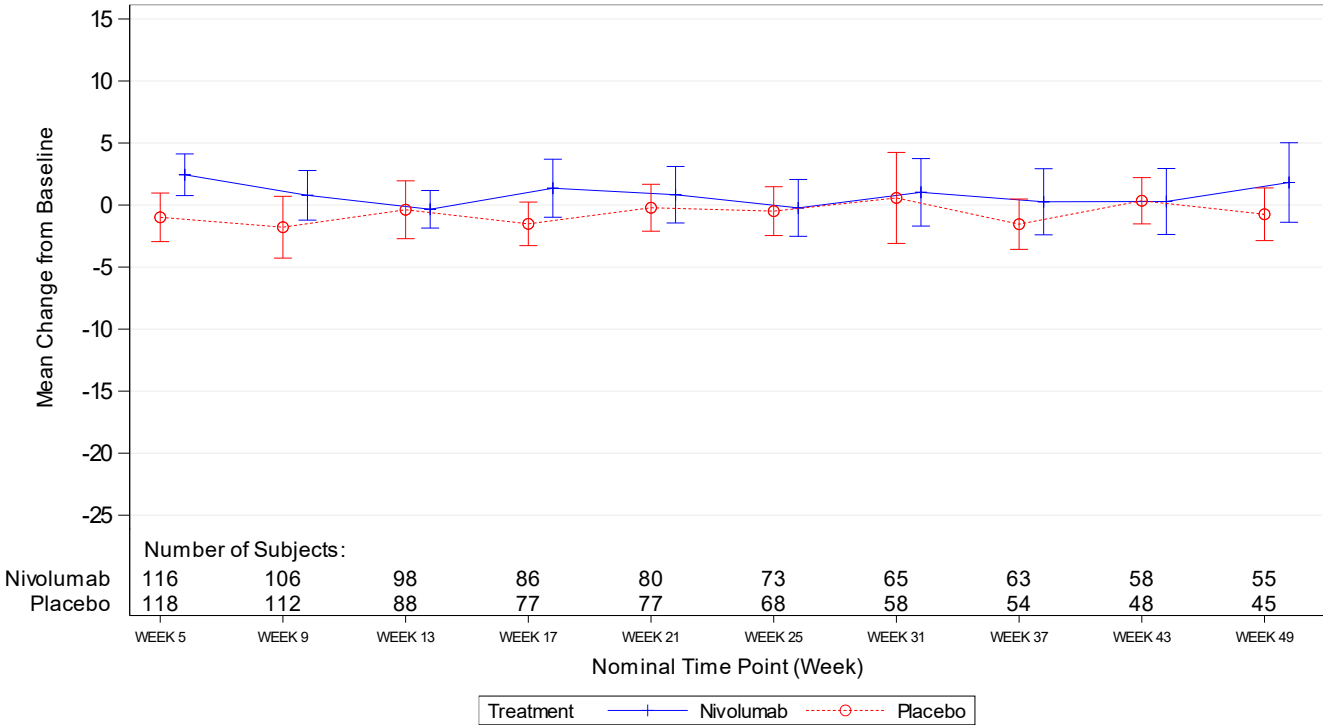
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24JUL2025:04:04:24

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

Figure 12.1
Line plot of Mean Change from Baseline - EORTC QLQ-C30 - PROS

Nausea and vomiting

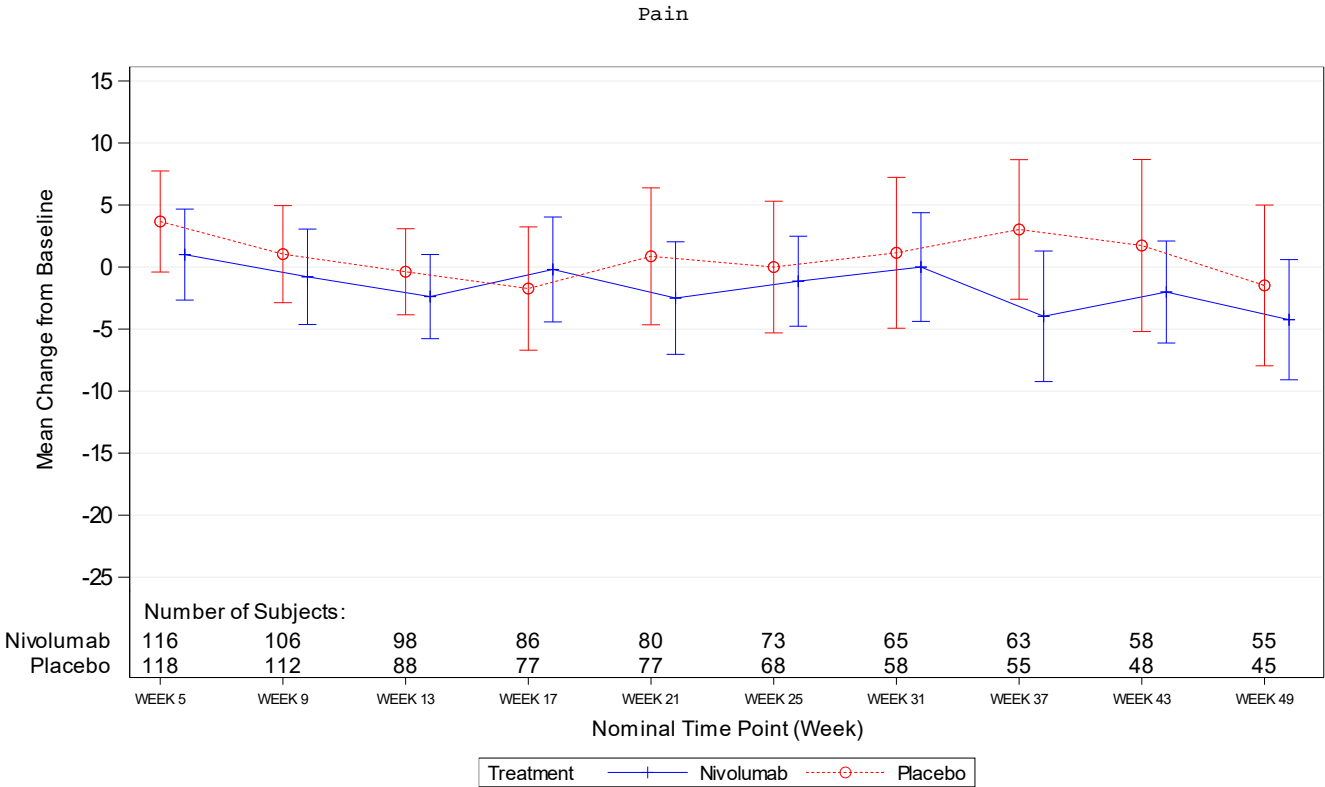


Error bars represent 95% CI for the mean change.
Only on-treatment visits with data for at least 10 patients across both treatment groups are plotted.
FEB2025 DBL
Program Path: /projects/bms214671/stats/market/ma274_202502/prog/figures
Program Name: rg-ef-lp-ebr45.sas

24JUL2025:04:04:24

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

Figure 12.1
Line plot of Mean Change from Baseline - EORTC QLQ-C30 - PROS

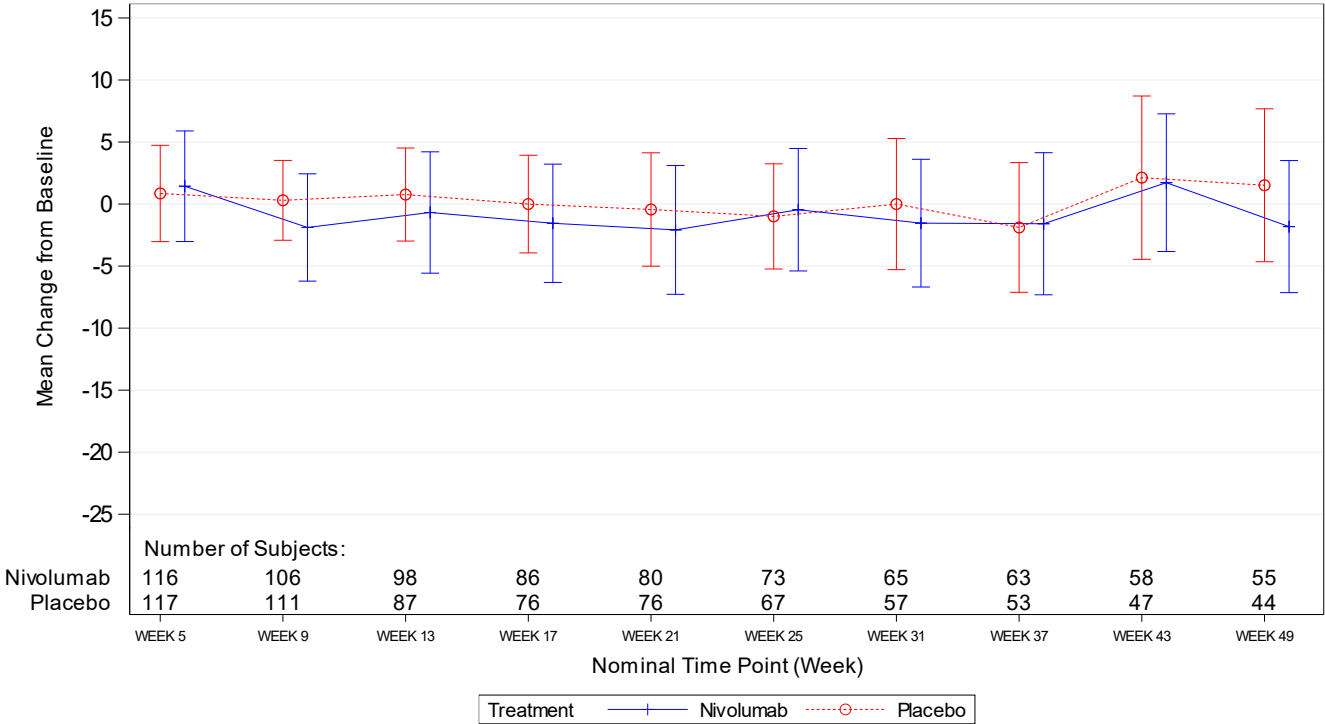


Error bars represent 95% CI for the mean change.
Only on-treatment visits with data for at least 10 patients across both treatment groups are plotted.
FEB2025 DBL
Program Path: /projects/bms214671/stats/market/ma274_202502/prog/figures
Program Name: rg-ef-lp-ebr45.sas

24JUL2025:04:04:24

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

Figure 12.1
Line plot of Mean Change from Baseline - EORTC QLQ-C30 - PROS
Dyspnea

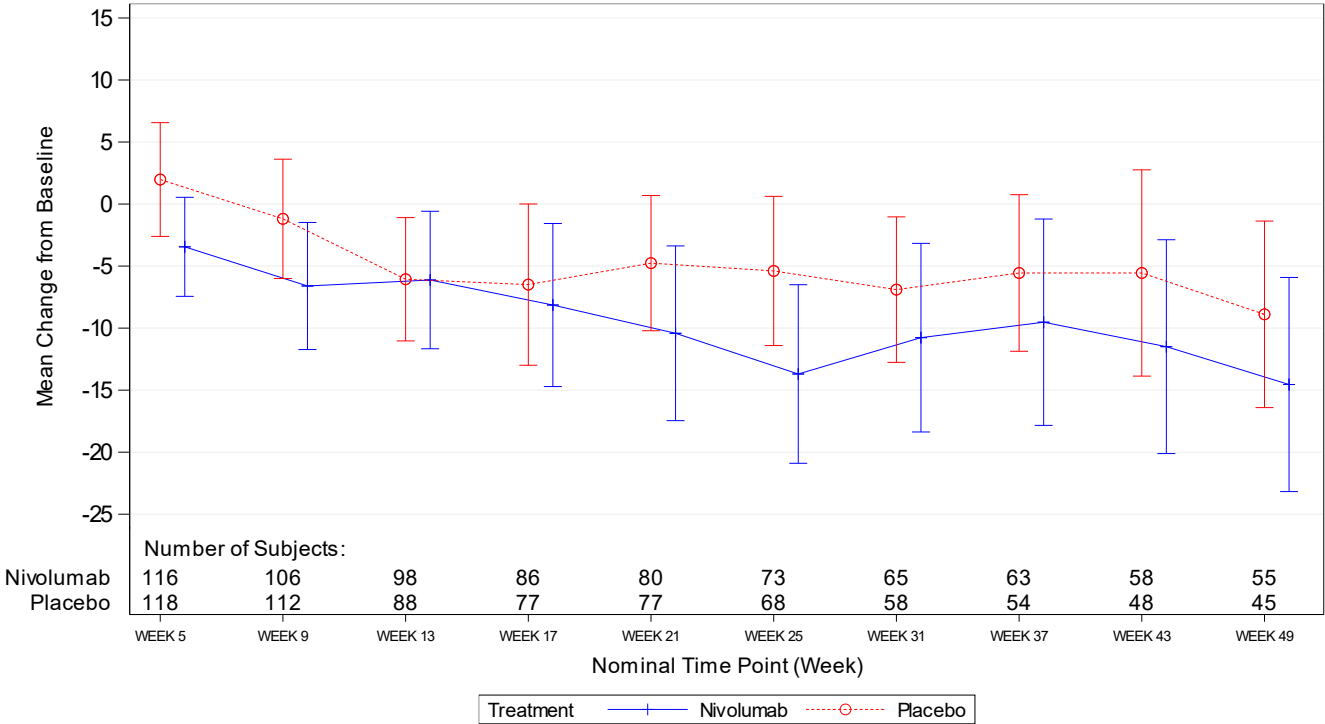


Error bars represent 95% CI for the mean change.
Only on-treatment visits with data for at least 10 patients across both treatment groups are plotted.
FEB2025 DBL
Program Path: /projects/bms214671/stats/market/ma274_202502/prog/figures
Program Name: rg-ef-lp-ebr45.sas

24JUL2025:04:04:24

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

Figure 12.1
Line plot of Mean Change from Baseline - EORTC QLQ-C30 - PROS
Insomnia

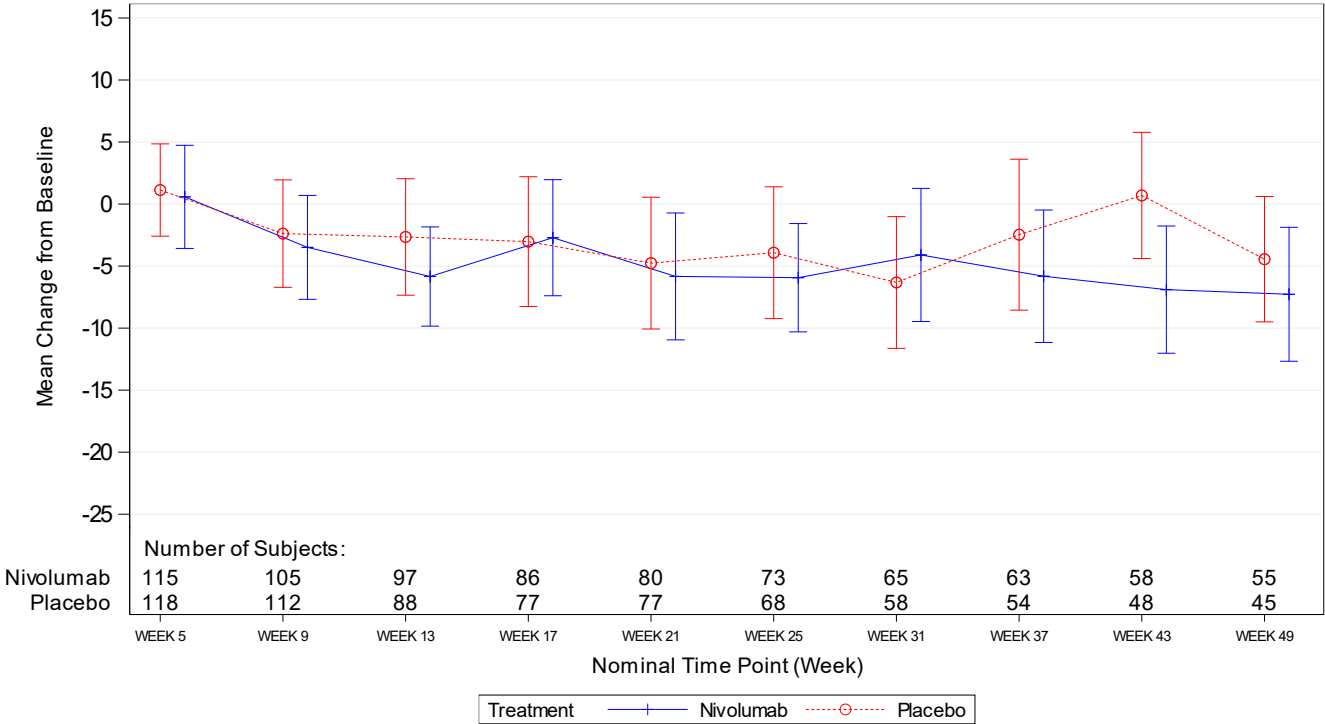


Error bars represent 95% CI for the mean change.
Only on-treatment visits with data for at least 10 patients across both treatment groups are plotted.
FEB2025 DBL
Program Path: /projects/bms214671/stats/market/ma274_202502/prog/figures
Program Name: rg-ef-lp-ebr45.sas

24JUL2025:04:04:24

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

Figure 12.1
Line plot of Mean Change from Baseline - EORTC QLQ-C30 - PROS
Appetite loss

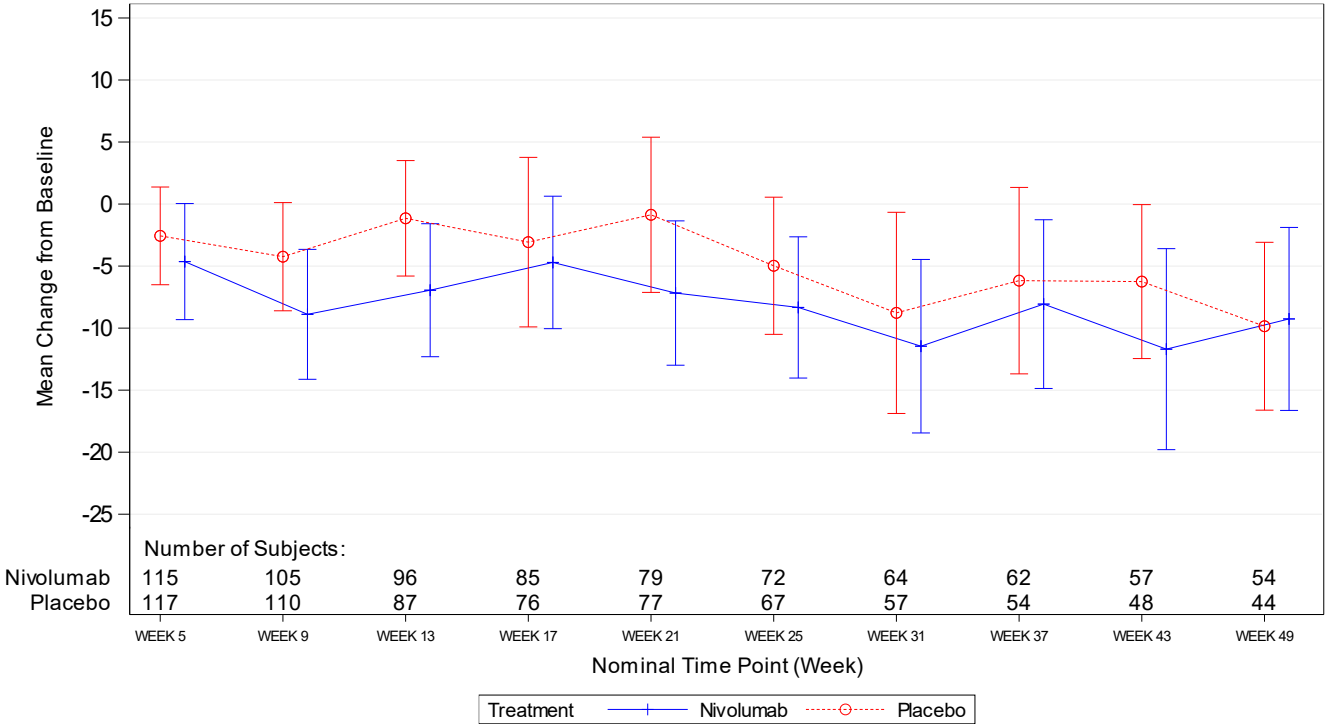


Error bars represent 95% CI for the mean change.
Only on-treatment visits with data for at least 10 patients across both treatment groups are plotted.
FEB2025 DBL
Program Path: /projects/bms214671/stats/market/ma274_202502/prog/figures
Program Name: rg-ef-lp-ebr45.sas

24JUL2025:04:04:24

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

Figure 12.1
Line plot of Mean Change from Baseline - EORTC QLQ-C30 - PROS
Constipation



Error bars represent 95% CI for the mean change.
Only on-treatment visits with data for at least 10 patients across both treatment groups are plotted.
FEB2025 DBL
Program Path: /projects/bms214671/stats/market/ma274_202502/prog/figures
Program Name: rg-ef-lp-ebr45.sas

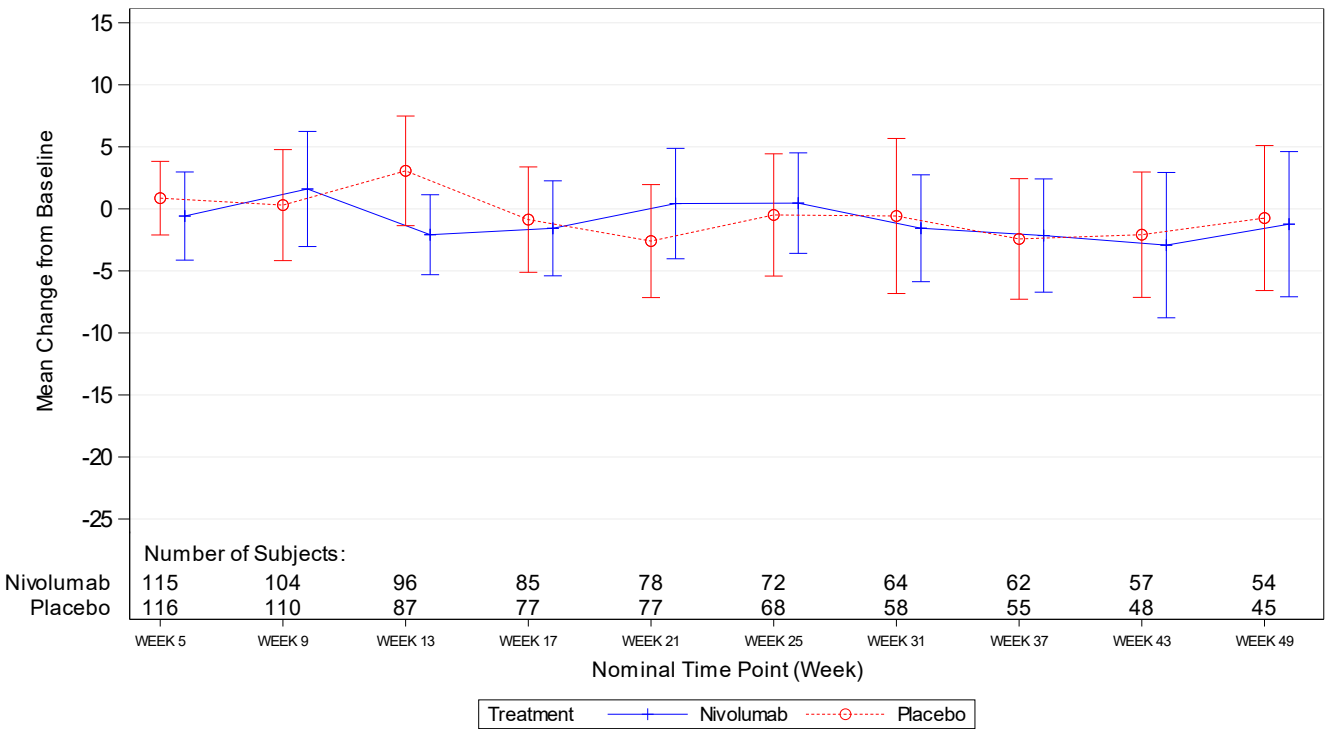
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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

Figure 12.1

Line plot of Mean Change from Baseline - EORTC QLQ-C30 - PROS

Diarrhea



Error bars represent 95% CI for the mean change.
Only on-treatment visits with data for at least 10 patients across both treatment groups are plotted.
FEB2025 DBL
Program Path: /projects/bms214671/stats/market/ma274_202502/prog/figures
Program Name: rg-ef-lp-ebr45.sas

24JUL2025:04:04:24

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

3.2.3 Subgruppenanalysen

Table 4.1
Subgroup Analyses of EORTC QLQ-C30 Time to First Deterioration
PROS

Fatigue Scale (MID=10)

Subgroup	Placebo				Nivolumab				Nivolumab vs. Placebo	
	N	Subjects with Event n (%)	Censored subjects n (%)	KME [95%CI] (mon) (1)	N	Subjects with Event n (%)	Censored subjects n (%)	KME [95%CI] (mon) (1)	HR [95%CI] P-value (2)	Test for Interaction P-value (3) (4)
OVERALL	128	82 (64.1)	46 (35.9)	3.78 (2.50, 5.19)	123	77 (62.6)	46 (37.4)	4.90 (2.04, 7.39)	1.000 (0.731, 1.367) 0.9987	
PRIOR NEO-ADJUVANT CISPLATIN THERAPY										0.4803
YES	54	35 (64.8)	19 (35.2)	3.94 (1.97, 9.20)	49	33 (67.3)	16 (32.7)	3.58 (1.02, 6.60)	1.079 (0.669, 1.739) 0.7565	
NO	74	47 (63.5)	27 (36.5)	3.71 (1.91, 5.59)	74	44 (59.5)	30 (40.5)	5.65 (2.04, 16.43)	0.909 (0.600, 1.376) 0.6512	

FEB2025 DBL. HR = hazard ratio; KME=Kaplan-Meier estimate; N.M.E = Not meaningful estimate.

(1) KME of median time to event.

(2) Unstratified Cox proportional hazard model, with baseline PRO score as a covariate. HR is Nivolumab over Placebo.

(3) Unstratified Cox proportional hazard model with treatment, subgroup and treatment*subgroup interaction to assess the significance of the interaction between treatment and the subgroup, with baseline PRO score as a covariate. (4) P-values <0.05 are indicated by 1 asterisk (indicates potential effect modification).

IUC = invasive urothelial carcinoma.

Program Path: /projects/bms214671/stats/market/ma274_202502/prog/tables

Program Name: rt-sy-tdd-eortc-comm-ebr45.sas

16JUL2025:07:44:05

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

Table 4.1
Subgroup Analyses of EORTC QLQ-C30 Time to First Deterioration
PROS

Fatigue Scale (MID=10)

Subgroup	Placebo				Nivolumab				Nivolumab vs. Placebo	
	N	Subjects with Event n (%)	Censored subjects n (%)	KME [95%CI] (mon) (1)	N	Subjects with Event n (%)	Censored subjects n (%)	KME [95%CI] (mon) (1)	HR [95%CI] P-value (2)	Test for Interaction P-value (3) (4)
PRIOR CISPLATIN STATUS										0.7767
RECEIVED NEO-ADJUVANT	54	35 (64.8)	19 (35.2)	3.94 (1.97, 9.20)	49	33 (67.3)	16 (32.7)	3.58 (1.02, 6.60)	1.079 (0.669, 1.739)	
UNWILLING TO RECEIVE NEO-ADJUVANT	42	28 (66.7)	14 (33.3)	3.75 (1.87, 7.39)	46	27 (58.7)	19 (41.3)	5.75 (1.84, N.A.)	0.919 (0.541, 1.561)	
NOT ELIGIBLE TO RECEIVE NEO-ADJUVANT	31	19 (61.3)	12 (38.7)	2.83 (1.87, 9.26)	23	17 (73.9)	6 (26.1)	3.98 (1.97, 9.26)	0.959 (0.489, 1.878)	

FEB2025 DBL. HR = hazard ratio; KME=Kaplan-Meier estimate; N.M.E = Not meaningful estimate.

(1) KME of median time to event.

(2) Unstratified Cox proportional hazard model, with baseline PRO score as a covariate. HR is Nivolumab over Placebo.

(3) Unstratified Cox proportional hazard model with treatment, subgroup and treatment*subgroup

interaction to assess the significance of the interaction between treatment and the subgroup, with baseline PRO score as a covariate. (4) P-values <0.05 are indicated by 1 asterisk (indicates potential effect modification).

IUC = invasive urothelial carcinoma.

Program Path: /projects/bms214671/stats/market/ma274_202502/prog/tables

Program Name: rt-sy-tdd-eortc-comm-ebr45.sas

16JUL2025:07:44:05

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

Table 4.1
Subgroup Analyses of EORTC QLQ-C30 Time to First Deterioration
PROS

Fatigue Scale (MID=10)

Subgroup	Placebo				Nivolumab				Nivolumab vs. Placebo	
	N	Subjects with Event n (%)	Censored subjects n (%)	KME [95%CI] (mon) (1)	N	Subjects with Event n (%)	Censored subjects n (%)	KME [95%CI] (mon) (1)	HR [95%CI] P-value (2)	Test for Interaction P-value (3) (4)
USE OF ANY PRIOR NEO-ADJUVANT SYSTEMIC THERAPY										0.3543
YES	55	35 (63.6)	20 (36.4)	3.94 (1.97, 9.20)	53	36 (67.9)	17 (32.1)	3.58 (1.02, 6.60)	1.131 (0.708, 1.804) 0.6069	
NO	73	47 (64.4)	26 (35.6)	3.71 (1.91, 4.73)	70	41 (58.6)	29 (41.4)	5.65 (2.04, 12.88)	0.895 (0.588, 1.362) 0.6032	

FEB2025 DBL. HR = hazard ratio; KME=Kaplan-Meier estimate; N.M.E = Not meaningful estimate.

(1) KME of median time to event.

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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

Table 4.1
Subgroup Analyses of EORTC QLQ-C30 Time to First Deterioration
PROS

Fatigue Scale (MID=10)

Subgroup	Placebo				Nivolumab				Nivolumab vs. Placebo	
	N	Subjects with Event n (%)	Censored subjects n (%)	KME [95%CI] (mon) (1)	N	Subjects with Event n (%)	Censored subjects n (%)	KME [95%CI] (mon) (1)	HR [95%CI] P-value (2)	Test for Interaction P-value (3) (4)
PATHOLOGICAL LYMPH NODE STATUS										0.7830
N+	57	36 (63.2)	21 (36.8)	3.78 (1.91, 6.93)	51	28 (54.9)	23 (45.1)	5.55 (1.18, N.A.)	0.869 (0.527, 1.431)	
N0/X WITH <10 NODES REMOVED	37	23 (62.2)	14 (37.8)	1.91 (1.87, N.A.)	35	24 (68.6)	11 (31.4)	3.58 (1.08, 11.07)	0.5803 (0.583, 1.856)	
N0 WITH >= 10 NODES REMOVED	34	23 (67.6)	11 (32.4)	3.94 (2.83, 9.26)	37	25 (67.6)	12 (32.4)	4.90 (1.97, 6.60)	1.120 (0.634, 1.979)	

FEB2025 DBL. HR = hazard ratio; KME=Kaplan-Meier estimate; N.M.E = Not meaningful estimate.

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Subgroup	Placebo				Nivolumab				Nivolumab vs. Placebo	
	N	Subjects with Event n (%)	Censored subjects n (%)	KME [95%CI] (mon) (1)	N	Subjects with Event n (%)	Censored subjects n (%)	KME [95%CI] (mon) (1)	HR [95%CI] P-value (2)	Test for Interaction P-value (3) (4)
PATHOLOGICAL STATUS										0.5253
PT0-2	29	21 (72.4)	8 (27.6)	2.83 (1.05, 6.93)	21	14 (66.7)	7 (33.3)	3.58 (0.99, N.A.)	0.868 (0.441, 1.710)	
PT3	73	46 (63.0)	27 (37.0)	3.94 (1.91, 7.39)	78	49 (62.8)	29 (37.2)	5.55 (2.33, 9.26)	0.6827 0.977 (0.651, 1.465)	
PT4A	25	15 (60.0)	10 (40.0)	3.78 (2.83, N.A.)	21	14 (66.7)	7 (33.3)	1.94 (0.99, N.A.)	0.9088 1.462 (0.703, 3.041)	

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	N	Subjects with Event n (%)	Censored subjects n (%)	KME [95%CI] (mon) (1)	N	Subjects with Event n (%)	Censored subjects n (%)	KME [95%CI] (mon) (1)	HR [95%CI] P-value (2)	Test for Interaction P-value (3) (4)
AGE CATEGORY I										0.7589
< 65	54	34 (63.0)	20 (37.0)	4.70 (1.97, 10.32)	57	35 (61.4)	22 (38.6)	3.98 (1.18, 16.59)	1.053 (0.656, 1.689) 0.8312	
>= 65	74	48 (64.9)	26 (35.1)	3.02 (1.91, 4.63)	66	42 (63.6)	24 (36.4)	4.90 (2.33, 9.26)	0.974 (0.639, 1.484) 0.9028	

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Fatigue Scale (MID=10)

Subgroup	Placebo				Nivolumab				Nivolumab vs. Placebo	
	N	Subjects with Event n (%)	Censored subjects n (%)	KME [95%CI] (mon) (1)	N	Subjects with Event n (%)	Censored subjects n (%)	KME [95%CI] (mon) (1)	HR [95%CI] P-value (2)	Test for Interaction P-value (3) (4)
AGE CATEGORY II										0.0588
< 65	54	34 (63.0)	20 (37.0)	4.70 (1.97, 10.32)	57	35 (61.4)	22 (38.6)	3.98 (1.18, 16.59)	1.053 (0.656, 1.689) 0.8312	
>= 65 AND < 75	54	36 (66.7)	18 (33.3)	3.02 (1.91, 4.24)	45	24 (53.3)	21 (46.7)	6.60 (3.32, N.A.)	0.648 (0.381, 1.102) 0.1093	
>= 75	20	12 (60.0)	8 (40.0)	3.75 (1.02, N.A.)	21	18 (85.7)	3 (14.3)	2.04 (0.99, 8.28)	1.990 (0.944, 4.197) 0.0707	

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Subgroup	Placebo				Nivolumab				Nivolumab vs. Placebo	
	N	Subjects with Event n (%)	Censored subjects n (%)	KME [95%CI] (mon) (1)	N	Subjects with Event n (%)	Censored subjects n (%)	KME [95%CI] (mon) (1)	HR [95%CI] P-value (2)	Test for Interaction P-value (3) (4)
REGION										0.0291*
US	21	15 (71.4)	6 (28.6)	2.83 (1.02, 7.13)	14	9 (64.3)	5 (35.7)	3.32 (0.99, N.A.)	0.815 (0.345, 1.925) 0.6410	
EUROPE	62	41 (66.1)	21 (33.9)	3.02 (1.97, 4.63)	65	45 (69.2)	20 (30.8)	2.83 (1.84, 5.85)	1.137 (0.738, 1.752) 0.5597	
ASIA	27	17 (63.0)	10 (37.0)	3.78 (1.84, N.A.)	28	10 (35.7)	18 (64.3)	N.A. (8.28, N.A.)	0.400 (0.180, 0.888) 0.0244	
REST OF WORLD	18	9 (50.0)	9 (50.0)	10.32 (1.45, N.A.)	16	13 (81.3)	3 (18.8)	1.87 (0.99, 5.55)	2.324 (0.984, 5.488) 0.0544	

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(3) Unstratified Cox proportional hazard model with treatment, subgroup and treatment*subgroup interaction to assess the significance of the interaction between treatment and the subgroup, with baseline PRO score as a covariate. (4) P-values <0.05 are indicated by 1 asterisk (indicates potential effect modification).

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	N	Subjects with Event n (%)	Censored subjects n (%)	KME [95%CI] (mon) (1)	N	Subjects with Event n (%)	Censored subjects n (%)	KME [95%CI] (mon) (1)	HR [95%CI] P-value (2)	Test for Interaction P-value (3) (4)
GENDER										0.6318
MALE	101	62 (61.4)	39 (38.6)	4.24 (2.83, 7.39)	90	54 (60.0)	36 (40.0)	4.63 (1.94, 12.88)	1.023 (0.709, 1.477) 0.9026	
FEMALE	27	20 (74.1)	7 (25.9)	1.87 (1.02, 4.63)	33	23 (69.7)	10 (30.3)	5.09 (1.94, 6.60)	0.818 (0.446, 1.501) 0.5170	
RACE										0.0263*
WHITE	96	63 (65.6)	33 (34.4)	3.02 (1.97, 4.73)	94	66 (70.2)	28 (29.8)	2.56 (1.84, 5.55)	1.167 (0.824, 1.652) 0.3848	
ASIAN	27	17 (63.0)	10 (37.0)	3.78 (1.84, N.A.)	28	10 (35.7)	18 (64.3)	N.A. (8.28, N.A.)	0.400 (0.180, 0.888) 0.0244	

FEB2025 DBL. HR = hazard ratio; KME=Kaplan-Meier estimate; N.M.E = Not meaningful estimate.

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	N	Subjects with Event n (%)	Censored subjects n (%)	KME [95%CI] (mon) (1)	N	Subjects with Event n (%)	Censored subjects n (%)	KME [95%CI] (mon) (1)	HR [95%CI] P-value (2)	Test for Interaction P-value (3) (4)
BASELINE ECOG STATUS										0.9823
0	80	53 (66.3)	27 (33.8)	3.94 (1.97, 6.93)	76	49 (64.5)	27 (35.5)	4.90 (1.91, 7.39)	0.987 (0.668, 1.459)	
1	44	27 (61.4)	17 (38.6)	2.96 (1.45, N.A.)	45	27 (60.0)	18 (40.0)	4.63 (1.87, 12.88)	0.9482 1.120 (0.650, 1.929)	
SMOKING STATUS										0.8492
NEVER SMOKED	36	20 (55.6)	16 (44.4)	4.70 (1.91, N.A.)	36	20 (55.6)	16 (44.4)	6.60 (2.96, N.A.)	1.080 (0.579, 2.016)	
CURRENT/FORMER	91	61 (67.0)	30 (33.0)	3.71 (1.97, 4.73)	86	56 (65.1)	30 (34.9)	2.79 (1.87, 7.39)	0.8091 0.979 (0.679, 1.410)	

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BASELINE HEMOGLOBIN										0.0161*
<10 G/DL	13	3 (23.1)	10 (76.9)	N.A. (1.87, N.A.)	6	5 (83.3)	1 (16.7)	1.49 (0.95, N.A.)	4.289 (0.920, 20.000)	
>=10 G/DL	115	79 (68.7)	36 (31.3)	3.02 (1.97, 4.67)	117	72 (61.5)	45 (38.5)	5.09 (2.79, 9.26)	0.0639 0.889 (0.643, 1.227) 0.4735	
BASELINE CREATININE CLEARANCE										0.2039
<60 ML/MIN	57	32 (56.1)	25 (43.9)	5.59 (1.91, N.A.)	47	31 (66.0)	16 (34.0)	5.55 (2.04, 11.56)	1.300 (0.785, 2.152)	
>=60 ML/MIN	71	50 (70.4)	21 (29.6)	2.86 (1.91, 4.70)	75	45 (60.0)	30 (40.0)	3.58 (1.87, 12.88)	0.3075 0.837 (0.558, 1.253) 0.3867	

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TIME FROM IUC SURGERY TO RANDOMIZATION (DAYS)										0.9928
>30-60	28	16 (57.1)	12 (42.9)	4.73 (1.87, N.A.)	30	18 (60.0)	12 (40.0)	5.55 (2.04, N.A.)	0.993 (0.505, 1.951)	
>60-90	57	37 (64.9)	20 (35.1)	2.86 (1.91, 7.39)	51	32 (62.7)	19 (37.3)	5.09 (1.84, 12.88)	0.9832 0.952 (0.587, 1.544)	
>90-120	38	26 (68.4)	12 (31.6)	3.78 (1.91, 7.13)	40	26 (65.0)	14 (35.0)	2.83 (1.05, 11.56)	0.8409 0.998 (0.577, 1.725)	

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INITIAL TUMOR ORIGIN										0.6430
URINARY BLADDER	104	65 (62.5)	39 (37.5)	3.94 (2.83, 6.93)	102	61 (59.8)	41 (40.2)	5.09 (1.94, 11.56)	1.011 (0.711, 1.438) 0.9501	
RENAL PELVIS	13	8 (61.5)	5 (38.5)	4.17 (1.45, N.A.)	15	13 (86.7)	2 (13.3)	2.86 (1.02, 8.28)	1.214 (0.494, 2.983) 0.6732	
URETER	11	9 (81.8)	2 (18.2)	1.91 (0.95, 4.73)	6	3 (50.0)	3 (50.0)	16.43 (0.95, N.A.)	0.551 (0.112, 2.721) 0.4648	

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MINOR HISTOLOGICAL VARIANTS										0.6010
PRESENCE	54	36 (66.7)	18 (33.3)	4.63 (1.97, 7.13)	53	34 (64.2)	19 (35.8)	2.86 (1.87, 6.60)	1.148 (0.716, 1.841) 0.5656	
ABSENCE	74	46 (62.2)	28 (37.8)	3.02 (1.91, 7.39)	70	43 (61.4)	27 (38.6)	5.55 (2.04, 12.88)	0.892 (0.586, 1.357) 0.5938	

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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

Table 4.1
Subgroup Analyses of EORTC QLQ-C30 Time to First Deterioration
PROS

Nausea and Vomiting Scale (MID=10)

Subgroup	Placebo				Nivolumab				Nivolumab vs. Placebo	
	N	Subjects with Event n (%)	Censored subjects n (%)	KME [95%CI] (mon) (1)	N	Subjects with Event n (%)	Censored subjects n (%)	KME [95%CI] (mon) (1)	HR [95%CI] P-value (2)	Test for Interaction P-value (3) (4)
OVERALL	128	35 (27.3)	93 (72.7)	N.A. (N.A., N.A.)	123	44 (35.8)	79 (64.2)	N.A. (15.41, N.A.)	1.349 (0.865, 2.104) 0.1869	
PRIOR NEO-ADJUVANT CISPLATIN THERAPY										0.2018
YES	54	16 (29.6)	38 (70.4)	N.A. (13.14, N.A.)	49	13 (26.5)	36 (73.5)	N.A. (15.90, N.A.)	0.925 (0.444, 1.924) 0.8340	
NO	74	19 (25.7)	55 (74.3)	N.A. (15.28, N.A.)	74	31 (41.9)	43 (58.1)	N.A. (6.67, N.A.)	1.716 (0.966, 3.049) 0.0655	

FEB2025 DBL. HR = hazard ratio; KME=Kaplan-Meier estimate; N.M.E = Not meaningful estimate.

(1) KME of median time to event.

(2) Unstratified Cox proportional hazard model, with baseline PRO score as a covariate. HR is Nivolumab over Placebo.

(3) Unstratified Cox proportional hazard model with treatment, subgroup and treatment*subgroup

interaction to assess the significance of the interaction between treatment and the subgroup, with baseline PRO score as a covariate. (4) P-values <0.05 are indicated by 1 asterisk (indicates potential effect modification).

IUC = invasive urothelial carcinoma.

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PROS

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Subgroup	Placebo				Nivolumab				Nivolumab vs. Placebo	
	N	Subjects with Event n (%)	Censored subjects n (%)	KME [95%CI] (mon) (1)	N	Subjects with Event n (%)	Censored subjects n (%)	KME [95%CI] (mon) (1)	HR [95%CI] P-value (2)	Test for Interaction P-value (3) (4)
PRIOR CISPLATIN STATUS										0.3183
RECEIVED NEO-ADJUVANT	54	16 (29.6)	38 (70.4)	N.A. (13.14, N.A.)	49	13 (26.5)	36 (73.5)	N.A. (15.90, N.A.)	0.925 (0.444, 1.924) 0.8340	
UNWILLING TO RECEIVE NEO-ADJUVANT	42	13 (31.0)	29 (69.0)	N.A. (11.73, N.A.)	46	21 (45.7)	25 (54.3)	15.41 (5.75, N.A.)	1.592 (0.789, 3.212) 0.1944	
NOT ELIGIBLE TO RECEIVE NEO-ADJUVANT	31	6 (19.4)	25 (80.6)	N.A. (9.26, N.A.)	23	10 (43.5)	13 (56.5)	N.A. (3.32, N.A.)	2.683 (0.910, 7.912) 0.0737	

FEB2025 DBL. HR = hazard ratio; KME=Kaplan-Meier estimate; N.M.E = Not meaningful estimate.

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	N	Subjects with Event n (%)	Censored subjects n (%)	KME [95%CI] (mon) (1)	N	Subjects with Event n (%)	Censored subjects n (%)	KME [95%CI] (mon) (1)	HR [95%CI] P-value (2)	Test for Interaction P-value (3) (4)
USE OF ANY PRIOR NEO-ADJUVANT SYSTEMIC THERAPY										0.2112
YES	55	16 (29.1)	39 (70.9)	N.A. (13.14, N.A.)	53	14 (26.4)	39 (73.6)	N.A. (15.90, N.A.)	0.937 (0.457, 1.922) 0.8601	
NO	73	19 (26.0)	54 (74.0)	N.A. (15.28, N.A.)	70	30 (42.9)	40 (57.1)	N.A. (5.75, N.A.)	1.717 (0.964, 3.058) 0.0664	

FEB2025 DBL. HR = hazard ratio; KME=Kaplan-Meier estimate; N.M.E = Not meaningful estimate.

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Subgroup	Placebo				Nivolumab				Nivolumab vs. Placebo	
	N	Subjects with Event n (%)	Censored subjects n (%)	KME [95%CI] (mon) (1)	N	Subjects with Event n (%)	Censored subjects n (%)	KME [95%CI] (mon) (1)	HR [95%CI] P-value (2)	Test for Interaction P-value (3) (4)
PATHOLOGICAL LYMPH NODE STATUS										0.1759
N+	57	19 (33.3)	38 (66.7)	N.A. (9.43, N.A.)	51	16 (31.4)	35 (68.6)	N.A. (15.41, N.A.)	0.854 (0.437, 1.668)	
NO/X WITH <10 NODES REMOVED	37	7 (18.9)	30 (81.1)	N.A. (N.A., N.A.)	35	10 (28.6)	25 (71.4)	N.A. (11.07, N.A.)	0.6442 1.486 (0.553, 3.992)	
NO WITH >= 10 NODES REMOVED	34	9 (26.5)	25 (73.5)	N.A. (9.26, N.A.)	37	18 (48.6)	19 (51.4)	15.90 (3.32, N.A.)	2.241 (1.004, 5.001)	0.4320 0.0489

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Subgroup	Placebo				Nivolumab				Nivolumab vs. Placebo	
	N	Subjects with Event n (%)	Censored subjects n (%)	KME [95%CI] (mon) (1)	N	Subjects with Event n (%)	Censored subjects n (%)	KME [95%CI] (mon) (1)	HR [95%CI] P-value (2)	Test for Interaction P-value (3) (4)
PATHOLOGICAL STATUS										0.2892
PT0-2	29	10 (34.5)	19 (65.5)	N.A. (11.73, N.A.)	21	5 (23.8)	16 (76.2)	N.A. (N.A., N.A.)	0.732 (0.250, 2.146)	
PT3	73	18 (24.7)	55 (75.3)	N.A. (N.A., N.A.)	78	27 (34.6)	51 (65.4)	N.A. (15.41, N.A.)	0.5701 1.354 (0.744, 2.464)	
PT4A	25	7 (28.0)	18 (72.0)	N.A. (7.16, N.A.)	21	11 (52.4)	10 (47.6)	8.97 (3.09, N.A.)	0.3208 2.329 (0.896, 6.055)	

FEB2025 DBL. HR = hazard ratio; KME=Kaplan-Meier estimate; N.M.E = Not meaningful estimate.

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Subgroup	Placebo				Nivolumab				Nivolumab vs. Placebo	
	N	Subjects with Event n (%)	Censored subjects n (%)	KME [95%CI] (mon) (1)	N	Subjects with Event n (%)	Censored subjects n (%)	KME [95%CI] (mon) (1)	HR [95%CI] P-value (2)	Test for Interaction P-value (3) (4)
AGE CATEGORY I										0.3214
< 65	54	21 (38.9)	33 (61.1)	N.A. (9.43, N.A.)	57	24 (42.1)	33 (57.9)	15.90 (8.90, N.A.)	1.072 (0.596, 1.928) 0.8160	
>= 65	74	14 (18.9)	60 (81.1)	N.A. (N.A., N.A.)	66	20 (30.3)	46 (69.7)	N.A. (N.A., N.A.)	1.732 (0.874, 3.432) 0.1153	

FEB2025 DBL. HR = hazard ratio; KME=Kaplan-Meier estimate; N.M.E = Not meaningful estimate.

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Subgroup	Placebo				Nivolumab				Nivolumab vs. Placebo	
	N	Subjects with Event n (%)	Censored subjects n (%)	KME [95%CI] (mon) (1)	N	Subjects with Event n (%)	Censored subjects n (%)	KME [95%CI] (mon) (1)	HR [95%CI] P-value (2)	Test for Interaction P-value (3) (4)
AGE CATEGORY II										0.6185
< 65	54	21 (38.9)	33 (61.1)	N.A. (9.43, N.A.)	57	24 (42.1)	33 (57.9)	15.90 (8.90, N.A.)	1.072 (0.596, 1.928) 0.8160	
>= 65 AND < 75	54	10 (18.5)	44 (81.5)	N.A. (N.A., N.A.)	45	13 (28.9)	32 (71.1)	N.A. (N.A., N.A.)	1.715 (0.750, 3.923) 0.2009	
>= 75	20	4 (20.0)	16 (80.0)	N.A. (9.26, N.A.)	21	7 (33.3)	14 (66.7)	N.A. (5.59, N.A.)	1.639 (0.478, 5.619) 0.4321	

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(3) Unstratified Cox proportional hazard model with treatment, subgroup and treatment*subgroup interaction to assess the significance of the interaction between treatment and the subgroup, with baseline PRO score as a covariate. (4) P-values <0.05 are indicated by 1 asterisk (indicates potential effect modification).

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	N	Subjects with Event n (%)	Censored subjects n (%)	KME [95%CI] (mon) (1)	N	Subjects with Event n (%)	Censored subjects n (%)	KME [95%CI] (mon) (1)	HR [95%CI] P-value (2)	Test for Interaction P-value (3) (4)
REGION										0.2694
US	21	7 (33.3)	14 (66.7)	N.A. (4.73, N.A.)	14	4 (28.6)	10 (71.4)	N.A. (3.32, N.A.)	0.891 (0.259, 3.059) 0.8545	
EUROPE	62	17 (27.4)	45 (72.6)	N.A. (15.28, N.A.)	65	28 (43.1)	37 (56.9)	15.90 (5.75, N.A.)	1.723 (0.942, 3.152) 0.0773	
ASIA	27	5 (18.5)	22 (81.5)	N.A. (N.A., N.A.)	28	9 (32.1)	19 (67.9)	N.A. (5.59, N.A.)	1.834 (0.613, 5.488) 0.2779	
REST OF WORLD	18	6 (33.3)	12 (66.7)	N.A. (2.83, N.A.)	16	3 (18.8)	13 (81.3)	N.A. (8.90, N.A.)	0.525 (0.123, 2.240) 0.3837	

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(3) Unstratified Cox proportional hazard model with treatment, subgroup and treatment*subgroup interaction to assess the significance of the interaction between treatment and the subgroup, with baseline PRO score as a covariate. (4) P-values <0.05 are indicated by 1 asterisk (indicates potential effect modification).

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	N	Subjects with Event n (%)	Censored subjects n (%)	KME [95%CI] (mon) (1)	N	Subjects with Event n (%)	Censored subjects n (%)	KME [95%CI] (mon) (1)	HR [95%CI] P-value (2)	Test for Interaction P-value (3) (4)
GENDER										
MALE	101	25 (24.8)	76 (75.2)	N.A. (N.A., N.A.)	90	28 (31.1)	62 (68.9)	N.A. (15.90, N.A.)	1.213 (0.706, 2.085) 0.4851	0.5512
FEMALE	27	10 (37.0)	17 (63.0)	N.A. (5.55, N.A.)	33	16 (48.5)	17 (51.5)	4.67 (1.97, N.A.)	1.665 (0.746, 3.714) 0.2131	
RACE										
WHITE	96	28 (29.2)	68 (70.8)	N.A. (15.28, N.A.)	94	35 (37.2)	59 (62.8)	N.A. (11.20, N.A.)	1.305 (0.793, 2.146) 0.2948	0.6083
ASIAN	27	5 (18.5)	22 (81.5)	N.A. (N.A., N.A.)	28	9 (32.1)	19 (67.9)	N.A. (5.59, N.A.)	1.834 (0.613, 5.488) 0.2779	

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BASELINE ECOG STATUS										0.7716
0	80	22 (27.5)	58 (72.5)	N.A. (N.A., N.A.)	76	26 (34.2)	50 (65.8)	15.90 (15.41, N.A.)	1.315 (0.745, 2.321) 0.3454	
1	44	12 (27.3)	32 (72.7)	N.A. (13.14, N.A.)	45	18 (40.0)	27 (60.0)	N.A. (5.82, N.A.)	1.561 (0.751, 3.243) 0.2326	
SMOKING STATUS										0.3355
NEVER SMOKED	36	8 (22.2)	28 (77.8)	N.A. (N.A., N.A.)	36	14 (38.9)	22 (61.1)	N.A. (4.63, N.A.)	1.931 (0.808, 4.610) 0.1385	
CURRENT/FORMER	91	27 (29.7)	64 (70.3)	N.A. (13.14, N.A.)	86	30 (34.9)	56 (65.1)	N.A. (15.41, N.A.)	1.159 (0.689, 1.952) 0.5779	

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	N	Subjects with Event n (%)	Censored subjects n (%)	KME [95%CI] (mon) (1)	N	Subjects with Event n (%)	Censored subjects n (%)	KME [95%CI] (mon) (1)	HR [95%CI] P-value (2)	Test for Interaction P-value (3) (4)
BASELINE HEMOGLOBIN										0.1628
<10 G/DL	13	2 (15.4)	11 (84.6)	N.A. (15.28, N.A.)	6	3 (50.0)	3 (50.0)	5.82 (0.95, N.A.)	3.318 (0.544, 20.257)	
>=10 G/DL	115	33 (28.7)	82 (71.3)	N.A. (N.A., N.A.)	117	41 (35.0)	76 (65.0)	N.A. (15.41, N.A.)	1.232 (0.779, 1.949)	
BASELINE CREATININE CLEARANCE										0.4000
<60 ML/MIN	57	15 (26.3)	42 (73.7)	N.A. (N.A., N.A.)	47	20 (42.6)	27 (57.4)	N.A. (4.67, N.A.)	1.767 (0.903, 3.455)	
>=60 ML/MIN	71	20 (28.2)	51 (71.8)	N.A. (15.28, N.A.)	75	24 (32.0)	51 (68.0)	N.A. (15.41, N.A.)	1.145 (0.632, 2.073)	

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	N	Subjects with Event n (%)	Censored subjects n (%)	KME [95%CI] (mon) (1)	N	Subjects with Event n (%)	Censored subjects n (%)	KME [95%CI] (mon) (1)	HR [95%CI] P-value (2)	Test for Interaction P-value (3) (4)
TIME FROM IUC SURGERY TO RANDOMIZATION (DAYS)										0.7601
>30-60	28	5 (17.9)	23 (82.1)	N.A. (N.A., N.A.)	30	9 (30.0)	21 (70.0)	N.A. (11.20, N.A.)	1.678 (0.559, 5.040)	
>60-90	57	19 (33.3)	38 (66.7)	N.A. (9.43, N.A.)	51	20 (39.2)	31 (60.8)	15.90 (8.90, N.A.)	1.172 (0.624, 2.202)	
>90-120	38	10 (26.3)	28 (73.7)	N.A. (11.73, N.A.)	40	15 (37.5)	25 (62.5)	N.A. (4.67, N.A.)	1.615 (0.722, 3.613)	

FEB2025 DBL. HR = hazard ratio; KME=Kaplan-Meier estimate; N.M.E = Not meaningful estimate.

(1) KME of median time to event.

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interaction to assess the significance of the interaction between treatment and the subgroup, with baseline PRO score as a covariate. (4) P-values <0.05 are indicated by 1 asterisk (indicates potential effect modification).

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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

Table 4.1
Subgroup Analyses of EORTC QLQ-C30 Time to First Deterioration
PROS

Nausea and Vomiting Scale (MID=10)

Subgroup	Placebo				Nivolumab				Nivolumab vs. Placebo	
	N	Subjects with Event n (%)	Censored subjects n (%)	KME [95%CI] (mon) (1)	N	Subjects with Event n (%)	Censored subjects n (%)	KME [95%CI] (mon) (1)	HR [95%CI] P-value (2)	Test for Interaction P-value (3) (4)
INITIAL TUMOR ORIGIN										0.5280
URINARY BLADDER	104	28 (26.9)	76 (73.1)	N.A. (N.A., N.A.)	102	37 (36.3)	65 (63.7)	N.A. (15.41, N.A.)	1.428 (0.873, 2.335) 0.1563	
RENAL PELVIS	13	2 (15.4)	11 (84.6)	N.A. (4.27, N.A.)	15	5 (33.3)	10 (66.7)	N.A. (4.63, N.A.)	2.355 (0.456, 12.148) 0.3062	
URETER	11	5 (45.5)	6 (54.5)	N.A. (0.99, N.A.)	6	2 (33.3)	4 (66.7)	N.A. (1.02, N.A.)	0.607 (0.112, 3.290) 0.5624	

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MINOR HISTOLOGICAL VARIANTS										0.4348
PRESENCE	54	13 (24.1)	41 (75.9)	N.A. (N.A., N.A.)	53	19 (35.8)	34 (64.2)	15.90 (11.07, N.A.)	1.595 (0.786, 3.237)	
ABSENCE	74	22 (29.7)	52 (70.3)	N.A. (13.14, N.A.)	70	25 (35.7)	45 (64.3)	N.A. (8.90, N.A.)	1.171 (0.660, 2.079)	

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OVERALL	128	81 (63.3)	47 (36.7)	4.76 (3.25, 7.16)	123	67 (54.5)	56 (45.5)	9.69 (5.16, 15.64)	0.751 (0.543, 1.039) 0.0836	
PRIOR NEO-ADJUVANT CISPLATIN THERAPY										0.2074
YES	54	33 (61.1)	21 (38.9)	4.63 (2.83, 9.72)	49	31 (63.3)	18 (36.7)	5.55 (2.83, 15.64)	0.971 (0.594, 1.587) 0.9069	
NO	74	48 (64.9)	26 (35.1)	4.76 (2.83, 7.16)	74	36 (48.6)	38 (51.4)	11.60 (5.52, N.A.)	0.634 (0.411, 0.978) 0.0392	

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Subgroup	Placebo				Nivolumab				Nivolumab vs. Placebo	
	N	Subjects with Event n (%)	Censored subjects n (%)	KME [95%CI] (mon) (1)	N	Subjects with Event n (%)	Censored subjects n (%)	KME [95%CI] (mon) (1)	HR [95%CI] P-value (2)	Test for Interaction P-value (3) (4)
PRIOR CISPLATIN STATUS										0.4226
RECEIVED NEO-ADJUVANT	54	33 (61.1)	21 (38.9)	4.63 (2.83, 9.72)	49	31 (63.3)	18 (36.7)	5.55 (2.83, 15.64)	0.971 (0.594, 1.587)	
UNWILLING TO RECEIVE NEO-ADJUVANT	42	27 (64.3)	15 (35.7)	6.08 (2.86, 11.10)	46	20 (43.5)	26 (56.5)	12.88 (7.13, N.A.)	0.552 (0.307, 0.992)	
NOT ELIGIBLE TO RECEIVE NEO-ADJUVANT	31	21 (67.7)	10 (32.3)	2.83 (1.87, 9.26)	23	14 (60.9)	9 (39.1)	9.99 (1.97, N.A.)	0.680 (0.337, 1.373)	

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Subgroup	Placebo				Nivolumab				Nivolumab vs. Placebo	
	N	Subjects with Event n (%)	Censored subjects n (%)	KME [95%CI] (mon) (1)	N	Subjects with Event n (%)	Censored subjects n (%)	KME [95%CI] (mon) (1)	HR [95%CI] P-value (2)	Test for Interaction P-value (3) (4)
USE OF ANY PRIOR NEO-ADJUVANT SYSTEMIC THERAPY										0.2470
YES	55	34 (61.8)	21 (38.2)	4.63 (2.83, 9.72)	53	34 (64.2)	19 (35.8)	5.55 (2.86, 10.94)	0.926 (0.575, 1.491) 0.7504	
NO	73	47 (64.4)	26 (35.6)	4.76 (2.83, 7.16)	70	33 (47.1)	37 (52.9)	12.88 (5.16, N.A.)	0.631 (0.404, 0.987) 0.0438	

FEB2025 DBL. HR = hazard ratio; KME=Kaplan-Meier estimate; N.M.E = Not meaningful estimate.

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Subgroup	Placebo				Nivolumab				Nivolumab vs. Placebo	
	N	Subjects with Event n (%)	Censored subjects n (%)	KME [95%CI] (mon) (1)	N	Subjects with Event n (%)	Censored subjects n (%)	KME [95%CI] (mon) (1)	HR [95%CI] P-value (2)	Test for Interaction P-value (3) (4)
PATHOLOGICAL LYMPH NODE STATUS										0.9472
N+	57	36 (63.2)	21 (36.8)	4.63 (2.83, 7.16)	51	28 (54.9)	23 (45.1)	9.99 (4.63, N.A.)	0.707 (0.427, 1.171)	
NO/X WITH <10 NODES REMOVED	37	22 (59.5)	15 (40.5)	5.52 (1.91, N.A.)	35	18 (51.4)	17 (48.6)	8.80 (1.97, N.A.)	0.673 (0.357, 1.272)	
NO WITH >= 10 NODES REMOVED	34	23 (67.6)	11 (32.4)	4.32 (2.79, 9.72)	37	21 (56.8)	16 (43.2)	7.13 (3.71, N.A.)	0.756 (0.417, 1.371)	

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	N	Subjects with Event n (%)	Censored subjects n (%)	KME [95%CI] (mon) (1)	N	Subjects with Event n (%)	Censored subjects n (%)	KME [95%CI] (mon) (1)	HR [95%CI] P-value (2)	Test for Interaction P-value (3) (4)
PATHOLOGICAL STATUS										0.9953
PT0-2	29	18 (62.1)	11 (37.9)	4.63 (1.05, N.A.)	21	12 (57.1)	9 (42.9)	5.55 (1.97, N.A.)	0.739 (0.348, 1.570)	
PT3	73	45 (61.6)	28 (38.4)	4.73 (2.86, 7.79)	78	42 (53.8)	36 (46.2)	10.64 (4.67, 15.64)	0.4317 0.767 (0.503, 1.169)	
PT4A	25	18 (72.0)	7 (28.0)	5.68 (2.83, 9.72)	21	12 (57.1)	9 (42.9)	9.69 (2.86, N.A.)	0.2171 0.637 (0.300, 1.353)	

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AGE CATEGORY I										0.1552
< 65	54	29 (53.7)	25 (46.3)	6.90 (3.71, N.A.)	57	33 (57.9)	24 (42.1)	8.80 (4.01, 16.20)	1.035 (0.624, 1.718) 0.8930	
>= 65	74	52 (70.3)	22 (29.7)	3.94 (2.79, 7.03)	66	34 (51.5)	32 (48.5)	11.07 (4.50, N.A.)	0.620 (0.401, 0.960) 0.0320	

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AGE CATEGORY II										0.3222
< 65	54	29 (53.7)	25 (46.3)	6.90 (3.71, N.A.)	57	33 (57.9)	24 (42.1)	8.80 (4.01, 16.20)	1.035 (0.624, 1.718) 0.8930	
>= 65 AND < 75	54	37 (68.5)	17 (31.5)	4.63 (2.76, 7.03)	45	21 (46.7)	24 (53.3)	13.01 (4.67, N.A.)	0.577 (0.336, 0.990) 0.0459	
>= 75	20	15 (75.0)	5 (25.0)	3.83 (1.05, 9.26)	21	13 (61.9)	8 (38.1)	4.90 (2.33, N.A.)	0.715 (0.336, 1.521) 0.3834	

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REGION										0.9530
US	21	15 (71.4)	6 (28.6)	3.25 (1.97, 8.48)	14	7 (50.0)	7 (50.0)	5.59 (1.02, N.A.)	0.599 (0.242, 1.481) 0.2672	
EUROPE	62	40 (64.5)	22 (35.5)	4.63 (2.76, 9.63)	65	37 (56.9)	28 (43.1)	9.69 (4.67, 15.64)	0.782 (0.500, 1.225) 0.2832	
ASIA	27	14 (51.9)	13 (48.1)	9.26 (4.01, N.A.)	28	13 (46.4)	15 (53.6)	10.94 (3.71, N.A.)	0.785 (0.366, 1.684) 0.5345	
REST OF WORLD	18	12 (66.7)	6 (33.3)	3.71 (1.05, N.A.)	16	10 (62.5)	6 (37.5)	3.94 (1.87, N.A.)	0.699 (0.293, 1.666) 0.4189	

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GENDER										0.9327
MALE	101	61 (60.4)	40 (39.6)	5.52 (3.94, 9.26)	90	47 (52.2)	43 (47.8)	10.94 (4.90, N.A.)	0.733 (0.500, 1.075) 0.1115	
FEMALE	27	20 (74.1)	7 (25.9)	2.86 (1.15, 6.08)	33	20 (60.6)	13 (39.4)	5.55 (2.04, 11.60)	0.721 (0.387, 1.342) 0.3020	
RACE										0.7483
WHITE	96	64 (66.7)	32 (33.3)	4.47 (2.83, 6.97)	94	53 (56.4)	41 (43.6)	9.69 (4.67, 15.64)	0.725 (0.503, 1.044) 0.0839	
ASIAN	27	14 (51.9)	13 (48.1)	9.26 (4.01, N.A.)	28	13 (46.4)	15 (53.6)	10.94 (3.71, N.A.)	0.785 (0.366, 1.684) 0.5345	

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BASELINE ECOG STATUS										0.8399
0	80	47 (58.8)	33 (41.3)	5.68 (2.96, 10.61)	76	40 (52.6)	36 (47.4)	10.94 (5.52, N.A.)	0.735 (0.480, 1.125)	
1	44	30 (68.2)	14 (31.8)	4.01 (2.76, 7.16)	45	25 (55.6)	20 (44.4)	8.28 (2.99, N.A.)	0.1564 0.782 (0.459, 1.333)	
SMOKING STATUS										0.1664
NEVER SMOKED	36	21 (58.3)	15 (41.7)	6.97 (2.83, N.A.)	36	22 (61.1)	14 (38.9)	8.80 (3.71, 15.64)	1.053 (0.574, 1.930)	
CURRENT/FORMER	91	59 (64.8)	32 (35.2)	4.47 (2.83, 7.03)	86	45 (52.3)	41 (47.7)	10.64 (4.63, N.A.)	0.8673 0.658 (0.446, 0.972)	
									0.0354	

FEB2025 DBL. HR = hazard ratio; KME=Kaplan-Meier estimate; N.M.E = Not meaningful estimate.

(1) KME of median time to event.

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interaction to assess the significance of the interaction between treatment and the subgroup, with baseline PRO score as a covariate. (4) P-values <0.05 are indicated by 1 asterisk (indicates potential effect modification).

IUC = invasive urothelial carcinoma.

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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

Table 4.1
Subgroup Analyses of EORTC QLQ-C30 Time to First Deterioration
PROS

Pain Scale (MID=10)

Subgroup	Placebo				Nivolumab				Nivolumab vs. Placebo	
	N	Subjects with Event n (%)	Censored subjects n (%)	KME [95%CI] (mon) (1)	N	Subjects with Event n (%)	Censored subjects n (%)	KME [95%CI] (mon) (1)	HR [95%CI] P-value (2)	Test for Interaction P-value (3) (4)
BASELINE HEMOGLOBIN										0.9749
<10 G/DL	13	9 (69.2)	4 (30.8)	4.76 (1.15, N.A.)	6	4 (66.7)	2 (33.3)	8.28 (1.02, N.A.)	0.583 (0.171, 1.992)	
>=10 G/DL	115	72 (62.6)	43 (37.4)	4.73 (2.96, 7.16)	117	63 (53.8)	54 (46.2)	9.69 (5.16, 15.64)	0.3895 0.761 (0.542, 1.068) 0.1145	
BASELINE CREATININE CLEARANCE										0.9916
<60 ML/MIN	57	35 (61.4)	22 (38.6)	6.90 (2.83, 9.63)	47	25 (53.2)	22 (46.8)	9.99 (3.75, N.A.)	0.750 (0.447, 1.260) 0.2772	
>=60 ML/MIN	71	46 (64.8)	25 (35.2)	4.63 (2.83, 7.03)	75	41 (54.7)	34 (45.3)	9.69 (4.63, 16.20)	0.752 (0.492, 1.149) 0.1879	

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TIME FROM IUC SURGERY TO RANDOMIZATION (DAYS)										0.2879
>30-60	28	17 (60.7)	11 (39.3)	4.73 (2.04, N.A.)	30	16 (53.3)	14 (46.7)	11.07 (3.61, N.A.)	0.709 (0.352, 1.428)	
>60-90	57	31 (54.4)	26 (45.6)	8.48 (3.71, N.A.)	51	29 (56.9)	22 (43.1)	7.39 (4.67, 13.01)	0.3351 1.015 (0.611, 1.686)	
>90-120	38	31 (81.6)	7 (18.4)	3.48 (2.76, 6.08)	40	22 (55.0)	18 (45.0)	8.28 (2.33, N.A.)	0.9542 0.538 (0.309, 0.938)	

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INITIAL TUMOR ORIGIN										0.7101
URINARY BLADDER	104	67 (64.4)	37 (35.6)	4.63 (2.86, 6.97)	102	59 (57.8)	43 (42.2)	6.97 (4.01, 13.01)	0.791 (0.557, 1.123)	
RENAL PELVIS	13	8 (61.5)	5 (38.5)	7.16 (1.05, N.A.)	15	6 (40.0)	9 (60.0)	11.07 (7.13, N.A.)	0.1903 0.524 (0.178, 1.537)	
URETER	11	6 (54.5)	5 (45.5)	7.03 (0.99, N.A.)	6	2 (33.3)	4 (66.7)	N.A. (0.95, N.A.)	0.2392 0.490 (0.087, 2.752)	

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	N	Subjects with Event n (%)	Censored subjects n (%)	KME [95%CI] (mon) (1)	N	Subjects with Event n (%)	Censored subjects n (%)	KME [95%CI] (mon) (1)	HR [95%CI] P-value (2)	Test for Interaction P-value (3) (4)
MINOR HISTOLOGICAL VARIANTS										0.9859
PRESENCE	54	35 (64.8)	19 (35.2)	5.19 (2.83, 9.63)	53	29 (54.7)	24 (45.3)	10.64 (4.90, 15.64)	0.751 (0.458, 1.230) 0.2551	
ABSENCE	74	46 (62.2)	28 (37.8)	4.63 (2.86, 7.16)	70	38 (54.3)	32 (45.7)	7.39 (3.61, N.A.)	0.771 (0.501, 1.187) 0.2382	

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Table 4.1
Subgroup Analyses of EORTC QLQ-C30 Time to First Deterioration
PROS

Dyspnea Scale (MID=10)

Subgroup	Placebo				Nivolumab				Nivolumab vs. Placebo	
	N	Subjects with Event n (%)	Censored subjects n (%)	KME [95%CI] (mon) (1)	N	Subjects with Event n (%)	Censored subjects n (%)	KME [95%CI] (mon) (1)	HR [95%CI] P-value (2)	Test for Interaction P-value (3) (4)
OVERALL	127	44 (34.6)	83 (65.4)	N.A. (12.91, N.A.)	123	51 (41.5)	72 (58.5)	15.93 (8.90, N.A.)	1.191 (0.795, 1.783) 0.3967	
PRIOR NEO-ADJUVANT CISPLATIN THERAPY										0.0409*
YES	53	16 (30.2)	37 (69.8)	N.A. (11.01, N.A.)	49	24 (49.0)	25 (51.0)	11.56 (4.04, N.A.)	1.987 (1.051, 3.755) 0.0345	
NO	74	28 (37.8)	46 (62.2)	N.A. (9.79, N.A.)	74	27 (36.5)	47 (63.5)	N.A. (8.90, N.A.)	0.829 (0.488, 1.407) 0.4863	

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Subgroup	Placebo				Nivolumab				Nivolumab vs. Placebo	
	N	Subjects with Event n (%)	Censored subjects n (%)	KME [95%CI] (mon) (1)	N	Subjects with Event n (%)	Censored subjects n (%)	KME [95%CI] (mon) (1)	HR [95%CI] P-value (2)	Test for Interaction P-value (3) (4)
PRIOR CISPLATIN STATUS										0.1562
RECEIVED NEO-ADJUVANT	53	16 (30.2)	37 (69.8)	N.A. (11.01, N.A.)	49	24 (49.0)	25 (51.0)	11.56 (4.04, N.A.)	1.987 (1.051, 3.755)	
UNWILLING TO RECEIVE NEO-ADJUVANT	42	14 (33.3)	28 (66.7)	N.A. (9.79, N.A.)	46	15 (32.6)	31 (67.4)	N.A. (9.95, N.A.)	0.813 (0.390, 1.693)	
NOT ELIGIBLE TO RECEIVE NEO-ADJUVANT	31	14 (45.2)	17 (54.8)	12.91 (2.83, N.A.)	23	11 (47.8)	12 (52.2)	11.07 (3.09, N.A.)	0.934 (0.419, 2.079)	

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	N	Subjects with Event n (%)	Censored subjects n (%)	KME [95%CI] (mon) (1)	N	Subjects with Event n (%)	Censored subjects n (%)	KME [95%CI] (mon) (1)	HR [95%CI] P-value (2)	Test for Interaction P-value (3) (4)
USE OF ANY PRIOR NEO-ADJUVANT SYSTEMIC THERAPY										0.0841
YES	54	16 (29.6)	38 (70.4)	N.A. (11.01, N.A.)	53	24 (45.3)	29 (54.7)	15.93 (4.50, N.A.)	1.843 (0.975, 3.485) 0.0598	
NO	73	28 (38.4)	45 (61.6)	N.A. (9.79, N.A.)	70	27 (38.6)	43 (61.4)	N.A. (8.28, N.A.)	0.872 (0.513, 1.480) 0.6108	

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	N	Subjects with Event n (%)	Censored subjects n (%)	KME [95%CI] (mon) (1)	N	Subjects with Event n (%)	Censored subjects n (%)	KME [95%CI] (mon) (1)	HR [95%CI] P-value (2)	Test for Interaction P-value (3) (4)
PATHOLOGICAL LYMPH NODE STATUS										0.6922
N+	56	18 (32.1)	38 (67.9)	N.A. (9.66, N.A.)	51	18 (35.3)	33 (64.7)	N.A. (7.23, N.A.)	0.995 (0.516, 1.920)	
N0/X WITH <10 NODES REMOVED	37	15 (40.5)	22 (59.5)	13.14 (5.65, N.A.)	35	17 (48.6)	18 (51.4)	11.07 (4.63, N.A.)	0.9892 1.234 (0.615, 2.479)	
N0 WITH >= 10 NODES REMOVED	34	11 (32.4)	23 (67.6)	N.A. (11.10, N.A.)	37	16 (43.2)	21 (56.8)	N.A. (5.65, N.A.)	0.5537 1.356 (0.621, 2.964)	
									0.4447	

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PATHOLOGICAL STATUS										0.6998
PT0-2	29	9 (31.0)	20 (69.0)	N.A. (9.66, N.A.)	21	9 (42.9)	12 (57.1)	15.93 (2.86, N.A.)	1.349 (0.533, 3.415)	
PT3	72	25 (34.7)	47 (65.3)	N.A. (12.91, N.A.)	78	29 (37.2)	49 (62.8)	N.A. (8.90, N.A.)	0.5278 (0.580, 1.692)	
PT4A	25	10 (40.0)	15 (60.0)	N.A. (3.02, N.A.)	21	11 (52.4)	10 (47.6)	4.04 (1.87, N.A.)	0.9726 (0.620, 3.476)	

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AGE CATEGORY I										
< 65	53	17 (32.1)	36 (67.9)	N.A. (11.01, N.A.)	57	18 (31.6)	39 (68.4)	N.A. (N.A., N.A.)	1.066 (0.548, 2.075) 0.8502	0.6413
>= 65	74	27 (36.5)	47 (63.5)	N.A. (9.63, N.A.)	66	33 (50.0)	33 (50.0)	9.95 (4.63, N.A.)	1.296 (0.779, 2.156) 0.3174	

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	N	Subjects with Event n (%)	Censored subjects n (%)	KME [95%CI] (mon) (1)	N	Subjects with Event n (%)	Censored subjects n (%)	KME [95%CI] (mon) (1)	HR [95%CI] P-value (2)	Test for Interaction P-value (3) (4)
AGE CATEGORY II										0.7832
< 65	53	17 (32.1)	36 (67.9)	N.A. (11.01, N.A.)	57	18 (31.6)	39 (68.4)	N.A. (N.A., N.A.)	1.066 (0.548, 2.075) 0.8502	
>= 65 AND < 75	54	18 (33.3)	36 (66.7)	N.A. (12.91, N.A.)	45	20 (44.4)	25 (55.6)	15.93 (4.63, N.A.)	1.184 (0.625, 2.244) 0.6040	
>= 75	20	9 (45.0)	11 (55.0)	9.63 (2.83, N.A.)	21	13 (61.9)	8 (38.1)	6.97 (2.83, 11.07)	1.566 (0.661, 3.708) 0.3081	

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	N	Subjects with Event n (%)	Censored subjects n (%)	KME [95%CI] (mon) (1)	N	Subjects with Event n (%)	Censored subjects n (%)	KME [95%CI] (mon) (1)	HR [95%CI] P-value (2)	Test for Interaction P-value (3) (4)
REGION										0.4403
US	21	8 (38.1)	13 (61.9)	12.94 (5.59, N.A.)	14	7 (50.0)	7 (50.0)	5.85 (1.87, N.A.)	1.466 (0.527, 4.079) 0.4640	
EUROPE	61	25 (41.0)	36 (59.0)	N.A. (9.63, N.A.)	65	29 (44.6)	36 (55.4)	15.93 (7.23, N.A.)	1.078 (0.630, 1.844) 0.7854	
ASIA	27	8 (29.6)	19 (70.4)	N.A. (13.14, N.A.)	28	9 (32.1)	19 (67.9)	N.A. (8.05, N.A.)	0.771 (0.295, 2.012) 0.5949	
REST OF WORLD	18	3 (16.7)	15 (83.3)	N.A. (5.62, N.A.)	16	6 (37.5)	10 (62.5)	N.A. (1.15, N.A.)	3.917 (0.969, 15.836) 0.0554	

FEB2025 DBL. HR = hazard ratio; KME=Kaplan-Meier estimate; N.M.E = Not meaningful estimate.

(1) KME of median time to event.

(2) Unstratified Cox proportional hazard model, with baseline PRO score as a covariate. HR is Nivolumab over Placebo.

(3) Unstratified Cox proportional hazard model with treatment, subgroup and treatment*subgroup interaction to assess the significance of the interaction between treatment and the subgroup, with baseline PRO score as a covariate. (4) P-values <0.05 are indicated by 1 asterisk (indicates potential effect modification).

IUC = invasive urothelial carcinoma.

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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

Table 4.1
Subgroup Analyses of EORTC QLQ-C30 Time to First Deterioration
PROS

Dyspnea Scale (MID=10)

Subgroup	Placebo				Nivolumab				Nivolumab vs. Placebo	
	N	Subjects with Event n (%)	Censored subjects n (%)	KME [95%CI] (mon) (1)	N	Subjects with Event n (%)	Censored subjects n (%)	KME [95%CI] (mon) (1)	HR [95%CI] P-value (2)	Test for Interaction P-value (3) (4)
GENDER										
MALE	100	34 (34.0)	66 (66.0)	N.A. (12.91, N.A.)	90	37 (41.1)	53 (58.9)	15.93 (9.69, N.A.)	1.143 (0.716, 1.823) 0.5756	0.7352
FEMALE	27	10 (37.0)	17 (63.0)	N.A. (1.87, N.A.)	33	14 (42.4)	19 (57.6)	8.28 (3.32, N.A.)	1.197 (0.525, 2.730) 0.6686	
RACE										
WHITE	95	34 (35.8)	61 (64.2)	N.A. (11.01, N.A.)	94	42 (44.7)	52 (55.3)	15.93 (7.23, N.A.)	1.312 (0.832, 2.067) 0.2424	0.3890
ASIAN	27	8 (29.6)	19 (70.4)	N.A. (13.14, N.A.)	28	9 (32.1)	19 (67.9)	N.A. (8.05, N.A.)	0.771 (0.295, 2.012) 0.5949	

FEB2025 DBL. HR = hazard ratio; KME=Kaplan-Meier estimate; N.M.E = Not meaningful estimate.

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	N	Subjects with Event n (%)	Censored subjects n (%)	KME [95%CI] (mon) (1)	N	Subjects with Event n (%)	Censored subjects n (%)	KME [95%CI] (mon) (1)	HR [95%CI] P-value (2)	Test for Interaction P-value (3) (4)
BASELINE ECOG STATUS										0.4195
0	80	25 (31.3)	55 (68.8)	N.A. (12.94, N.A.)	76	32 (42.1)	44 (57.9)	N.A. (8.90, N.A.)	1.367 (0.809, 2.308) 0.2425	
1	43	17 (39.5)	26 (60.5)	11.10 (5.59, N.A.)	45	18 (40.0)	27 (60.0)	15.93 (6.01, N.A.)	0.995 (0.512, 1.933) 0.9873	
SMOKING STATUS										0.7475
NEVER SMOKED	36	11 (30.6)	25 (69.4)	N.A. (12.94, N.A.)	36	13 (36.1)	23 (63.9)	N.A. (6.01, N.A.)	1.218 (0.542, 2.737) 0.6328	
CURRENT/FORMER	90	33 (36.7)	57 (63.3)	N.A. (9.79, N.A.)	86	37 (43.0)	49 (57.0)	15.93 (8.05, N.A.)	1.106 (0.690, 1.772) 0.6755	

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	N	Subjects with Event n (%)	Censored subjects n (%)	KME [95%CI] (mon) (1)	N	Subjects with Event n (%)	Censored subjects n (%)	KME [95%CI] (mon) (1)	HR [95%CI] P-value (2)	Test for Interaction P-value (3) (4)
BASELINE HEMOGLOBIN										0.3375
<10 G/DL	13	4 (30.8)	9 (69.2)	N.A. (5.62, N.A.)	6	4 (66.7)	2 (33.3)	6.05 (1.02, N.A.)	3.011 (0.641, 14.145)	
>=10 G/DL	114	40 (35.1)	74 (64.9)	N.A. (12.91, N.A.)	117	47 (40.2)	70 (59.8)	15.93 (9.69, N.A.)	1.134 (0.743, 1.731)	
BASELINE CREATININE CLEARANCE										0.1954
<60 ML/MIN	57	19 (33.3)	38 (66.7)	N.A. (11.10, N.A.)	47	23 (48.9)	24 (51.1)	8.28 (4.63, N.A.)	1.695 (0.921, 3.119)	
>=60 ML/MIN	70	25 (35.7)	45 (64.3)	N.A. (9.79, N.A.)	75	27 (36.0)	48 (64.0)	N.A. (9.95, N.A.)	0.956 (0.554, 1.648)	

FEB2025 DBL. HR = hazard ratio; KME=Kaplan-Meier estimate; N.M.E = Not meaningful estimate.

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	N	Subjects with Event n (%)	Censored subjects n (%)	KME [95%CI] (mon) (1)	N	Subjects with Event n (%)	Censored subjects n (%)	KME [95%CI] (mon) (1)	HR [95%CI] P-value (2)	Test for Interaction P-value (3) (4)
TIME FROM IUC SURGERY TO RANDOMIZATION (DAYS)										0.8637
>30-60	28	9 (32.1)	19 (67.9)	N.A. (9.79, N.A.)	30	11 (36.7)	19 (63.3)	15.93 (6.01, N.A.)	1.427 (0.585, 3.482)	
>60-90	56	21 (37.5)	35 (62.5)	N.A. (9.63, N.A.)	51	21 (41.2)	30 (58.8)	N.A. (5.65, N.A.)	1.067 (0.582, 1.956)	
>90-120	38	14 (36.8)	24 (63.2)	12.94 (9.66, N.A.)	40	19 (47.5)	21 (52.5)	11.56 (4.50, N.A.)	1.304 (0.651, 2.612)	

FEB2025 DBL. HR = hazard ratio; KME=Kaplan-Meier estimate; N.M.E = Not meaningful estimate.

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Subgroup	Placebo				Nivolumab				Nivolumab vs. Placebo	
	N	Subjects with Event n (%)	Censored subjects n (%)	KME [95%CI] (mon) (1)	N	Subjects with Event n (%)	Censored subjects n (%)	KME [95%CI] (mon) (1)	HR [95%CI] P-value (2)	Test for Interaction P-value (3) (4)
INITIAL TUMOR ORIGIN										0.5282
URINARY BLADDER	103	33 (32.0)	70 (68.0)	N.A. (12.91, N.A.)	102	42 (41.2)	60 (58.8)	15.93 (8.90, N.A.)	1.325 (0.839, 2.093)	
RENAL PELVIS	13	8 (61.5)	5 (38.5)	12.94 (0.99, N.A.)	15	8 (53.3)	7 (46.7)	9.95 (2.99, N.A.)	0.2275 0.833 (0.308, 2.249)	
URETER	11	3 (27.3)	8 (72.7)	N.A. (1.87, N.A.)	6	1 (16.7)	5 (83.3)	N.A. (1.94, N.A.)	0.7180 0.520 (0.049, 5.508)	

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(1) KME of median time to event.

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(3) Unstratified Cox proportional hazard model with treatment, subgroup and treatment*subgroup

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Subgroup	Placebo				Nivolumab				Nivolumab vs. Placebo	
	N	Subjects with Event n (%)	Censored subjects n (%)	KME [95%CI] (mon) (1)	N	Subjects with Event n (%)	Censored subjects n (%)	KME [95%CI] (mon) (1)	HR [95%CI] P-value (2)	Test for Interaction P-value (3) (4)
MINOR HISTOLOGICAL VARIANTS										0.7321
PRESENCE	54	20 (37.0)	34 (63.0)	N.A. (9.79, N.A.)	53	24 (45.3)	29 (54.7)	11.07 (6.97, N.A.)	1.296 (0.714, 2.350)	
ABSENCE	73	24 (32.9)	49 (67.1)	N.A. (11.01, N.A.)	70	27 (38.6)	43 (61.4)	N.A. (7.39, N.A.)	1.128 (0.650, 1.958)	

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Table 4.1
Subgroup Analyses of EORTC QLQ-C30 Time to First Deterioration
PROS

Insomnia Scale (MID=10)

Subgroup	Placebo				Nivolumab				Nivolumab vs. Placebo	
	N	Subjects with Event n (%)	Censored subjects n (%)	KME [95%CI] (mon) (1)	N	Subjects with Event n (%)	Censored subjects n (%)	KME [95%CI] (mon) (1)	HR [95%CI] P-value (2)	Test for Interaction P-value (3) (4)
OVERALL	128	64 (50.0)	64 (50.0)	10.61 (5.49, N.A.)	123	49 (39.8)	74 (60.2)	15.80 (11.07, N.A.)	0.773 (0.532, 1.123) 0.1767	
PRIOR NEO-ADJUVANT CISPLATIN THERAPY										0.6549
YES	54	28 (51.9)	26 (48.1)	10.32 (4.47, N.A.)	49	20 (40.8)	29 (59.2)	15.80 (8.77, N.A.)	0.869 (0.486, 1.553) 0.6346	
NO	74	36 (48.6)	38 (51.4)	11.73 (3.75, N.A.)	74	29 (39.2)	45 (60.8)	N.A. (7.89, N.A.)	0.726 (0.445, 1.186) 0.2011	

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	N	Subjects with Event n (%)	Censored subjects n (%)	KME [95%CI] (mon) (1)	N	Subjects with Event n (%)	Censored subjects n (%)	KME [95%CI] (mon) (1)	HR [95%CI] P-value (2)	Test for Interaction P-value (3) (4)
PRIOR CISPLATIN STATUS										0.5915
RECEIVED NEO-ADJUVANT	54	28 (51.9)	26 (48.1)	10.32 (4.47, N.A.)	49	20 (40.8)	29 (59.2)	15.80 (8.77, N.A.)	0.869 (0.486, 1.553)	
UNWILLING TO RECEIVE NEO-ADJUVANT	42	21 (50.0)	21 (50.0)	11.73 (3.75, N.A.)	46	19 (41.3)	27 (58.7)	N.A. (3.38, N.A.)	0.6346 0.813 (0.437, 1.514)	
NOT ELIGIBLE TO RECEIVE NEO-ADJUVANT	31	15 (48.4)	16 (51.6)	4.67 (1.87, N.A.)	23	8 (34.8)	15 (65.2)	N.A. (7.89, N.A.)	0.5139 0.497 (0.207, 1.196)	

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USE OF ANY PRIOR NEO-ADJUVANT SYSTEMIC THERAPY										0.9526
YES	55	29 (52.7)	26 (47.3)	10.32 (4.47, N.A.)	53	21 (39.6)	32 (60.4)	15.80 (8.87, N.A.)	0.766 (0.436, 1.348) 0.3558	
NO	73	35 (47.9)	38 (52.1)	11.73 (4.63, N.A.)	70	28 (40.0)	42 (60.0)	N.A. (7.89, N.A.)	0.785 (0.477, 1.291) 0.3401	

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PATHOLOGICAL LYMPH NODE STATUS										0.4270
N+	57	31 (54.4)	26 (45.6)	7.92 (3.94, 12.91)	51	21 (41.2)	30 (58.8)	15.31 (5.55, N.A.)	0.605 (0.346, 1.055)	
N0/X WITH <10 NODES REMOVED	37	17 (45.9)	20 (54.1)	12.91 (1.97, N.A.)	35	13 (37.1)	22 (62.9)	N.A. (5.52, N.A.)	0.0766 (0.354, 1.519)	
N0 WITH >= 10 NODES REMOVED	34	16 (47.1)	18 (52.9)	N.A. (2.96, N.A.)	37	15 (40.5)	22 (59.5)	15.80 (8.05, N.A.)	0.733 (0.580, 2.481)	

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PATHOLOGICAL STATUS										0.7677
PT0-2	29	15 (51.7)	14 (48.3)	11.73 (4.67, N.A.)	21	10 (47.6)	11 (52.4)	N.A. (1.87, N.A.)	0.938 (0.416, 2.116)	
PT3	73	33 (45.2)	40 (54.8)	12.91 (4.76, N.A.)	78	30 (38.5)	48 (61.5)	15.80 (8.87, N.A.)	0.8778 0.839 (0.510, 1.381)	
PT4A	25	16 (64.0)	9 (36.0)	3.75 (1.87, 10.61)	21	9 (42.9)	12 (57.1)	N.A. (2.07, N.A.)	0.4900 0.643 (0.280, 1.475)	

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IUC = invasive urothelial carcinoma.

Program Path: /projects/bms214671/stats/market/ma274_202502/prog/tables

Program Name: rt-sy-tdd-eortc-comm-ebr45.sas

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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

Table 4.1
Subgroup Analyses of EORTC QLQ-C30 Time to First Deterioration
PROS

Insomnia Scale (MID=10)

Subgroup	Placebo				Nivolumab				Nivolumab vs. Placebo	
	N	Subjects with Event n (%)	Censored subjects n (%)	KME [95%CI] (mon) (1)	N	Subjects with Event n (%)	Censored subjects n (%)	KME [95%CI] (mon) (1)	HR [95%CI] P-value (2)	Test for Interaction P-value (3) (4)
AGE CATEGORY I										0.8933
< 65	54	26 (48.1)	28 (51.9)	11.04 (5.49, N.A.)	57	21 (36.8)	36 (63.2)	N.A. (8.87, N.A.)	0.800 (0.449, 1.425) 0.4490	
>= 65	74	38 (51.4)	36 (48.6)	10.61 (3.75, N.A.)	66	28 (42.4)	38 (57.6)	12.75 (8.05, N.A.)	0.782 (0.479, 1.278) 0.3270	

FEB2025 DBL. HR = hazard ratio; KME=Kaplan-Meier estimate; N.M.E = Not meaningful estimate.

(1) KME of median time to event.

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Subgroup	Placebo				Nivolumab				Nivolumab vs. Placebo	
	N	Subjects with Event n (%)	Censored subjects n (%)	KME [95%CI] (mon) (1)	N	Subjects with Event n (%)	Censored subjects n (%)	KME [95%CI] (mon) (1)	HR [95%CI] P-value (2)	Test for Interaction P-value (3) (4)
AGE CATEGORY II										0.4361
< 65	54	26 (48.1)	28 (51.9)	11.04 (5.49, N.A.)	57	21 (36.8)	36 (63.2)	N.A. (8.87, N.A.)	0.800 (0.449, 1.425) 0.4490	
>= 65 AND < 75	54	28 (51.9)	26 (48.1)	7.92 (2.96, N.A.)	45	17 (37.8)	28 (62.2)	15.31 (8.71, N.A.)	0.610 (0.333, 1.115) 0.1081	
>= 75	20	10 (50.0)	10 (50.0)	11.73 (1.87, N.A.)	21	11 (52.4)	10 (47.6)	11.07 (4.57, N.A.)	1.518 (0.615, 3.743) 0.3652	

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REGION										0.5039
US	21	11 (52.4)	10 (47.6)	12.91 (1.94, N.A.)	14	3 (21.4)	11 (78.6)	N.A. (12.75, N.A.)	0.481 (0.131, 1.765) 0.2696	
EUROPE	62	31 (50.0)	31 (50.0)	11.73 (5.49, N.A.)	65	30 (46.2)	35 (53.8)	15.80 (5.55, N.A.)	0.950 (0.575, 1.571) 0.8430	
ASIA	27	14 (51.9)	13 (48.1)	11.04 (1.45, N.A.)	28	9 (32.1)	19 (67.9)	N.A. (8.05, N.A.)	0.531 (0.227, 1.245) 0.1457	
REST OF WORLD	18	8 (44.4)	10 (55.6)	10.32 (1.87, N.A.)	16	7 (43.8)	9 (56.3)	8.77 (3.38, N.A.)	1.058 (0.365, 3.063) 0.9173	

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	N	Subjects with Event n (%)	Censored subjects n (%)	KME [95%CI] (mon) (1)	N	Subjects with Event n (%)	Censored subjects n (%)	KME [95%CI] (mon) (1)	HR [95%CI] P-value (2)	Test for Interaction P-value (3) (4)
GENDER										
MALE	101	47 (46.5)	54 (53.5)	12.91 (9.43, N.A.)	90	34 (37.8)	56 (62.2)	N.A. (8.87, N.A.)	0.828 (0.531, 1.291) 0.4047	0.4232
FEMALE	27	17 (63.0)	10 (37.0)	3.75 (1.45, N.A.)	33	15 (45.5)	18 (54.5)	11.10 (3.81, N.A.)	0.581 (0.288, 1.172) 0.1294	
RACE										
WHITE	96	49 (51.0)	47 (49.0)	10.61 (6.57, N.A.)	94	40 (42.6)	54 (57.4)	15.80 (8.71, N.A.)	0.855 (0.562, 1.300) 0.4635	0.2549
ASIAN	27	14 (51.9)	13 (48.1)	11.04 (1.45, N.A.)	28	9 (32.1)	19 (67.9)	N.A. (8.05, N.A.)	0.531 (0.227, 1.245) 0.1457	

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	N	Subjects with Event n (%)	Censored subjects n (%)	KME [95%CI] (mon) (1)	N	Subjects with Event n (%)	Censored subjects n (%)	KME [95%CI] (mon) (1)	HR [95%CI] P-value (2)	Test for Interaction P-value (3) (4)
BASELINE ECOG STATUS										0.9400
0	80	37 (46.3)	43 (53.8)	12.91 (9.43, N.A.)	76	29 (38.2)	47 (61.8)	15.80 (11.07, N.A.)	0.786 (0.483, 1.279)	
1	44	24 (54.5)	20 (45.5)	5.49 (2.76, N.A.)	45	19 (42.2)	26 (57.8)	N.A. (4.63, N.A.)	0.3326 0.814 (0.443, 1.496)	
SMOKING STATUS										0.4317
NEVER SMOKED	36	15 (41.7)	21 (58.3)	N.A. (3.75, N.A.)	36	13 (36.1)	23 (63.9)	N.A. (6.60, N.A.)	1.008 (0.477, 2.130)	
CURRENT/FORMER	91	48 (52.7)	43 (47.3)	9.69 (4.47, 15.64)	86	36 (41.9)	50 (58.1)	15.80 (8.05, N.A.)	0.9841 0.713 (0.462, 1.099)	
									0.1255	

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BASELINE HEMOGLOBIN										0.4320
<10 G/DL	13	7 (53.8)	6 (46.2)	8.34 (0.95, N.A.)	6	3 (50.0)	3 (50.0)	8.71 (0.95, N.A.)	1.362 (0.326, 5.688)	
>=10 G/DL	115	57 (49.6)	58 (50.4)	11.04 (5.49, N.A.)	117	46 (39.3)	71 (60.7)	15.80 (11.07, N.A.)	0.6722 0.764 (0.517, 1.128)	
BASELINE CREATININE CLEARANCE										0.8279
<60 ML/MIN	57	29 (50.9)	28 (49.1)	7.13 (3.29, N.A.)	47	19 (40.4)	28 (59.6)	15.31 (8.77, N.A.)	0.783 (0.431, 1.424)	
>=60 ML/MIN	71	35 (49.3)	36 (50.7)	11.73 (7.92, N.A.)	75	29 (38.7)	46 (61.3)	15.80 (7.46, N.A.)	0.4233 0.734 (0.448, 1.203)	

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TIME FROM IUC SURGERY TO RANDOMIZATION (DAYS)										0.2298
>30-60	28	18 (64.3)	10 (35.7)	3.75 (1.45, 12.91)	30	12 (40.0)	18 (60.0)	N.A. (5.55, N.A.)	0.505 (0.240, 1.066)	
>60-90	57	24 (42.1)	33 (57.9)	N.A. (9.43, N.A.)	51	23 (45.1)	28 (54.9)	15.80 (8.71, N.A.)	0.0730 1.115 (0.628, 1.979)	
>90-120	38	20 (52.6)	18 (47.4)	8.34 (4.47, N.A.)	40	14 (35.0)	26 (65.0)	N.A. (6.60, N.A.)	0.660 (0.333, 1.308)	

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INITIAL TUMOR ORIGIN										0.9098
URINARY BLADDER	104	52 (50.0)	52 (50.0)	10.61 (5.49, N.A.)	102	42 (41.2)	60 (58.8)	15.80 (8.77, N.A.)	0.811 (0.540, 1.219)	
RENAL PELVIS	13	6 (46.2)	7 (53.8)	11.04 (1.15, N.A.)	15	5 (33.3)	10 (66.7)	N.A. (7.89, N.A.)	0.3140 0.783 (0.221, 2.772)	
URETER	11	6 (54.5)	5 (45.5)	12.91 (0.99, N.A.)	6	2 (33.3)	4 (66.7)	N.A. (0.95, N.A.)	0.7044 0.542 (0.103, 2.848)	

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MINOR HISTOLOGICAL VARIANTS										0.0716
PRESENCE	54	25 (46.3)	29 (53.7)	15.64 (7.13, N.A.)	53	26 (49.1)	27 (50.9)	8.87 (4.67, N.A.)	1.124 (0.647, 1.952)	
ABSENCE	74	39 (52.7)	35 (47.3)	10.32 (3.29, 12.91)	70	23 (32.9)	47 (67.1)	N.A. (15.31, N.A.)	0.540 (0.320, 0.912)	

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PROS

Appetite Loss Scale (MID=10)

Subgroup	Placebo				Nivolumab				Nivolumab vs. Placebo	
	N	Subjects with Event n (%)	Censored subjects n (%)	KME [95%CI] (mon) (1)	N	Subjects with Event n (%)	Censored subjects n (%)	KME [95%CI] (mon) (1)	HR [95%CI] P-value (2)	Test for Interaction P-value (3) (4)
OVERALL	128	49 (38.3)	79 (61.7)	N.A. (11.24, N.A.)	122	52 (42.6)	70 (57.4)	15.93 (9.23, N.A.)	1.177 (0.795, 1.742) 0.4163	
PRIOR NEO-ADJUVANT CISPLATIN THERAPY										0.7634
YES	54	21 (38.9)	33 (61.1)	N.A. (10.32, N.A.)	49	22 (44.9)	27 (55.1)	15.90 (5.55, 16.13)	1.209 (0.664, 2.202) 0.5346	
NO	74	28 (37.8)	46 (62.2)	N.A. (10.05, N.A.)	73	30 (41.1)	43 (58.9)	16.59 (8.38, N.A.)	1.139 (0.675, 1.921) 0.6260	

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PRIOR CISPLATIN STATUS										0.7429
RECEIVED NEO-ADJUVANT	54	21 (38.9)	33 (61.1)	N.A. (10.32, N.A.)	49	22 (44.9)	27 (55.1)	15.90 (5.55, 16.13)	1.209 (0.664, 2.202)	
UNWILLING TO RECEIVE NEO-ADJUVANT	42	18 (42.9)	24 (57.1)	N.A. (8.34, N.A.)	46	22 (47.8)	24 (52.2)	8.97 (4.24, N.A.)	1.375 (0.730, 2.589)	
NOT ELIGIBLE TO RECEIVE NEO-ADJUVANT	31	10 (32.3)	21 (67.7)	N.A. (4.17, N.A.)	22	8 (36.4)	14 (63.6)	16.59 (3.98, N.A.)	0.911 (0.342, 2.425)	

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USE OF ANY PRIOR NEO-ADJUVANT SYSTEMIC THERAPY										0.8272
YES	55	21 (38.2)	34 (61.8)	N.A. (10.32, N.A.)	53	24 (45.3)	29 (54.7)	15.90 (8.80, N.A.)	1.216 (0.676, 2.190) 0.5139	
NO	73	28 (38.4)	45 (61.6)	N.A. (10.05, N.A.)	69	28 (40.6)	41 (59.4)	N.A. (8.08, N.A.)	1.186 (0.700, 2.011) 0.5253	

FEB2025 DBL. HR = hazard ratio; KME=Kaplan-Meier estimate; N.M.E = Not meaningful estimate.

(1) KME of median time to event.

(2) Unstratified Cox proportional hazard model, with baseline PRO score as a covariate. HR is Nivolumab over Placebo.

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IUC = invasive urothelial carcinoma.

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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

Table 4.1
Subgroup Analyses of EORTC QLQ-C30 Time to First Deterioration
PROS

Appetite Loss Scale (MID=10)

Subgroup	Placebo				Nivolumab				Nivolumab vs. Placebo	
	N	Subjects with Event n (%)	Censored subjects n (%)	KME [95%CI] (mon) (1)	N	Subjects with Event n (%)	Censored subjects n (%)	KME [95%CI] (mon) (1)	HR [95%CI] P-value (2)	Test for Interaction P-value (3) (4)
PATHOLOGICAL LYMPH NODE STATUS										0.3094
N+	57	25 (43.9)	32 (56.1)	11.24 (8.34, N.A.)	50	19 (38.0)	31 (62.0)	16.13 (8.97, N.A.)	0.774 (0.421, 1.424)	
NO/X WITH <10 NODES REMOVED	37	13 (35.1)	24 (64.9)	N.A. (7.16, N.A.)	35	18 (51.4)	17 (48.6)	11.56 (3.75, N.A.)	1.584 (0.756, 3.317)	
NO WITH >= 10 NODES REMOVED	34	11 (32.4)	23 (67.6)	N.A. (4.63, N.A.)	37	15 (40.5)	22 (59.5)	15.90 (8.08, N.A.)	1.387 (0.637, 3.022)	

FEB2025 DBL. HR = hazard ratio; KME=Kaplan-Meier estimate; N.M.E = Not meaningful estimate.

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Subgroup	Placebo				Nivolumab				Nivolumab vs. Placebo	
	N	Subjects with Event n (%)	Censored subjects n (%)	KME [95%CI] (mon) (1)	N	Subjects with Event n (%)	Censored subjects n (%)	KME [95%CI] (mon) (1)	HR [95%CI] P-value (2)	Test for Interaction P-value (3) (4)
PATHOLOGICAL STATUS										0.7447
PT0-2	29	12 (41.4)	17 (58.6)	13.14 (10.32, N.A.)	21	11 (52.4)	10 (47.6)	15.93 (3.65, N.A.)	1.014 (0.435, 2.366) 0.9740	
PT3	73	30 (41.1)	43 (58.9)	N.A. (7.49, N.A.)	77	33 (42.9)	44 (57.1)	15.90 (8.80, N.A.)	1.077 (0.653, 1.777) 0.7701	
PT4A	25	7 (28.0)	18 (72.0)	N.A. (3.78, N.A.)	21	8 (38.1)	13 (61.9)	N.A. (3.61, N.A.)	1.781 (0.635, 4.994) 0.2727	

FEB2025 DBL. HR = hazard ratio; KME=Kaplan-Meier estimate; N.M.E = Not meaningful estimate.

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Appetite Loss Scale (MID=10)

Subgroup	Placebo				Nivolumab				Nivolumab vs. Placebo	
	N	Subjects with Event n (%)	Censored subjects n (%)	KME [95%CI] (mon) (1)	N	Subjects with Event n (%)	Censored subjects n (%)	KME [95%CI] (mon) (1)	HR [95%CI] P-value (2)	Test for Interaction P-value (3) (4)
AGE CATEGORY I										0.2535
< 65	54	25 (46.3)	29 (53.7)	13.14 (7.66, N.A.)	56	23 (41.1)	33 (58.9)	16.13 (11.56, N.A.)	0.921 (0.519, 1.634) 0.7787	
>= 65	74	24 (32.4)	50 (67.6)	N.A. (11.73, N.A.)	66	29 (43.9)	37 (56.1)	15.93 (8.05, N.A.)	1.477 (0.858, 2.542) 0.1598	

FEB2025 DBL. HR = hazard ratio; KME=Kaplan-Meier estimate; N.M.E = Not meaningful estimate.

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IUC = invasive urothelial carcinoma.

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PROS

Appetite Loss Scale (MID=10)

Subgroup	Placebo				Nivolumab				Nivolumab vs. Placebo	
	N	Subjects with Event n (%)	Censored subjects n (%)	KME [95%CI] (mon) (1)	N	Subjects with Event n (%)	Censored subjects n (%)	KME [95%CI] (mon) (1)	HR [95%CI] P-value (2)	Test for Interaction P-value (3) (4)
AGE CATEGORY II										0.4686
< 65	54	25 (46.3)	29 (53.7)	13.14 (7.66, N.A.)	56	23 (41.1)	33 (58.9)	16.13 (11.56, N.A.)	0.921 (0.519, 1.634) 0.7787	
>= 65 AND < 75	54	17 (31.5)	37 (68.5)	N.A. (10.05, N.A.)	45	20 (44.4)	25 (55.6)	9.23 (4.47, N.A.)	1.601 (0.835, 3.067) 0.1562	
>= 75	20	7 (35.0)	13 (65.0)	N.A. (7.16, N.A.)	21	9 (42.9)	12 (57.1)	N.A. (2.92, N.A.)	1.216 (0.451, 3.280) 0.6998	

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Appetite Loss Scale (MID=10)

Subgroup	Placebo				Nivolumab				Nivolumab vs. Placebo	
	N	Subjects with Event n (%)	Censored subjects n (%)	KME [95%CI] (mon) (1)	N	Subjects with Event n (%)	Censored subjects n (%)	KME [95%CI] (mon) (1)	HR [95%CI] P-value (2)	Test for Interaction P-value (3) (4)
REGION										0.8711
US	21	10 (47.6)	11 (52.4)	10.35 (1.91, N.A.)	13	6 (46.2)	7 (53.8)	4.01 (1.91, N.A.)	0.859 (0.309, 2.387) 0.7700	
EUROPE	62	24 (38.7)	38 (61.3)	N.A. (10.05, N.A.)	65	32 (49.2)	33 (50.8)	15.90 (8.08, N.A.)	1.340 (0.786, 2.285) 0.2820	
ASIA	27	7 (25.9)	20 (74.1)	N.A. (7.16, N.A.)	28	6 (21.4)	22 (78.6)	N.A. (9.26, N.A.)	0.806 (0.259, 2.502) 0.7085	
REST OF WORLD	18	8 (44.4)	10 (55.6)	10.32 (5.09, N.A.)	16	8 (50.0)	8 (50.0)	4.47 (1.15, N.A.)	1.146 (0.428, 3.067) 0.7862	

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(3) Unstratified Cox proportional hazard model with treatment, subgroup and treatment*subgroup interaction to assess the significance of the interaction between treatment and the subgroup, with baseline PRO score as a covariate. (4) P-values <0.05 are indicated by 1 asterisk (indicates potential effect modification).

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Subgroup	Placebo				Nivolumab				Nivolumab vs. Placebo	
	N	Subjects with Event n (%)	Censored subjects n (%)	KME [95%CI] (mon) (1)	N	Subjects with Event n (%)	Censored subjects n (%)	KME [95%CI] (mon) (1)	HR [95%CI] P-value (2)	Test for Interaction P-value (3) (4)
GENDER										0.0471*
MALE	101	34 (33.7)	67 (66.3)	N.A. (11.73, N.A.)	89	40 (44.9)	49 (55.1)	15.90 (8.97, 16.59)	1.437 (0.907, 2.276) 0.1229	
FEMALE	27	15 (55.6)	12 (44.4)	4.63 (1.87, N.A.)	33	12 (36.4)	21 (63.6)	N.A. (4.24, N.A.)	0.608 (0.284, 1.302) 0.2003	
RACE										0.5690
WHITE	96	40 (41.7)	56 (58.3)	13.14 (10.32, N.A.)	93	45 (48.4)	48 (51.6)	15.90 (5.55, N.A.)	1.214 (0.792, 1.861) 0.3741	
ASIAN	27	7 (25.9)	20 (74.1)	N.A. (7.16, N.A.)	28	6 (21.4)	22 (78.6)	N.A. (9.26, N.A.)	0.806 (0.259, 2.502) 0.7085	

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Subgroup	Placebo				Nivolumab				Nivolumab vs. Placebo	
	N	Subjects with Event n (%)	Censored subjects n (%)	KME [95%CI] (mon) (1)	N	Subjects with Event n (%)	Censored subjects n (%)	KME [95%CI] (mon) (1)	HR [95%CI] P-value (2)	Test for Interaction P-value (3) (4)
BASELINE ECOG STATUS										0.0596
0	80	30 (37.5)	50 (62.5)	N.A. (10.32, N.A.)	76	25 (32.9)	51 (67.1)	16.13 (15.90, N.A.)	0.854 (0.501, 1.454) 0.5610	
1	44	17 (38.6)	27 (61.4)	N.A. (7.16, N.A.)	44	25 (56.8)	19 (43.2)	8.97 (3.58, 15.93)	1.950 (1.044, 3.639) 0.0361	
SMOKING STATUS										0.3655
NEVER SMOKED	36	13 (36.1)	23 (63.9)	N.A. (10.05, N.A.)	35	9 (25.7)	26 (74.3)	N.A. (N.A., N.A.)	0.883 (0.375, 2.080) 0.7754	
CURRENT/FORMER	91	36 (39.6)	55 (60.4)	N.A. (11.24, N.A.)	86	42 (48.8)	44 (51.2)	15.90 (8.08, 16.13)	1.253 (0.801, 1.959) 0.3233	

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	N	Subjects with Event n (%)	Censored subjects n (%)	KME [95%CI] (mon) (1)	N	Subjects with Event n (%)	Censored subjects n (%)	KME [95%CI] (mon) (1)	HR [95%CI] P-value (2)	Test for Interaction P-value (3) (4)
BASELINE HEMOGLOBIN										0.1079
<10 G/DL	13	5 (38.5)	8 (61.5)	N.A. (3.25, N.A.)	6	3 (50.0)	3 (50.0)	N.A. (0.95, N.A.)	14.107 (1.425, >99.999)	
>=10 G/DL	115	44 (38.3)	71 (61.7)	N.A. (11.24, N.A.)	116	49 (42.2)	67 (57.8)	15.93 (9.26, N.A.)	1.127 (0.749, 1.695)	0.0236
BASELINE CREATININE CLEARANCE										0.8815
<60 ML/MIN	57	18 (31.6)	39 (68.4)	N.A. (12.16, N.A.)	46	17 (37.0)	29 (63.0)	16.59 (9.26, N.A.)	1.176 (0.596, 2.320)	0.6409
>=60 ML/MIN	71	31 (43.7)	40 (56.3)	13.14 (8.34, N.A.)	75	34 (45.3)	41 (54.7)	15.90 (5.55, N.A.)	1.118 (0.686, 1.823)	0.6546

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PROS

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Subgroup	Placebo				Nivolumab				Nivolumab vs. Placebo	
	N	Subjects with Event n (%)	Censored subjects n (%)	KME [95%CI] (mon) (1)	N	Subjects with Event n (%)	Censored subjects n (%)	KME [95%CI] (mon) (1)	HR [95%CI] P-value (2)	Test for Interaction P-value (3) (4)
TIME FROM IUC SURGERY TO RANDOMIZATION (DAYS)										0.5098
>30-60	28	9 (32.1)	19 (67.9)	N.A. (10.32, N.A.)	30	12 (40.0)	18 (60.0)	15.93 (8.05, N.A.)	1.718 (0.717, 4.116)	
>60-90	57	20 (35.1)	37 (64.9)	N.A. (10.35, N.A.)	51	24 (47.1)	27 (52.9)	15.90 (4.67, N.A.)	1.345 (0.739, 2.445)	
>90-120	38	17 (44.7)	21 (55.3)	12.16 (5.09, N.A.)	39	16 (41.0)	23 (59.0)	N.A. (4.01, N.A.)	0.955 (0.482, 1.896)	

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	N	Subjects with Event n (%)	Censored subjects n (%)	KME [95%CI] (mon) (1)	N	Subjects with Event n (%)	Censored subjects n (%)	KME [95%CI] (mon) (1)	HR [95%CI] P-value (2)	Test for Interaction P-value (3) (4)
INITIAL TUMOR ORIGIN										0.6989
URINARY BLADDER	104	40 (38.5)	64 (61.5)	N.A. (10.35, N.A.)	101	46 (45.5)	55 (54.5)	15.90 (8.38, 16.59)	1.242 (0.811, 1.900)	
RENAL PELVIS	13	4 (30.8)	9 (69.2)	N.A. (1.91, N.A.)	15	5 (33.3)	10 (66.7)	N.A. (8.05, N.A.)	0.3190 0.898 (0.228, 3.540)	
URETER	11	5 (45.5)	6 (54.5)	11.24 (0.99, N.A.)	6	1 (16.7)	5 (83.3)	N.A. (2.92, N.A.)	0.8774 0.366 (0.022, 5.989)	
									0.4810	

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Subgroup	Placebo				Nivolumab				Nivolumab vs. Placebo	
	N	Subjects with Event n (%)	Censored subjects n (%)	KME [95%CI] (mon) (1)	N	Subjects with Event n (%)	Censored subjects n (%)	KME [95%CI] (mon) (1)	HR [95%CI] P-value (2)	Test for Interaction P-value (3) (4)
MINOR HISTOLOGICAL VARIANTS										0.1507
PRESENCE	54	19 (35.2)	35 (64.8)	N.A. (11.73, N.A.)	53	27 (50.9)	26 (49.1)	15.90 (3.98, 16.13)	1.527 (0.846, 2.756)	
ABSENCE	74	30 (40.5)	44 (59.5)	N.A. (7.49, N.A.)	69	25 (36.2)	44 (63.8)	16.59 (9.26, N.A.)	0.1605 0.900 (0.526, 1.538) 0.6989	

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Subgroup Analyses of EORTC QLQ-C30 Time to First Deterioration
PROS

Constipation Scale (MID=10)

Subgroup	Placebo				Nivolumab				Nivolumab vs. Placebo	
	N	Subjects with Event n (%)	Censored subjects n (%)	KME [95%CI] (mon) (1)	N	Subjects with Event n (%)	Censored subjects n (%)	KME [95%CI] (mon) (1)	HR [95%CI] P-value (2)	Test for Interaction P-value (3) (4)
OVERALL	127	43 (33.9)	84 (66.1)	N.A. (N.A., N.A.)	122	37 (30.3)	85 (69.7)	N.A. (N.A., N.A.)	0.859 (0.553, 1.334) 0.4982	
PRIOR NEO-ADJUVANT CISPLATIN THERAPY										0.8132
YES	53	21 (39.6)	32 (60.4)	N.A. (6.77, N.A.)	49	15 (30.6)	34 (69.4)	N.A. (15.61, N.A.)	0.795 (0.409, 1.546) 0.4989	
NO	74	22 (29.7)	52 (70.3)	N.A. (N.A., N.A.)	73	22 (30.1)	51 (69.9)	N.A. (N.A., N.A.)	0.892 (0.493, 1.613) 0.7047	

FEB2025 DBL. HR = hazard ratio; KME=Kaplan-Meier estimate; N.M.E = Not meaningful estimate.

(1) KME of median time to event.

(2) Unstratified Cox proportional hazard model, with baseline PRO score as a covariate. HR is Nivolumab over Placebo.

(3) Unstratified Cox proportional hazard model with treatment, subgroup and treatment*subgroup

interaction to assess the significance of the interaction between treatment and the subgroup, with baseline PRO score as a covariate. (4) P-values <0.05 are indicated by 1 asterisk (indicates potential effect modification).

IUC = invasive urothelial carcinoma.

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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

Table 4.1
Subgroup Analyses of EORTC QLQ-C30 Time to First Deterioration
PROS

Constipation Scale (MID=10)

Subgroup	Placebo				Nivolumab				Nivolumab vs. Placebo	
	N	Subjects with Event n (%)	Censored subjects n (%)	KME [95%CI] (mon) (1)	N	Subjects with Event n (%)	Censored subjects n (%)	KME [95%CI] (mon) (1)	HR [95%CI] P-value (2)	Test for Interaction P-value (3) (4)
PRIOR CISPLATIN STATUS										0.8710
RECEIVED NEO-ADJUVANT	53	21 (39.6)	32 (60.4)	N.A. (6.77, N.A.)	49	15 (30.6)	34 (69.4)	N.A. (15.61, N.A.)	0.795 (0.409, 1.546)	
UNWILLING TO RECEIVE NEO-ADJUVANT	42	10 (23.8)	32 (76.2)	N.A. (N.A., N.A.)	45	12 (26.7)	33 (73.3)	N.A. (N.A., N.A.)	1.040 (0.448, 2.414)	
NOT ELIGIBLE TO RECEIVE NEO-ADJUVANT	31	12 (38.7)	19 (61.3)	N.A. (4.17, N.A.)	23	9 (39.1)	14 (60.9)	N.A. (5.55, N.A.)	0.9275 (0.338, 1.910)	
									0.803 0.6201	

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	N	Subjects with Event n (%)	Censored subjects n (%)	KME [95%CI] (mon) (1)	N	Subjects with Event n (%)	Censored subjects n (%)	KME [95%CI] (mon) (1)	HR [95%CI] P-value (2)	Test for Interaction P-value (3) (4)
USE OF ANY PRIOR NEO-ADJUVANT SYSTEMIC THERAPY										0.5974
YES	54	22 (40.7)	32 (59.3)	N.A. (6.77, N.A.)	53	16 (30.2)	37 (69.8)	N.A. (15.61, N.A.)	0.748 (0.392, 1.427) 0.3783	
NO	73	21 (28.8)	52 (71.2)	N.A. (N.A., N.A.)	69	21 (30.4)	48 (69.6)	N.A. (N.A., N.A.)	0.951 (0.519, 1.743) 0.8707	

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	N	Subjects with Event n (%)	Censored subjects n (%)	KME [95%CI] (mon) (1)	N	Subjects with Event n (%)	Censored subjects n (%)	KME [95%CI] (mon) (1)	HR [95%CI] P-value (2)	Test for Interaction P-value (3) (4)
PATHOLOGICAL LYMPH NODE STATUS										0.6482
N+	56	18 (32.1)	38 (67.9)	N.A. (10.32, N.A.)	51	12 (23.5)	39 (76.5)	N.A. (N.A., N.A.)	0.647 (0.311, 1.343) 0.2425	
N0/X WITH <10 NODES REMOVED	37	12 (32.4)	25 (67.6)	N.A. (7.29, N.A.)	35	10 (28.6)	25 (71.4)	N.A. (6.44, N.A.)	0.961 (0.411, 2.245) 0.9269	
N0 WITH >= 10 NODES REMOVED	34	13 (38.2)	21 (61.8)	N.A. (6.37, N.A.)	36	15 (41.7)	21 (58.3)	N.A. (5.55, N.A.)	1.130 (0.533, 2.396) 0.7506	

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Constipation Scale (MID=10)

Subgroup	Placebo				Nivolumab				Nivolumab vs. Placebo	
	N	Subjects with Event n (%)	Censored subjects n (%)	KME [95%CI] (mon) (1)	N	Subjects with Event n (%)	Censored subjects n (%)	KME [95%CI] (mon) (1)	HR [95%CI] P-value (2)	Test for Interaction P-value (3) (4)
PATHOLOGICAL STATUS										0.2025
PT0-2	29	14 (48.3)	15 (51.7)	N.A. (5.32, N.A.)	21	4 (19.0)	17 (81.0)	N.A. (11.07, N.A.)	0.372 (0.122, 1.130) 0.0812	
PT3	73	23 (31.5)	50 (68.5)	N.A. (7.29, N.A.)	77	25 (32.5)	52 (67.5)	N.A. (15.61, N.A.)	1.025 (0.581, 1.808) 0.9333	
PT4A	25	6 (24.0)	19 (76.0)	N.A. (N.A., N.A.)	21	7 (33.3)	14 (66.7)	N.A. (3.68, N.A.)	1.294 (0.423, 3.952) 0.6514	

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Subgroup	Placebo				Nivolumab				Nivolumab vs. Placebo	
	N	Subjects with Event n (%)	Censored subjects n (%)	KME [95%CI] (mon) (1)	N	Subjects with Event n (%)	Censored subjects n (%)	KME [95%CI] (mon) (1)	HR [95%CI] P-value (2)	Test for Interaction P-value (3) (4)
AGE CATEGORY I										
< 65	53	18 (34.0)	35 (66.0)	N.A. (10.32, N.A.)	56	15 (26.8)	41 (73.2)	N.A. (N.A., N.A.)	0.734 (0.369, 1.458) 0.3769	0.5760
>= 65	74	25 (33.8)	49 (66.2)	N.A. (7.29, N.A.)	66	22 (33.3)	44 (66.7)	N.A. (7.59, N.A.)	0.976 (0.550, 1.731) 0.9332	

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Constipation Scale (MID=10)

Subgroup	Placebo				Nivolumab				Nivolumab vs. Placebo	
	N	Subjects with Event n (%)	Censored subjects n (%)	KME [95%CI] (mon) (1)	N	Subjects with Event n (%)	Censored subjects n (%)	KME [95%CI] (mon) (1)	HR [95%CI] P-value (2)	Test for Interaction P-value (3) (4)
AGE CATEGORY II										0.6066
< 65	53	18 (34.0)	35 (66.0)	N.A. (10.32, N.A.)	56	15 (26.8)	41 (73.2)	N.A. (N.A., N.A.)	0.734 (0.369, 1.458) 0.3769	
>= 65 AND < 75	54	20 (37.0)	34 (63.0)	N.A. (6.37, N.A.)	45	15 (33.3)	30 (66.7)	N.A. (7.23, N.A.)	0.861 (0.440, 1.683) 0.6617	
>= 75	20	5 (25.0)	15 (75.0)	N.A. (7.29, N.A.)	21	7 (33.3)	14 (66.7)	N.A. (6.44, N.A.)	1.563 (0.493, 4.952) 0.4476	

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Constipation Scale (MID=10)

Subgroup	Placebo				Nivolumab				Nivolumab vs. Placebo	
	N	Subjects with Event n (%)	Censored subjects n (%)	KME [95%CI] (mon) (1)	N	Subjects with Event n (%)	Censored subjects n (%)	KME [95%CI] (mon) (1)	HR [95%CI] P-value (2)	Test for Interaction P-value (3) (4)
REGION										0.6741
US	21	8 (38.1)	13 (61.9)	N.A. (4.67, N.A.)	14	2 (14.3)	12 (85.7)	N.A. (15.61, N.A.)	0.318 (0.065, 1.560) 0.1580	
EUROPE	61	21 (34.4)	40 (65.6)	N.A. (9.69, N.A.)	64	20 (31.3)	44 (68.8)	N.A. (N.A., N.A.)	0.926 (0.501, 1.708) 0.8047	
ASIA	27	7 (25.9)	20 (74.1)	N.A. (6.74, N.A.)	28	7 (25.0)	21 (75.0)	N.A. (7.59, N.A.)	0.879 (0.308, 2.508) 0.8095	
REST OF WORLD	18	7 (38.9)	11 (61.1)	N.A. (1.45, N.A.)	16	8 (50.0)	8 (50.0)	5.55 (1.91, N.A.)	1.203 (0.432, 3.350) 0.7238	

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	N	Subjects with Event n (%)	Censored subjects n (%)	KME [95%CI] (mon) (1)	N	Subjects with Event n (%)	Censored subjects n (%)	KME [95%CI] (mon) (1)	HR [95%CI] P-value (2)	Test for Interaction P-value (3) (4)
GENDER										
MALE	100	32 (32.0)	68 (68.0)	N.A. (N.A., N.A.)	89	27 (30.3)	62 (69.7)	N.A. (N.A., N.A.)	0.870 (0.520, 1.454) 0.5946	0.9088
FEMALE	27	11 (40.7)	16 (59.3)	N.A. (4.70, N.A.)	33	10 (30.3)	23 (69.7)	N.A. (5.55, N.A.)	0.841 (0.354, 2.000) 0.6958	
RACE										
WHITE	95	36 (37.9)	59 (62.1)	N.A. (9.69, N.A.)	93	29 (31.2)	64 (68.8)	N.A. (N.A., N.A.)	0.815 (0.499, 1.329) 0.4121	0.9452
ASIAN	27	7 (25.9)	20 (74.1)	N.A. (6.74, N.A.)	28	7 (25.0)	21 (75.0)	N.A. (7.59, N.A.)	0.879 (0.308, 2.508) 0.8095	

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BASELINE ECOG STATUS										0.3639
0	79	27 (34.2)	52 (65.8)	N.A. (9.69, N.A.)	75	20 (26.7)	55 (73.3)	N.A. (N.A., N.A.)	0.737 (0.413, 1.315)	
1	44	16 (36.4)	28 (63.6)	N.A. (7.29, N.A.)	45	17 (37.8)	28 (62.2)	N.A. (6.44, N.A.)	0.3017 1.123 (0.564, 2.234)	
SMOKING STATUS										0.5508
NEVER SMOKED	36	10 (27.8)	26 (72.2)	N.A. (10.32, N.A.)	36	7 (19.4)	29 (80.6)	N.A. (N.A., N.A.)	0.659 (0.250, 1.734)	
CURRENT/FORMER	90	33 (36.7)	57 (63.3)	N.A. (9.69, N.A.)	85	30 (35.3)	55 (64.7)	N.A. (15.61, N.A.)	0.3980 0.925 (0.564, 1.518)	

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BASELINE HEMOGLOBIN										0.6832
<10 G/DL	13	4 (30.8)	9 (69.2)	N.A. (1.91, N.A.)	6	1 (16.7)	5 (83.3)	N.A. (15.61, N.A.)	0.310 (0.029, 3.328)	
>=10 G/DL	114	39 (34.2)	75 (65.8)	N.A. (13.14, N.A.)	116	36 (31.0)	80 (69.0)	N.A. (N.A., N.A.)	0.3336 0.869 (0.552, 1.368) 0.5443	
BASELINE CREATININE CLEARANCE										0.2437
<60 ML/MIN	57	19 (33.3)	38 (66.7)	N.A. (7.29, N.A.)	47	18 (38.3)	29 (61.7)	N.A. (6.44, N.A.)	1.171 (0.614, 2.233)	
>=60 ML/MIN	70	24 (34.3)	46 (65.7)	N.A. (10.32, N.A.)	74	19 (25.7)	55 (74.3)	N.A. (N.A., N.A.)	0.6328 0.692 (0.379, 1.265) 0.2315	

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	N	Subjects with Event n (%)	Censored subjects n (%)	KME [95%CI] (mon) (1)	N	Subjects with Event n (%)	Censored subjects n (%)	KME [95%CI] (mon) (1)	HR [95%CI] P-value (2)	Test for Interaction P-value (3) (4)
TIME FROM IUC SURGERY TO RANDOMIZATION (DAYS)										0.8703
>30-60	28	9 (32.1)	19 (67.9)	N.A. (7.29, N.A.)	30	10 (33.3)	20 (66.7)	N.A. (5.55, N.A.)	1.124 (0.452, 2.792)	
>60-90	57	22 (38.6)	35 (61.4)	N.A. (6.97, N.A.)	50	16 (32.0)	34 (68.0)	N.A. (8.28, N.A.)	0.8018 0.813 (0.427, 1.549)	
>90-120	37	9 (24.3)	28 (75.7)	N.A. (N.A., N.A.)	40	10 (25.0)	30 (75.0)	N.A. (15.61, N.A.)	0.5292 0.902 (0.364, 2.233)	
									0.8238	

FEB2025 DBL. HR = hazard ratio; KME=Kaplan-Meier estimate; N.M.E = Not meaningful estimate.

(1) KME of median time to event.

(2) Unstratified Cox proportional hazard model, with baseline PRO score as a covariate. HR is Nivolumab over Placebo.

(3) Unstratified Cox proportional hazard model with treatment, subgroup and treatment*subgroup

interaction to assess the significance of the interaction between treatment and the subgroup, with baseline PRO score as a covariate. (4) P-values <0.05 are indicated by 1 asterisk (indicates potential effect modification).

IUC = invasive urothelial carcinoma.

Program Path: /projects/bms214671/stats/market/ma274_202502/prog/tables

Program Name: rt-sy-tdd-eortc-comm-eb45.sas

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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

Table 4.1
Subgroup Analyses of EORTC QLQ-C30 Time to First Deterioration
PROS

Constipation Scale (MID=10)

Subgroup	Placebo				Nivolumab				Nivolumab vs. Placebo	
	N	Subjects with Event n (%)	Censored subjects n (%)	KME [95%CI] (mon) (1)	N	Subjects with Event n (%)	Censored subjects n (%)	KME [95%CI] (mon) (1)	HR [95%CI] P-value (2)	Test for Interaction P-value (3) (4)
INITIAL TUMOR ORIGIN										0.9965
URINARY BLADDER	103	34 (33.0)	69 (67.0)	N.A. (N.A., N.A.)	101	31 (30.7)	70 (69.3)	N.A. (N.A., N.A.)	0.902 (0.554, 1.469) 0.6779	
RENAL PELVIS	13	5 (38.5)	8 (61.5)	7.29 (1.05, N.A.)	15	6 (40.0)	9 (60.0)	N.A. (4.63, N.A.)	0.964 (0.293, 3.166) 0.9515	
URETER	11	4 (36.4)	7 (63.6)	N.A. (1.94, N.A.)	6	0	6 (100.0)	N.A. (N.A., N.A.)	N.M.E. 0.9980	

FEB2025 DBL. HR = hazard ratio; KME=Kaplan-Meier estimate; N.M.E = Not meaningful estimate.

(1) KME of median time to event.

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interaction to assess the significance of the interaction between treatment and the subgroup, with baseline PRO score as a covariate. (4) P-values <0.05 are indicated by 1 asterisk (indicates potential effect modification).

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PROS

Constipation Scale (MID=10)

Subgroup	Placebo				Nivolumab				Nivolumab vs. Placebo	
	N	Subjects with Event n (%)	Censored subjects n (%)	KME [95%CI] (mon) (1)	N	Subjects with Event n (%)	Censored subjects n (%)	KME [95%CI] (mon) (1)	HR [95%CI] P-value (2)	Test for Interaction P-value (3) (4)
MINOR HISTOLOGICAL VARIANTS										0.6733
PRESENCE	54	19 (35.2)	35 (64.8)	N.A. (8.31, N.A.)	53	17 (32.1)	36 (67.9)	N.A. (11.07, N.A.)	0.967 (0.502, 1.862)	
ABSENCE	73	24 (32.9)	49 (67.1)	N.A. (10.32, N.A.)	69	20 (29.0)	49 (71.0)	N.A. (15.61, N.A.)	0.9207 0.783 (0.432, 1.419) 0.4203	

FEB2025 DBL. HR = hazard ratio; KME=Kaplan-Meier estimate; N.M.E = Not meaningful estimate.

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Table 4.1
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PROS

Diarrhea Scale (MID=10)

Subgroup	Placebo				Nivolumab				Nivolumab vs. Placebo	
	N	Subjects with Event n (%)	Censored subjects n (%)	KME [95%CI] (mon) (1)	N	Subjects with Event n (%)	Censored subjects n (%)	KME [95%CI] (mon) (1)	HR [95%CI] P-value (2)	Test for Interaction P-value (3) (4)
OVERALL	127	41 (32.3)	86 (67.7)	N.A. (N.A., N.A.)	122	41 (33.6)	81 (66.4)	N.A. (13.83, N.A.)	0.995 (0.645, 1.535) 0.9815	
PRIOR NEO-ADJUVANT CISPLATIN THERAPY										0.6973
YES	53	20 (37.7)	33 (62.3)	N.A. (3.75, N.A.)	49	18 (36.7)	31 (63.3)	N.A. (11.27, N.A.)	0.939 (0.496, 1.778) 0.8474	
NO	74	21 (28.4)	53 (71.6)	N.A. (N.A., N.A.)	73	23 (31.5)	50 (68.5)	N.A. (13.11, N.A.)	1.065 (0.589, 1.927) 0.8352	

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PROS

Diarrhea Scale (MID=10)

Subgroup	Placebo				Nivolumab				Nivolumab vs. Placebo	
	N	Subjects with Event n (%)	Censored subjects n (%)	KME [95%CI] (mon) (1)	N	Subjects with Event n (%)	Censored subjects n (%)	KME [95%CI] (mon) (1)	HR [95%CI] P-value (2)	Test for Interaction P-value (3) (4)
PRIOR CISPLATIN STATUS										0.8926
RECEIVED NEO-ADJUVANT	53	20 (37.7)	33 (62.3)	N.A. (3.75, N.A.)	49	18 (36.7)	31 (63.3)	N.A. (11.27, N.A.)	0.939 (0.496, 1.778)	
UNWILLING TO RECEIVE NEO-ADJUVANT	42	11 (26.2)	31 (73.8)	N.A. (N.A., N.A.)	45	14 (31.1)	31 (68.9)	N.A. (11.33, N.A.)	1.159 (0.525, 2.559)	
NOT ELIGIBLE TO RECEIVE NEO-ADJUVANT	31	10 (32.3)	21 (67.7)	N.A. (6.97, N.A.)	23	7 (30.4)	16 (69.6)	N.A. (7.23, N.A.)	1.066 (0.404, 2.814)	

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interaction to assess the significance of the interaction between treatment and the subgroup, with baseline PRO score as a covariate. (4) P-values <0.05 are indicated by 1 asterisk (indicates potential effect modification).

IUC = invasive urothelial carcinoma.

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Table 4.1
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PROS

Diarrhea Scale (MID=10)

Subgroup	Placebo				Nivolumab				Nivolumab vs. Placebo	
	N	Subjects with Event n (%)	Censored subjects n (%)	KME [95%CI] (mon) (1)	N	Subjects with Event n (%)	Censored subjects n (%)	KME [95%CI] (mon) (1)	HR [95%CI] P-value (2)	Test for Interaction P-value (3) (4)
USE OF ANY PRIOR NEO-ADJUVANT SYSTEMIC THERAPY										0.7117
YES	54	20 (37.0)	34 (63.0)	N.A. (3.75, N.A.)	53	19 (35.8)	34 (64.2)	N.A. (11.33, N.A.)	0.926 (0.493, 1.739) 0.8113	
NO	73	21 (28.8)	52 (71.2)	N.A. (N.A., N.A.)	69	22 (31.9)	47 (68.1)	N.A. (13.11, N.A.)	1.061 (0.583, 1.931) 0.8471	

FEB2025 DBL. HR = hazard ratio; KME=Kaplan-Meier estimate; N.M.E = Not meaningful estimate.

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IUC = invasive urothelial carcinoma.

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PROS

Diarrhea Scale (MID=10)

Subgroup	Placebo				Nivolumab				Nivolumab vs. Placebo	
	N	Subjects with Event n (%)	Censored subjects n (%)	KME [95%CI] (mon) (1)	N	Subjects with Event n (%)	Censored subjects n (%)	KME [95%CI] (mon) (1)	HR [95%CI] P-value (2)	Test for Interaction P-value (3) (4)
PATHOLOGICAL LYMPH NODE STATUS										0.5776
N+	56	18 (32.1)	38 (67.9)	N.A. (8.44, N.A.)	51	15 (29.4)	36 (70.6)	N.A. (13.11, N.A.)	0.745 (0.374, 1.484)	
N0/X WITH <10 NODES REMOVED	37	12 (32.4)	25 (67.6)	N.A. (7.16, N.A.)	35	11 (31.4)	24 (68.6)	N.A. (13.08, N.A.)	0.4024 0.970 (0.425, 2.216)	
N0 WITH >= 10 NODES REMOVED	34	11 (32.4)	23 (67.6)	N.A. (7.62, N.A.)	36	15 (41.7)	21 (58.3)	N.A. (4.70, N.A.)	0.9432 1.330 (0.610, 2.897)	
									0.4735	

FEB2025 DBL. HR = hazard ratio; KME=Kaplan-Meier estimate; N.M.E = Not meaningful estimate.

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PROS

Diarrhea Scale (MID=10)

Subgroup	Placebo				Nivolumab				Nivolumab vs. Placebo	
	N	Subjects with Event n (%)	Censored subjects n (%)	KME [95%CI] (mon) (1)	N	Subjects with Event n (%)	Censored subjects n (%)	KME [95%CI] (mon) (1)	HR [95%CI] P-value (2)	Test for Interaction P-value (3) (4)
PATHOLOGICAL STATUS										0.0948
PT0-2	29	7 (24.1)	22 (75.9)	N.A. (N.A., N.A.)	21	7 (33.3)	14 (66.7)	N.A. (4.90, N.A.)	1.259 (0.441, 3.597) 0.6671	
PT3	73	27 (37.0)	46 (63.0)	N.A. (7.16, N.A.)	77	22 (28.6)	55 (71.4)	N.A. (N.A., N.A.)	0.673 (0.381, 1.187) 0.1710	
PT4A	25	7 (28.0)	18 (72.0)	N.A. (8.44, N.A.)	21	10 (47.6)	11 (52.4)	11.27 (3.81, N.A.)	2.268 (0.854, 6.023) 0.1002	

FEB2025 DBL. HR = hazard ratio; KME=Kaplan-Meier estimate; N.M.E = Not meaningful estimate.

(1) KME of median time to event.

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(3) Unstratified Cox proportional hazard model with treatment, subgroup and treatment*subgroup

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IUC = invasive urothelial carcinoma.

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Table 4.1
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PROS

Diarrhea Scale (MID=10)

Subgroup	Placebo				Nivolumab				Nivolumab vs. Placebo	
	N	Subjects with Event n (%)	Censored subjects n (%)	KME [95%CI] (mon) (1)	N	Subjects with Event n (%)	Censored subjects n (%)	KME [95%CI] (mon) (1)	HR [95%CI] P-value (2)	Test for Interaction P-value (3) (4)
AGE CATEGORY I										
< 65	53	25 (47.2)	28 (52.8)	9.66 (2.83, N.A.)	56	20 (35.7)	36 (64.3)	N.A. (11.27, N.A.)	0.675 (0.374, 1.217) 0.1912	0.0733
>= 65	74	16 (21.6)	58 (78.4)	N.A. (N.A., N.A.)	66	21 (31.8)	45 (68.2)	N.A. (13.11, N.A.)	1.471 (0.766, 2.823) 0.2459	

FEB2025 DBL. HR = hazard ratio; KME=Kaplan-Meier estimate; N.M.E = Not meaningful estimate.

(1) KME of median time to event.

(2) Unstratified Cox proportional hazard model, with baseline PRO score as a covariate. HR is Nivolumab over Placebo.

(3) Unstratified Cox proportional hazard model with treatment, subgroup and treatment*subgroup interaction to assess the significance of the interaction between treatment and the subgroup, with baseline PRO score as a covariate. (4) P-values <0.05 are indicated by 1 asterisk (indicates potential effect modification).

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Diarrhea Scale (MID=10)

Subgroup	Placebo				Nivolumab				Nivolumab vs. Placebo	
	N	Subjects with Event n (%)	Censored subjects n (%)	KME [95%CI] (mon) (1)	N	Subjects with Event n (%)	Censored subjects n (%)	KME [95%CI] (mon) (1)	HR [95%CI] P-value (2)	Test for Interaction P-value (3) (4)
AGE CATEGORY II										0.1763
< 65	53	25 (47.2)	28 (52.8)	9.66 (2.83, N.A.)	56	20 (35.7)	36 (64.3)	N.A. (11.27, N.A.)	0.675 (0.374, 1.217) 0.1912	
>= 65 AND < 75	54	13 (24.1)	41 (75.9)	N.A. (N.A., N.A.)	45	15 (33.3)	30 (66.7)	N.A. (8.38, N.A.)	1.321 (0.627, 2.781) 0.4638	
>= 75	20	3 (15.0)	17 (85.0)	N.A. (N.A., N.A.)	21	6 (28.6)	15 (71.4)	N.A. (13.11, N.A.)	2.022 (0.501, 8.160) 0.3228	

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REGION										0.9815
US	21	8 (38.1)	13 (61.9)	N.A. (2.79, N.A.)	14	5 (35.7)	9 (64.3)	N.A. (1.91, N.A.)	0.776 (0.253, 2.378) 0.6575	
EUROPE	61	21 (34.4)	40 (65.6)	N.A. (7.62, N.A.)	64	24 (37.5)	40 (62.5)	N.A. (8.74, N.A.)	1.020 (0.567, 1.833) 0.9484	
ASIA	27	5 (18.5)	22 (81.5)	N.A. (N.A., N.A.)	28	5 (17.9)	23 (82.1)	N.A. (13.83, N.A.)	1.091 (0.312, 3.823) 0.8913	
REST OF WORLD	18	7 (38.9)	11 (61.1)	N.A. (2.60, N.A.)	16	7 (43.8)	9 (56.3)	13.11 (2.99, N.A.)	0.789 (0.265, 2.349) 0.6707	

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GENDER										
MALE	100	31 (31.0)	69 (69.0)	N.A. (N.A., N.A.)	89	30 (33.7)	59 (66.3)	N.A. (13.11, N.A.)	1.022 (0.617, 1.692) 0.9328	0.7139
FEMALE	27	10 (37.0)	17 (63.0)	N.A. (2.79, N.A.)	33	11 (33.3)	22 (66.7)	N.A. (4.73, N.A.)	0.906 (0.384, 2.138) 0.8209	
RACE										
WHITE	95	34 (35.8)	61 (64.2)	N.A. (8.44, N.A.)	93	36 (38.7)	57 (61.3)	N.A. (11.27, N.A.)	0.987 (0.617, 1.579) 0.9569	0.8311
ASIAN	27	5 (18.5)	22 (81.5)	N.A. (N.A., N.A.)	28	5 (17.9)	23 (82.1)	N.A. (13.83, N.A.)	1.091 (0.312, 3.823) 0.8913	

FEB2025 DBL. HR = hazard ratio; KME=Kaplan-Meier estimate; N.M.E = Not meaningful estimate.

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	N	Subjects with Event n (%)	Censored subjects n (%)	KME [95%CI] (mon) (1)	N	Subjects with Event n (%)	Censored subjects n (%)	KME [95%CI] (mon) (1)	HR [95%CI] P-value (2)	Test for Interaction P-value (3) (4)
BASELINE ECOG STATUS										0.5171
0	79	26 (32.9)	53 (67.1)	N.A. (9.66, N.A.)	75	27 (36.0)	48 (64.0)	N.A. (13.08, N.A.)	1.046 (0.610, 1.797) 0.8691	
1	44	14 (31.8)	30 (68.2)	N.A. (7.62, N.A.)	45	12 (26.7)	33 (73.3)	N.A. (N.A., N.A.)	0.801 (0.370, 1.734) 0.5736	
SMOKING STATUS										0.7636
NEVER SMOKED	36	12 (33.3)	24 (66.7)	N.A. (2.83, N.A.)	36	11 (30.6)	25 (69.4)	N.A. (11.33, N.A.)	0.896 (0.393, 2.043) 0.7937	
CURRENT/FORMER	90	29 (32.2)	61 (67.8)	N.A. (N.A., N.A.)	85	29 (34.1)	56 (65.9)	N.A. (13.11, N.A.)	1.017 (0.606, 1.704) 0.9498	

FEB2025 DBL. HR = hazard ratio; KME=Kaplan-Meier estimate; N.M.E = Not meaningful estimate.

(1) KME of median time to event.

(2) Unstratified Cox proportional hazard model, with baseline PRO score as a covariate. HR is Nivolumab over Placebo.

(3) Unstratified Cox proportional hazard model with treatment, subgroup and treatment*subgroup

interaction to assess the significance of the interaction between treatment and the subgroup, with baseline PRO score as a covariate. (4) P-values <0.05 are indicated by 1 asterisk (indicates potential effect modification).

IUC = invasive urothelial carcinoma.

Program Path: /projects/bms214671/stats/market/ma274_202502/prog/tables

Program Name: rt-sy-tdd-eortc-comm-eb45.sas

16JUL2025:07:44:05

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

Table 4.1
Subgroup Analyses of EORTC QLQ-C30 Time to First Deterioration
PROS

Diarrhea Scale (MID=10)

Subgroup	Placebo				Nivolumab				Nivolumab vs. Placebo	
	N	Subjects with Event n (%)	Censored subjects n (%)	KME [95%CI] (mon) (1)	N	Subjects with Event n (%)	Censored subjects n (%)	KME [95%CI] (mon) (1)	HR [95%CI] P-value (2)	Test for Interaction P-value (3) (4)
BASELINE HEMOGLOBIN										0.6520
<10 G/DL	13	5 (38.5)	8 (61.5)	N.A. (2.10, N.A.)	6	3 (50.0)	3 (50.0)	4.90 (1.91, N.A.)	0.538 (0.125, 2.313)	
>=10 G/DL	114	36 (31.6)	78 (68.4)	N.A. (N.A., N.A.)	116	38 (32.8)	78 (67.2)	N.A. (13.83, N.A.)	1.026 (0.649, 1.621)	
BASELINE CREATININE CLEARANCE										0.2893
<60 ML/MIN	57	16 (28.1)	41 (71.9)	N.A. (N.A., N.A.)	47	17 (36.2)	30 (63.8)	N.A. (10.22, N.A.)	1.353 (0.682, 2.682)	
>=60 ML/MIN	70	25 (35.7)	45 (64.3)	N.A. (8.44, N.A.)	74	24 (32.4)	50 (67.6)	N.A. (13.08, N.A.)	0.822 (0.469, 1.442)	

FEB2025 DBL. HR = hazard ratio; KME=Kaplan-Meier estimate; N.M.E = Not meaningful estimate.

(1) KME of median time to event.

(2) Unstratified Cox proportional hazard model, with baseline PRO score as a covariate. HR is Nivolumab over Placebo.

(3) Unstratified Cox proportional hazard model with treatment, subgroup and treatment*subgroup

interaction to assess the significance of the interaction between treatment and the subgroup, with baseline PRO score as a covariate. (4) P-values <0.05 are indicated by 1 asterisk (indicates potential effect modification).

IUC = invasive urothelial carcinoma.

Program Path: /projects/bms214671/stats/market/ma274_202502/prog/tables

Program Name: rt-sy-tdd-eortc-comm-ebr45.sas

16JUL2025:07:44:05

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

Table 4.1
Subgroup Analyses of EORTC QLQ-C30 Time to First Deterioration
PROS

Diarrhea Scale (MID=10)

Subgroup	Placebo				Nivolumab				Nivolumab vs. Placebo	
	N	Subjects with Event n (%)	Censored subjects n (%)	KME [95%CI] (mon) (1)	N	Subjects with Event n (%)	Censored subjects n (%)	KME [95%CI] (mon) (1)	HR [95%CI] P-value (2)	Test for Interaction P-value (3) (4)
TIME FROM IUC SURGERY TO RANDOMIZATION (DAYS)										0.4490
>30-60	28	8 (28.6)	20 (71.4)	N.A. (5.52, N.A.)	30	6 (20.0)	24 (80.0)	N.A. (13.11, N.A.)	0.569 (0.196, 1.646)	
>60-90	57	21 (36.8)	36 (63.2)	N.A. (7.16, N.A.)	50	18 (36.0)	32 (64.0)	N.A. (8.38, N.A.)	0.2980 0.985 (0.524, 1.852)	
>90-120	37	12 (32.4)	25 (67.6)	N.A. (8.44, N.A.)	40	17 (42.5)	23 (57.5)	N.A. (4.73, N.A.)	0.9635 1.378 (0.657, 2.891)	

FEB2025 DBL. HR = hazard ratio; KME=Kaplan-Meier estimate; N.M.E = Not meaningful estimate.

(1) KME of median time to event.

(2) Unstratified Cox proportional hazard model, with baseline PRO score as a covariate. HR is Nivolumab over Placebo.

(3) Unstratified Cox proportional hazard model with treatment, subgroup and treatment*subgroup

interaction to assess the significance of the interaction between treatment and the subgroup, with baseline PRO score as a covariate. (4) P-values <0.05 are indicated by 1 asterisk (indicates potential effect modification).

IUC = invasive urothelial carcinoma.

Program Path: /projects/bms214671/stats/market/ma274_202502/prog/tables

Program Name: rt-sy-tdd-eortc-comm-ebr45.sas

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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

Table 4.1
Subgroup Analyses of EORTC QLQ-C30 Time to First Deterioration
PROS

Diarrhea Scale (MID=10)

Subgroup	Placebo				Nivolumab				Nivolumab vs. Placebo	
	N	Subjects with Event n (%)	Censored subjects n (%)	KME [95%CI] (mon) (1)	N	Subjects with Event n (%)	Censored subjects n (%)	KME [95%CI] (mon) (1)	HR [95%CI] P-value (2)	Test for Interaction P-value (3) (4)
INITIAL TUMOR ORIGIN										0.9431
URINARY BLADDER	103	33 (32.0)	70 (68.0)	N.A. (N.A., N.A.)	101	35 (34.7)	66 (65.3)	N.A. (13.11, N.A.)	1.048 (0.651, 1.687)	
RENAL PELVIS	13	2 (15.4)	11 (84.6)	N.A. (7.16, N.A.)	15	3 (20.0)	12 (80.0)	N.A. (11.33, N.A.)	1.005 (0.163, 6.209)	
URETER	11	6 (54.5)	5 (45.5)	3.81 (1.08, N.A.)	6	3 (50.0)	3 (50.0)	13.11 (0.99, N.A.)	0.795 (0.193, 3.269)	

FEB2025 DBL. HR = hazard ratio; KME=Kaplan-Meier estimate; N.M.E = Not meaningful estimate.

(1) KME of median time to event.

(2) Unstratified Cox proportional hazard model, with baseline PRO score as a covariate. HR is Nivolumab over Placebo.

(3) Unstratified Cox proportional hazard model with treatment, subgroup and treatment*subgroup interaction to assess the significance of the interaction between treatment and the subgroup, with baseline PRO score as a covariate. (4) P-values <0.05 are indicated by 1 asterisk (indicates potential effect modification).

IUC = invasive urothelial carcinoma.

Program Path: /projects/bms214671/stats/market/ma274_202502/prog/tables

Program Name: rt-sy-tdd-eortc-comm-ebr45.sas

16JUL2025:07:44:05

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

Table 4.1
Subgroup Analyses of EORTC QLQ-C30 Time to First Deterioration
PROS

Diarrhea Scale (MID=10)

Subgroup	Placebo				Nivolumab				Nivolumab vs. Placebo	
	N	Subjects with Event n (%)	Censored subjects n (%)	KME [95%CI] (mon) (1)	N	Subjects with Event n (%)	Censored subjects n (%)	KME [95%CI] (mon) (1)	HR [95%CI] P-value (2)	Test for Interaction P-value (3) (4)
MINOR HISTOLOGICAL VARIANTS										0.3652
PRESENCE	54	20 (37.0)	34 (63.0)	N.A. (7.16, N.A.)	53	17 (32.1)	36 (67.9)	N.A. (13.83, N.A.)	0.818 (0.428, 1.565)	
ABSENCE	73	21 (28.8)	52 (71.2)	N.A. (N.A., N.A.)	69	24 (34.8)	45 (65.2)	N.A. (11.33, N.A.)	0.5444 1.189 (0.661, 2.142) 0.5633	

FEB2025 DBL. HR = hazard ratio; KME=Kaplan-Meier estimate; N.M.E = Not meaningful estimate.

(1) KME of median time to event.

(2) Unstratified Cox proportional hazard model, with baseline PRO score as a covariate. HR is Nivolumab over Placebo.

(3) Unstratified Cox proportional hazard model with treatment, subgroup and treatment*subgroup

interaction to assess the significance of the interaction between treatment and the subgroup, with baseline PRO score as a covariate. (4) P-values <0.05 are indicated by 1 asterisk (indicates potential effect modification).

IUC = invasive urothelial carcinoma.

Program Path: /projects/bms214671/stats/market/ma274_202502/prog/tables

Program Name: rt-sy-tdd-eortc-comm-ebr45.sas

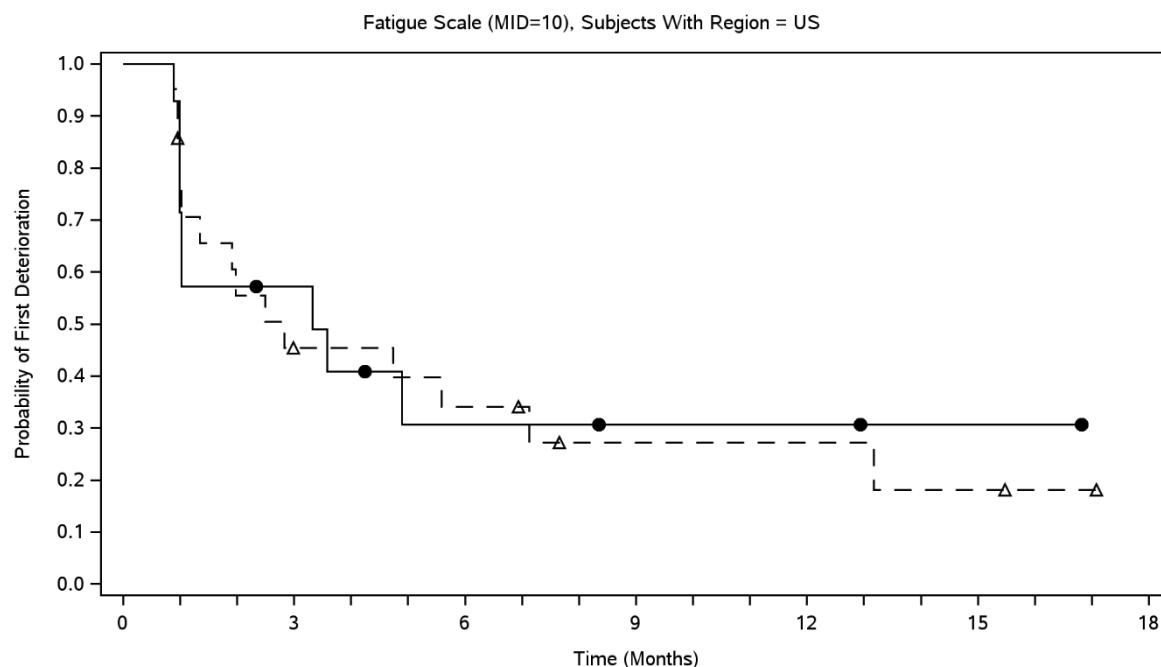
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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

3.2.4 Kaplan-Meier Kurven für Subgruppen mit statistisch signifikantem Interaktionsterm

Figure 4.1

Kaplan-Meier Plot of EORTC QLQ-C30 Time to First Deterioration - by Significant Subgroups - PROS



Number of Subjects at Risk

Placebo

21 8 6 3 3 2 0

Nivolumab

14 7 3 2 2 1 0

— Δ — Placebo (events: 15/21), median and 95% CI: 2.83 (1.02, 7.13)

— ● — Nivolumab (events: 9/14), median and 95% CI: 3.32 (0.99, N.A.)

Hazard Ratio (Nivolumab vs. Placebo) and 95% CI: 0.815 (0.345, 1.925)

FEB2025 DBL.

Symbols represent censored observations.

Unstratified Cox proportional hazard model,
with baseline PRO score as a covariate.

Program Path: /projects/bms214671/stats/market/ma274_202502/prog/figures

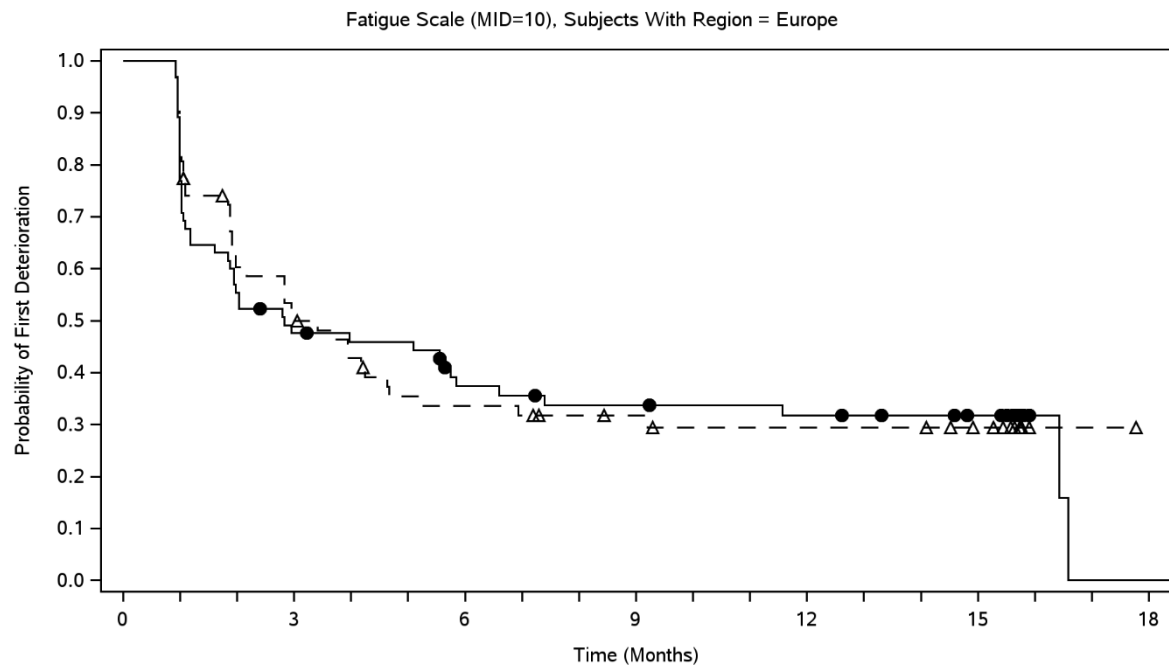
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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

Figure 4.1

Kaplan-Meier Plot of EORTC QLQ-C30 Time to First Deterioration - by Significant Subgroups - PROS



FEB2025 DBL.

Symbols represent censored observations.

Unstratified Cox proportional hazard model,
with baseline PRO score as a covariate.

Program Path: /projects/bms214671/stats/market/ma274_202502/prog/figures

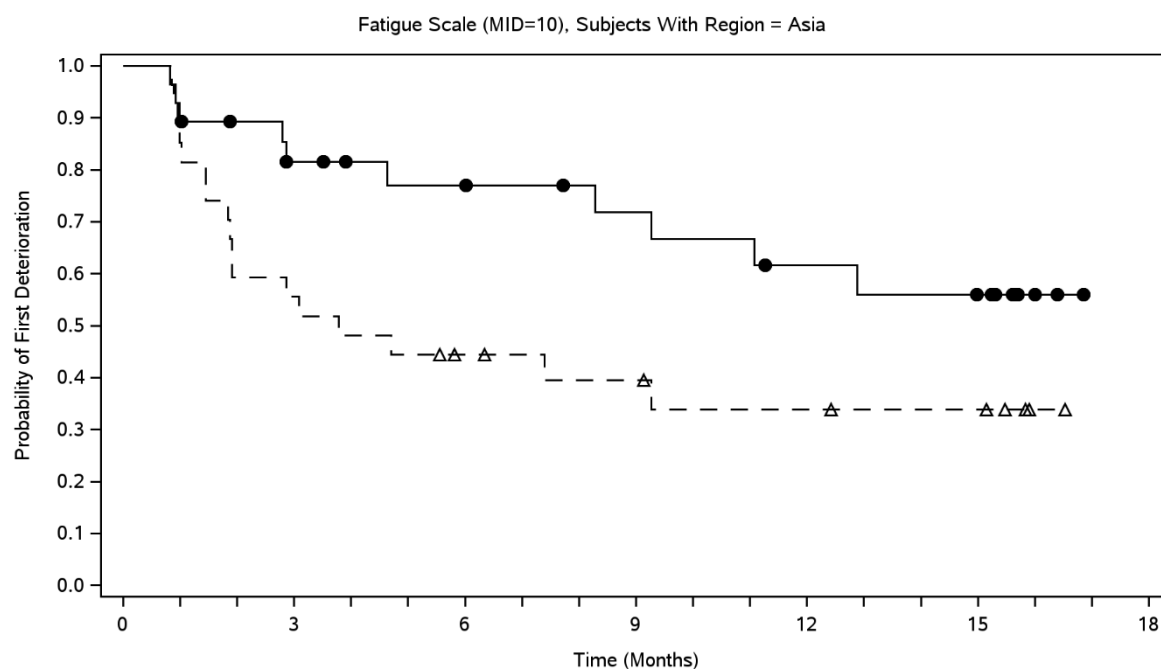
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24JUL2025:04:03:27

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

Figure 4.1

Kaplan-Meier Plot of EORTC QLQ-C30 Time to First Deterioration - by Significant Subgroups - PROS



Number of Subjects at Risk

Placebo

27 15 10 8 6 5 0

Nivolumab

28 20 17 14 11 9 0

— △ — Placebo (events: 17/27), median and 95% CI: 3.78 (1.84, N.A.)

— ● — Nivolumab (events: 10/28), median and 95% CI: N.A. (8.28, N.A.)

Hazard Ratio (Nivolumab vs. Placebo) and 95% CI: 0.400 (0.180, 0.888)

FEB2025 DBL.

Symbols represent censored observations.

Unstratified Cox proportional hazard model,
with baseline PRO score as a covariate.

Program Path: /projects/bms214671/stats/market/ma274_202502/prog/figures

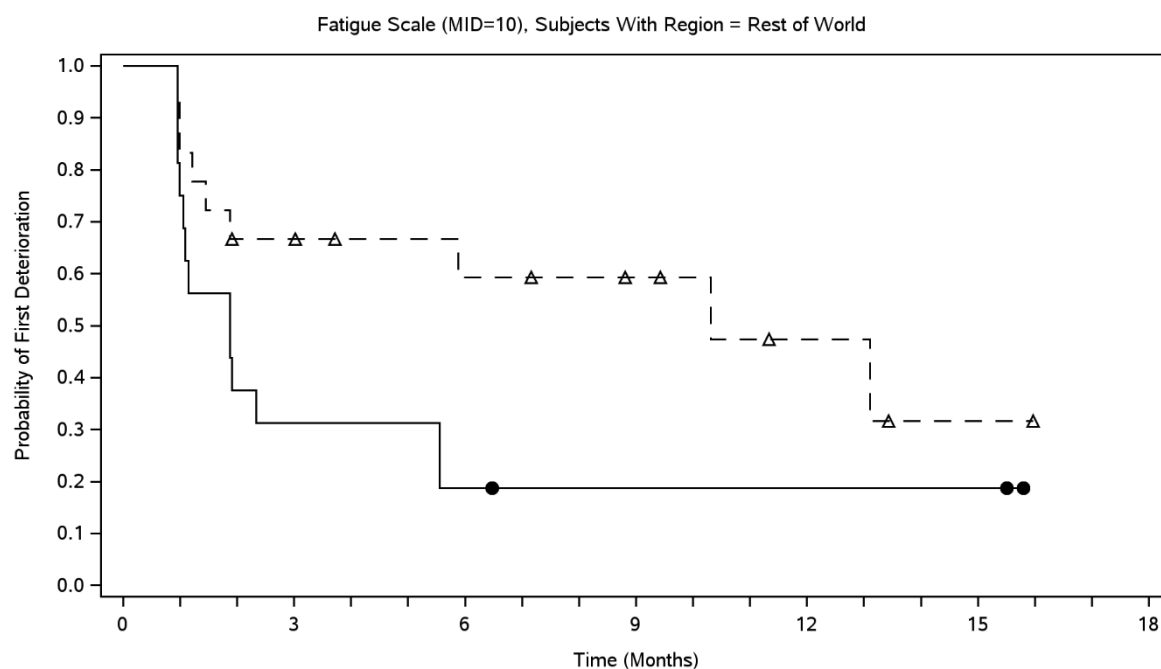
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24JUL2025:04:03:27

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

Figure 4.1

Kaplan-Meier Plot of EORTC QLQ-C30 Time to First Deterioration - by Significant Subgroups - PROS



Number of Subjects at Risk

Placebo

18 11 8 6 3 1 0

Nivolumab

16 5 3 2 2 2 0

— △ — Placebo (events: 9/18), median and 95% CI: 10.32 (1.45, N.A.)

— ● — Nivolumab (events: 13/16), median and 95% CI: 1.87 (0.99, 5.55)

Hazard Ratio (Nivolumab vs. Placebo) and 95% CI: 2.324 (0.984, 5.488)

FEB2025 DBL.

Symbols represent censored observations.

Unstratified Cox proportional hazard model,

with baseline PRO score as a covariate.

Program Path: /projects/bms214671/stats/market/ma274_202502/prog/figures

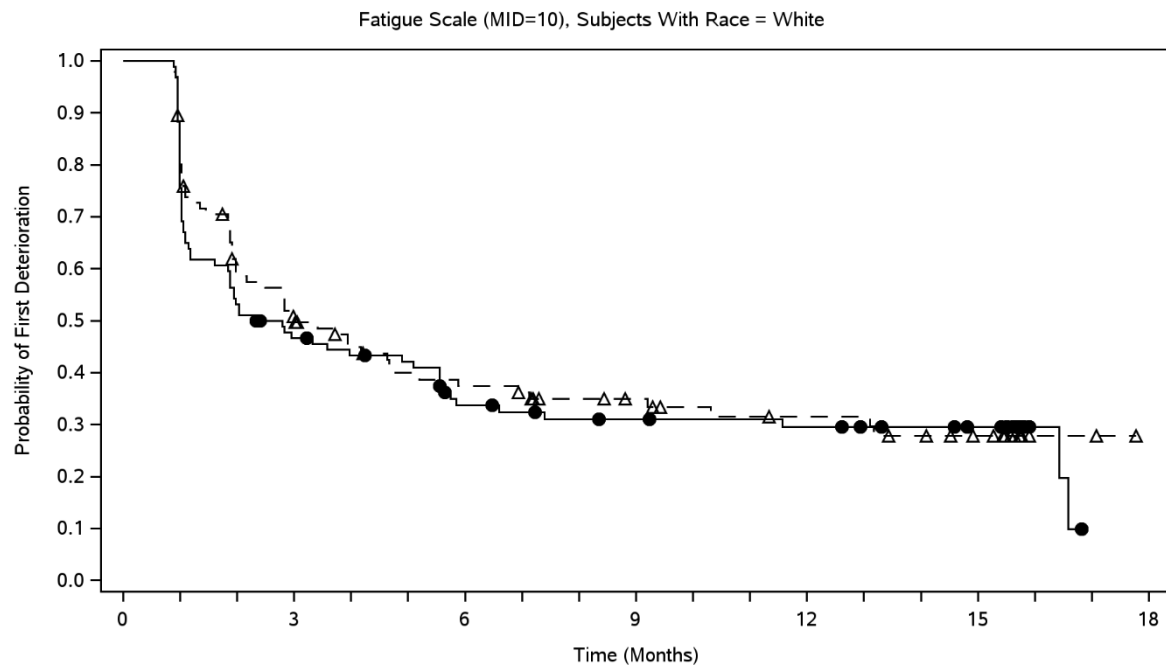
Program Name: rg-sy-subpdllrpro-ebr45.sas

24JUL2025:04:03:27

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

Figure 4.1

Kaplan-Meier Plot of EORTC QLQ-C30 Time to First Deterioration - by Significant Subgroups - PROS



Hazard Ratio (Nivolumab vs. Placebo) and 95% CI: 1.167 (0.824, 1.652)

FEB2025 DBL.

Symbols represent censored observations.

Unstratified Cox proportional hazard model,
with baseline PRO score as a covariate.

Program Path: /projects/bms214671/stats/market/ma274_202502/prog/figures

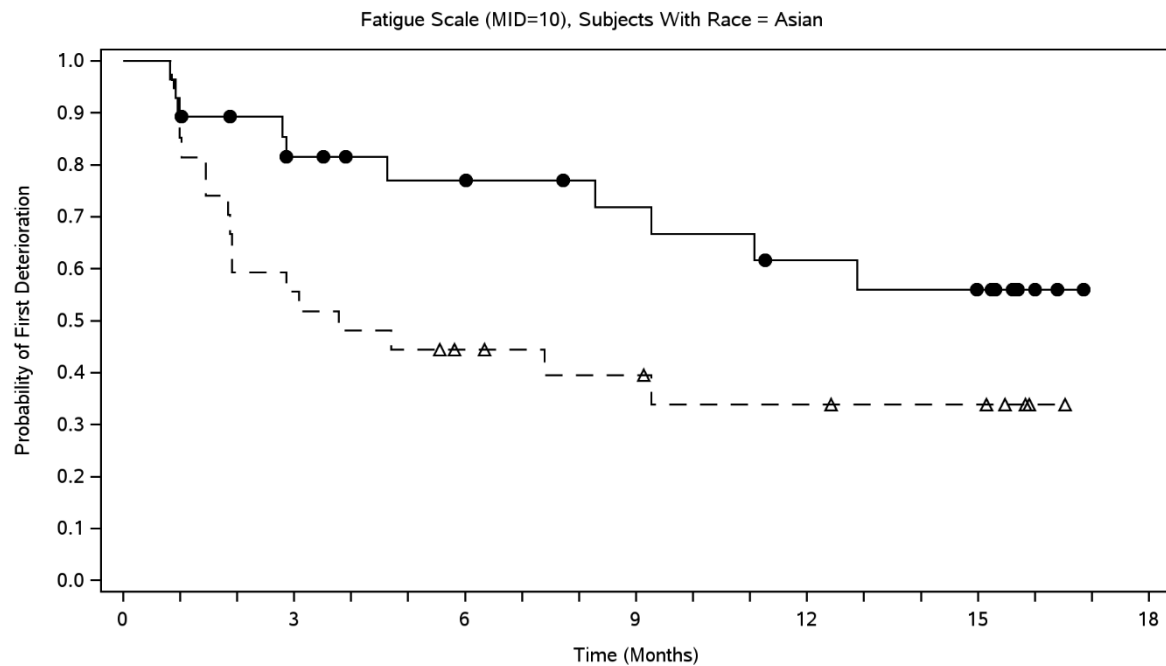
Program Name: rg-sy-subpdllrpro-ebr45.sas

24JUL2025:04:03:27

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

Figure 4.1

Kaplan-Meier Plot of EORTC QLQ-C30 Time to First Deterioration - by Significant Subgroups - PROS



Number of Subjects at Risk

Placebo

27 15 10 8 6 5 0

Nivolumab

28 20 17 14 11 9 0

— △ — Placebo (events: 17/27), median and 95% CI: 3.78 (1.84, N.A.)

— ● — Nivolumab (events: 10/28), median and 95% CI: N.A. (8.28, N.A.)

Hazard Ratio (Nivolumab vs. Placebo) and 95% CI: 0.400 (0.180, 0.888)

FEB2025 DBL.

Symbols represent censored observations.

Unstratified Cox proportional hazard model,
with baseline PRO score as a covariate.

Program Path: /projects/bms214671/stats/market/ma274_202502/prog/figures

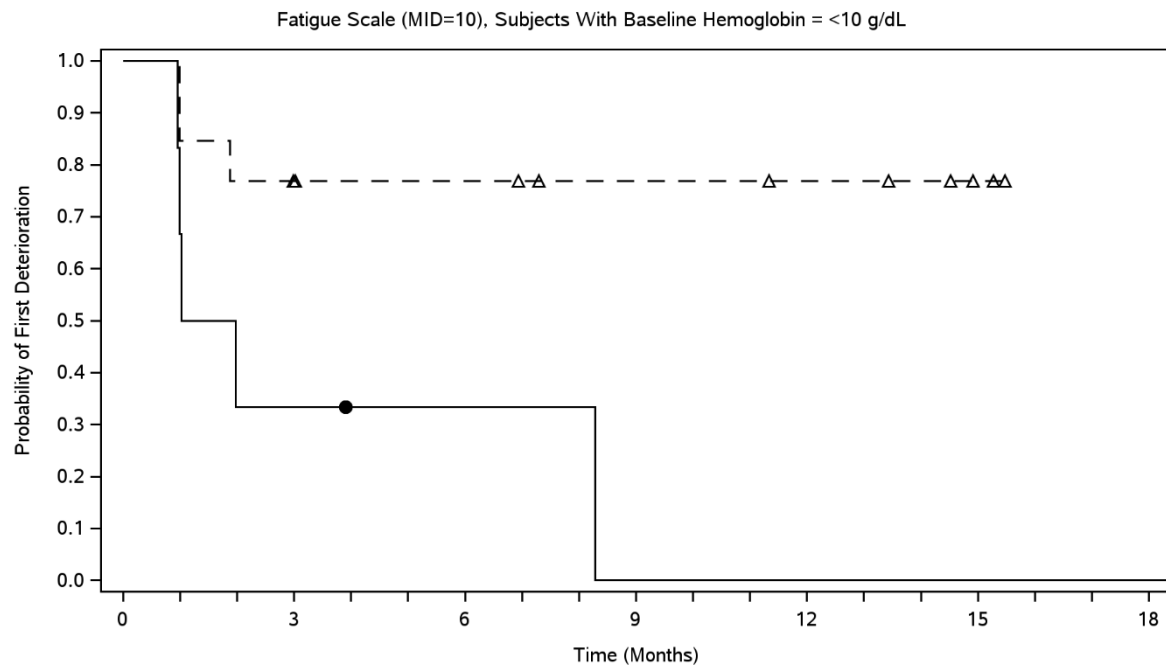
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24JUL2025:04:03:27

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

Figure 4.1

Kaplan-Meier Plot of EORTC QLQ-C30 Time to First Deterioration - by Significant Subgroups - PROS



Hazard Ratio (Nivolumab vs. Placebo) and 95% CI: 4.289 (0.920, 20.000)

FEB2025 DBL.

Symbols represent censored observations.

Unstratified Cox proportional hazard model,
with baseline PRO score as a covariate.

Program Path: /projects/bms214671/stats/market/ma274_202502/prog/figures

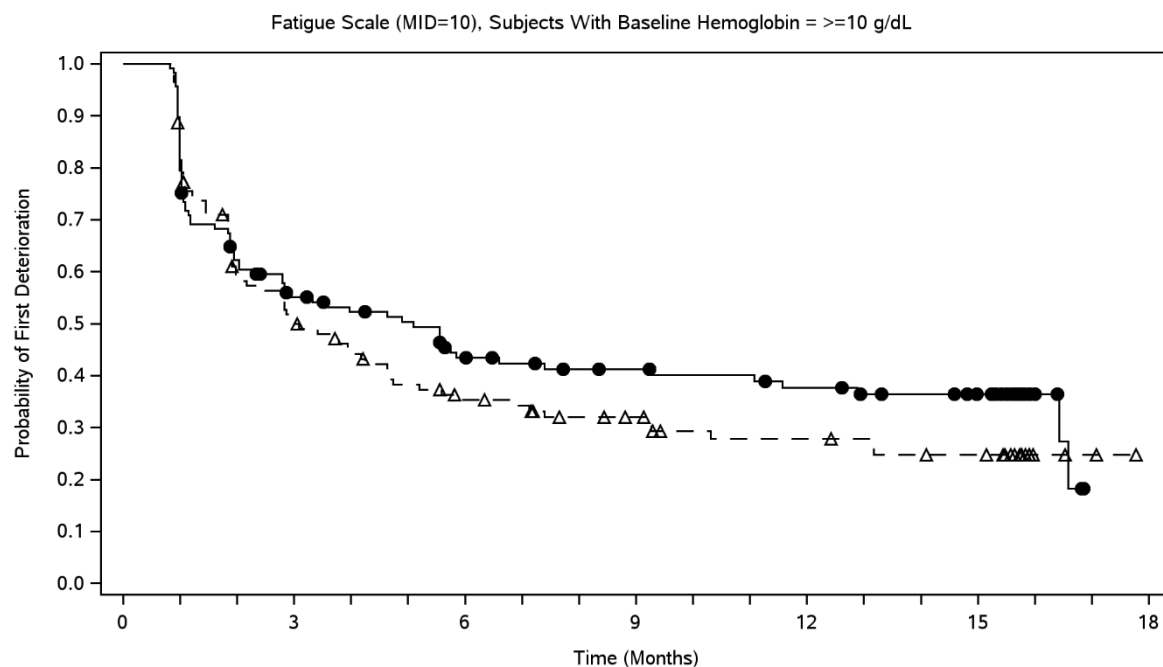
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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

Figure 4.1

Kaplan-Meier Plot of EORTC QLQ-C30 Time to First Deterioration - by Significant Subgroups - PROS



Hazard Ratio (Nivolumab vs. Placebo) and 95% CI: 0.889 (0.643, 1.227)

FEB2025 DBL.

Symbols represent censored observations.

Unstratified Cox proportional hazard model,
with baseline PRO score as a covariate.

Program Path: /projects/bms214671/stats/market/ma274_202502/prog/figures

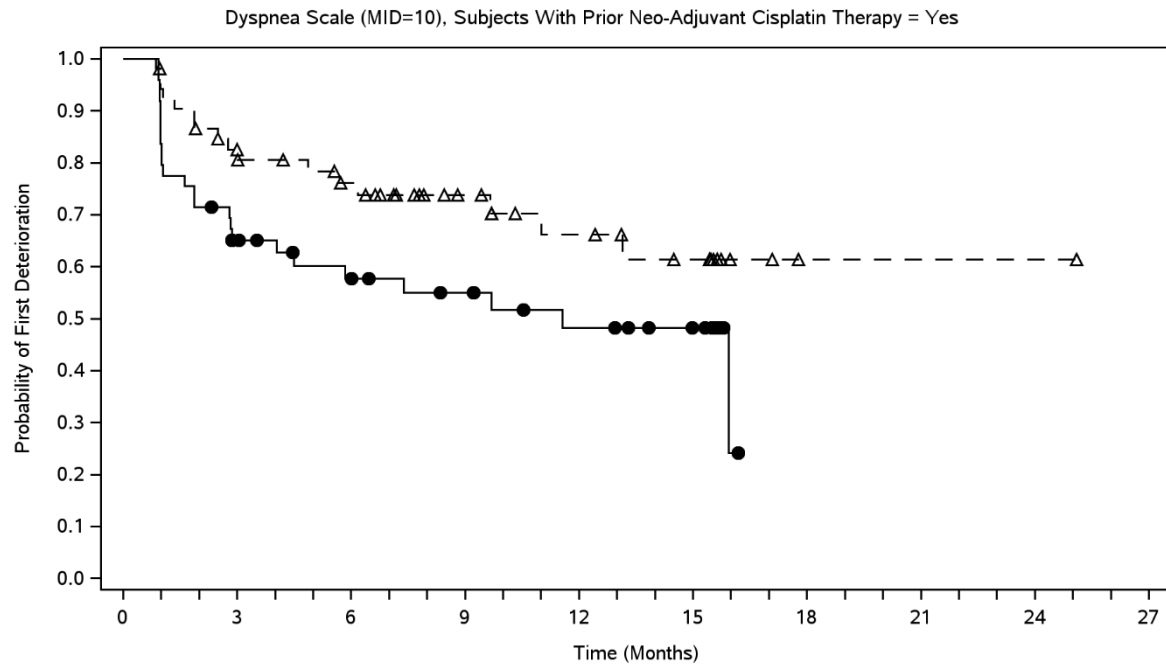
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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

Figure 4.1

Kaplan-Meier Plot of EORTC QLQ-C30 Time to First Deterioration - by Significant Subgroups - PROS



FEB2025 DBL.

Symbols represent censored observations.

Unstratified Cox proportional hazard model,
with baseline PRO score as a covariate.

Program Path: /projects/bms214671/stats/market/ma274_202502/prog/figures

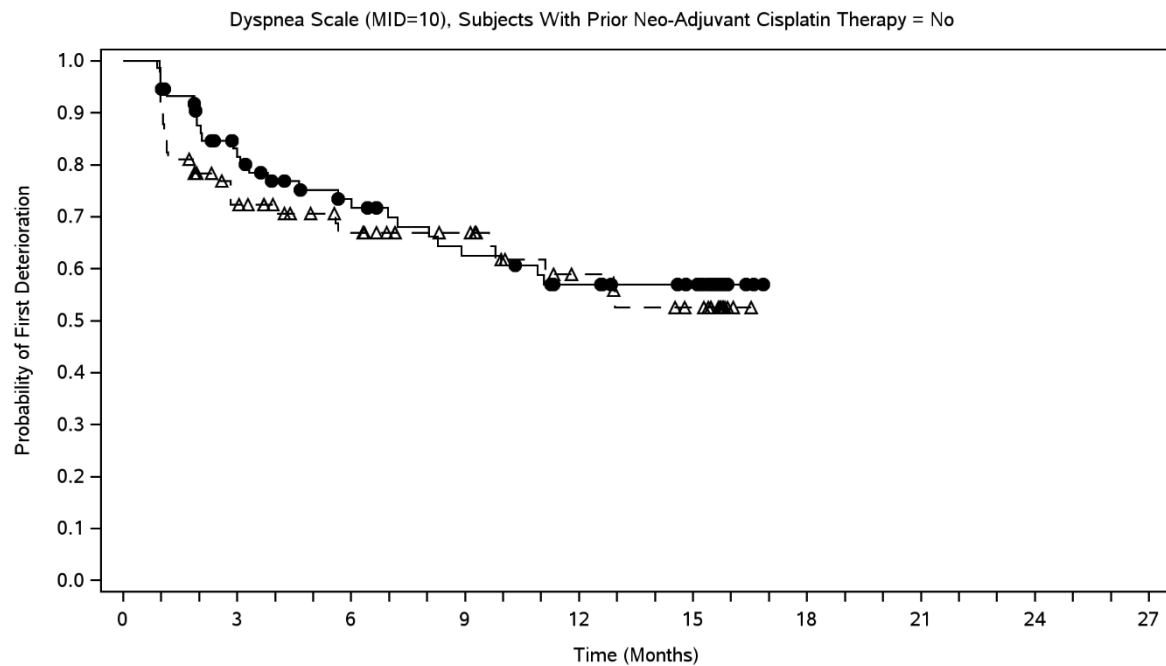
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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

Figure 4.1

Kaplan-Meier Plot of EORTC QLQ-C30 Time to First Deterioration - by Significant Subgroups - PROS



FEB2025 DBL.

Symbols represent censored observations.

Unstratified Cox proportional hazard model,
with baseline PRO score as a covariate.

Program Path: /projects/bms214671/stats/market/ma274_202502/prog/figures

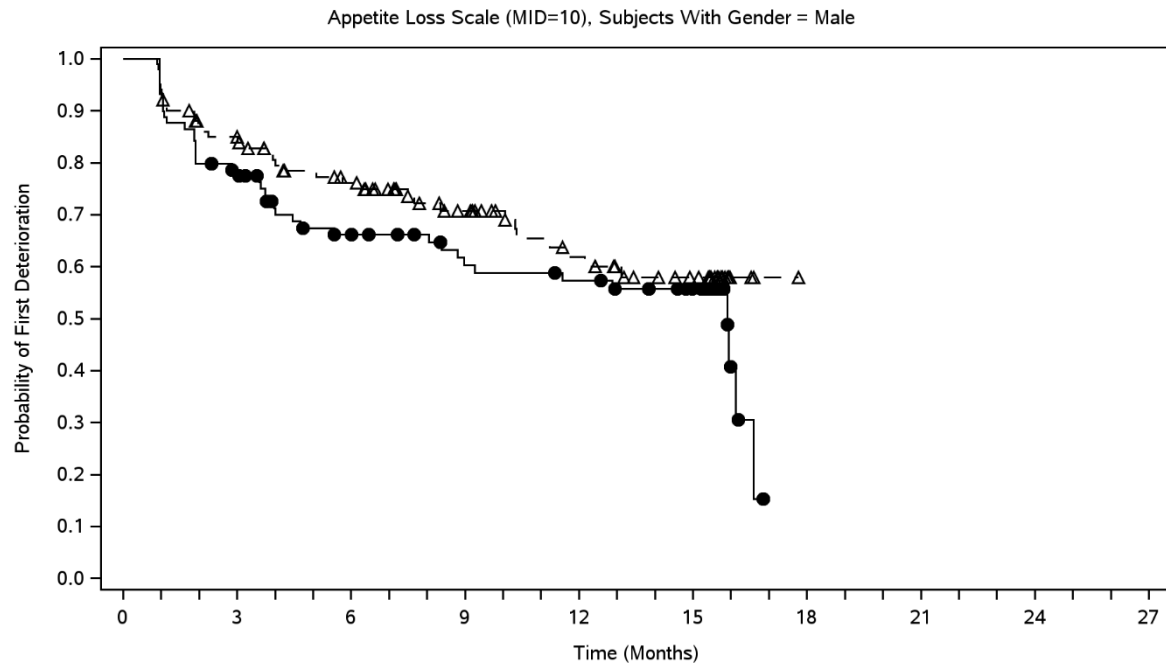
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24JUL2025:04:03:27

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

Figure 4.1

Kaplan-Meier Plot of EORTC QLQ-C30 Time to First Deterioration - by Significant Subgroups - PROS



Hazard Ratio (Nivolumab vs. Placebo) and 95% CI: 1.437 (0.907, 2.276)

FEB2025 DBL.

Symbols represent censored observations.

Unstratified Cox proportional hazard model,
with baseline PRO score as a covariate.

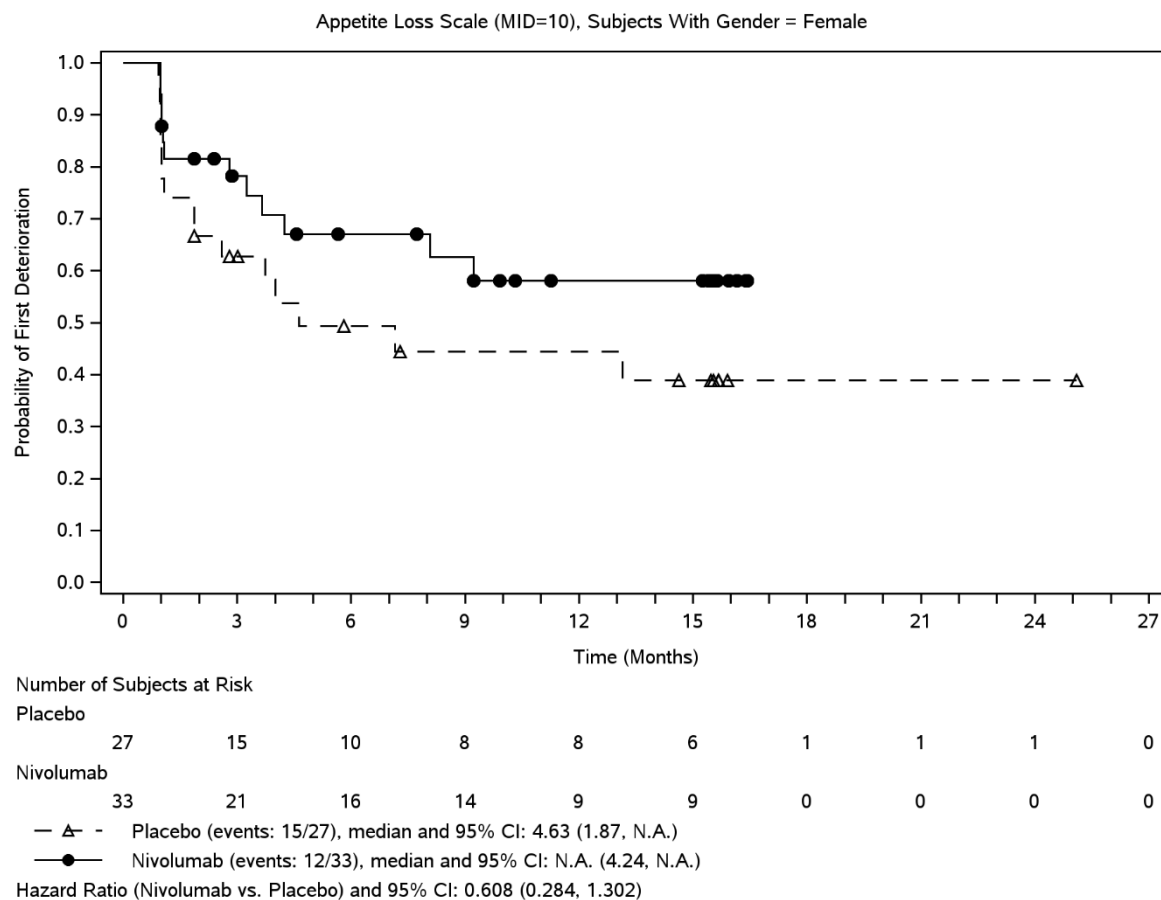
Program Path: /projects/bms214671/stats/market/ma274_202502/prog/figures

Program Name: rg-sy-subpdllrpro-ebr45.sas

24JUL2025:04:03:27

Figure 4.1

Kaplan-Meier Plot of EORTC QLQ-C30 Time to First Deterioration - by Significant Subgroups - PROS



FEB2025 DBL.

Symbols represent censored observations.

Unstratified Cox proportional hazard model,
with baseline PRO score as a covariate.

Program Path: /projects/bms214671/stats/market/ma274_202502/prog/figures

Program Name: rg-sy-subpdllrpro-ebr45.sas

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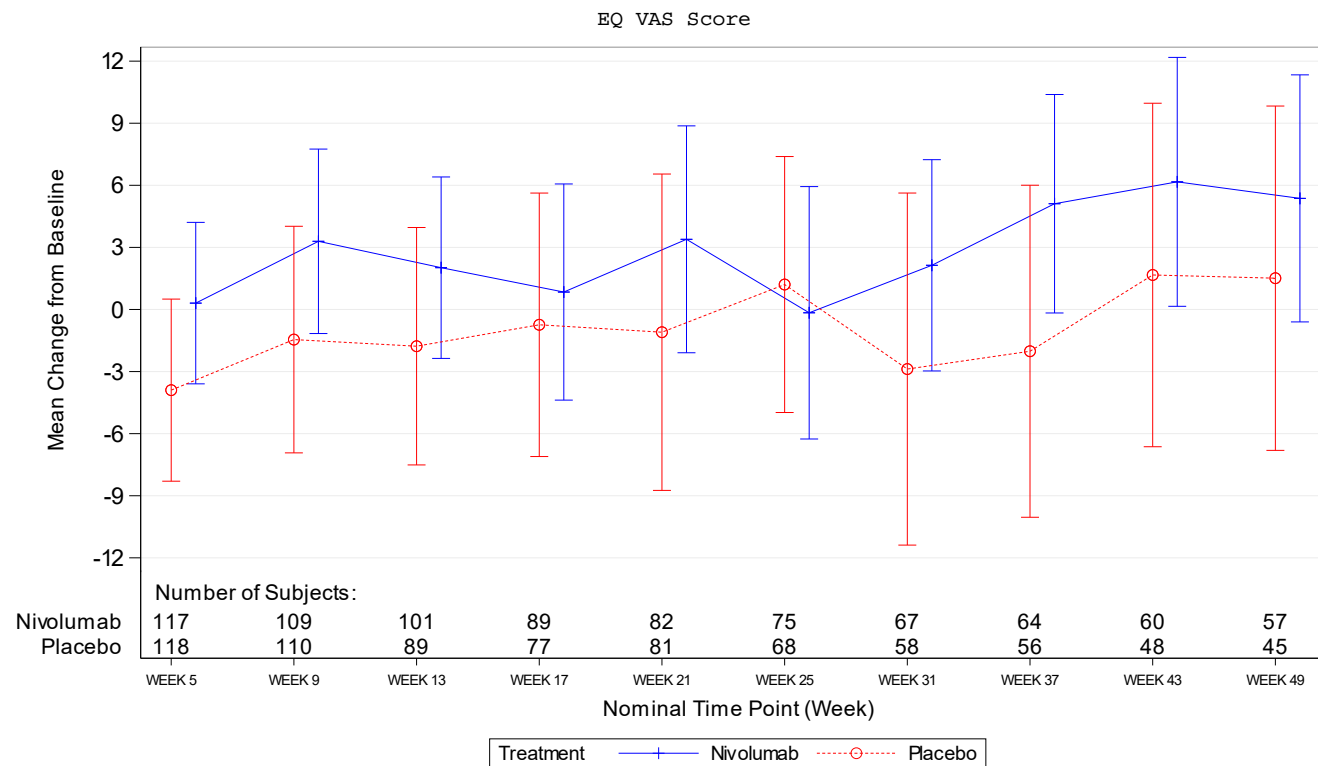
3.3 Gesundheitszustand: Endpunkt Zeit bis zur ersten Verschlechterung des Gesundheitszustands gemäß EQ-5D-3L VAS

Für die Auswertungen wurde PRO-Population herangezogen. Eine Verschlechterung wurde als klinisch relevante Verschlechterung im EQ-5D-3L VAS um ≥ 15 Punkte gegenüber Baseline definiert.

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

3.3.1 Grafische Darstellung der mittleren Veränderung gegenüber Baseline im zeitlichen Verlauf

Figure 12.2
Line plot of Mean Change from Baseline - EQ-5D-3L - PROS



Error bars represent 95% CI for the mean change.

Only on-treatment visits with data for at least 10 patients across both treatment groups are plotted.

FEB2025 DBL

Program Path: /projects/bms214671/stats/market/ma274_202502/prog/figures

Program Name: rg-ef-lp-ebr45.sas

24JUL2025:04:04:32

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

3.3.2 Subgruppenanalysen

Table 5.1.1
Subgroup Analyses of EQ-5D-3L VAS Time to First Deterioration
PROS

VAS (MID=15)

Subgroup	Placebo				Nivolumab				Nivolumab vs. Placebo	
	N	Subjects with Event n (%)	Censored subjects n (%)	KME [95%CI] (mon) (1)	N	Subjects with Event n (%)	Censored subjects n (%)	KME [95%CI] (mon) (1)	HR [95%CI] P-value (2)	Test for Interaction P-value (3) (4)
OVERALL	129	80 (62.0)	49 (38.0)	9.43 (5.88, 17.25)	127	68 (53.5)	59 (46.5)	25.13 (12.02, 63.61)	0.626 (0.452, 0.866) 0.0048	
PRIOR NEO-ADJUVANT CISPLATIN THERAPY										0.4034
YES	55	32 (58.2)	23 (41.8)	10.61 (4.44, 69.06)	51	29 (56.9)	22 (43.1)	25.13 (9.72, 78.06)	0.732 (0.440, 1.218) 0.2302	
NO	74	48 (64.9)	26 (35.1)	7.56 (4.24, 15.01)	76	39 (51.3)	37 (48.7)	21.29 (10.18, N.A.)	0.550 (0.360, 0.843) 0.0060	

FEB2025 DBL. HR = hazard ratio; KME=Kaplan-Meier estimate; N.M.E = Not meaningful estimate.

(1) KME of median time to event.

(2) Unstratified Cox proportional hazard model, with baseline PRO score as a covariate. HR is Nivolumab over Placebo.

(3) Unstratified Cox proportional hazard model with treatment, subgroup and treatment*subgroup interaction to assess the significance of the interaction between treatment and the subgroup, with baseline PRO score as a covariate. (4) P-values <0.05 are indicated by 1 asterisk (indicates potential effect modification).

IUC = invasive urothelial carcinoma

Program Path: /projects/bms214671/stats/market/ma274_202502/prog/tables

Program Name: rt-sy-tdd-eortc-comm-ebr45.sas

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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

Table 5.1.1
Subgroup Analyses of EQ-5D-3L VAS Time to First Deterioration
PROS

VAS (MID=15)

Subgroup	Placebo				Nivolumab				Nivolumab vs. Placebo	
	N	Subjects with Event n (%)	Censored subjects n (%)	KME [95%CI] (mon) (1)	N	Subjects with Event n (%)	Censored subjects n (%)	KME [95%CI] (mon) (1)	HR [95%CI] P-value (2)	Test for Interaction P-value (3) (4)
PRIOR CISPLATIN STATUS										0.1236
RECEIVED NEO-ADJUVANT	55	32 (58.2)	23 (41.8)	10.61 (4.44, 69.06)	51	29 (56.9)	22 (43.1)	25.13 (9.72, 78.06)	0.732 (0.440, 1.218)	
UNWILLING TO RECEIVE NEO-ADJUVANT	42	25 (59.5)	17 (40.5)	15.01 (6.67, 70.83)	47	24 (51.1)	23 (48.9)	21.29 (9.95, N.A.)	0.2302 (0.437, 1.345)	
NOT ELIGIBLE TO RECEIVE NEO-ADJUVANT	31	23 (74.2)	8 (25.8)	3.94 (1.87, 8.61)	24	12 (50.0)	12 (50.0)	58.22 (5.55, N.A.)	0.767 (0.162, 0.701)	

FEB2025 DBL. HR = hazard ratio; KME=Kaplan-Meier estimate; N.M.E = Not meaningful estimate.

(1) KME of median time to event.

(2) Unstratified Cox proportional hazard model, with baseline PRO score as a covariate. HR is Nivolumab over Placebo.

(3) Unstratified Cox proportional hazard model with treatment, subgroup and treatment*subgroup

interaction to assess the significance of the interaction between treatment and the subgroup, with baseline PRO score as a covariate. (4) P-values <0.05 are indicated by 1 asterisk (indicates potential effect modification).

IUC = invasive urothelial carcinoma

Program Path: /projects/bms214671/stats/market/ma274_202502/prog/tables

Program Name: rt-sy-tdd-eortc-comm-ebr45.sas

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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

Table 5.1.1
Subgroup Analyses of EQ-5D-3L VAS Time to First Deterioration
PROS

VAS (MID=15)

Subgroup	Placebo				Nivolumab				Nivolumab vs. Placebo	
	N	Subjects with Event n (%)	Censored subjects n (%)	KME [95%CI] (mon) (1)	N	Subjects with Event n (%)	Censored subjects n (%)	KME [95%CI] (mon) (1)	HR [95%CI] P-value (2)	Test for Interaction P-value (3) (4)
USE OF ANY PRIOR NEO-ADJUVANT SYSTEMIC THERAPY										0.5043
YES	56	33 (58.9)	23 (41.1)	10.61 (4.44, 30.00)	55	31 (56.4)	24 (43.6)	25.13 (9.72, 78.06)	0.710 (0.432, 1.168) 0.1773	
NO	73	47 (64.4)	26 (35.6)	8.41 (4.60, 15.01)	72	37 (51.4)	35 (48.6)	21.29 (11.07, N.A.)	0.558 (0.361, 0.860) 0.0083	

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	N	Subjects with Event n (%)	Censored subjects n (%)	KME [95%CI] (mon) (1)	N	Subjects with Event n (%)	Censored subjects n (%)	KME [95%CI] (mon) (1)	HR [95%CI] P-value (2)	Test for Interaction P-value (3) (4)
PATHOLOGICAL LYMPH NODE STATUS										0.4709
N+	58	35 (60.3)	23 (39.7)	9.00 (2.76, 17.25)	51	26 (51.0)	25 (49.0)	29.80 (10.18, N.A.)	0.516 (0.308, 0.866)	
NO/X WITH <10 NODES REMOVED	37	25 (67.6)	12 (32.4)	4.73 (2.83, 50.96)	36	17 (47.2)	19 (52.8)	26.45 (9.72, N.A.)	0.0122 (0.334, 1.164)	
NO WITH >= 10 NODES REMOVED	34	20 (58.8)	14 (41.2)	17.77 (6.67, 70.83)	40	25 (62.5)	15 (37.5)	21.29 (7.59, 63.61)	0.624 (0.461, 1.527)	
									0.1381 0.839 0.5661	

FEB2025 DBL. HR = hazard ratio; KME=Kaplan-Meier estimate; N.M.E = Not meaningful estimate.

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PROS

VAS (MID=15)

Subgroup	Placebo				Nivolumab				Nivolumab vs. Placebo	
	N	Subjects with Event n (%)	Censored subjects n (%)	KME [95%CI] (mon) (1)	N	Subjects with Event n (%)	Censored subjects n (%)	KME [95%CI] (mon) (1)	HR [95%CI] P-value (2)	Test for Interaction P-value (3) (4)
PATHOLOGICAL STATUS										0.1327
PT0-2	30	18 (60.0)	12 (40.0)	10.32 (2.50, N.A.)	21	13 (61.9)	8 (38.1)	12.58 (3.84, N.A.)	0.897 (0.432, 1.860)	
PT3	73	43 (58.9)	30 (41.1)	12.16 (4.76, 30.49)	82	48 (58.5)	34 (41.5)	15.18 (9.95, 46.95)	0.7695 0.753 (0.497, 1.141)	
PT4A	26	19 (73.1)	7 (26.9)	6.05 (1.91, 10.61)	21	6 (28.6)	15 (71.4)	N.A. (21.29, N.A.)	0.1806 0.298 (0.117, 0.758)	
									0.0110	

FEB2025 DBL. HR = hazard ratio; KME=Kaplan-Meier estimate; N.M.E = Not meaningful estimate.

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Table 5.1.1
Subgroup Analyses of EQ-5D-3L VAS Time to First Deterioration
PROS

VAS (MID=15)

Subgroup	Placebo				Nivolumab				Nivolumab vs. Placebo	
	N	Subjects with Event n (%)	Censored subjects n (%)	KME [95%CI] (mon) (1)	N	Subjects with Event n (%)	Censored subjects n (%)	KME [95%CI] (mon) (1)	HR [95%CI] P-value (2)	Test for Interaction P-value (3) (4)
AGE CATEGORY I										0.9460
< 65	54	30 (55.6)	24 (44.4)	18.50 (5.88, 70.83)	59	31 (52.5)	28 (47.5)	25.13 (10.18, N.A.)	0.648 (0.388, 1.083) 0.0980	
>= 65	75	50 (66.7)	25 (33.3)	7.29 (3.94, 13.60)	68	37 (54.4)	31 (45.6)	18.37 (9.95, 58.22)	0.653 (0.424, 1.004) 0.0520	

FEB2025 DBL. HR = hazard ratio; KME=Kaplan-Meier estimate; N.M.E = Not meaningful estimate.

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(3) Unstratified Cox proportional hazard model with treatment, subgroup and treatment*subgroup interaction to assess the significance of the interaction between treatment and the subgroup, with baseline PRO score as a covariate. (4) P-values <0.05 are indicated by 1 asterisk (indicates potential effect modification).

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PROS

VAS (MID=15)

Subgroup	Placebo				Nivolumab				Nivolumab vs. Placebo	
	N	Subjects with Event n (%)	Censored subjects n (%)	KME [95%CI] (mon) (1)	N	Subjects with Event n (%)	Censored subjects n (%)	KME [95%CI] (mon) (1)	HR [95%CI] P-value (2)	Test for Interaction P-value (3) (4)
AGE CATEGORY II										0.8701
< 65	54	30 (55.6)	24 (44.4)	18.50 (5.88, 70.83)	59	31 (52.5)	28 (47.5)	25.13 (10.18, N.A.)	0.648 (0.388, 1.083) 0.0980	
>= 65 AND < 75	55	39 (70.9)	16 (29.1)	7.56 (3.94, 13.60)	47	22 (46.8)	25 (53.2)	46.95 (8.08, N.A.)	0.564 (0.332, 0.959) 0.0345	
>= 75	20	11 (55.0)	9 (45.0)	4.70 (1.45, N.A.)	21	15 (71.4)	6 (28.6)	11.07 (2.86, 44.62)	0.784 (0.354, 1.737) 0.5486	

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PROS

VAS (MID=15)

Subgroup	Placebo				Nivolumab				Nivolumab vs. Placebo	
	N	Subjects with Event n (%)	Censored subjects n (%)	KME [95%CI] (mon) (1)	N	Subjects with Event n (%)	Censored subjects n (%)	KME [95%CI] (mon) (1)	HR [95%CI] P-value (2)	Test for Interaction P-value (3) (4)
REGION										0.5010
US	21	14 (66.7)	7 (33.3)	4.73 (1.97, 30.00)	14	7 (50.0)	7 (50.0)	25.13 (1.91, N.A.)	0.368 (0.141, 0.959) 0.0408	
EUROPE	63	38 (60.3)	25 (39.7)	10.61 (4.70, 30.49)	68	37 (54.4)	31 (45.6)	15.41 (9.49, N.A.)	0.710 (0.450, 1.119) 0.1400	
ASIA	27	15 (55.6)	12 (44.4)	12.16 (2.79, N.A.)	29	14 (48.3)	15 (51.7)	44.62 (11.14, N.A.)	0.775 (0.373, 1.608) 0.4933	
REST OF WORLD	18	13 (72.2)	5 (27.8)	9.00 (2.83, 50.96)	16	10 (62.5)	6 (37.5)	21.29 (2.33, N.A.)	0.555 (0.237, 1.299) 0.1744	

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(3) Unstratified Cox proportional hazard model with treatment, subgroup and treatment*subgroup interaction to assess the significance of the interaction between treatment and the subgroup, with baseline PRO score as a covariate. (4) P-values <0.05 are indicated by 1 asterisk (indicates potential effect modification).

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Subgroup	Placebo				Nivolumab				Nivolumab vs. Placebo	
	N	Subjects with Event n (%)	Censored subjects n (%)	KME [95%CI] (mon) (1)	N	Subjects with Event n (%)	Censored subjects n (%)	KME [95%CI] (mon) (1)	HR [95%CI] P-value (2)	Test for Interaction P-value (3) (4)
GENDER										0.0902
MALE	102	66 (64.7)	36 (35.3)	8.41 (4.70, 13.60)	92	44 (47.8)	48 (52.2)	44.62 (13.14, N.A.)	0.520 (0.354, 0.765) 0.0009	
FEMALE	27	14 (51.9)	13 (48.1)	30.00 (2.04, N.A.)	35	24 (68.6)	11 (31.4)	11.10 (2.89, 24.11)	0.968 (0.497, 1.887) 0.9243	
RACE										0.5918
WHITE	97	62 (63.9)	35 (36.1)	9.00 (4.73, 17.25)	96	53 (55.2)	43 (44.8)	21.29 (9.95, 78.06)	0.607 (0.419, 0.879) 0.0083	
ASIAN	27	15 (55.6)	12 (44.4)	12.16 (2.79, N.A.)	29	14 (48.3)	15 (51.7)	44.62 (11.14, N.A.)	0.775 (0.373, 1.608) 0.4933	

FEB2025 DBL. HR = hazard ratio; KME=Kaplan-Meier estimate; N.M.E = Not meaningful estimate.

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VAS (MID=15)

Subgroup	Placebo				Nivolumab				Nivolumab vs. Placebo	
	N	Subjects with Event n (%)	Censored subjects n (%)	KME [95%CI] (mon) (1)	N	Subjects with Event n (%)	Censored subjects n (%)	KME [95%CI] (mon) (1)	HR [95%CI] P-value (2)	Test for Interaction P-value (3) (4)
BASELINE ECOG STATUS										0.7236
0	81	53 (65.4)	28 (34.6)	9.00 (4.17, 23.72)	78	43 (55.1)	35 (44.9)	29.80 (11.07, 69.06)	0.611 (0.407, 0.916) 0.0170	
1	44	27 (61.4)	17 (38.6)	11.14 (4.76, 30.00)	47	25 (53.2)	22 (46.8)	18.37 (7.59, N.A.)	0.686 (0.397, 1.185) 0.1767	
SMOKING STATUS										0.6377
NEVER SMOKED	36	23 (63.9)	13 (36.1)	6.67 (3.78, 17.25)	37	20 (54.1)	17 (45.9)	15.18 (4.63, N.A.)	0.596 (0.323, 1.102) 0.0988	
CURRENT/FORMER	92	56 (60.9)	36 (39.1)	11.14 (5.88, 30.49)	89	47 (52.8)	42 (47.2)	29.80 (11.14, 78.06)	0.652 (0.442, 0.962) 0.0312	

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	N	Subjects with Event n (%)	Censored subjects n (%)	KME [95%CI] (mon) (1)	N	Subjects with Event n (%)	Censored subjects n (%)	KME [95%CI] (mon) (1)	HR [95%CI] P-value (2)	Test for Interaction P-value (3) (4)
BASELINE HEMOGLOBIN										0.0793
<10 G/DL	13	8 (61.5)	5 (38.5)	17.25 (1.84, N.A.)	6	2 (33.3)	4 (66.7)	N.A. (18.37, N.A.)	0.053 (0.006, 0.458)	
>=10 G/DL	116	72 (62.1)	44 (37.9)	9.43 (5.88, 17.77)	121	66 (54.5)	55 (45.5)	24.11 (11.10, 58.22)	0.0076 0.683 (0.488, 0.955) 0.0258	
BASELINE CREATININE CLEARANCE										0.5109
<60 ML/MIN	57	38 (66.7)	19 (33.3)	8.61 (3.94, 30.00)	49	25 (51.0)	24 (49.0)	44.62 (11.07, N.A.)	0.573 (0.345, 0.952)	
>=60 ML/MIN	72	42 (58.3)	30 (41.7)	10.61 (4.73, 23.72)	77	43 (55.8)	34 (44.2)	21.29 (9.95, 54.90)	0.0316 0.684 (0.444, 1.054) 0.0849	

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TIME FROM IUC SURGERY TO RANDOMIZATION (DAYS)										0.1525
>30-60	28	14 (50.0)	14 (50.0)	13.60 (6.67, N.A.)	31	16 (51.6)	15 (48.4)	13.14 (5.55, N.A.)	1.084 (0.526, 2.234)	
>60-90	58	42 (72.4)	16 (27.6)	6.05 (2.86, 23.72)	53	26 (49.1)	27 (50.9)	54.90 (15.18, N.A.)	0.8265 (0.272, 0.733)	
>90-120	38	23 (60.5)	15 (39.5)	8.61 (2.50, 17.77)	41	25 (61.0)	16 (39.0)	14.29 (3.09, 78.06)	0.447 (0.0014, 0.701)	
									0.2263	

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	N	Subjects with Event n (%)	Censored subjects n (%)	KME [95%CI] (mon) (1)	N	Subjects with Event n (%)	Censored subjects n (%)	KME [95%CI] (mon) (1)	HR [95%CI] P-value (2)	Test for Interaction P-value (3) (4)
INITIAL TUMOR ORIGIN										0.7433
URINARY BLADDER	105	67 (63.8)	38 (36.2)	8.61 (4.70, 15.01)	105	57 (54.3)	48 (45.7)	25.13 (12.02, 69.06)	0.571 (0.398, 0.817) 0.0022	
RENAL PELVIS	13	8 (61.5)	5 (38.5)	6.05 (0.99, N.A.)	15	9 (60.0)	6 (40.0)	11.14 (1.91, N.A.)	0.834 (0.313, 2.219) 0.7163	
URETER	11	5 (45.5)	6 (54.5)	88.18 (2.04, N.A.)	7	2 (28.6)	5 (71.4)	N.A. (0.95, N.A.)	0.691 (0.127, 3.766) 0.6696	

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(2) Unstratified Cox proportional hazard model, with baseline PRO score as a covariate. HR is Nivolumab over Placebo.

(3) Unstratified Cox proportional hazard model with treatment, subgroup and treatment*subgroup

interaction to assess the significance of the interaction between treatment and the subgroup, with baseline PRO score as a covariate. (4) P-values <0.05 are indicated by 1 asterisk (indicates potential effect modification).

IUC = invasive urothelial carcinoma

Program Path: /projects/bms214671/stats/market/ma274_202502/prog/tables

Program Name: rt-sy-tdd-eortc-comm-ebr45.sas

16JUL2025:07:43:43

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

Table 5.1.1
Subgroup Analyses of EQ-5D-3L VAS Time to First Deterioration
PROS

VAS (MID=15)

Subgroup	Placebo				Nivolumab				Nivolumab vs. Placebo	
	N	Subjects with Event n (%)	Censored subjects n (%)	KME [95%CI] (mon) (1)	N	Subjects with Event n (%)	Censored subjects n (%)	KME [95%CI] (mon) (1)	HR [95%CI] P-value (2)	Test for Interaction P-value (3) (4)
MINOR HISTOLOGICAL VARIANTS										0.2245
PRESENCE	54	35 (64.8)	19 (35.2)	9.00 (4.70, 30.00)	56	32 (57.1)	24 (42.9)	15.18 (10.18, 63.61)	0.765 (0.472, 1.240)	
ABSENCE	75	45 (60.0)	30 (40.0)	10.32 (3.94, 23.72)	71	36 (50.7)	35 (49.3)	33.41 (12.02, N.A.)	0.521 (0.333, 0.814) 0.0042	

FEB2025 DBL. HR = hazard ratio; KME=Kaplan-Meier estimate; N.M.E = Not meaningful estimate.

(1) KME of median time to event.

(2) Unstratified Cox proportional hazard model, with baseline PRO score as a covariate. HR is Nivolumab over Placebo.

(3) Unstratified Cox proportional hazard model with treatment, subgroup and treatment*subgroup

interaction to assess the significance of the interaction between treatment and the subgroup, with baseline PRO score as a covariate. (4) P-values <0.05 are indicated by 1 asterisk (indicates potential effect modification).

IUC = invasive urothelial carcinoma

Program Path: /projects/bms214671/stats/market/ma274_202502/prog/tables

Program Name: rt-sy-tdd-eortc-comm-ebr45.sas

16JUL2025:07:43:43

3.3.3 Kaplan-Meier Kurven für Subgruppen mit statistisch signifikantem Interaktionsterm

Nicht zutreffend.

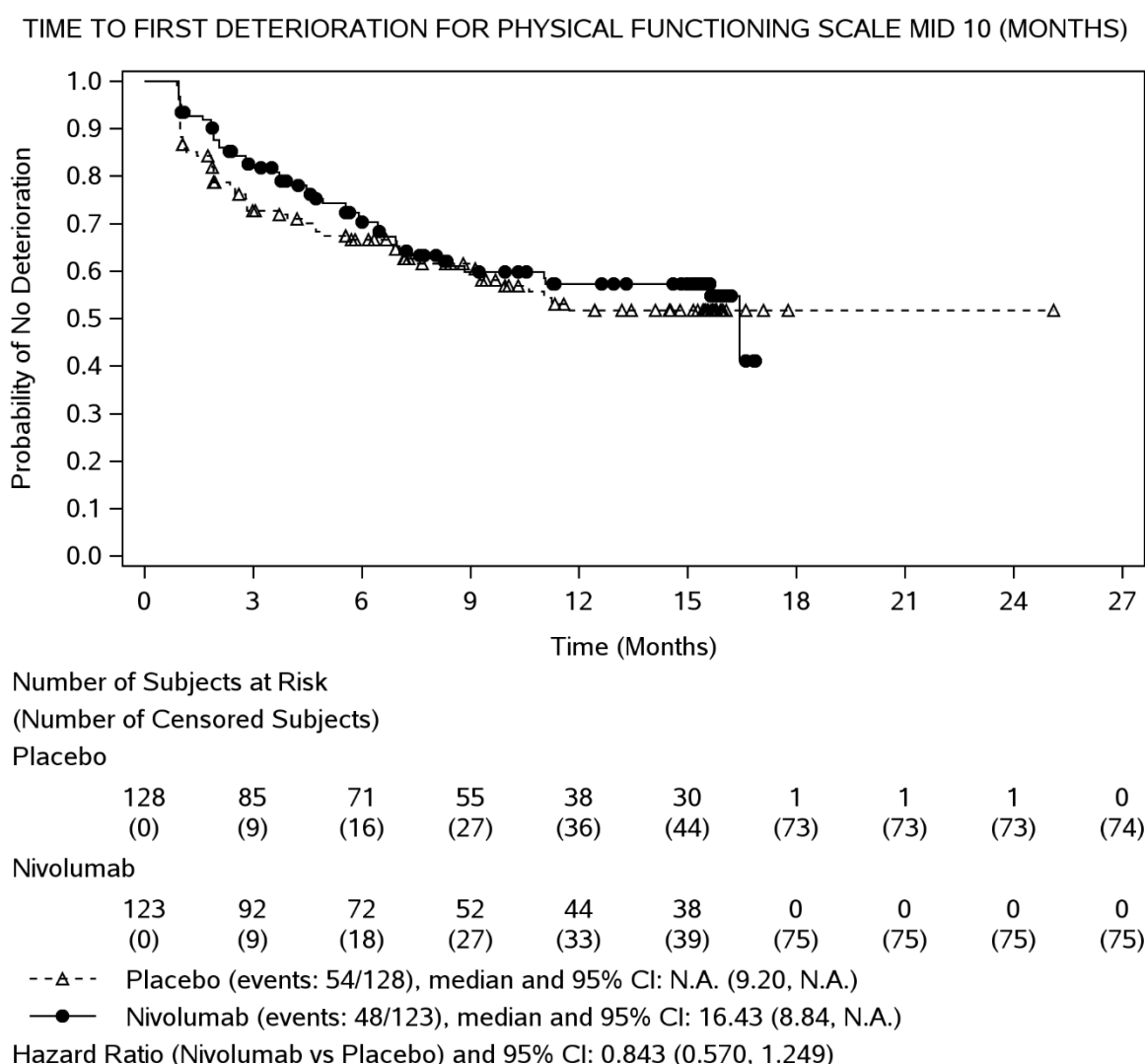
Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

4 Gesundheitsbezogene Lebensqualität: Endpunkt Zeit bis zur ersten Verschlechterung der gesundheitsbezogenen Lebensqualität gemäß den Domänen des EORTC QLQ-C30

Für die Auswertungen wurde PRO-Population herangezogen. Eine Verschlechterung wurde als klinisch relevante Verschlechterung der jeweiligen Domäne des EORTC-QLQ-C30 um ≥ 10 Punkte gegenüber Baseline definiert.

4.1 Kaplan-Meier-Kurven

Figure 1.1
Kaplan-Meier Plot of EORTC QLQ-C30 Time to First Deterioration - PROS



FEB2025 DBL

Symbols represent censored observations.

Stratified Cox proportional hazard model

with baseline PRO score as a covariate.

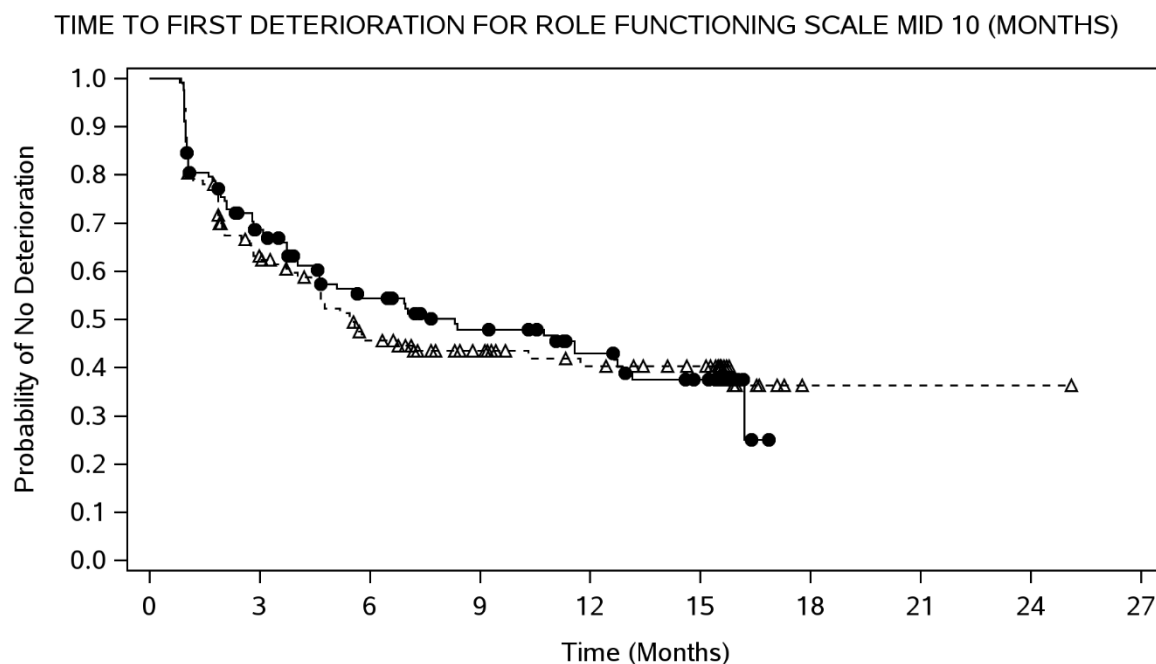
Program Path: /projects/bms214671/stats/market/ma274_202502/prog/figures

Program Name: rg-sy-tdd-eb45.sas

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Figure 1.1

Kaplan-Meier Plot of EORTC QLQ-C30 Time to First Deterioration - PROS



Number of Subjects at Risk

(Number of Censored Subjects)

Placebo

128	73	47	33	25	20	1	1	1	0
(0)	(9)	(16)	(28)	(34)	(39)	(57)	(57)	(57)	(58)

Nivolumab

123	76	54	43	33	25	0	0	0	0
(0)	(9)	(16)	(21)	(27)	(31)	(55)	(55)	(55)	(55)

--△-- Placebo (events: 70/128), median and 95% CI: 5.55 (4.04, 11.73)

—●— Nivolumab (events: 68/123), median and 95% CI: 8.31 (4.63, 12.75)

Hazard Ratio (Nivolumab vs Placebo) and 95% CI: 0.925 (0.657, 1.303)

FEB2025 DBL

Symbols represent censored observations.

Stratified Cox proportional hazard model

with baseline PRO score as a covariate.

Program Path: /projects/bms214671/stats/market/ma274_202502/prog/figures

Program Name: rg-sy-tdd-ebr45.sas

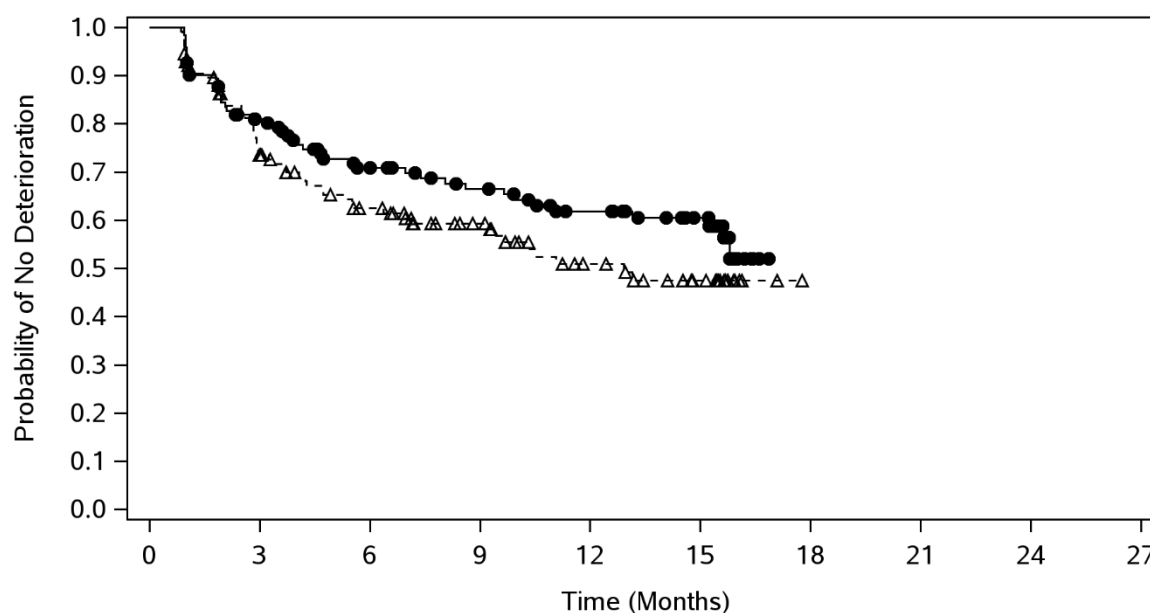
21NOV2025:14:45:48

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

Figure 1.1

Kaplan-Meier Plot of EORTC QLQ-C30 Time to First Deterioration - PROS

TIME TO FIRST DETERIORATION FOR EMOTIONAL FUNCTIONING SCALE MID 10 (MONTHS)



Number of Subjects at Risk

(Number of Censored Subjects)

Placebo

127	85	64	48	31	20	0	0	0	0
(0)	(10)	(19)	(32)	(43)	(52)	(72)	(72)	(72)	(72)

Nivolumab

123	93	70	60	49	39	0	0	0	0
(0)	(7)	(19)	(25)	(32)	(41)	(77)	(77)	(77)	(77)

--△-- Placebo (events: 55/127), median and 95% CI: 12.91 (7.16, N.A.)

—●— Nivolumab (events: 46/123), median and 95% CI: N.A. (15.24, N.A.)

Hazard Ratio (Nivolumab vs Placebo) and 95% CI: 0.780 (0.525, 1.158)

FEB2025 DBL

Symbols represent censored observations.

Stratified Cox proportional hazard model

with baseline PRO score as a covariate.

Program Path: /projects/bms214671/stats/market/ma274_202502/prog/figures

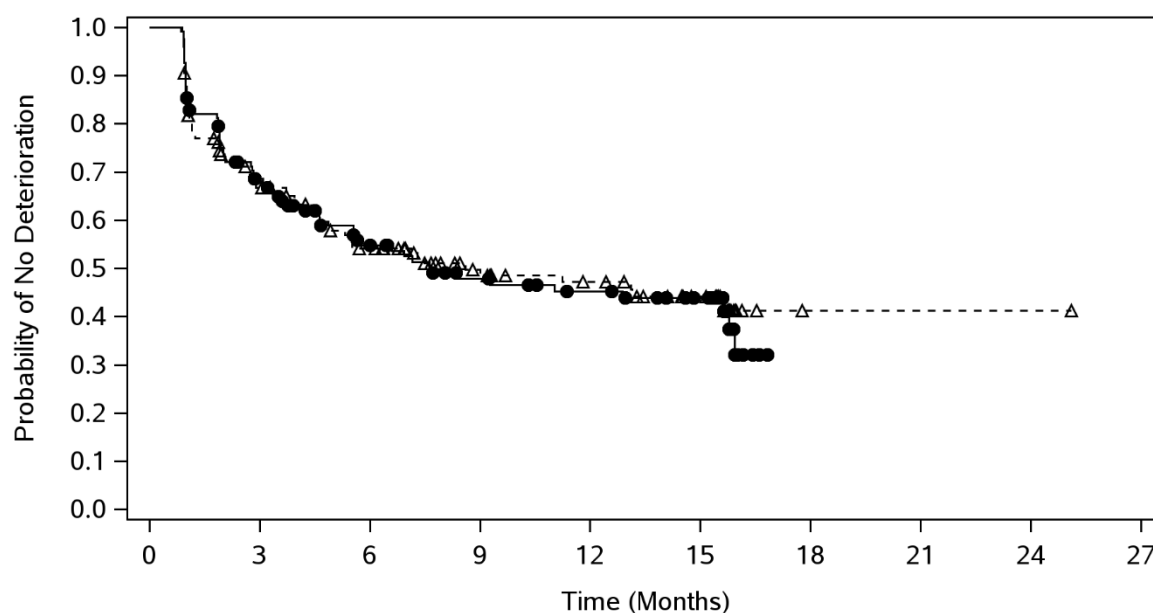
Program Name: rg-sy-tdd-ebr45.sas

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Figure 1.1

Kaplan-Meier Plot of EORTC QLQ-C30 Time to First Deterioration - PROS

TIME TO FIRST DETERIORATION FOR COGNITIVE FUNCTIONING SCALE MID 10 (MONTHS)



Number of Subjects at Risk

(Number of Censored Subjects)

Placebo

127	78	58	40	33	22	1	1	1	0
(0)	(8)	(14)	(28)	(33)	(42)	(62)	(62)	(62)	(63)

Nivolumab

123	75	51	39	33	26	0	0	0	0
(0)	(10)	(20)	(26)	(30)	(36)	(59)	(59)	(59)	(59)

--△-- Placebo (events: 64/127), median and 95% CI: 8.61 (4.86, N.A.)

—●— Nivolumab (events: 64/123), median and 95% CI: 7.66 (4.67, 15.77)

Hazard Ratio (Nivolumab vs Placebo) and 95% CI: 1.006 (0.708, 1.429)

FEB2025 DBL

Symbols represent censored observations.

Stratified Cox proportional hazard model

with baseline PRO score as a covariate.

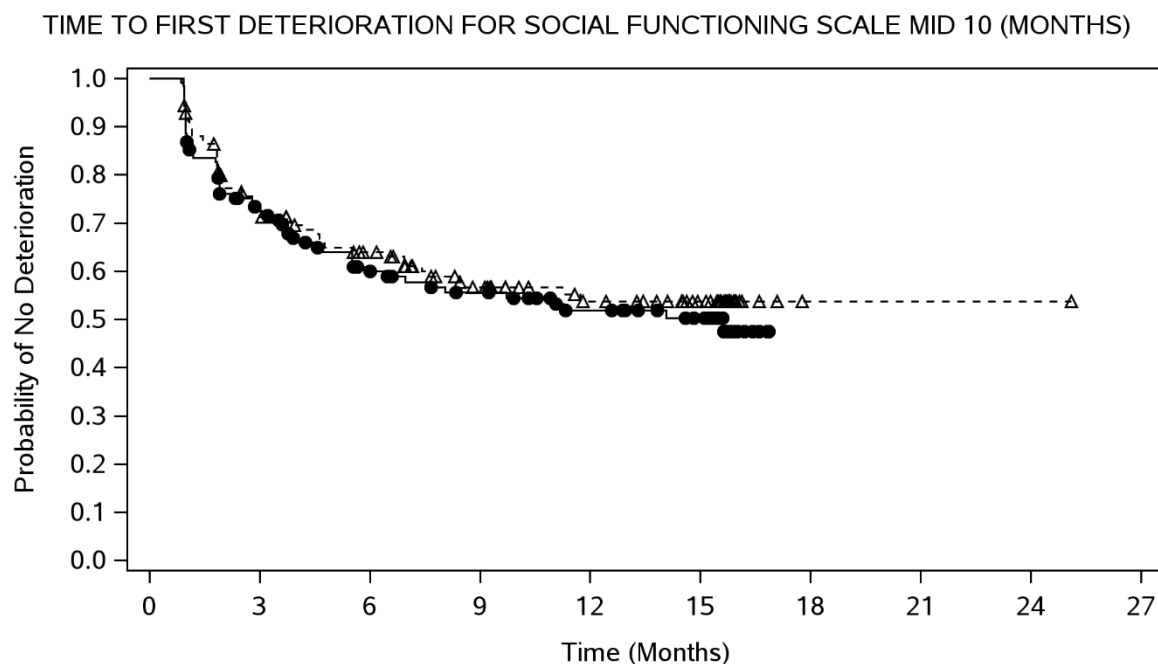
Program Path: /projects/bms214671/stats/market/ma274_202502/prog/figures

Program Name: rg-sy-tdd-ebr45.sas

21NOV2025:14:45:48

Figure 1.1

Kaplan-Meier Plot of EORTC QLQ-C30 Time to First Deterioration - PROS



Number of Subjects at Risk

(Number of Censored Subjects)

Placebo

126	83	67	48	36	26	1	1	1	0
(0)	(8)	(16)	(28)	(38)	(48)	(73)	(73)	(73)	(74)

Nivolumab

122	80	59	49	39	31	0	0	0	0
(0)	(9)	(18)	(23)	(30)	(37)	(67)	(67)	(67)	(67)

--△-- Placebo (events: 52/126), median and 95% CI: N.A. (7.56, N.A.)

—●— Nivolumab (events: 55/122), median and 95% CI: 15.64 (6.47, N.A.)

Hazard Ratio (Nivolumab vs Placebo) and 95% CI: 1.060 (0.723, 1.553)

FEB2025 DBL

Symbols represent censored observations.

Stratified Cox proportional hazard model

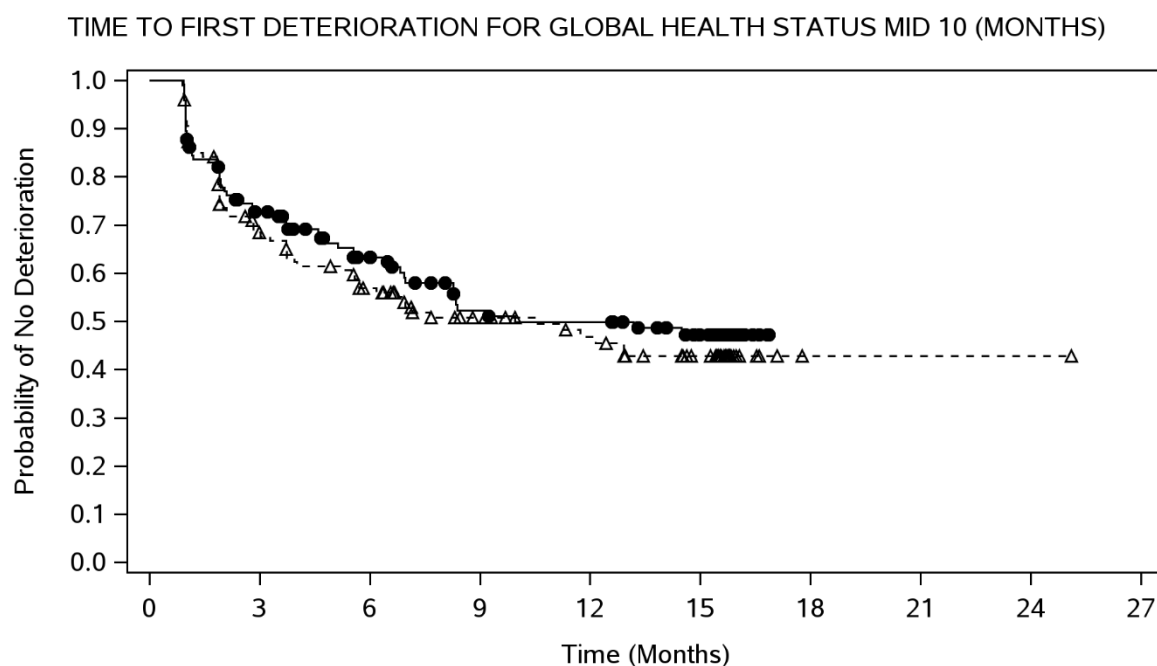
with baseline PRO score as a covariate.

Program Path: /projects/bms214671/stats/market/ma274_202502/prog/figures

Program Name: rg-sy-tdd-ebr45.sas

21NOV2025:14:45:48

Figure 1.1
Kaplan-Meier Plot of EORTC QLQ-C30 Time to First Deterioration - PROS



Number of Subjects at Risk

(Number of Censored Subjects)

Placebo

127	79	61	43	35	24	1	1	1	0
(0)	(9)	(14)	(26)	(31)	(39)	(62)	(62)	(62)	(63)

Nivolumab

123	83	63	45	42	31	0	0	0	0
(0)	(7)	(17)	(25)	(26)	(35)	(66)	(66)	(66)	(66)

--△-- Placebo (events: 64/127), median and 95% CI: 10.51 (5.59, N.A.)

—●— Nivolumab (events: 57/123), median and 95% CI: 9.95 (6.93, N.A.)

Hazard Ratio (Nivolumab vs Placebo) and 95% CI: 0.942 (0.655, 1.355)

FEB2025 DBL

Symbols represent censored observations.

Stratified Cox proportional hazard model

with baseline PRO score as a covariate.

Program Path: /projects/bms214671/stats/market/ma274_202502/prog/figures

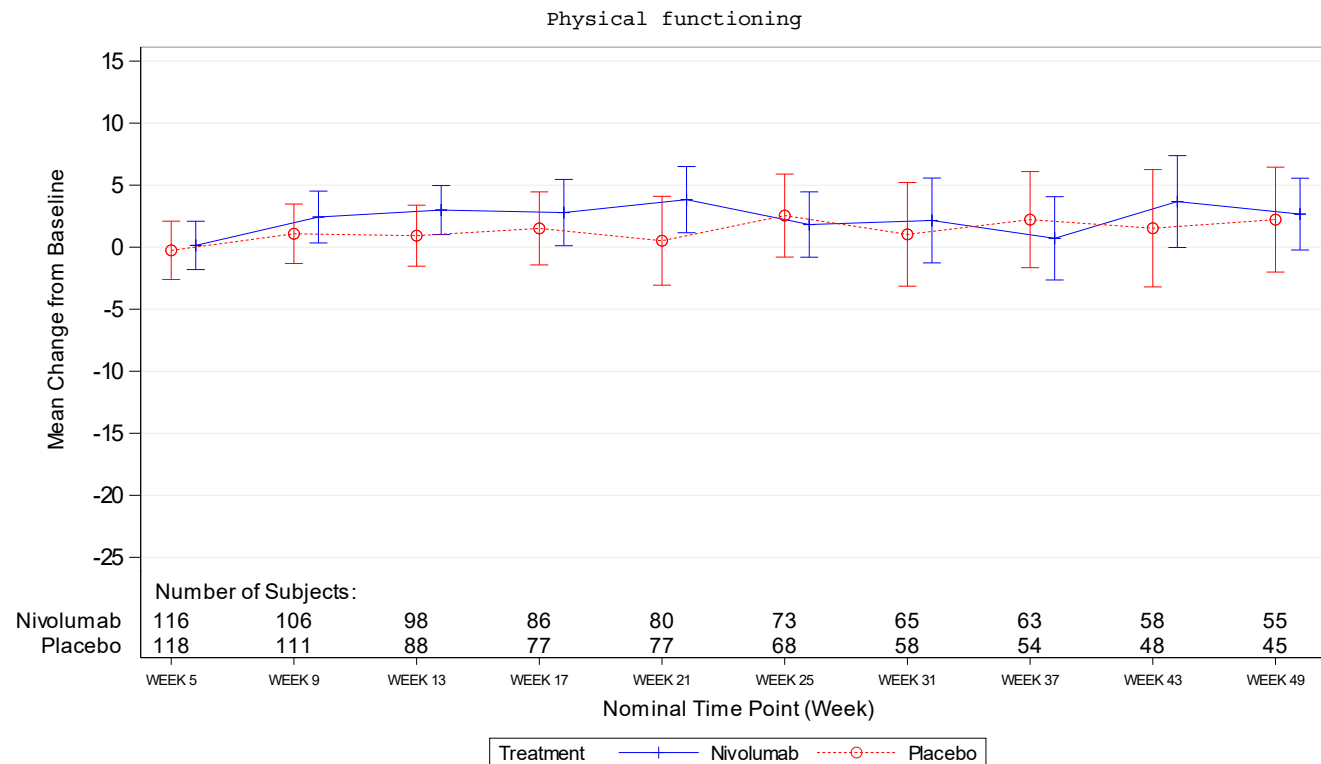
Program Name: rg-sy-tdd-ebr45.sas

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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

4.2 Grafische Darstellung der mittleren Veränderung gegenüber Baseline im zeitlichen Verlauf

Figure 12.1
Line plot of Mean Change from Baseline - EORTC QLQ-C30 - PROS



Error bars represent 95% CI for the mean change.

Only on-treatment visits with data for at least 10 patients across both treatment groups are plotted.

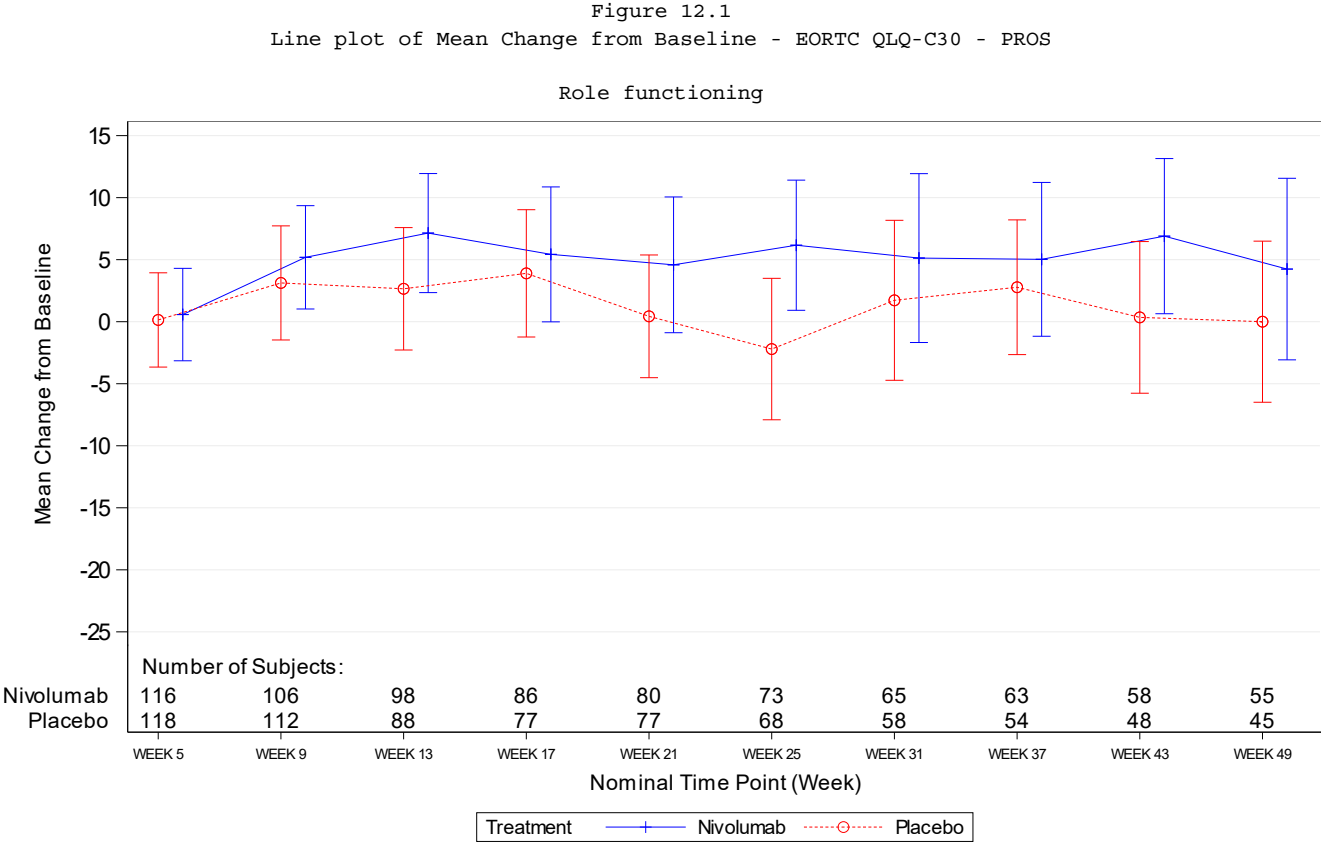
FEB2025 DBL

Program Path: /projects/bms214671/stats/market/ma274_202502/prog/figures

Program Name: rg-ef-lp-ebr45.sas

24JUL2025:04:04:24

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

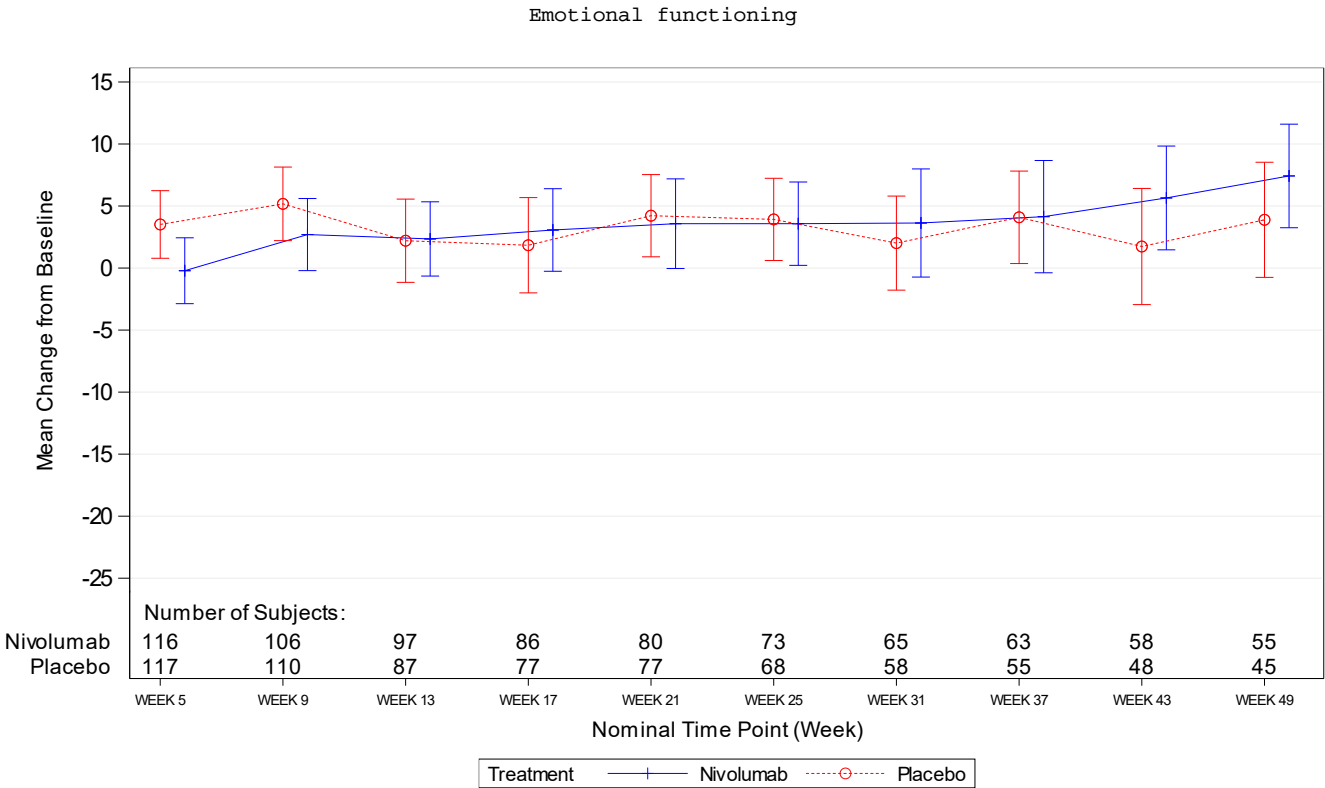


Error bars represent 95% CI for the mean change.
Only on-treatment visits with data for at least 10 patients across both treatment groups are plotted.
FEB2025 DBL
Program Path: /projects/bms214671/stats/market/ma274_202502/prog/figures
Program Name: rg-ef-lp-ebr45.sas

24JUL2025:04:04:24

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

Figure 12.1
Line plot of Mean Change from Baseline - EORTC QLQ-C30 - PROS

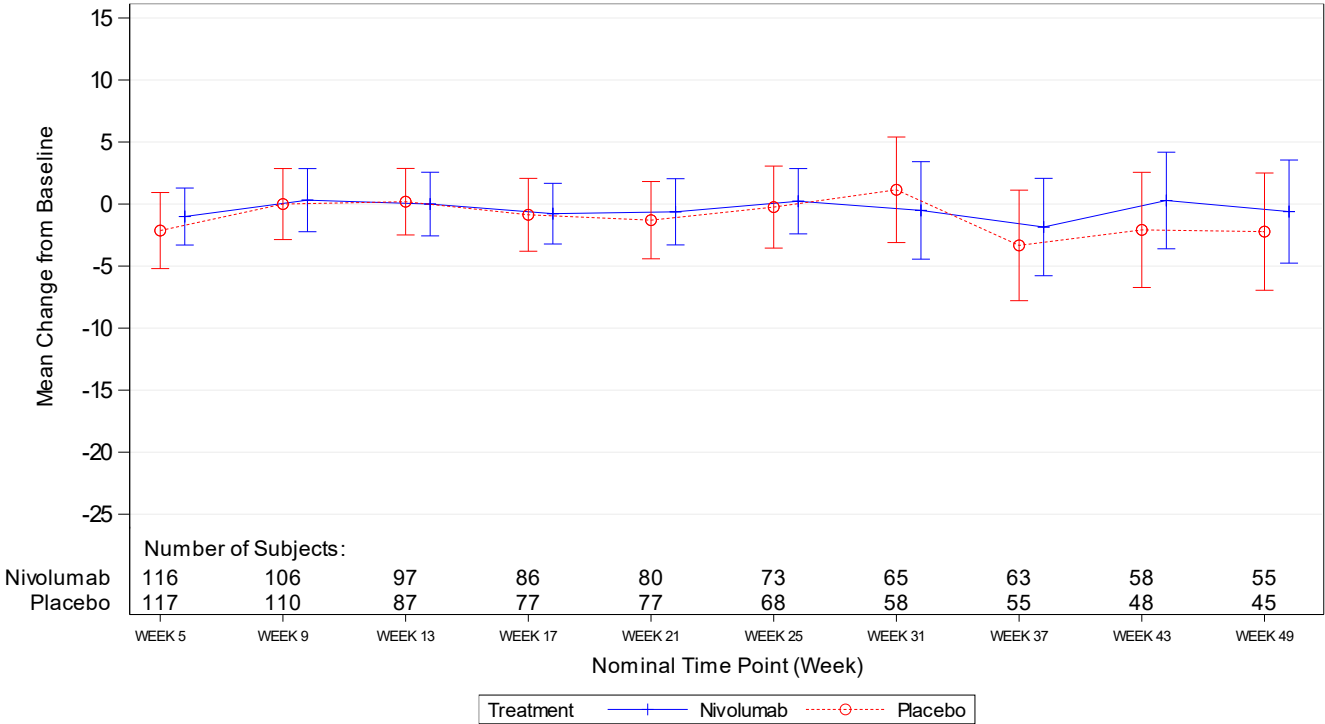


Error bars represent 95% CI for the mean change.
Only on-treatment visits with data for at least 10 patients across both treatment groups are plotted.
FEB2025 DBL
Program Path: /projects/bms214671/stats/market/ma274_202502/prog/figures
Program Name: rg-ef-lp-ebr45.sas

24JUL2025:04:04:24

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

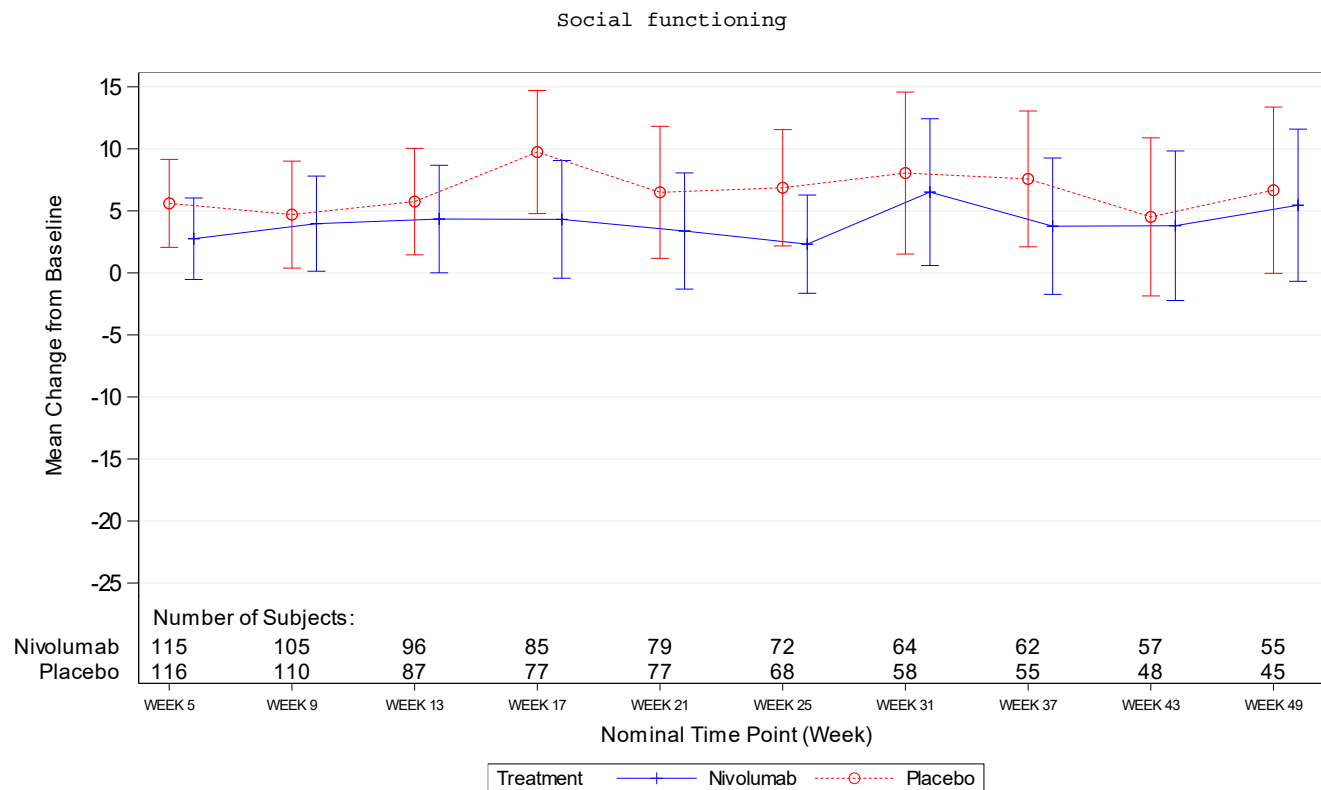
Figure 12.1
Line plot of Mean Change from Baseline - EORTC QLQ-C30 - PROS
Cognitive functioning



Error bars represent 95% CI for the mean change.
Only on-treatment visits with data for at least 10 patients across both treatment groups are plotted.
FEB2025 DBL
Program Path: /projects/bms214671/stats/market/ma274_202502/prog/figures
Program Name: rg-ef-lp-ebr45.sas

24JUL2025:04:04:24

Figure 12.1
Line plot of Mean Change from Baseline - EORTC QLQ-C30 - PROS



Error bars represent 95% CI for the mean change.

Only on-treatment visits with data for at least 10 patients across both treatment groups are plotted.

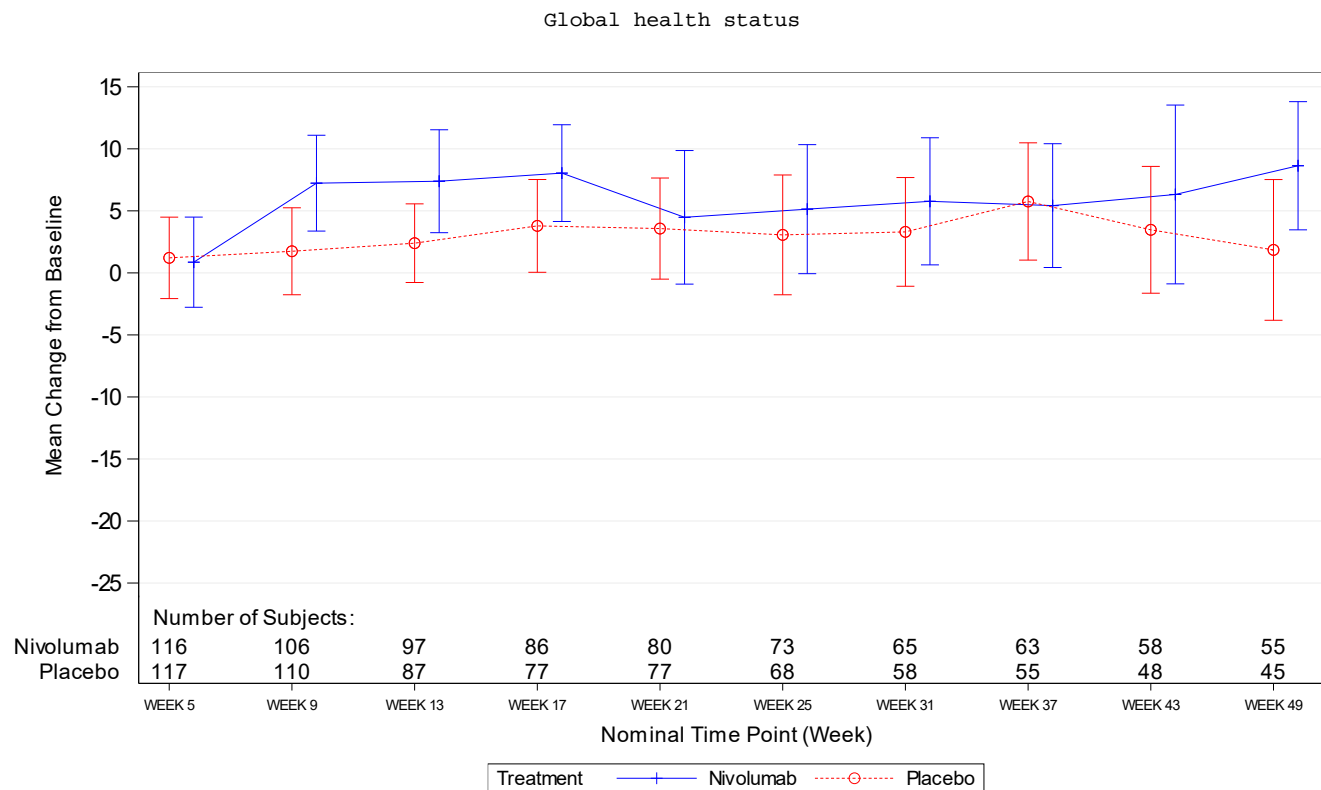
FEB2025 DBL

Program Path: /projects/bms214671/stats/market/ma274_202502/prog/figures

Program Name: rg-ef-lp-ebr45.sas

24JUL2025:04:04:24

Figure 12.1
Line plot of Mean Change from Baseline - EORTC QLQ-C30 - PROS



Error bars represent 95% CI for the mean change.

Only on-treatment visits with data for at least 10 patients across both treatment groups are plotted.

FEB2025 DBL

Program Path: /projects/bms214671/stats/market/ma274_202502/prog/figures

Program Name: rg-ef-lp-ebr45.sas

24JUL2025:04:04:24

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

4.3 Subgruppenanalysen

Table 4.1
Subgroup Analyses of EORTC QLQ-C30 Time to First Deterioration
PROS

Physical Functioning Scale (MID=10)

Subgroup	Placebo				Nivolumab				Nivolumab vs. Placebo	
	N	Subjects with Event n (%)	Censored subjects n (%)	KME [95%CI] (mon) (1)	N	Subjects with Event n (%)	Censored subjects n (%)	KME [95%CI] (mon) (1)	HR [95%CI] P-value (2)	Test for Interaction P-value (3) (4)
OVERALL	128	54 (42.2)	74 (57.8)	N.A. (9.20, N.A.)	123	48 (39.0)	75 (61.0)	16.43 (8.84, N.A.)	0.858 (0.581, 1.266) 0.4394	
PRIOR NEO-ADJUVANT CISPLATIN THERAPY										0.8949
YES	54	23 (42.6)	31 (57.4)	N.A. (6.87, N.A.)	49	19 (38.8)	30 (61.2)	N.A. (6.93, N.A.)	0.861 (0.468, 1.581) 0.6282	
NO	74	31 (41.9)	43 (58.1)	N.A. (7.49, N.A.)	74	29 (39.2)	45 (60.8)	16.43 (8.08, N.A.)	0.808 (0.484, 1.347) 0.4130	

FEB2025 DBL. HR = hazard ratio; KME=Kaplan-Meier estimate; N.M.E = Not meaningful estimate.

(1) KME of median time to event.

(2) Unstratified Cox proportional hazard model, with baseline PRO score as a covariate. HR is Nivolumab over Placebo.

(3) Unstratified Cox proportional hazard model with treatment, subgroup and treatment*subgroup

interaction to assess the significance of the interaction between treatment and the subgroup, with baseline PRO score as a covariate. (4) P-values <0.05 are indicated by 1 asterisk (indicates potential effect modification).

IUC = invasive urothelial carcinoma.

Program Path: /projects/bms214671/stats/market/ma274_202502/prog/tables

Program Name: rt-sy-tdd-eortc-comm-eb45.sas

16JUL2025:07:44:05

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

Table 4.1
Subgroup Analyses of EORTC QLQ-C30 Time to First Deterioration
PROS

Physical Functioning Scale (MID=10)

Subgroup	Placebo				Nivolumab				Nivolumab vs. Placebo	
	N	Subjects with Event n (%)	Censored subjects n (%)	KME [95%CI] (mon) (1)	N	Subjects with Event n (%)	Censored subjects n (%)	KME [95%CI] (mon) (1)	HR [95%CI] P-value (2)	Test for Interaction P-value (3) (4)
PRIOR CISPLATIN STATUS										0.9418
RECEIVED NEO-ADJUVANT	54	23 (42.6)	31 (57.4)	N.A. (6.87, N.A.)	49	19 (38.8)	30 (61.2)	N.A. (6.93, N.A.)	0.861 (0.468, 1.581)	
UNWILLING TO RECEIVE NEO-ADJUVANT	42	18 (42.9)	24 (57.1)	N.A. (7.03, N.A.)	46	18 (39.1)	28 (60.9)	16.43 (8.08, N.A.)	0.6282 (0.440, 1.658)	
NOT ELIGIBLE TO RECEIVE NEO-ADJUVANT	31	13 (41.9)	18 (58.1)	9.26 (2.83, N.A.)	23	10 (43.5)	13 (56.5)	11.07 (4.93, N.A.)	0.854 (0.324, 1.699)	
									0.6416 0.743 0.4810	

FEB2025 DBL. HR = hazard ratio; KME=Kaplan-Meier estimate; N.M.E = Not meaningful estimate.

(1) KME of median time to event.

(2) Unstratified Cox proportional hazard model, with baseline PRO score as a covariate. HR is Nivolumab over Placebo.

(3) Unstratified Cox proportional hazard model with treatment, subgroup and treatment*subgroup interaction to assess the significance of the interaction between treatment and the subgroup, with baseline PRO score as a covariate. (4) P-values <0.05 are indicated by 1 asterisk (indicates potential effect modification).

IUC = invasive urothelial carcinoma.

Program Path: /projects/bms214671/stats/market/ma274_202502/prog/tables

Program Name: rt-sy-tdd-eortc-comm-ebr45.sas

16JUL2025:07:44:05

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

Table 4.1
Subgroup Analyses of EORTC QLQ-C30 Time to First Deterioration
PROS

Physical Functioning Scale (MID=10)

Subgroup	Placebo				Nivolumab				Nivolumab vs. Placebo	
	N	Subjects with Event n (%)	Censored subjects n (%)	KME [95%CI] (mon) (1)	N	Subjects with Event n (%)	Censored subjects n (%)	KME [95%CI] (mon) (1)	HR [95%CI] P-value (2)	Test for Interaction P-value (3) (4)
USE OF ANY PRIOR NEO-ADJUVANT SYSTEMIC THERAPY										0.8120
YES	55	23 (41.8)	32 (58.2)	N.A. (6.87, N.A.)	53	19 (35.8)	34 (64.2)	N.A. (7.39, N.A.)	0.809 (0.440, 1.487) 0.4951	
NO	73	31 (42.5)	42 (57.5)	N.A. (7.49, N.A.)	70	29 (41.4)	41 (58.6)	16.43 (7.03, N.A.)	0.864 (0.518, 1.440) 0.5741	

FEB2025 DBL. HR = hazard ratio; KME=Kaplan-Meier estimate; N.M.E = Not meaningful estimate.

(1) KME of median time to event.

(2) Unstratified Cox proportional hazard model, with baseline PRO score as a covariate. HR is Nivolumab over Placebo.

(3) Unstratified Cox proportional hazard model with treatment, subgroup and treatment*subgroup

interaction to assess the significance of the interaction between treatment and the subgroup, with baseline PRO score as a covariate. (4) P-values <0.05 are indicated by 1 asterisk (indicates potential effect modification).

IUC = invasive urothelial carcinoma.

Program Path: /projects/bms214671/stats/market/ma274_202502/prog/tables

Program Name: rt-sy-tdd-eortc-comm-ebr45.sas

16JUL2025:07:44:05

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

Table 4.1
Subgroup Analyses of EORTC QLQ-C30 Time to First Deterioration
PROS

Physical Functioning Scale (MID=10)

Subgroup	Placebo				Nivolumab				Nivolumab vs. Placebo	
	N	Subjects with Event n (%)	Censored subjects n (%)	KME [95%CI] (mon) (1)	N	Subjects with Event n (%)	Censored subjects n (%)	KME [95%CI] (mon) (1)	HR [95%CI] P-value (2)	Test for Interaction P-value (3) (4)
PATHOLOGICAL LYMPH NODE STATUS										0.5332
N+	57	24 (42.1)	33 (57.9)	N.A. (4.40, N.A.)	51	18 (35.3)	33 (64.7)	N.A. (6.97, N.A.)	0.704 (0.382, 1.300) 0.2621	
NO/X WITH <10 NODES REMOVED	37	17 (45.9)	20 (54.1)	11.73 (4.73, N.A.)	35	14 (40.0)	21 (60.0)	N.A. (6.01, N.A.)	0.818 (0.402, 1.664) 0.5802	
NO WITH >= 10 NODES REMOVED	34	13 (38.2)	21 (61.8)	N.A. (9.20, N.A.)	37	16 (43.2)	21 (56.8)	15.64 (7.03, N.A.)	1.224 (0.584, 2.567) 0.5927	

FEB2025 DBL. HR = hazard ratio; KME=Kaplan-Meier estimate; N.M.E = Not meaningful estimate.

(1) KME of median time to event.

(2) Unstratified Cox proportional hazard model, with baseline PRO score as a covariate. HR is Nivolumab over Placebo.

(3) Unstratified Cox proportional hazard model with treatment, subgroup and treatment*subgroup interaction to assess the significance of the interaction between treatment and the subgroup, with baseline PRO score as a covariate. (4) P-values <0.05 are indicated by 1 asterisk (indicates potential effect modification).

IUC = invasive urothelial carcinoma.

Program Path: /projects/bms214671/stats/market/ma274_202502/prog/tables

Program Name: rt-sy-tdd-eortc-comm-ebr45.sas

16JUL2025:07:44:05

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

Table 4.1
Subgroup Analyses of EORTC QLQ-C30 Time to First Deterioration
PROS

Physical Functioning Scale (MID=10)

Subgroup	Placebo				Nivolumab				Nivolumab vs. Placebo	
	N	Subjects with Event n (%)	Censored subjects n (%)	KME [95%CI] (mon) (1)	N	Subjects with Event n (%)	Censored subjects n (%)	KME [95%CI] (mon) (1)	HR [95%CI] P-value (2)	Test for Interaction P-value (3) (4)
PATHOLOGICAL STATUS										0.3823
PT0-2	29	12 (41.4)	17 (58.6)	N.A. (4.67, N.A.)	21	5 (23.8)	16 (76.2)	N.A. (6.93, N.A.)	0.470 (0.164, 1.348)	
PT3	73	32 (43.8)	41 (56.2)	11.24 (7.03, N.A.)	78	33 (42.3)	45 (57.7)	16.43 (7.39, N.A.)	0.1601 0.844 (0.519, 1.374)	
PT4A	25	10 (40.0)	15 (60.0)	N.A. (4.40, N.A.)	21	10 (47.6)	11 (52.4)	8.38 (2.07, N.A.)	0.4956 1.192 (0.487, 2.917)	
									0.7009	

FEB2025 DBL. HR = hazard ratio; KME=Kaplan-Meier estimate; N.M.E = Not meaningful estimate.

(1) KME of median time to event.

(2) Unstratified Cox proportional hazard model, with baseline PRO score as a covariate. HR is Nivolumab over Placebo.

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IUC = invasive urothelial carcinoma.

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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

Table 4.1
Subgroup Analyses of EORTC QLQ-C30 Time to First Deterioration
PROS

Physical Functioning Scale (MID=10)

Subgroup	Placebo				Nivolumab				Nivolumab vs. Placebo	
	N	Subjects with Event n (%)	Censored subjects n (%)	KME [95%CI] (mon) (1)	N	Subjects with Event n (%)	Censored subjects n (%)	KME [95%CI] (mon) (1)	HR [95%CI] P-value (2)	Test for Interaction P-value (3) (4)
AGE CATEGORY I										
< 65	54	19 (35.2)	35 (64.8)	N.A. (11.04, N.A.)	57	20 (35.1)	37 (64.9)	N.A. (6.93, N.A.)	1.029 (0.548, 1.932) 0.9288	0.4913
>= 65	74	35 (47.3)	39 (52.7)	9.95 (4.93, N.A.)	66	28 (42.4)	38 (57.6)	15.64 (7.39, N.A.)	0.770 (0.468, 1.267) 0.3040	

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	N	Subjects with Event n (%)	Censored subjects n (%)	KME [95%CI] (mon) (1)	N	Subjects with Event n (%)	Censored subjects n (%)	KME [95%CI] (mon) (1)	HR [95%CI] P-value (2)	Test for Interaction P-value (3) (4)
AGE CATEGORY II										0.6969
< 65	54	19 (35.2)	35 (64.8)	N.A. (11.04, N.A.)	57	20 (35.1)	37 (64.9)	N.A. (6.93, N.A.)	1.029 (0.548, 1.932) 0.9288	
>= 65 AND < 75	54	25 (46.3)	29 (53.7)	10.61 (3.94, N.A.)	45	17 (37.8)	28 (62.2)	15.64 (7.39, N.A.)	0.696 (0.375, 1.292) 0.2512	
>= 75	20	10 (50.0)	10 (50.0)	9.26 (1.45, N.A.)	21	11 (52.4)	10 (47.6)	11.04 (4.50, N.A.)	0.886 (0.375, 2.094) 0.7828	

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REGION										0.5946
US	21	9 (42.9)	12 (57.1)	N.A. (4.73, N.A.)	14	2 (14.3)	12 (85.7)	N.A. (8.84, N.A.)	0.303 (0.065, 1.406) 0.1272	
EUROPE	62	29 (46.8)	33 (53.2)	11.24 (6.77, N.A.)	65	30 (46.2)	35 (53.8)	15.64 (6.60, N.A.)	0.935 (0.561, 1.558) 0.7960	
ASIA	27	9 (33.3)	18 (66.7)	N.A. (9.26, N.A.)	28	9 (32.1)	19 (67.9)	N.A. (6.44, N.A.)	0.905 (0.358, 2.283) 0.8321	
REST OF WORLD	18	7 (38.9)	11 (61.1)	N.A. (1.87, N.A.)	16	7 (43.8)	9 (56.3)	N.A. (2.33, N.A.)	1.023 (0.349, 2.994) 0.9672	

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Subgroup	Placebo				Nivolumab				Nivolumab vs. Placebo	
	N	Subjects with Event n (%)	Censored subjects n (%)	KME [95%CI] (mon) (1)	N	Subjects with Event n (%)	Censored subjects n (%)	KME [95%CI] (mon) (1)	HR [95%CI] P-value (2)	Test for Interaction P-value (3) (4)
GENDER										
MALE	101	43 (42.6)	58 (57.4)	N.A. (9.20, N.A.)	90	34 (37.8)	56 (62.2)	N.A. (8.38, N.A.)	0.812 (0.518, 1.274) 0.3656	0.6534
FEMALE	27	11 (40.7)	16 (59.3)	N.A. (2.79, N.A.)	33	14 (42.4)	19 (57.6)	11.04 (6.97, N.A.)	0.987 (0.443, 2.200) 0.9751	
RACE										
WHITE	96	44 (45.8)	52 (54.2)	11.24 (7.03, N.A.)	94	38 (40.4)	56 (59.6)	16.43 (8.08, N.A.)	0.807 (0.523, 1.246) 0.3326	0.7909
ASIAN	27	9 (33.3)	18 (66.7)	N.A. (9.26, N.A.)	28	9 (32.1)	19 (67.9)	N.A. (6.44, N.A.)	0.905 (0.358, 2.283) 0.8321	

FEB2025 DBL. HR = hazard ratio; KME=Kaplan-Meier estimate; N.M.E = Not meaningful estimate.

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Subgroup	Placebo				Nivolumab				Nivolumab vs. Placebo	
	N	Subjects with Event n (%)	Censored subjects n (%)	KME [95%CI] (mon) (1)	N	Subjects with Event n (%)	Censored subjects n (%)	KME [95%CI] (mon) (1)	HR [95%CI] P-value (2)	Test for Interaction P-value (3) (4)
BASELINE ECOG STATUS										0.1556
0	80	33 (41.3)	47 (58.8)	N.A. (9.00, N.A.)	76	33 (43.4)	43 (56.6)	15.64 (7.39, N.A.)	1.082 (0.666, 1.756)	
1	44	20 (45.5)	24 (54.5)	N.A. (2.50, N.A.)	45	14 (31.1)	31 (68.9)	N.A. (11.04, N.A.)	0.7512 0.595 (0.300, 1.179)	
SMOKING STATUS										0.3055
NEVER SMOKED	36	11 (30.6)	25 (69.4)	N.A. (9.95, N.A.)	36	13 (36.1)	23 (63.9)	15.64 (8.84, N.A.)	1.083 (0.471, 2.491)	
CURRENT/FORMER	91	42 (46.2)	49 (53.8)	11.73 (6.77, N.A.)	86	35 (40.7)	51 (59.3)	N.A. (7.03, N.A.)	0.8516 0.767 (0.490, 1.202)	
									0.2478	

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Subgroup	Placebo				Nivolumab				Nivolumab vs. Placebo	
	N	Subjects with Event n (%)	Censored subjects n (%)	KME [95%CI] (mon) (1)	N	Subjects with Event n (%)	Censored subjects n (%)	KME [95%CI] (mon) (1)	HR [95%CI] P-value (2)	Test for Interaction P-value (3) (4)
BASELINE HEMOGLOBIN										0.3861
<10 G/DL	13	5 (38.5)	8 (61.5)	N.A. (0.99, N.A.)	6	4 (66.7)	2 (33.3)	8.84 (6.60, N.A.)	1.737 (0.460, 6.555)	
>=10 G/DL	115	49 (42.6)	66 (57.4)	N.A. (9.00, N.A.)	117	44 (37.6)	73 (62.4)	16.43 (11.07, N.A.)	0.4150 0.820 (0.546, 1.232) 0.3394	
BASELINE CREATININE CLEARANCE										0.8002
<60 ML/MIN	57	24 (42.1)	33 (57.9)	N.A. (7.49, N.A.)	47	21 (44.7)	26 (55.3)	16.43 (6.47, N.A.)	0.927 (0.515, 1.668) 0.7992	
>=60 ML/MIN	71	30 (42.3)	41 (57.7)	N.A. (6.87, N.A.)	75	27 (36.0)	48 (64.0)	N.A. (8.84, N.A.)	0.829 (0.493, 1.395) 0.4804	

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	N	Subjects with Event n (%)	Censored subjects n (%)	KME [95%CI] (mon) (1)	N	Subjects with Event n (%)	Censored subjects n (%)	KME [95%CI] (mon) (1)	HR [95%CI] P-value (2)	Test for Interaction P-value (3) (4)
TIME FROM IUC SURGERY TO RANDOMIZATION (DAYS)										0.4185
>30-60	28	7 (25.0)	21 (75.0)	N.A. (9.00, N.A.)	30	10 (33.3)	20 (66.7)	N.A. (6.01, N.A.)	1.286 (0.488, 3.386)	
>60-90	57	27 (47.4)	30 (52.6)	11.24 (4.93, N.A.)	51	24 (47.1)	27 (52.9)	8.84 (6.47, N.A.)	0.6110 0.935 (0.539, 1.622)	
>90-120	38	20 (52.6)	18 (47.4)	9.95 (3.71, N.A.)	40	14 (35.0)	26 (65.0)	N.A. (11.04, N.A.)	0.574 (0.288, 1.141)	

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INITIAL TUMOR ORIGIN										0.2928
URINARY BLADDER	104	42 (40.4)	62 (59.6)	N.A. (9.20, N.A.)	102	42 (41.2)	60 (58.8)	N.A. (7.03, N.A.)	0.994 (0.648, 1.526)	
RENAL PELVIS	13	6 (46.2)	7 (53.8)	11.04 (0.99, N.A.)	15	4 (26.7)	11 (73.3)	N.A. (6.44, N.A.)	0.9798 0.331 (0.090, 1.213)	
URETER	11	6 (54.5)	5 (45.5)	7.03 (0.99, N.A.)	6	2 (33.3)	4 (66.7)	16.43 (0.95, N.A.)	0.0950 0.262 (0.030, 2.257)	

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MINOR HISTOLOGICAL VARIANTS										0.3100
PRESENCE	54	21 (38.9)	33 (61.1)	N.A. (9.00, N.A.)	53	22 (41.5)	31 (58.5)	15.64 (6.97, N.A.)	1.091 (0.598, 1.990) 0.7763	
ABSENCE	74	33 (44.6)	41 (55.4)	11.04 (6.77, N.A.)	70	26 (37.1)	44 (62.9)	16.43 (7.39, N.A.)	0.720 (0.430, 1.205) 0.2108	

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PROS

Role Functioning Scale (MID=10)

Subgroup	Placebo				Nivolumab				Nivolumab vs. Placebo	
	N	Subjects with Event n (%)	Censored subjects n (%)	KME [95%CI] (mon) (1)	N	Subjects with Event n (%)	Censored subjects n (%)	KME [95%CI] (mon) (1)	HR [95%CI] P-value (2)	Test for Interaction P-value (3) (4)
OVERALL	128	70 (54.7)	58 (45.3)	5.55 (4.04, 11.73)	123	68 (55.3)	55 (44.7)	8.31 (4.63, 12.75)	0.950 (0.680, 1.328) 0.7647	
PRIOR NEO-ADJUVANT CISPLATIN THERAPY										0.2678
YES	54	27 (50.0)	27 (50.0)	10.32 (4.63, N.A.)	49	29 (59.2)	20 (40.8)	7.39 (3.58, N.A.)	1.196 (0.706, 2.026) 0.5064	
NO	74	43 (58.1)	31 (41.9)	4.67 (2.73, 7.16)	74	39 (52.7)	35 (47.3)	8.38 (3.98, N.A.)	0.807 (0.523, 1.247) 0.3343	

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	N	Subjects with Event n (%)	Censored subjects n (%)	KME [95%CI] (mon) (1)	N	Subjects with Event n (%)	Censored subjects n (%)	KME [95%CI] (mon) (1)	HR [95%CI] P-value (2)	Test for Interaction P-value (3) (4)
PRIOR CISPLATIN STATUS										0.2497
RECEIVED NEO-ADJUVANT	54	27 (50.0)	27 (50.0)	10.32 (4.63, N.A.)	49	29 (59.2)	20 (40.8)	7.39 (3.58, N.A.)	1.196 (0.706, 2.026)	
UNWILLING TO RECEIVE NEO-ADJUVANT	42	27 (64.3)	15 (35.7)	4.63 (1.91, 11.73)	46	22 (47.8)	24 (52.2)	11.56 (3.78, N.A.)	0.651 (0.370, 1.145)	
NOT ELIGIBLE TO RECEIVE NEO-ADJUVANT	31	16 (51.6)	15 (48.4)	5.59 (1.87, N.A.)	23	16 (69.6)	7 (30.4)	4.63 (1.08, 11.07)	1.184 (0.586, 2.391)	

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	N	Subjects with Event n (%)	Censored subjects n (%)	KME [95%CI] (mon) (1)	N	Subjects with Event n (%)	Censored subjects n (%)	KME [95%CI] (mon) (1)	HR [95%CI] P-value (2)	Test for Interaction P-value (3) (4)
USE OF ANY PRIOR NEO-ADJUVANT SYSTEMIC THERAPY										0.2491
YES	55	27 (49.1)	28 (50.9)	10.32 (4.63, N.A.)	53	31 (58.5)	22 (41.5)	7.39 (3.75, 12.88)	1.194 (0.710, 2.007) 0.5031	
NO	73	43 (58.9)	30 (41.1)	4.63 (2.73, 7.16)	70	37 (52.9)	33 (47.1)	8.38 (3.78, N.A.)	0.800 (0.515, 1.243) 0.3202	

FEB2025 DBL. HR = hazard ratio; KME=Kaplan-Meier estimate; N.M.E = Not meaningful estimate.

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IUC = invasive urothelial carcinoma.

Program Path: /projects/bms214671/stats/market/ma274_202502/prog/tables

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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

Table 4.1
Subgroup Analyses of EORTC QLQ-C30 Time to First Deterioration
PROS

Role Functioning Scale (MID=10)

Subgroup	Placebo				Nivolumab				Nivolumab vs. Placebo	
	N	Subjects with Event n (%)	Censored subjects n (%)	KME [95%CI] (mon) (1)	N	Subjects with Event n (%)	Censored subjects n (%)	KME [95%CI] (mon) (1)	HR [95%CI] P-value (2)	Test for Interaction P-value (3) (4)
PATHOLOGICAL LYMPH NODE STATUS										0.7430
N+	57	31 (54.4)	26 (45.6)	5.59 (3.38, 15.80)	51	26 (51.0)	25 (49.0)	8.31 (4.04, N.A.)	0.801 (0.471, 1.363) 0.4139	
NO/X WITH <10 NODES REMOVED	37	21 (56.8)	16 (43.2)	4.73 (1.91, N.A.)	35	21 (60.0)	14 (40.0)	10.74 (3.09, 13.14)	0.904 (0.493, 1.658) 0.7441	
NO WITH >= 10 NODES REMOVED	34	18 (52.9)	16 (47.1)	4.76 (2.76, N.A.)	37	21 (56.8)	16 (43.2)	5.75 (2.33, N.A.)	1.136 (0.605, 2.133) 0.6918	

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PATHOLOGICAL STATUS										0.2693
PT0-2	29	20 (69.0)	9 (31.0)	5.45 (1.87, 10.32)	21	12 (57.1)	9 (42.9)	6.93 (3.78, N.A.)	0.725 (0.352, 1.490)	
PT3	73	38 (52.1)	35 (47.9)	5.19 (2.76, N.A.)	78	43 (55.1)	35 (44.9)	11.07 (3.98, 13.14)	0.816 (0.526, 1.265)	
PT4A	25	12 (48.0)	13 (52.0)	15.80 (3.02, N.A.)	21	12 (57.1)	9 (42.9)	7.03 (0.99, N.A.)	1.755 (0.768, 4.007)	

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	N	Subjects with Event n (%)	Censored subjects n (%)	KME [95%CI] (mon) (1)	N	Subjects with Event n (%)	Censored subjects n (%)	KME [95%CI] (mon) (1)	HR [95%CI] P-value (2)	Test for Interaction P-value (3) (4)
AGE CATEGORY I										0.0752
< 65	54	26 (48.1)	28 (51.9)	15.80 (3.91, N.A.)	57	34 (59.6)	23 (40.4)	5.75 (2.10, 16.20)	1.357 (0.812, 2.266) 0.2438	
>= 65	74	44 (59.5)	30 (40.5)	4.63 (2.83, 6.74)	66	34 (51.5)	32 (48.5)	11.07 (4.63, N.A.)	0.707 (0.451, 1.108) 0.1300	

FEB2025 DBL. HR = hazard ratio; KME=Kaplan-Meier estimate; N.M.E = Not meaningful estimate.

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Role Functioning Scale (MID=10)

Subgroup	Placebo				Nivolumab				Nivolumab vs. Placebo	
	N	Subjects with Event n (%)	Censored subjects n (%)	KME [95%CI] (mon) (1)	N	Subjects with Event n (%)	Censored subjects n (%)	KME [95%CI] (mon) (1)	HR [95%CI] P-value (2)	Test for Interaction P-value (3) (4)
AGE CATEGORY II										0.1917
< 65	54	26 (48.1)	28 (51.9)	15.80 (3.91, N.A.)	57	34 (59.6)	23 (40.4)	5.75 (2.10, 16.20)	1.357 (0.812, 2.266) 0.2438	
>= 65 AND < 75	54	31 (57.4)	23 (42.6)	4.63 (2.76, N.A.)	45	21 (46.7)	24 (53.3)	12.75 (4.63, N.A.)	0.682 (0.391, 1.191) 0.1782	
>= 75	20	13 (65.0)	7 (35.0)	5.82 (1.87, 11.73)	21	13 (61.9)	8 (38.1)	6.97 (3.75, 13.14)	0.658 (0.301, 1.442) 0.2958	

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Subgroup	Placebo				Nivolumab				Nivolumab vs. Placebo	
	N	Subjects with Event n (%)	Censored subjects n (%)	KME [95%CI] (mon) (1)	N	Subjects with Event n (%)	Censored subjects n (%)	KME [95%CI] (mon) (1)	HR [95%CI] P-value (2)	Test for Interaction P-value (3) (4)
REGION										0.8815
US	21	12 (57.1)	9 (42.9)	5.59 (1.87, N.A.)	14	8 (57.1)	6 (42.9)	4.50 (1.05, N.A.)	1.023 (0.415, 2.524) 0.9603	
EUROPE	62	35 (56.5)	27 (43.5)	4.67 (2.73, N.A.)	65	36 (55.4)	29 (44.6)	8.38 (5.09, N.A.)	0.857 (0.537, 1.369) 0.5180	
ASIA	27	15 (55.6)	12 (44.4)	6.74 (1.91, N.A.)	28	14 (50.0)	14 (50.0)	4.63 (3.75, N.A.)	0.953 (0.459, 1.981) 0.8979	
REST OF WORLD	18	8 (44.4)	10 (55.6)	10.32 (1.97, N.A.)	16	10 (62.5)	6 (37.5)	5.01 (1.91, N.A.)	1.413 (0.538, 3.707) 0.4827	

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	N	Subjects with Event n (%)	Censored subjects n (%)	KME [95%CI] (mon) (1)	N	Subjects with Event n (%)	Censored subjects n (%)	KME [95%CI] (mon) (1)	HR [95%CI] P-value (2)	Test for Interaction P-value (3) (4)
GENDER										0.4082
MALE	101	52 (51.5)	49 (48.5)	5.65 (4.40, N.A.)	90	51 (56.7)	39 (43.3)	8.31 (4.04, N.A.)	1.032 (0.700, 1.521) 0.8731	
FEMALE	27	18 (66.7)	9 (33.3)	4.63 (1.08, 7.16)	33	17 (51.5)	16 (48.5)	7.39 (1.94, 12.88)	0.748 (0.385, 1.455) 0.3927	
RACE										0.9608
WHITE	96	53 (55.2)	43 (44.8)	4.76 (3.02, 11.73)	94	53 (56.4)	41 (43.6)	8.31 (4.63, 13.14)	0.927 (0.632, 1.360) 0.6994	
ASIAN	27	15 (55.6)	12 (44.4)	6.74 (1.91, N.A.)	28	14 (50.0)	14 (50.0)	4.63 (3.75, N.A.)	0.953 (0.459, 1.981) 0.8979	

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	N	Subjects with Event n (%)	Censored subjects n (%)	KME [95%CI] (mon) (1)	N	Subjects with Event n (%)	Censored subjects n (%)	KME [95%CI] (mon) (1)	HR [95%CI] P-value (2)	Test for Interaction P-value (3) (4)
BASELINE ECOG STATUS										0.3920
0	80	40 (50.0)	40 (50.0)	6.74 (4.67, N.A.)	76	42 (55.3)	34 (44.7)	8.31 (4.50, N.A.)	1.067 (0.691, 1.647) 0.7714	
1	44	28 (63.6)	16 (36.4)	4.63 (2.50, 7.16)	45	25 (55.6)	20 (44.4)	5.09 (3.58, N.A.)	0.795 (0.460, 1.374) 0.4121	
SMOKING STATUS										0.6386
NEVER SMOKED	36	18 (50.0)	18 (50.0)	7.16 (2.50, N.A.)	36	19 (52.8)	17 (47.2)	12.65 (3.75, 16.20)	1.059 (0.554, 2.023) 0.8624	
CURRENT/FORMER	91	51 (56.0)	40 (44.0)	4.73 (3.38, 15.80)	86	48 (55.8)	38 (44.2)	7.39 (4.04, 13.14)	0.894 (0.602, 1.328) 0.5786	

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BASELINE HEMOGLOBIN										0.9177
<10 G/DL	13	7 (53.8)	6 (46.2)	5.78 (0.99, N.A.)	6	3 (50.0)	3 (50.0)	12.65 (1.02, N.A.)	1.437 (0.301, 6.852)	
>=10 G/DL	115	63 (54.8)	52 (45.2)	5.45 (4.04, 11.73)	117	65 (55.6)	52 (44.4)	7.39 (4.50, 12.88)	0.6495 0.956 (0.676, 1.353) 0.8004	
BASELINE CREATININE CLEARANCE										0.3590
<60 ML/MIN	57	31 (54.4)	26 (45.6)	5.78 (2.04, N.A.)	47	29 (61.7)	18 (38.3)	7.39 (3.09, 12.65)	1.148 (0.688, 1.917) 0.5971	
>=60 ML/MIN	71	39 (54.9)	32 (45.1)	5.45 (4.04, 15.80)	75	39 (52.0)	36 (48.0)	8.31 (3.98, N.A.)	0.862 (0.551, 1.347) 0.5138	

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TIME FROM IUC SURGERY TO RANDOMIZATION (DAYS)										0.1697
>30-60	28	13 (46.4)	15 (53.6)	10.32 (1.87, N.A.)	30	16 (53.3)	14 (46.7)	11.56 (3.98, N.A.)	1.089 (0.516, 2.296)	
>60-90	57	30 (52.6)	27 (47.4)	5.82 (3.91, N.A.)	51	30 (58.8)	21 (41.2)	6.93 (2.83, 10.74)	0.8233 1.209 (0.727, 2.011)	
>90-120	38	25 (65.8)	13 (34.2)	3.71 (1.91, 11.73)	40	21 (52.5)	19 (47.5)	11.56 (3.09, N.A.)	0.4651 0.569 (0.312, 1.038)	

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INITIAL TUMOR ORIGIN										0.6308
URINARY BLADDER	104	56 (53.8)	48 (46.2)	5.55 (3.91, 15.80)	102	57 (55.9)	45 (44.1)	7.03 (3.98, 12.88)	0.995 (0.688, 1.440)	
RENAL PELVIS	13	7 (53.8)	6 (46.2)	5.82 (0.99, N.A.)	15	9 (60.0)	6 (40.0)	12.65 (3.75, 13.14)	0.9809 1.024 (0.372, 2.819)	
URETER	11	7 (63.6)	4 (36.4)	4.67 (0.95, N.A.)	6	2 (33.3)	4 (66.7)	N.A. (0.95, N.A.)	0.9635 0.517 (0.104, 2.586)	

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	N	Subjects with Event n (%)	Censored subjects n (%)	KME [95%CI] (mon) (1)	N	Subjects with Event n (%)	Censored subjects n (%)	KME [95%CI] (mon) (1)	HR [95%CI] P-value (2)	Test for Interaction P-value (3) (4)
MINOR HISTOLOGICAL VARIANTS										0.8888
PRESENCE	54	29 (53.7)	25 (46.3)	5.45 (2.83, N.A.)	53	30 (56.6)	23 (43.4)	8.31 (3.58, 13.14)	0.889 (0.531, 1.488) 0.6536	
ABSENCE	74	41 (55.4)	33 (44.6)	5.55 (3.02, 15.80)	70	38 (54.3)	32 (45.7)	7.39 (4.63, N.A.)	0.948 (0.608, 1.478) 0.8136	

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Table 4.1
Subgroup Analyses of EORTC QLQ-C30 Time to First Deterioration
PROS

Emotional Functioning Scale (MID=10)

Subgroup	Placebo				Nivolumab				Nivolumab vs. Placebo	
	N	Subjects with Event n (%)	Censored subjects n (%)	KME [95%CI] (mon) (1)	N	Subjects with Event n (%)	Censored subjects n (%)	KME [95%CI] (mon) (1)	HR [95%CI] P-value (2)	Test for Interaction P-value (3) (4)
OVERALL	127	55 (43.3)	72 (56.7)	12.91 (7.16, N.A.)	123	46 (37.4)	77 (62.6)	N.A. (15.24, N.A.)	0.752 (0.508, 1.115) 0.1560	
PRIOR NEO-ADJUVANT CISPLATIN THERAPY										0.4097
YES	53	22 (41.5)	31 (58.5)	N.A. (5.32, N.A.)	49	20 (40.8)	29 (59.2)	15.64 (7.39, N.A.)	0.931 (0.507, 1.709) 0.8164	
NO	74	33 (44.6)	41 (55.4)	11.07 (5.55, N.A.)	74	26 (35.1)	48 (64.9)	N.A. (11.07, N.A.)	0.655 (0.389, 1.103) 0.1113	

FEB2025 DBL. HR = hazard ratio; KME=Kaplan-Meier estimate; N.M.E = Not meaningful estimate.

(1) KME of median time to event.

(2) Unstratified Cox proportional hazard model, with baseline PRO score as a covariate. HR is Nivolumab over Placebo.

(3) Unstratified Cox proportional hazard model with treatment, subgroup and treatment*subgroup

interaction to assess the significance of the interaction between treatment and the subgroup, with baseline PRO score as a covariate. (4) P-values <0.05 are indicated by 1 asterisk (indicates potential effect modification).

IUC = invasive urothelial carcinoma.

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Program Name: rt-sy-tdd-eortc-comm-ebr45.sas

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Subgroup	Placebo				Nivolumab				Nivolumab vs. Placebo	
	N	Subjects with Event n (%)	Censored subjects n (%)	KME [95%CI] (mon) (1)	N	Subjects with Event n (%)	Censored subjects n (%)	KME [95%CI] (mon) (1)	HR [95%CI] P-value (2)	Test for Interaction P-value (3) (4)
PRIOR CISPLATIN STATUS										0.5392
RECEIVED NEO-ADJUVANT	53	22 (41.5)	31 (58.5)	N.A. (5.32, N.A.)	49	20 (40.8)	29 (59.2)	15.64 (7.39, N.A.)	0.931 (0.507, 1.709)	
UNWILLING TO RECEIVE NEO-ADJUVANT	42	22 (52.4)	20 (47.6)	9.40 (4.07, N.A.)	46	16 (34.8)	30 (65.2)	N.A. (9.66, N.A.)	0.602 (0.315, 1.151)	
NOT ELIGIBLE TO RECEIVE NEO-ADJUVANT	31	10 (32.3)	21 (67.7)	12.91 (7.16, N.A.)	23	9 (39.1)	14 (60.9)	N.A. (4.63, N.A.)	0.960 (0.382, 2.410)	

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	N	Subjects with Event n (%)	Censored subjects n (%)	KME [95%CI] (mon) (1)	N	Subjects with Event n (%)	Censored subjects n (%)	KME [95%CI] (mon) (1)	HR [95%CI] P-value (2)	Test for Interaction P-value (3) (4)
USE OF ANY PRIOR NEO-ADJUVANT SYSTEMIC THERAPY										0.4735
YES	54	22 (40.7)	32 (59.3)	N.A. (5.32, N.A.)	53	21 (39.6)	32 (60.4)	15.64 (8.61, N.A.)	0.909 (0.498, 1.657) 0.7546	
NO	73	33 (45.2)	40 (54.8)	10.51 (5.52, N.A.)	70	25 (35.7)	45 (64.3)	N.A. (10.35, N.A.)	0.677 (0.400, 1.144) 0.1453	

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	N	Subjects with Event n (%)	Censored subjects n (%)	KME [95%CI] (mon) (1)	N	Subjects with Event n (%)	Censored subjects n (%)	KME [95%CI] (mon) (1)	HR [95%CI] P-value (2)	Test for Interaction P-value (3) (4)
PATHOLOGICAL LYMPH NODE STATUS										0.5896
N+	56	21 (37.5)	35 (62.5)	13.14 (7.16, N.A.)	51	19 (37.3)	32 (62.7)	15.80 (7.39, N.A.)	0.916 (0.486, 1.728)	
N0/X WITH <10 NODES REMOVED	37	19 (51.4)	18 (48.6)	5.55 (2.99, N.A.)	35	12 (34.3)	23 (65.7)	N.A. (9.66, N.A.)	0.7867 (0.280, 1.193)	
N0 WITH >= 10 NODES REMOVED	34	15 (44.1)	19 (55.9)	12.91 (6.37, N.A.)	37	15 (40.5)	22 (59.5)	15.64 (8.61, N.A.)	0.578 (0.1382, 0.866)	
									0.6988	

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Subgroup	Placebo				Nivolumab				Nivolumab vs. Placebo	
	N	Subjects with Event n (%)	Censored subjects n (%)	KME [95%CI] (mon) (1)	N	Subjects with Event n (%)	Censored subjects n (%)	KME [95%CI] (mon) (1)	HR [95%CI] P-value (2)	Test for Interaction P-value (3) (4)
PATHOLOGICAL STATUS										0.9323
PT0-2	29	12 (41.4)	17 (58.6)	N.A. (2.96, N.A.)	21	9 (42.9)	12 (57.1)	N.A. (4.17, N.A.)	1.020 (0.429, 2.428) 0.9635	
PT3	73	28 (38.4)	45 (61.6)	N.A. (9.20, N.A.)	78	27 (34.6)	51 (65.4)	N.A. (13.14, N.A.)	0.791 (0.465, 1.345) 0.3862	
PT4A	25	15 (60.0)	10 (40.0)	7.16 (2.92, N.A.)	21	10 (47.6)	11 (52.4)	15.52 (1.87, N.A.)	0.719 (0.314, 1.644) 0.4345	

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Subgroup	Placebo				Nivolumab				Nivolumab vs. Placebo	
	N	Subjects with Event n (%)	Censored subjects n (%)	KME [95%CI] (mon) (1)	N	Subjects with Event n (%)	Censored subjects n (%)	KME [95%CI] (mon) (1)	HR [95%CI] P-value (2)	Test for Interaction P-value (3) (4)
AGE CATEGORY I										
< 65	53	26 (49.1)	27 (50.9)	10.35 (4.07, N.A.)	57	26 (45.6)	31 (54.4)	N.A. (3.98, N.A.)	0.973 (0.562, 1.684) 0.9211	0.3550
>= 65	74	29 (39.2)	45 (60.8)	12.91 (7.16, N.A.)	66	20 (30.3)	46 (69.7)	N.A. (15.64, N.A.)	0.648 (0.365, 1.151) 0.1390	

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(3) Unstratified Cox proportional hazard model with treatment, subgroup and treatment*subgroup interaction to assess the significance of the interaction between treatment and the subgroup, with baseline PRO score as a covariate. (4) P-values <0.05 are indicated by 1 asterisk (indicates potential effect modification).

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Subgroup	Placebo				Nivolumab				Nivolumab vs. Placebo	
	N	Subjects with Event n (%)	Censored subjects n (%)	KME [95%CI] (mon) (1)	N	Subjects with Event n (%)	Censored subjects n (%)	KME [95%CI] (mon) (1)	HR [95%CI] P-value (2)	Test for Interaction P-value (3) (4)
AGE CATEGORY II										0.2973
< 65	53	26 (49.1)	27 (50.9)	10.35 (4.07, N.A.)	57	26 (45.6)	31 (54.4)	N.A. (3.98, N.A.)	0.973 (0.562, 1.684) 0.9211	
>= 65 AND < 75	54	21 (38.9)	33 (61.1)	12.91 (6.37, N.A.)	45	10 (22.2)	35 (77.8)	N.A. (15.64, N.A.)	0.484 (0.226, 1.034) 0.0609	
>= 75	20	8 (40.0)	12 (60.0)	N.A. (2.73, N.A.)	21	10 (47.6)	11 (52.4)	11.07 (4.63, N.A.)	0.883 (0.338, 2.307) 0.8002	

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	N	Subjects with Event n (%)	Censored subjects n (%)	KME [95%CI] (mon) (1)	N	Subjects with Event n (%)	Censored subjects n (%)	KME [95%CI] (mon) (1)	HR [95%CI] P-value (2)	Test for Interaction P-value (3) (4)
REGION										0.6546
US	21	8 (38.1)	13 (61.9)	N.A. (2.89, N.A.)	14	6 (42.9)	8 (57.1)	8.61 (1.94, N.A.)	1.212 (0.418, 3.511) 0.7229	
EUROPE	61	28 (45.9)	33 (54.1)	12.91 (4.27, N.A.)	65	24 (36.9)	41 (63.1)	N.A. (13.14, N.A.)	0.694 (0.402, 1.200) 0.1914	
ASIA	27	11 (40.7)	16 (59.3)	N.A. (3.71, N.A.)	28	8 (28.6)	20 (71.4)	N.A. (9.66, N.A.)	0.595 (0.239, 1.486) 0.2665	
REST OF WORLD	18	8 (44.4)	10 (55.6)	10.35 (2.92, N.A.)	16	8 (50.0)	8 (50.0)	15.80 (1.94, N.A.)	1.009 (0.362, 2.809) 0.9868	

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GENDER										
MALE	100	42 (42.0)	58 (58.0)	12.91 (9.20, N.A.)	90	31 (34.4)	59 (65.6)	N.A. (15.80, N.A.)	0.687 (0.430, 1.097) 0.1156	0.5465
FEMALE	27	13 (48.1)	14 (51.9)	13.14 (2.83, N.A.)	33	15 (45.5)	18 (54.5)	15.24 (4.73, N.A.)	0.892 (0.423, 1.879) 0.7628	
RACE										
WHITE	95	42 (44.2)	53 (55.8)	12.91 (6.97, N.A.)	94	37 (39.4)	57 (60.6)	15.80 (13.14, N.A.)	0.787 (0.505, 1.227) 0.2903	0.5609
ASIAN	27	11 (40.7)	16 (59.3)	N.A. (3.71, N.A.)	28	8 (28.6)	20 (71.4)	N.A. (9.66, N.A.)	0.595 (0.239, 1.486) 0.2665	

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BASELINE ECOG STATUS										0.8818
0	79	34 (43.0)	45 (57.0)	12.91 (5.55, N.A.)	76	29 (38.2)	47 (61.8)	15.80 (13.14, N.A.)	0.766 (0.466, 1.259) 0.2929	
1	44	19 (43.2)	25 (56.8)	13.14 (4.70, N.A.)	45	17 (37.8)	28 (62.2)	N.A. (8.05, N.A.)	0.840 (0.436, 1.620) 0.6026	
SMOKING STATUS										0.9701
NEVER SMOKED	36	15 (41.7)	21 (58.3)	N.A. (3.25, N.A.)	36	12 (33.3)	24 (66.7)	N.A. (9.66, N.A.)	0.735 (0.342, 1.579) 0.4296	
CURRENT/FORMER	90	40 (44.4)	50 (55.6)	11.07 (6.37, N.A.)	86	33 (38.4)	53 (61.6)	N.A. (13.14, N.A.)	0.713 (0.448, 1.133) 0.1525	

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BASELINE HEMOGLOBIN										0.4540
<10 G/DL	13	5 (38.5)	8 (61.5)	N.A. (1.91, N.A.)	6	3 (50.0)	3 (50.0)	9.66 (1.02, N.A.)	1.708 (0.380, 7.678)	
>=10 G/DL	114	50 (43.9)	64 (56.1)	12.91 (6.97, N.A.)	117	43 (36.8)	74 (63.2)	N.A. (15.24, N.A.)	0.4850 0.723 (0.480, 1.089)	
BASELINE CREATININE CLEARANCE										0.3162
<60 ML/MIN	57	23 (40.4)	34 (59.6)	N.A. (6.97, N.A.)	47	20 (42.6)	27 (57.4)	15.80 (6.97, N.A.)	1.023 (0.560, 1.868)	
>=60 ML/MIN	70	32 (45.7)	38 (54.3)	11.07 (4.73, N.A.)	75	26 (34.7)	49 (65.3)	N.A. (15.24, N.A.)	0.9421 0.650 (0.386, 1.094)	

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	N	Subjects with Event n (%)	Censored subjects n (%)	KME [95%CI] (mon) (1)	N	Subjects with Event n (%)	Censored subjects n (%)	KME [95%CI] (mon) (1)	HR [95%CI] P-value (2)	Test for Interaction P-value (3) (4)
TIME FROM IUC SURGERY TO RANDOMIZATION (DAYS)										0.1543
>30-60	28	16 (57.1)	12 (42.9)	4.73 (2.96, N.A.)	30	9 (30.0)	21 (70.0)	N.A. (8.05, N.A.)	0.409 (0.180, 0.931)	
>60-90	57	24 (42.1)	33 (57.9)	13.14 (6.37, N.A.)	51	19 (37.3)	32 (62.7)	N.A. (9.95, N.A.)	0.0330 0.812 (0.443, 1.486)	
>90-120	37	15 (40.5)	22 (59.5)	N.A. (4.24, N.A.)	40	18 (45.0)	22 (55.0)	15.64 (6.97, N.A.)	1.105 (0.557, 2.196)	

FEB2025 DBL. HR = hazard ratio; KME=Kaplan-Meier estimate; N.M.E = Not meaningful estimate.

(1) KME of median time to event.

(2) Unstratified Cox proportional hazard model, with baseline PRO score as a covariate. HR is Nivolumab over Placebo.

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interaction to assess the significance of the interaction between treatment and the subgroup, with baseline PRO score as a covariate. (4) P-values <0.05 are indicated by 1 asterisk (indicates potential effect modification).

IUC = invasive urothelial carcinoma.

Program Path: /projects/bms214671/stats/market/ma274_202502/prog/tables

Program Name: rt-sy-tdd-eortc-comm-eb45.sas

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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

Table 4.1
Subgroup Analyses of EORTC QLQ-C30 Time to First Deterioration
PROS

Emotional Functioning Scale (MID=10)

Subgroup	Placebo				Nivolumab				Nivolumab vs. Placebo	
	N	Subjects with Event n (%)	Censored subjects n (%)	KME [95%CI] (mon) (1)	N	Subjects with Event n (%)	Censored subjects n (%)	KME [95%CI] (mon) (1)	HR [95%CI] P-value (2)	Test for Interaction P-value (3) (4)
INITIAL TUMOR ORIGIN										0.9212
URINARY BLADDER	103	45 (43.7)	58 (56.3)	12.91 (9.20, N.A.)	102	39 (38.2)	63 (61.8)	N.A. (13.14, N.A.)	0.791 (0.515, 1.216)	
RENAL PELVIS	13	5 (38.5)	8 (61.5)	N.A. (1.91, N.A.)	15	5 (33.3)	10 (66.7)	N.A. (8.05, N.A.)	0.2861 0.591 (0.162, 2.147)	
URETER	11	5 (45.5)	6 (54.5)	N.A. (2.96, N.A.)	6	2 (33.3)	4 (66.7)	15.80 (0.95, N.A.)	0.4239 0.416 (0.048, 3.582)	

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	N	Subjects with Event n (%)	Censored subjects n (%)	KME [95%CI] (mon) (1)	N	Subjects with Event n (%)	Censored subjects n (%)	KME [95%CI] (mon) (1)	HR [95%CI] P-value (2)	Test for Interaction P-value (3) (4)
MINOR HISTOLOGICAL VARIANTS										0.7387
PRESENCE	54	22 (40.7)	32 (59.3)	N.A. (4.73, N.A.)	53	19 (35.8)	34 (64.2)	N.A. (11.07, N.A.)	0.848 (0.456, 1.578) 0.6027	
ABSENCE	73	33 (45.2)	40 (54.8)	10.51 (6.37, N.A.)	70	27 (38.6)	43 (61.4)	15.80 (9.66, N.A.)	0.700 (0.420, 1.167) 0.1718	

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	N	Subjects with Event n (%)	Censored subjects n (%)	KME [95%CI] (mon) (1)	N	Subjects with Event n (%)	Censored subjects n (%)	KME [95%CI] (mon) (1)	HR [95%CI] P-value (2)	Test for Interaction P-value (3) (4)
OVERALL	127	64 (50.4)	63 (49.6)	8.61 (4.86, N.A.)	123	64 (52.0)	59 (48.0)	7.66 (4.67, 15.77)	1.018 (0.720, 1.440) 0.9209	
PRIOR NEO-ADJUVANT CISPLATIN THERAPY										0.4825
YES	53	25 (47.2)	28 (52.8)	15.64 (4.63, N.A.)	49	27 (55.1)	22 (44.9)	6.93 (3.75, N.A.)	1.185 (0.686, 2.045) 0.5433	
NO	74	39 (52.7)	35 (47.3)	5.52 (4.01, N.A.)	74	37 (50.0)	37 (50.0)	9.26 (3.38, N.A.)	0.922 (0.588, 1.445) 0.7219	

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Subgroup	Placebo				Nivolumab				Nivolumab vs. Placebo	
	N	Subjects with Event n (%)	Censored subjects n (%)	KME [95%CI] (mon) (1)	N	Subjects with Event n (%)	Censored subjects n (%)	KME [95%CI] (mon) (1)	HR [95%CI] P-value (2)	Test for Interaction P-value (3) (4)
PRIOR CISPLATIN STATUS										0.7449
RECEIVED NEO-ADJUVANT	53	25 (47.2)	28 (52.8)	15.64 (4.63, N.A.)	49	27 (55.1)	22 (44.9)	6.93 (3.75, N.A.)	1.185 (0.686, 2.045)	
UNWILLING TO RECEIVE NEO-ADJUVANT	42	22 (52.4)	20 (47.6)	5.52 (4.01, N.A.)	46	24 (52.2)	22 (47.8)	11.04 (2.86, N.A.)	1.056 (0.589, 1.891)	
NOT ELIGIBLE TO RECEIVE NEO-ADJUVANT	31	17 (54.8)	14 (45.2)	5.49 (1.91, N.A.)	23	12 (52.2)	11 (47.8)	7.62 (1.94, N.A.)	0.766 (0.359, 1.636)	

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interaction to assess the significance of the interaction between treatment and the subgroup, with baseline PRO score as a covariate. (4) P-values <0.05 are indicated by 1 asterisk (indicates potential effect modification).

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Subgroup	Placebo				Nivolumab				Nivolumab vs. Placebo	
	N	Subjects with Event n (%)	Censored subjects n (%)	KME [95%CI] (mon) (1)	N	Subjects with Event n (%)	Censored subjects n (%)	KME [95%CI] (mon) (1)	HR [95%CI] P-value (2)	Test for Interaction P-value (3) (4)
USE OF ANY PRIOR NEO-ADJUVANT SYSTEMIC THERAPY										0.3736
YES	54	25 (46.3)	29 (53.7)	15.64 (4.63, N.A.)	53	29 (54.7)	24 (45.3)	6.93 (3.75, N.A.)	1.233 (0.721, 2.109) 0.4434	
NO	73	39 (53.4)	34 (46.6)	5.52 (3.94, N.A.)	70	35 (50.0)	35 (50.0)	9.26 (3.38, N.A.)	0.888 (0.563, 1.402) 0.6112	

FEB2025 DBL. HR = hazard ratio; KME=Kaplan-Meier estimate; N.M.E = Not meaningful estimate.

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Subgroup	Placebo				Nivolumab				Nivolumab vs. Placebo	
	N	Subjects with Event n (%)	Censored subjects n (%)	KME [95%CI] (mon) (1)	N	Subjects with Event n (%)	Censored subjects n (%)	KME [95%CI] (mon) (1)	HR [95%CI] P-value (2)	Test for Interaction P-value (3) (4)
PATHOLOGICAL LYMPH NODE STATUS										0.3293
N+	56	25 (44.6)	31 (55.4)	11.24 (3.71, N.A.)	51	21 (41.2)	30 (58.8)	N.A. (5.55, N.A.)	0.835 (0.464, 1.502)	
NO/X WITH <10 NODES REMOVED	37	23 (62.2)	14 (37.8)	4.86 (2.33, 15.64)	35	21 (60.0)	14 (40.0)	5.55 (3.09, 15.93)	0.5465 (0.502, 1.647)	
NO WITH >= 10 NODES REMOVED	34	16 (47.1)	18 (52.9)	13.14 (4.63, N.A.)	37	22 (59.5)	15 (40.5)	5.68 (3.09, 15.77)	0.909 (0.806, 2.930)	

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Subgroup	Placebo				Nivolumab				Nivolumab vs. Placebo	
	N	Subjects with Event n (%)	Censored subjects n (%)	KME [95%CI] (mon) (1)	N	Subjects with Event n (%)	Censored subjects n (%)	KME [95%CI] (mon) (1)	HR [95%CI] P-value (2)	Test for Interaction P-value (3) (4)
PATHOLOGICAL STATUS										0.7055
PT0-2	29	18 (62.1)	11 (37.9)	4.63 (1.05, N.A.)	21	13 (61.9)	8 (38.1)	5.55 (2.86, N.A.)	0.825 (0.396, 1.716)	
PT3	73	34 (46.6)	39 (53.4)	11.24 (4.86, N.A.)	78	39 (50.0)	39 (50.0)	11.04 (4.63, N.A.)	0.6063 1.008 (0.636, 1.600)	
PT4A	25	12 (48.0)	13 (52.0)	13.14 (2.73, N.A.)	21	11 (52.4)	10 (47.6)	5.68 (1.87, N.A.)	0.9715 1.310 (0.575, 2.984)	

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Subgroup	Placebo				Nivolumab				Nivolumab vs. Placebo	
	N	Subjects with Event n (%)	Censored subjects n (%)	KME [95%CI] (mon) (1)	N	Subjects with Event n (%)	Censored subjects n (%)	KME [95%CI] (mon) (1)	HR [95%CI] P-value (2)	Test for Interaction P-value (3) (4)
AGE CATEGORY I										0.9155
< 65	53	26 (49.1)	27 (50.9)	15.64 (4.01, N.A.)	57	27 (47.4)	30 (52.6)	15.77 (3.38, N.A.)	1.017 (0.593, 1.747) 0.9501	
>= 65	74	38 (51.4)	36 (48.6)	7.29 (4.40, N.A.)	66	37 (56.1)	29 (43.9)	7.62 (4.57, 12.88)	1.005 (0.639, 1.581) 0.9818	

FEB2025 DBL. HR = hazard ratio; KME=Kaplan-Meier estimate; N.M.E = Not meaningful estimate.

(1) KME of median time to event.

(2) Unstratified Cox proportional hazard model, with baseline PRO score as a covariate. HR is Nivolumab over Placebo.

(3) Unstratified Cox proportional hazard model with treatment, subgroup and treatment*subgroup interaction to assess the significance of the interaction between treatment and the subgroup, with baseline PRO score as a covariate. (4) P-values <0.05 are indicated by 1 asterisk (indicates potential effect modification).

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	N	Subjects with Event n (%)	Censored subjects n (%)	KME [95%CI] (mon) (1)	N	Subjects with Event n (%)	Censored subjects n (%)	KME [95%CI] (mon) (1)	HR [95%CI] P-value (2)	Test for Interaction P-value (3) (4)
AGE CATEGORY II										0.7565
< 65	53	26 (49.1)	27 (50.9)	15.64 (4.01, N.A.)	57	27 (47.4)	30 (52.6)	15.77 (3.38, N.A.)	1.017 (0.593, 1.747) 0.9501	
>= 65 AND < 75	54	27 (50.0)	27 (50.0)	5.52 (3.94, N.A.)	45	23 (51.1)	22 (48.9)	8.38 (3.58, N.A.)	0.897 (0.514, 1.566) 0.7020	
>= 75	20	11 (55.0)	9 (45.0)	7.29 (1.91, N.A.)	21	14 (66.7)	7 (33.3)	5.55 (2.07, 11.04)	1.346 (0.609, 2.976) 0.4632	

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REGION										0.0830
US	21	12 (57.1)	9 (42.9)	5.32 (1.15, N.A.)	14	5 (35.7)	9 (64.3)	N.A. (3.58, N.A.)	0.487 (0.170, 1.394) 0.1800	
EUROPE	61	28 (45.9)	33 (54.1)	13.14 (5.49, N.A.)	65	37 (56.9)	28 (43.1)	6.60 (3.09, 15.77)	1.329 (0.809, 2.181) 0.2613	
ASIA	27	16 (59.3)	11 (40.7)	4.63 (1.15, N.A.)	28	10 (35.7)	18 (64.3)	N.A. (2.83, N.A.)	0.594 (0.269, 1.313) 0.1983	
REST OF WORLD	18	8 (44.4)	10 (55.6)	9.00 (1.25, N.A.)	16	12 (75.0)	4 (25.0)	3.38 (1.05, 7.16)	1.846 (0.751, 4.538) 0.1818	

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GENDER										0.6039
MALE	100	47 (47.0)	53 (53.0)	11.24 (5.32, N.A.)	90	47 (52.2)	43 (47.8)	7.62 (4.67, 15.93)	1.067 (0.712, 1.600) 0.7532	
FEMALE	27	17 (63.0)	10 (37.0)	4.86 (1.02, N.A.)	33	17 (51.5)	16 (48.5)	8.38 (2.04, N.A.)	0.900 (0.456, 1.776) 0.7617	
RACE										0.1229
WHITE	95	47 (49.5)	48 (50.5)	11.24 (4.86, N.A.)	94	53 (56.4)	41 (43.6)	6.93 (4.17, 15.64)	1.140 (0.768, 1.692) 0.5146	
ASIAN	27	16 (59.3)	11 (40.7)	4.63 (1.15, N.A.)	28	10 (35.7)	18 (64.3)	N.A. (2.83, N.A.)	0.594 (0.269, 1.313) 0.1983	

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BASELINE ECOG STATUS										0.6970
0	79	37 (46.8)	42 (53.2)	13.11 (4.86, N.A.)	76	39 (51.3)	37 (48.7)	7.66 (3.75, N.A.)	1.087 (0.691, 1.712)	
1	44	25 (56.8)	19 (43.2)	5.52 (2.83, N.A.)	45	23 (51.1)	22 (48.9)	9.26 (3.32, N.A.)	0.7172 0.945 (0.535, 1.669)	0.8449
SMOKING STATUS										0.7913
NEVER SMOKED	36	17 (47.2)	19 (52.8)	7.49 (2.33, N.A.)	36	16 (44.4)	20 (55.6)	12.88 (2.83, N.A.)	1.026 (0.517, 2.035)	
CURRENT/FORMER	90	47 (52.2)	43 (47.8)	8.61 (4.76, 15.64)	86	47 (54.7)	39 (45.3)	7.16 (4.63, 15.77)	0.9412 0.971 (0.648, 1.456)	0.8871

FEB2025 DBL. HR = hazard ratio; KME=Kaplan-Meier estimate; N.M.E = Not meaningful estimate.

(1) KME of median time to event.

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IUC = invasive urothelial carcinoma.

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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

Table 4.1
Subgroup Analyses of EORTC QLQ-C30 Time to First Deterioration
PROS

Cognitive Functioning Scale (MID=10)

Subgroup	Placebo				Nivolumab				Nivolumab vs. Placebo	
	N	Subjects with Event n (%)	Censored subjects n (%)	KME [95%CI] (mon) (1)	N	Subjects with Event n (%)	Censored subjects n (%)	KME [95%CI] (mon) (1)	HR [95%CI] P-value (2)	Test for Interaction P-value (3) (4)
BASELINE HEMOGLOBIN										0.8406
<10 G/DL	13	9 (69.2)	4 (30.8)	7.29 (0.99, N.A.)	6	4 (66.7)	2 (33.3)	6.60 (1.02, N.A.)	1.165 (0.342, 3.966)	
>=10 G/DL	114	55 (48.2)	59 (51.8)	11.24 (4.63, N.A.)	117	60 (51.3)	57 (48.7)	7.66 (4.57, 15.93)	1.049 (0.727, 1.512)	0.8075 0.7998
BASELINE CREATININE CLEARANCE										0.2634
<60 ML/MIN	57	32 (56.1)	25 (43.9)	7.13 (2.89, 13.11)	47	23 (48.9)	24 (51.1)	9.26 (3.09, N.A.)	0.821 (0.479, 1.406)	
>=60 ML/MIN	70	32 (45.7)	38 (54.3)	15.64 (4.76, N.A.)	75	40 (53.3)	35 (46.7)	7.16 (4.63, 15.77)	1.236 (0.774, 1.976)	0.4720 0.3751

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TIME FROM IUC SURGERY TO RANDOMIZATION (DAYS)										0.4570
>30-60	28	16 (57.1)	12 (42.9)	5.52 (2.83, N.A.)	30	13 (43.3)	17 (56.7)	15.77 (3.38, N.A.)	0.732 (0.351, 1.527)	
>60-90	57	25 (43.9)	32 (56.1)	N.A. (4.86, N.A.)	51	27 (52.9)	24 (47.1)	6.93 (2.86, N.A.)	1.247 (0.721, 2.157)	
>90-120	37	20 (54.1)	17 (45.9)	7.49 (2.83, N.A.)	40	23 (57.5)	17 (42.5)	5.59 (3.32, 15.64)	1.030 (0.565, 1.878)	

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	N	Subjects with Event n (%)	Censored subjects n (%)	KME [95%CI] (mon) (1)	N	Subjects with Event n (%)	Censored subjects n (%)	KME [95%CI] (mon) (1)	HR [95%CI] P-value (2)	Test for Interaction P-value (3) (4)
INITIAL TUMOR ORIGIN										0.1845
URINARY BLADDER	103	48 (46.6)	55 (53.4)	13.11 (5.32, N.A.)	102	54 (52.9)	48 (47.1)	7.16 (4.17, 15.77)	1.160 (0.786, 1.712) 0.4559	
RENAL PELVIS	13	10 (76.9)	3 (23.1)	2.37 (0.99, 7.29)	15	8 (53.3)	7 (46.7)	9.26 (1.94, N.A.)	0.402 (0.152, 1.059) 0.0651	
URETER	11	6 (54.5)	5 (45.5)	11.24 (1.02, N.A.)	6	2 (33.3)	4 (66.7)	N.A. (0.95, N.A.)	0.786 (0.151, 4.083) 0.7744	

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Subgroup	Placebo				Nivolumab				Nivolumab vs. Placebo	
	N	Subjects with Event n (%)	Censored subjects n (%)	KME [95%CI] (mon) (1)	N	Subjects with Event n (%)	Censored subjects n (%)	KME [95%CI] (mon) (1)	HR [95%CI] P-value (2)	Test for Interaction P-value (3) (4)
MINOR HISTOLOGICAL VARIANTS										0.5586
PRESENCE	54	28 (51.9)	26 (48.1)	8.61 (3.71, N.A.)	53	26 (49.1)	27 (50.9)	12.88 (4.63, N.A.)	0.881 (0.516, 1.505)	
ABSENCE	73	36 (49.3)	37 (50.7)	11.24 (4.40, N.A.)	70	38 (54.3)	32 (45.7)	6.93 (3.38, 15.64)	1.120 (0.709, 1.769)	0.6425 0.6266

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Social Functioning Scale (MID=10)

Subgroup	Placebo				Nivolumab				Nivolumab vs. Placebo	
	N	Subjects with Event n (%)	Censored subjects n (%)	KME [95%CI] (mon) (1)	N	Subjects with Event n (%)	Censored subjects n (%)	KME [95%CI] (mon) (1)	HR [95%CI] P-value (2)	Test for Interaction P-value (3) (4)
OVERALL	126	52 (41.3)	74 (58.7)	N.A. (7.56, N.A.)	122	55 (45.1)	67 (54.9)	15.64 (6.47, N.A.)	1.065 (0.728, 1.557) 0.7457	
PRIOR NEO-ADJUVANT CISPLATIN THERAPY										0.2633
YES	53	19 (35.8)	34 (64.2)	N.A. (7.43, N.A.)	49	23 (46.9)	26 (53.1)	15.64 (3.58, N.A.)	1.390 (0.757, 2.555) 0.2883	
NO	73	33 (45.2)	40 (54.8)	11.73 (4.76, N.A.)	73	32 (43.8)	41 (56.2)	11.27 (5.55, N.A.)	0.872 (0.535, 1.423) 0.5848	

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Subgroup	Placebo				Nivolumab				Nivolumab vs. Placebo	
	N	Subjects with Event n (%)	Censored subjects n (%)	KME [95%CI] (mon) (1)	N	Subjects with Event n (%)	Censored subjects n (%)	KME [95%CI] (mon) (1)	HR [95%CI] P-value (2)	Test for Interaction P-value (3) (4)
PRIOR CISPLATIN STATUS										0.0627
RECEIVED NEO-ADJUVANT	53	19 (35.8)	34 (64.2)	N.A. (7.43, N.A.)	49	23 (46.9)	26 (53.1)	15.64 (3.58, N.A.)	1.390 (0.757, 2.555)	
UNWILLING TO RECEIVE NEO-ADJUVANT	42	23 (54.8)	19 (45.2)	8.54 (2.60, N.A.)	46	18 (39.1)	28 (60.9)	N.A. (6.97, N.A.)	0.587 (0.315, 1.095)	
NOT ELIGIBLE TO RECEIVE NEO-ADJUVANT	30	10 (33.3)	20 (66.7)	N.A. (4.60, N.A.)	22	14 (63.6)	8 (36.4)	5.52 (3.32, 11.07)	1.962 (0.862, 4.466)	

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Subgroup	Placebo				Nivolumab				Nivolumab vs. Placebo	
	N	Subjects with Event n (%)	Censored subjects n (%)	KME [95%CI] (mon) (1)	N	Subjects with Event n (%)	Censored subjects n (%)	KME [95%CI] (mon) (1)	HR [95%CI] P-value (2)	Test for Interaction P-value (3) (4)
USE OF ANY PRIOR NEO-ADJUVANT SYSTEMIC THERAPY										0.4631
YES	54	20 (37.0)	34 (63.0)	N.A. (6.93, N.A.)	53	24 (45.3)	29 (54.7)	15.64 (3.71, N.A.)	1.272 (0.702, 2.304) 0.4275	
NO	72	32 (44.4)	40 (55.6)	11.73 (4.76, N.A.)	69	31 (44.9)	38 (55.1)	11.07 (5.55, N.A.)	0.927 (0.564, 1.522) 0.7632	

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	N	Subjects with Event n (%)	Censored subjects n (%)	KME [95%CI] (mon) (1)	N	Subjects with Event n (%)	Censored subjects n (%)	KME [95%CI] (mon) (1)	HR [95%CI] P-value (2)	Test for Interaction P-value (3) (4)
PATHOLOGICAL LYMPH NODE STATUS										0.8826
N+	55	17 (30.9)	38 (69.1)	N.A. (11.24, N.A.)	51	19 (37.3)	32 (62.7)	N.A. (6.97, N.A.)	1.008 (0.519, 1.955) 0.9817	
NO/X WITH <10 NODES REMOVED	37	21 (56.8)	16 (43.2)	7.56 (2.83, N.A.)	34	18 (52.9)	16 (47.1)	6.01 (2.89, N.A.)	1.004 (0.535, 1.887) 0.9892	
NO WITH >= 10 NODES REMOVED	34	14 (41.2)	20 (58.8)	N.A. (4.60, N.A.)	37	18 (48.6)	19 (51.4)	15.64 (3.32, N.A.)	1.274 (0.633, 2.565) 0.4973	

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PATHOLOGICAL STATUS										0.6693
PT0-2	29	11 (37.9)	18 (62.1)	N.A. (6.93, N.A.)	21	10 (47.6)	11 (52.4)	14.06 (3.71, N.A.)	1.355 (0.574, 3.196)	
PT3	72	31 (43.1)	41 (56.9)	11.24 (4.76, N.A.)	77	34 (44.2)	43 (55.8)	15.64 (5.55, N.A.)	0.4877 0.892 (0.547, 1.455)	
PT4A	25	10 (40.0)	15 (60.0)	N.A. (3.81, N.A.)	21	9 (42.9)	12 (57.1)	N.A. (1.81, N.A.)	0.6478 1.188 (0.479, 2.945)	

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AGE CATEGORY I										0.5482
< 65	53	22 (41.5)	31 (58.5)	N.A. (6.93, N.A.)	56	26 (46.4)	30 (53.6)	N.A. (3.06, N.A.)	1.227 (0.695, 2.166) 0.4815	
>= 65	73	30 (41.1)	43 (58.9)	N.A. (5.55, N.A.)	66	29 (43.9)	37 (56.1)	14.06 (6.47, N.A.)	0.960 (0.575, 1.602) 0.8765	

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	N	Subjects with Event n (%)	Censored subjects n (%)	KME [95%CI] (mon) (1)	N	Subjects with Event n (%)	Censored subjects n (%)	KME [95%CI] (mon) (1)	HR [95%CI] P-value (2)	Test for Interaction P-value (3) (4)
AGE CATEGORY II										0.1473
< 65	53	22 (41.5)	31 (58.5)	N.A. (6.93, N.A.)	56	26 (46.4)	30 (53.6)	N.A. (3.06, N.A.)	1.227 (0.695, 2.166) 0.4815	
>= 65 AND < 75	53	24 (45.3)	29 (54.7)	N.A. (4.24, N.A.)	45	17 (37.8)	28 (62.2)	15.64 (8.05, N.A.)	0.698 (0.374, 1.302) 0.2579	
>= 75	20	6 (30.0)	14 (70.0)	N.A. (4.76, N.A.)	21	12 (57.1)	9 (42.9)	6.01 (2.83, N.A.)	2.013 (0.752, 5.392) 0.1638	

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	N	Subjects with Event n (%)	Censored subjects n (%)	KME [95%CI] (mon) (1)	N	Subjects with Event n (%)	Censored subjects n (%)	KME [95%CI] (mon) (1)	HR [95%CI] P-value (2)	Test for Interaction P-value (3) (4)
REGION										0.9567
US	21	6 (28.6)	15 (71.4)	N.A. (4.73, N.A.)	14	5 (35.7)	9 (64.3)	N.A. (3.32, N.A.)	1.099 (0.323, 3.739) 0.8793	
EUROPE	60	27 (45.0)	33 (55.0)	N.A. (5.55, N.A.)	64	32 (50.0)	32 (50.0)	14.06 (3.98, N.A.)	1.118 (0.669, 1.870) 0.6702	
ASIA	27	13 (48.1)	14 (51.9)	7.56 (1.87, N.A.)	28	12 (42.9)	16 (57.1)	11.27 (5.52, N.A.)	0.816 (0.371, 1.795) 0.6132	
REST OF WORLD	18	6 (33.3)	12 (66.7)	N.A. (2.83, N.A.)	16	6 (37.5)	10 (62.5)	N.A. (2.33, N.A.)	1.290 (0.412, 4.041) 0.6619	

FEB2025 DBL. HR = hazard ratio; KME=Kaplan-Meier estimate; N.M.E = Not meaningful estimate.

(1) KME of median time to event.

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(3) Unstratified Cox proportional hazard model with treatment, subgroup and treatment*subgroup interaction to assess the significance of the interaction between treatment and the subgroup, with baseline PRO score as a covariate. (4) P-values <0.05 are indicated by 1 asterisk (indicates potential effect modification).

IUC = invasive urothelial carcinoma.

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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

Table 4.1
Subgroup Analyses of EORTC QLQ-C30 Time to First Deterioration
PROS

Social Functioning Scale (MID=10)

Subgroup	Placebo				Nivolumab				Nivolumab vs. Placebo	
	N	Subjects with Event n (%)	Censored subjects n (%)	KME [95%CI] (mon) (1)	N	Subjects with Event n (%)	Censored subjects n (%)	KME [95%CI] (mon) (1)	HR [95%CI] P-value (2)	Test for Interaction P-value (3) (4)
GENDER										
MALE	99	36 (36.4)	63 (63.6)	N.A. (11.24, N.A.)	90	41 (45.6)	49 (54.4)	N.A. (5.52, N.A.)	1.208 (0.771, 1.893) 0.4100	0.1730
FEMALE	27	16 (59.3)	11 (40.7)	4.63 (1.45, N.A.)	32	14 (43.8)	18 (56.3)	11.27 (3.32, N.A.)	0.690 (0.335, 1.419) 0.3131	
RACE										
WHITE	95	38 (40.0)	57 (60.0)	N.A. (8.44, N.A.)	93	43 (46.2)	50 (53.8)	15.64 (5.52, N.A.)	1.129 (0.729, 1.749) 0.5876	0.5719
ASIAN	27	13 (48.1)	14 (51.9)	7.56 (1.87, N.A.)	28	12 (42.9)	16 (57.1)	11.27 (5.52, N.A.)	0.816 (0.371, 1.795) 0.6132	

FEB2025 DBL. HR = hazard ratio; KME=Kaplan-Meier estimate; N.M.E = Not meaningful estimate.

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BASELINE ECOG STATUS										0.4037
0	79	28 (35.4)	51 (64.6)	N.A. (8.54, N.A.)	75	32 (42.7)	43 (57.3)	N.A. (5.52, N.A.)	1.207 (0.726, 2.008) 0.4684	
1	44	23 (52.3)	21 (47.7)	8.44 (2.50, N.A.)	45	21 (46.7)	24 (53.3)	9.72 (4.63, N.A.)	0.823 (0.454, 1.492) 0.5206	
SMOKING STATUS										0.4338
NEVER SMOKED	36	11 (30.6)	25 (69.4)	N.A. (4.76, N.A.)	36	13 (36.1)	23 (63.9)	15.64 (6.01, N.A.)	1.318 (0.589, 2.952) 0.5014	
CURRENT/FORMER	89	41 (46.1)	48 (53.9)	11.24 (6.37, N.A.)	85	41 (48.2)	44 (51.8)	9.72 (4.63, N.A.)	0.942 (0.608, 1.457) 0.7868	

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	N	Subjects with Event n (%)	Censored subjects n (%)	KME [95%CI] (mon) (1)	N	Subjects with Event n (%)	Censored subjects n (%)	KME [95%CI] (mon) (1)	HR [95%CI] P-value (2)	Test for Interaction P-value (3) (4)
BASELINE HEMOGLOBIN										0.3191
<10 G/DL	13	6 (46.2)	7 (53.8)	N.A. (2.99, N.A.)	6	4 (66.7)	2 (33.3)	2.86 (1.02, N.A.)	2.659 (0.612, 11.565)	
>=10 G/DL	113	46 (40.7)	67 (59.3)	N.A. (7.43, N.A.)	116	51 (44.0)	65 (56.0)	15.64 (6.97, N.A.)	1.041 (0.698, 1.552)	
BASELINE CREATININE CLEARANCE										0.0777
<60 ML/MIN	57	21 (36.8)	36 (63.2)	N.A. (6.93, N.A.)	46	25 (54.3)	21 (45.7)	6.97 (2.89, N.A.)	1.563 (0.874, 2.794)	
>=60 ML/MIN	69	31 (44.9)	38 (55.1)	11.73 (4.73, N.A.)	75	29 (38.7)	46 (61.3)	N.A. (7.62, N.A.)	0.781 (0.469, 1.299)	

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	N	Subjects with Event n (%)	Censored subjects n (%)	KME [95%CI] (mon) (1)	N	Subjects with Event n (%)	Censored subjects n (%)	KME [95%CI] (mon) (1)	HR [95%CI] P-value (2)	Test for Interaction P-value (3) (4)
TIME FROM IUC SURGERY TO RANDOMIZATION (DAYS)										0.4517
>30-60	27	15 (55.6)	12 (44.4)	4.73 (1.87, N.A.)	29	12 (41.4)	17 (58.6)	N.A. (4.63, N.A.)	0.674 (0.314, 1.445)	
>60-90	57	23 (40.4)	34 (59.6)	N.A. (6.37, N.A.)	51	22 (43.1)	29 (56.9)	N.A. (3.75, N.A.)	1.161 (0.647, 2.085)	
>90-120	37	12 (32.4)	25 (67.6)	N.A. (11.73, N.A.)	40	20 (50.0)	20 (50.0)	11.27 (3.32, N.A.)	1.277 (0.605, 2.695)	

FEB2025 DBL. HR = hazard ratio; KME=Kaplan-Meier estimate; N.M.E = Not meaningful estimate.

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Subgroup	Placebo				Nivolumab				Nivolumab vs. Placebo	
	N	Subjects with Event n (%)	Censored subjects n (%)	KME [95%CI] (mon) (1)	N	Subjects with Event n (%)	Censored subjects n (%)	KME [95%CI] (mon) (1)	HR [95%CI] P-value (2)	Test for Interaction P-value (3) (4)
INITIAL TUMOR ORIGIN										0.4063
URINARY BLADDER	102	40 (39.2)	62 (60.8)	N.A. (8.44, N.A.)	101	48 (47.5)	53 (52.5)	14.06 (5.52, N.A.)	1.189 (0.780, 1.814)	
RENAL PELVIS	13	6 (46.2)	7 (53.8)	N.A. (1.05, N.A.)	15	6 (40.0)	9 (60.0)	N.A. (2.83, N.A.)	0.4211 0.778 (0.247, 2.446)	
URETER	11	6 (54.5)	5 (45.5)	7.56 (0.95, N.A.)	6	1 (16.7)	5 (83.3)	N.A. (0.95, N.A.)	0.6670 0.300 (0.035, 2.606)	

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Subgroup	Placebo				Nivolumab				Nivolumab vs. Placebo	
	N	Subjects with Event n (%)	Censored subjects n (%)	KME [95%CI] (mon) (1)	N	Subjects with Event n (%)	Censored subjects n (%)	KME [95%CI] (mon) (1)	HR [95%CI] P-value (2)	Test for Interaction P-value (3) (4)
MINOR HISTOLOGICAL VARIANTS										0.1100
PRESENCE	54	18 (33.3)	36 (66.7)	N.A. (11.73, N.A.)	52	27 (51.9)	25 (48.1)	9.72 (4.50, N.A.)	1.470 (0.797, 2.714)	
ABSENCE	72	34 (47.2)	38 (52.8)	8.54 (4.24, N.A.)	70	28 (40.0)	42 (60.0)	N.A. (5.52, N.A.)	0.2174 0.816 (0.494, 1.347) 0.4259	

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PROS

Global Health Status (MID=10)

Subgroup	Placebo				Nivolumab				Nivolumab vs. Placebo	
	N	Subjects with Event n (%)	Censored subjects n (%)	KME [95%CI] (mon) (1)	N	Subjects with Event n (%)	Censored subjects n (%)	KME [95%CI] (mon) (1)	HR [95%CI] P-value (2)	Test for Interaction P-value (3) (4)
OVERALL	127	64 (50.4)	63 (49.6)	10.51 (5.59, N.A.)	123	57 (46.3)	66 (53.7)	9.95 (6.93, N.A.)	0.961 (0.672, 1.374) 0.8270	
PRIOR NEO-ADJUVANT CISPLATIN THERAPY										0.9528
YES	53	26 (49.1)	27 (50.9)	12.91 (4.01, N.A.)	49	23 (46.9)	26 (53.1)	13.17 (6.60, N.A.)	0.929 (0.530, 1.629) 0.7975	
NO	74	38 (51.4)	36 (48.6)	10.51 (3.29, N.A.)	74	34 (45.9)	40 (54.1)	9.95 (4.67, N.A.)	0.954 (0.600, 1.518) 0.8426	

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	N	Subjects with Event n (%)	Censored subjects n (%)	KME [95%CI] (mon) (1)	N	Subjects with Event n (%)	Censored subjects n (%)	KME [95%CI] (mon) (1)	HR [95%CI] P-value (2)	Test for Interaction P-value (3) (4)
PRIOR CISPLATIN STATUS										0.8819
RECEIVED NEO-ADJUVANT	53	26 (49.1)	27 (50.9)	12.91 (4.01, N.A.)	49	23 (46.9)	26 (53.1)	13.17 (6.60, N.A.)	0.929 (0.530, 1.629)	
UNWILLING TO RECEIVE NEO-ADJUVANT	42	19 (45.2)	23 (54.8)	12.16 (2.83, N.A.)	46	23 (50.0)	23 (50.0)	8.38 (2.46, N.A.)	1.127 (0.612, 2.075)	
NOT ELIGIBLE TO RECEIVE NEO-ADJUVANT	31	18 (58.1)	13 (41.9)	5.59 (1.91, N.A.)	23	11 (47.8)	12 (52.2)	9.23 (2.10, N.A.)	0.846 (0.390, 1.837)	

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USE OF ANY PRIOR NEO-ADJUVANT SYSTEMIC THERAPY										0.9496
YES	54	26 (48.1)	28 (51.9)	12.91 (5.19, N.A.)	53	25 (47.2)	28 (52.8)	13.17 (6.47, N.A.)	0.961 (0.554, 1.665) 0.8868	
NO	73	38 (52.1)	35 (47.9)	7.62 (2.83, N.A.)	70	32 (45.7)	38 (54.3)	9.95 (4.67, N.A.)	0.935 (0.583, 1.499) 0.7801	

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PATHOLOGICAL LYMPH NODE STATUS										0.7089
N+	56	30 (53.6)	26 (46.4)	7.16 (5.49, N.A.)	51	21 (41.2)	30 (58.8)	N.A. (5.13, N.A.)	0.829 (0.472, 1.455)	
N0/X WITH <10 NODES REMOVED	37	18 (48.6)	19 (51.4)	11.73 (2.79, N.A.)	35	15 (42.9)	20 (57.1)	14.49 (8.28, N.A.)	0.5142 1.093 (0.546, 2.185)	
N0 WITH >= 10 NODES REMOVED	34	16 (47.1)	18 (52.9)	7.62 (3.02, N.A.)	37	21 (56.8)	16 (43.2)	6.93 (3.78, N.A.)	1.111 (0.579, 2.130)	
									0.7523	

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PATHOLOGICAL STATUS										0.2652
PT0-2	29	14 (48.3)	15 (51.7)	12.91 (5.49, N.A.)	21	8 (38.1)	13 (61.9)	N.A. (4.67, N.A.)	0.816 (0.340, 1.957)	
PT3	73	33 (45.2)	40 (54.8)	11.24 (6.18, N.A.)	78	40 (51.3)	38 (48.7)	8.34 (5.13, N.A.)	0.6482 1.202 (0.757, 1.909)	
PT4A	25	17 (68.0)	8 (32.0)	2.83 (1.87, 7.16)	21	9 (42.9)	12 (57.1)	N.A. (1.94, N.A.)	0.4356 0.602 (0.266, 1.365)	
									0.2243	

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interaction to assess the significance of the interaction between treatment and the subgroup, with baseline PRO score as a covariate. (4) P-values <0.05 are indicated by 1 asterisk (indicates potential effect modification).

IUC = invasive urothelial carcinoma.

Program Path: /projects/bms214671/stats/market/ma274_202502/prog/tables

Program Name: rt-sy-tdd-eortc-comm-ebr45.sas

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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

Table 4.1
Subgroup Analyses of EORTC QLQ-C30 Time to First Deterioration
PROS

Global Health Status (MID=10)

Subgroup	Placebo				Nivolumab				Nivolumab vs. Placebo	
	N	Subjects with Event n (%)	Censored subjects n (%)	KME [95%CI] (mon) (1)	N	Subjects with Event n (%)	Censored subjects n (%)	KME [95%CI] (mon) (1)	HR [95%CI] P-value (2)	Test for Interaction P-value (3) (4)
AGE CATEGORY I										0.1272
< 65	53	22 (41.5)	31 (58.5)	N.A. (6.77, N.A.)	57	28 (49.1)	29 (50.9)	13.17 (4.76, N.A.)	1.359 (0.777, 2.378) 0.2825	
>= 65	74	42 (56.8)	32 (43.2)	5.59 (2.83, 12.16)	66	29 (43.9)	37 (56.1)	9.95 (6.60, N.A.)	0.773 (0.479, 1.248) 0.2925	

FEB2025 DBL. HR = hazard ratio; KME=Kaplan-Meier estimate; N.M.E = Not meaningful estimate.

(1) KME of median time to event.

(2) Unstratified Cox proportional hazard model, with baseline PRO score as a covariate. HR is Nivolumab over Placebo.

(3) Unstratified Cox proportional hazard model with treatment, subgroup and treatment*subgroup interaction to assess the significance of the interaction between treatment and the subgroup, with baseline PRO score as a covariate. (4) P-values <0.05 are indicated by 1 asterisk (indicates potential effect modification).

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Global Health Status (MID=10)

Subgroup	Placebo				Nivolumab				Nivolumab vs. Placebo	
	N	Subjects with Event n (%)	Censored subjects n (%)	KME [95%CI] (mon) (1)	N	Subjects with Event n (%)	Censored subjects n (%)	KME [95%CI] (mon) (1)	HR [95%CI] P-value (2)	Test for Interaction P-value (3) (4)
AGE CATEGORY II										0.2934
< 65	53	22 (41.5)	31 (58.5)	N.A. (6.77, N.A.)	57	28 (49.1)	29 (50.9)	13.17 (4.76, N.A.)	1.359 (0.777, 2.378) 0.2825	
>= 65 AND < 75	54	29 (53.7)	25 (46.3)	5.19 (2.14, N.A.)	45	18 (40.0)	27 (60.0)	N.A. (6.47, N.A.)	0.697 (0.383, 1.269) 0.2375	
>= 75	20	13 (65.0)	7 (35.0)	5.59 (1.05, 12.91)	21	11 (52.4)	10 (47.6)	9.23 (1.15, N.A.)	0.852 (0.380, 1.908) 0.6973	

FEB2025 DBL. HR = hazard ratio; KME=Kaplan-Meier estimate; N.M.E = Not meaningful estimate.

(1) KME of median time to event.

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(3) Unstratified Cox proportional hazard model with treatment, subgroup and treatment*subgroup

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IUC = invasive urothelial carcinoma.

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PROS

Global Health Status (MID=10)

Subgroup	Placebo				Nivolumab				Nivolumab vs. Placebo	
	N	Subjects with Event n (%)	Censored subjects n (%)	KME [95%CI] (mon) (1)	N	Subjects with Event n (%)	Censored subjects n (%)	KME [95%CI] (mon) (1)	HR [95%CI] P-value (2)	Test for Interaction P-value (3) (4)
REGION										0.5814
US	21	8 (38.1)	13 (61.9)	N.A. (2.83, N.A.)	14	6 (42.9)	8 (57.1)	6.97 (3.32, N.A.)	0.927 (0.313, 2.752)	
EUROPE	61	36 (59.0)	25 (41.0)	6.97 (4.01, 12.91)	65	33 (50.8)	32 (49.2)	8.38 (5.13, N.A.)	1.098 (0.672, 1.792)	
ASIA	27	9 (33.3)	18 (66.7)	N.A. (1.91, N.A.)	28	11 (39.3)	17 (60.7)	13.17 (4.67, N.A.)	0.823 (0.332, 2.039)	
REST OF WORLD	18	11 (61.1)	7 (38.9)	3.75 (1.45, N.A.)	16	7 (43.8)	9 (56.3)	N.A. (1.87, N.A.)	0.659 (0.254, 1.714)	

FEB2025 DBL. HR = hazard ratio; KME=Kaplan-Meier estimate; N.M.E = Not meaningful estimate.

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PROS

Global Health Status (MID=10)

Subgroup	Placebo				Nivolumab				Nivolumab vs. Placebo	
	N	Subjects with Event n (%)	Censored subjects n (%)	KME [95%CI] (mon) (1)	N	Subjects with Event n (%)	Censored subjects n (%)	KME [95%CI] (mon) (1)	HR [95%CI] P-value (2)	Test for Interaction P-value (3) (4)
GENDER										0.0500*
MALE	100	52 (52.0)	48 (48.0)	10.51 (5.19, N.A.)	90	37 (41.1)	53 (58.9)	N.A. (8.38, N.A.)	0.775 (0.508, 1.184) 0.2382	
FEMALE	27	12 (44.4)	15 (55.6)	N.A. (3.71, N.A.)	33	20 (60.6)	13 (39.4)	5.13 (2.04, 8.28)	1.752 (0.851, 3.606) 0.1280	
RACE										0.8244
WHITE	95	52 (54.7)	43 (45.3)	7.16 (4.01, 12.91)	94	45 (47.9)	49 (52.1)	9.95 (6.47, N.A.)	0.988 (0.660, 1.479) 0.9535	
ASIAN	27	9 (33.3)	18 (66.7)	N.A. (1.91, N.A.)	28	11 (39.3)	17 (60.7)	13.17 (4.67, N.A.)	0.823 (0.332, 2.039) 0.6739	

FEB2025 DBL. HR = hazard ratio; KME=Kaplan-Meier estimate; N.M.E = Not meaningful estimate.

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Global Health Status (MID=10)

Subgroup	Placebo				Nivolumab				Nivolumab vs. Placebo	
	N	Subjects with Event n (%)	Censored subjects n (%)	KME [95%CI] (mon) (1)	N	Subjects with Event n (%)	Censored subjects n (%)	KME [95%CI] (mon) (1)	HR [95%CI] P-value (2)	Test for Interaction P-value (3) (4)
BASELINE ECOG STATUS										0.1964
0	79	35 (44.3)	44 (55.7)	12.91 (5.72, N.A.)	76	38 (50.0)	38 (50.0)	9.23 (6.83, N.A.)	1.231 (0.777, 1.952)	
1	44	25 (56.8)	19 (43.2)	6.97 (3.29, N.A.)	45	19 (42.2)	26 (57.8)	N.A. (3.71, N.A.)	0.3757 0.743 (0.409, 1.350) 0.3289	
SMOKING STATUS										0.0054*
NEVER SMOKED	36	11 (30.6)	25 (69.4)	N.A. (10.51, N.A.)	36	20 (55.6)	16 (44.4)	6.97 (3.78, 13.17)	2.475 (1.174, 5.220) 0.0173	
CURRENT/FORMER	90	52 (57.8)	38 (42.2)	6.18 (3.71, 11.73)	86	37 (43.0)	49 (57.0)	N.A. (6.93, N.A.)	0.702 (0.459, 1.072) 0.1017	

FEB2025 DBL. HR = hazard ratio; KME=Kaplan-Meier estimate; N.M.E = Not meaningful estimate.

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PROS

Global Health Status (MID=10)

Subgroup	Placebo				Nivolumab				Nivolumab vs. Placebo	
	N	Subjects with Event n (%)	Censored subjects n (%)	KME [95%CI] (mon) (1)	N	Subjects with Event n (%)	Censored subjects n (%)	KME [95%CI] (mon) (1)	HR [95%CI] P-value (2)	Test for Interaction P-value (3) (4)
BASELINE HEMOGLOBIN										0.6878
<10 G/DL	13	6 (46.2)	7 (53.8)	N.A. (1.87, N.A.)	6	2 (33.3)	4 (66.7)	N.A. (1.02, N.A.)	1.162 (0.198, 6.831)	
>=10 G/DL	114	58 (50.9)	56 (49.1)	7.62 (5.49, N.A.)	117	55 (47.0)	62 (53.0)	9.95 (6.83, N.A.)	0.8680 0.980 (0.677, 1.419) 0.9141	
BASELINE CREATININE CLEARANCE										0.6215
<60 ML/MIN	57	29 (50.9)	28 (49.1)	7.16 (3.29, N.A.)	47	21 (44.7)	26 (55.3)	14.49 (5.55, N.A.)	1.099 (0.610, 1.981)	
>=60 ML/MIN	70	35 (50.0)	35 (50.0)	11.73 (5.19, N.A.)	75	35 (46.7)	40 (53.3)	8.38 (6.60, N.A.)	0.7522 0.903 (0.564, 1.444) 0.6695	

FEB2025 DBL. HR = hazard ratio; KME=Kaplan-Meier estimate; N.M.E = Not meaningful estimate.

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Subgroup	Placebo				Nivolumab				Nivolumab vs. Placebo	
	N	Subjects with Event n (%)	Censored subjects n (%)	KME [95%CI] (mon) (1)	N	Subjects with Event n (%)	Censored subjects n (%)	KME [95%CI] (mon) (1)	HR [95%CI] P-value (2)	Test for Interaction P-value (3) (4)
TIME FROM IUC SURGERY TO RANDOMIZATION (DAYS)										0.7799
>30-60	28	11 (39.3)	17 (60.7)	N.A. (1.91, N.A.)	30	13 (43.3)	17 (56.7)	N.A. (2.79, N.A.)	1.121 (0.502, 2.508)	
>60-90	57	29 (50.9)	28 (49.1)	11.24 (5.49, N.A.)	51	22 (43.1)	29 (56.9)	N.A. (8.28, N.A.)	0.7801 0.891 (0.507, 1.566)	
>90-120	37	22 (59.5)	15 (40.5)	7.16 (3.29, N.A.)	40	22 (55.0)	18 (45.0)	6.93 (3.65, N.A.)	0.6883 0.804 (0.443, 1.457)	

FEB2025 DBL. HR = hazard ratio; KME=Kaplan-Meier estimate; N.M.E = Not meaningful estimate.

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	N	Subjects with Event n (%)	Censored subjects n (%)	KME [95%CI] (mon) (1)	N	Subjects with Event n (%)	Censored subjects n (%)	KME [95%CI] (mon) (1)	HR [95%CI] P-value (2)	Test for Interaction P-value (3) (4)
INITIAL TUMOR ORIGIN										0.5140
URINARY BLADDER	103	54 (52.4)	49 (47.6)	7.62 (5.19, N.A.)	102	47 (46.1)	55 (53.9)	14.49 (6.60, N.A.)	0.885 (0.598, 1.309)	
RENAL PELVIS	13	5 (38.5)	8 (61.5)	N.A. (1.15, N.A.)	15	7 (46.7)	8 (53.3)	9.23 (4.60, N.A.)	0.5411 1.064 (0.334, 3.391)	
URETER	11	5 (45.5)	6 (54.5)	11.24 (0.99, N.A.)	6	3 (50.0)	3 (50.0)	13.17 (0.95, N.A.)	0.9171 2.021 (0.409, 9.984)	

FEB2025 DBL. HR = hazard ratio; KME=Kaplan-Meier estimate; N.M.E = Not meaningful estimate.

(1) KME of median time to event.

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MINOR HISTOLOGICAL VARIANTS										0.0296*
PRESENCE	54	21 (38.9)	33 (61.1)	N.A. (6.87, N.A.)	53	26 (49.1)	27 (50.9)	9.23 (5.13, N.A.)	1.591 (0.889, 2.849)	
ABSENCE	73	43 (58.9)	30 (41.1)	6.18 (3.29, 11.24)	70	31 (44.3)	39 (55.7)	14.49 (6.47, N.A.)	0.1182 0.672 (0.423, 1.068) 0.0930	

FEB2025 DBL. HR = hazard ratio; KME=Kaplan-Meier estimate; N.M.E = Not meaningful estimate.

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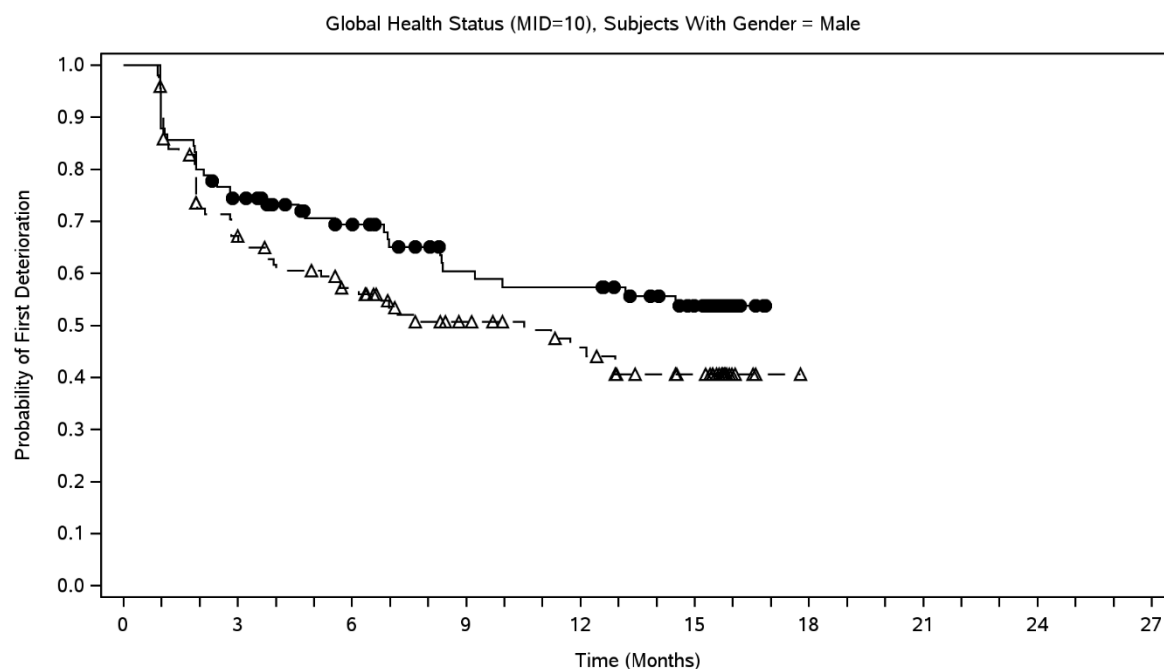
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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

4.4 Kaplan-Meier Kurven für Subgruppen mit statistisch signifikantem Interaktionsterm

Figure 4.1

Kaplan-Meier Plot of EORTC QLQ-C30 Time to First Deterioration - by Significant Subgroups - PROS



FEB2025 DBL.

Symbols represent censored observations.

Unstratified Cox proportional hazard model,
with baseline PRO score as a covariate.

Program Path: /projects/bms214671/stats/market/ma274_202502/prog/figures

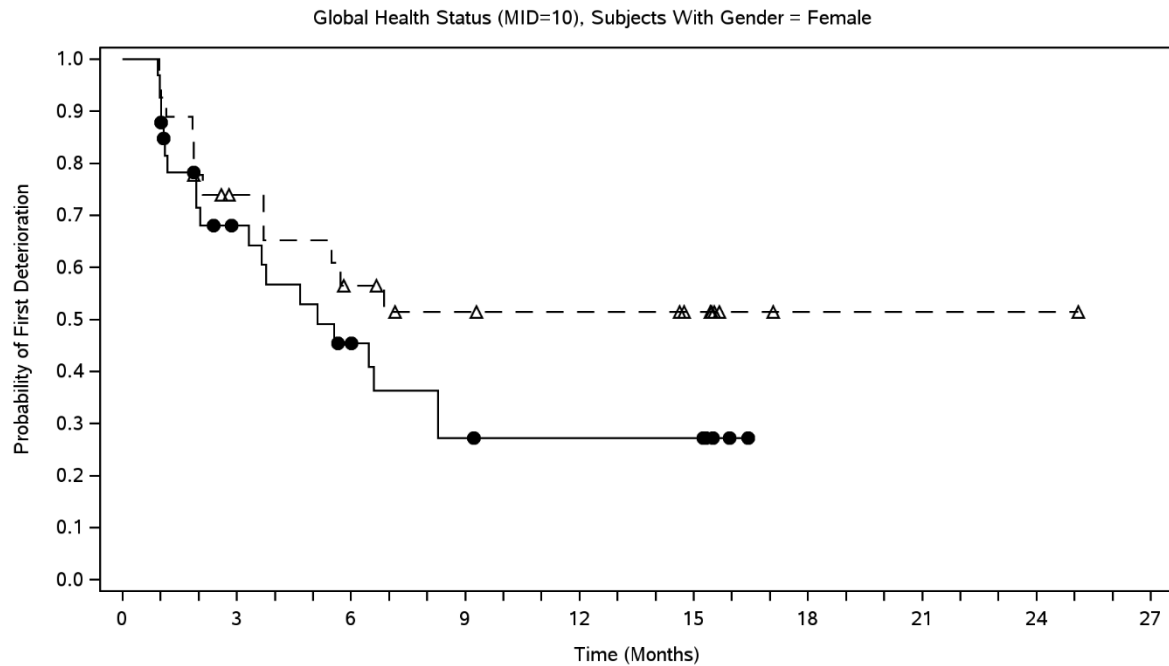
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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

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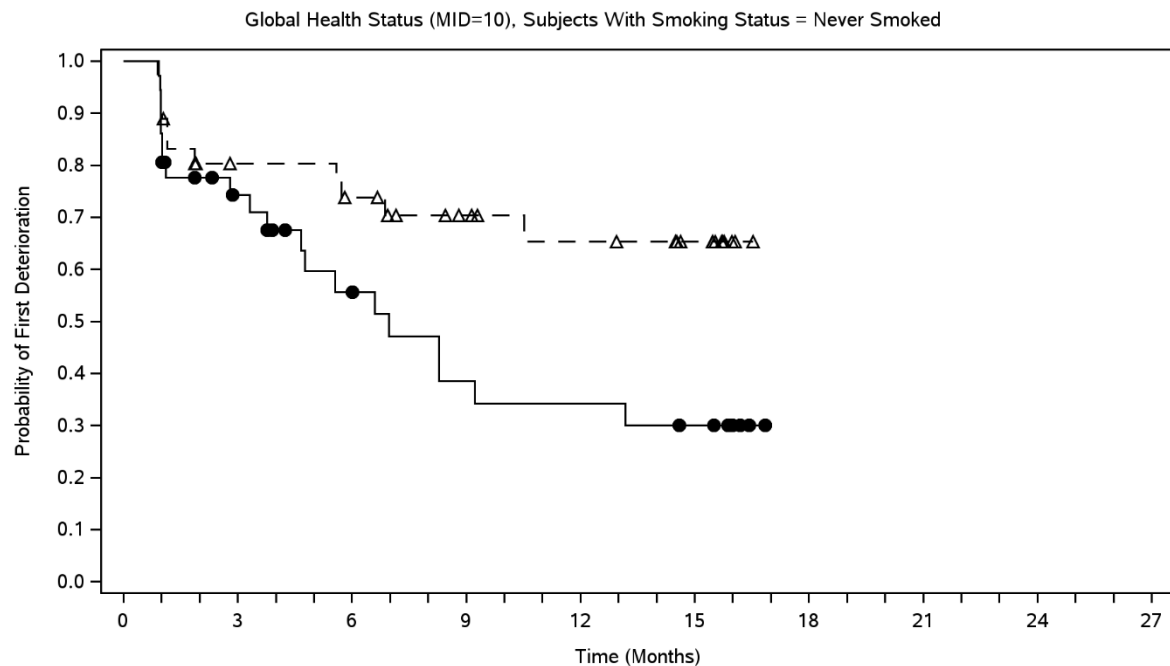
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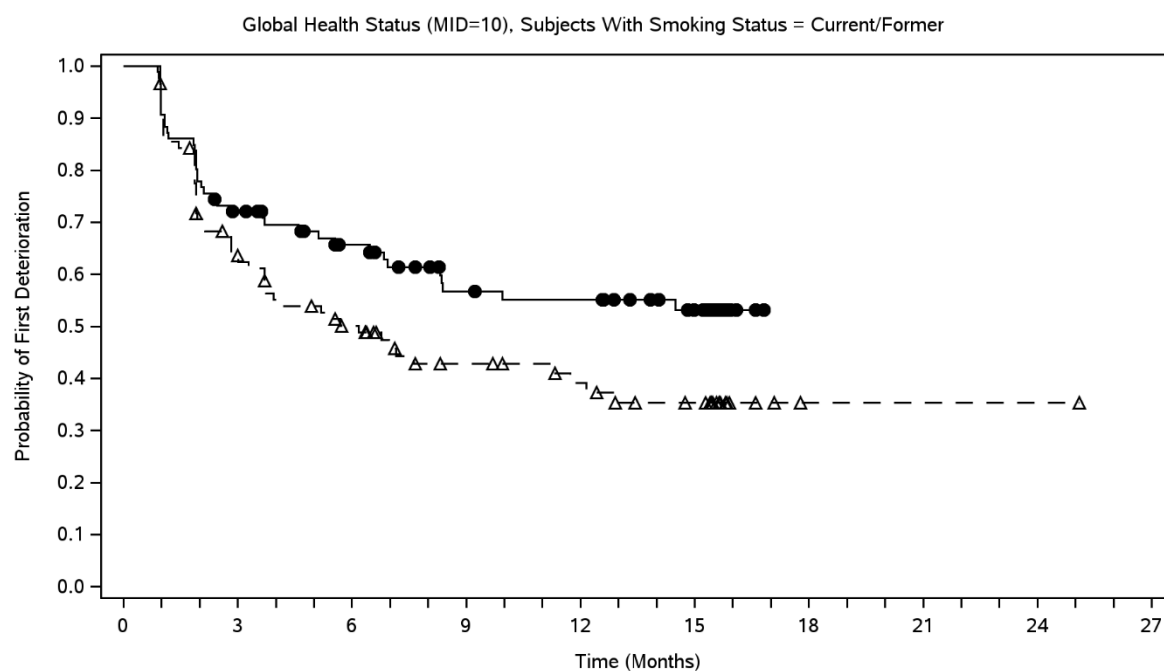
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Figure 4.1

Kaplan-Meier Plot of EORTC QLQ-C30 Time to First Deterioration - by Significant Subgroups - PROS



Number of Subjects at Risk

Placebo

90 53 38 26 21 15 1 1 1 0

Nivolumab

86 60 48 36 34 25 0 0 0 0

— △ — Placebo (events: 52/90), median and 95% CI: 6.18 (3.71, 11.73)

— ● — Nivolumab (events: 37/86), median and 95% CI: N.A. (6.93, N.A.)

Hazard Ratio (Nivolumab vs. Placebo) and 95% CI: 0.702 (0.459, 1.072)

FEB2025 DBL.

Symbols represent censored observations.

Unstratified Cox proportional hazard model,
with baseline PRO score as a covariate.

Program Path: /projects/bms214671/stats/market/ma274_202502/prog/figures

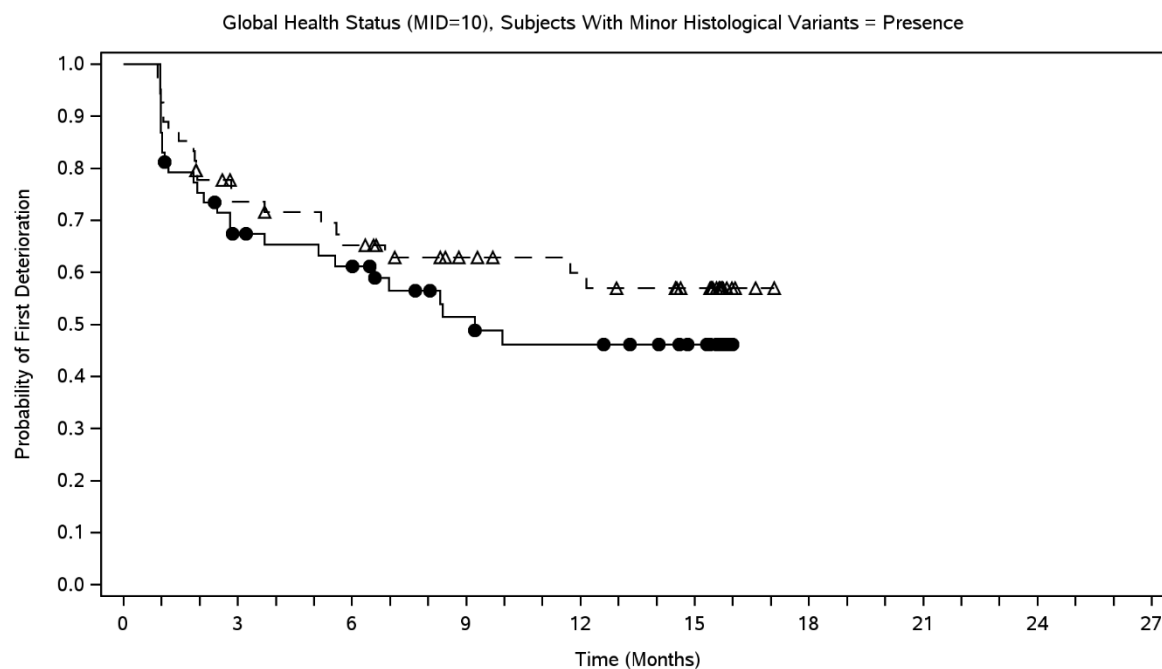
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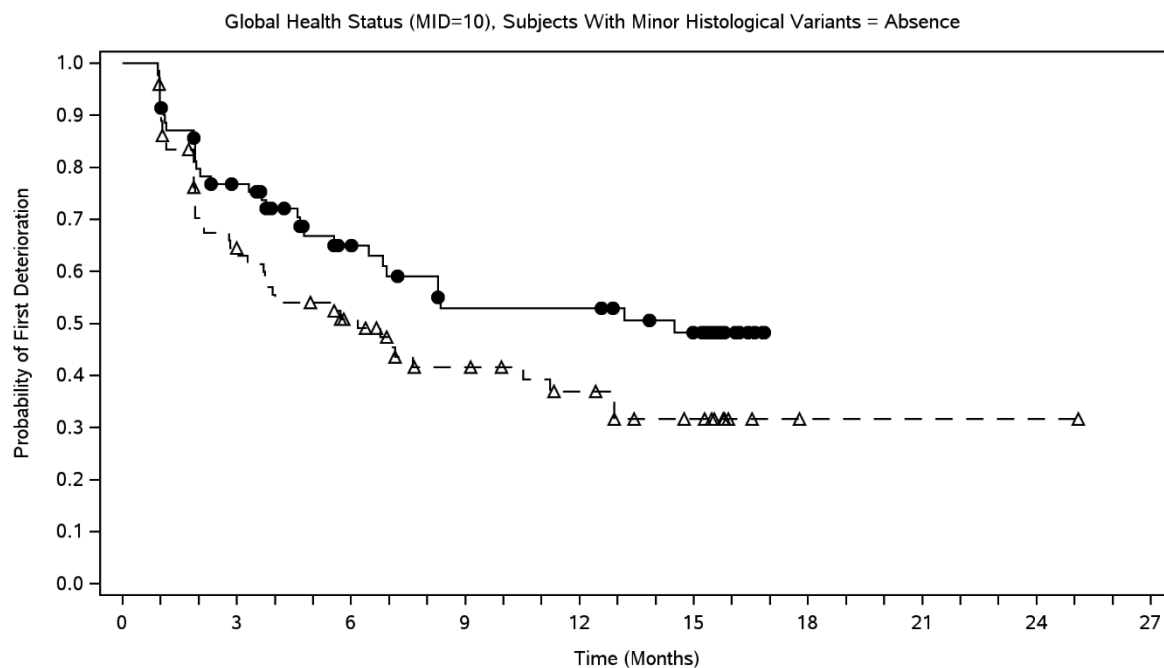
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5 Verträglichkeit: Endpunkt Zeit bis zum Auftreten des jeweiligen Ereignisses

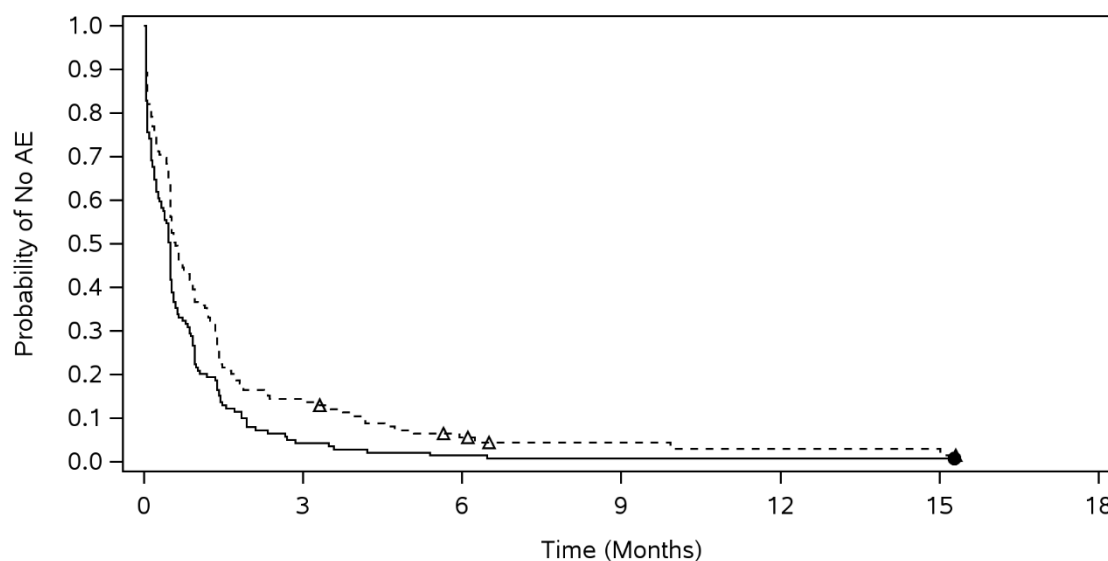
Für die Auswertungen wurde die *Safety*-Population herangezogen.

5.1 UE-Hauptkategorien (ohne Erfassung des Progresses der Grunderkrankung)

5.1.1 Kaplan-Meier Kurven

Figure 11.1

Kaplan-Meier Plot of Time to any Adverse Events - Excluding Progression Terms - SAF



Number of Subjects at Risk

(Number of Censored Subjects)

Placebo

139	20	6	3	2	2	0
(0)	(0)	(3)	(5)	(5)	(5)	(6)

Nivolumab

139	6	2	1	1	1	0
(0)	(0)	(0)	(0)	(0)	(0)	(1)

--△-- Placebo (events: 133/139), median and 95% CI: 0.59 (0.49, 0.85)

—●— Nivolumab (events: 138/139), median and 95% CI: 0.49 (0.33, 0.49)

Hazard Ratio (Nivolumab vs Placebo) and 95% CI: 1.466 (1.143, 1.881)

FEB2025 DBL.

Includes events reported between first dose and 100 days after last dose of study therapy.

Stratified Cox proportional hazard model.

Symbols represent censored observations.

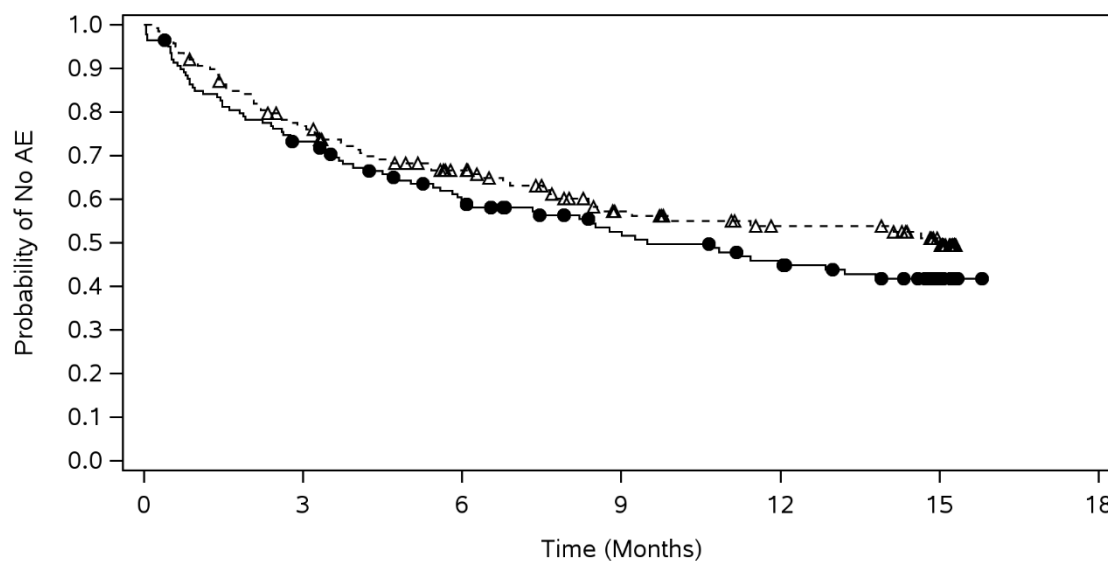
Program Path: /projects/bms214671/stats/market/ma274_202502/prog/figures

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Figure 11.2

Kaplan-Meier Plot of Time to any Adverse Events with CTCAE Grade ≥ 3 - Excluding Progression
Terms - SAF



Number of Subjects at Risk

(Number of Censored Subjects)

Placebo

139	103	78	53	43	32	0
(0)	(4)	(16)	(31)	(38)	(47)	(78)

Nivolumab

139	100	77	56	47	24	0
(0)	(2)	(7)	(20)	(22)	(41)	(65)

--△-- Placebo (events: 61/139), median and 95% CI: 15.01 (8.41, N.A.)

—●— Nivolumab (events: 74/139), median and 95% CI: 9.49 (6.11, N.A.)

Hazard Ratio (Nivolumab vs Placebo) and 95% CI: 1.230 (0.875, 1.728)

FEB2025 DBL.

Includes events reported between first dose and 100 days after last dose of study therapy.

Stratified Cox proportional hazard model.

Symbols represent censored observations.

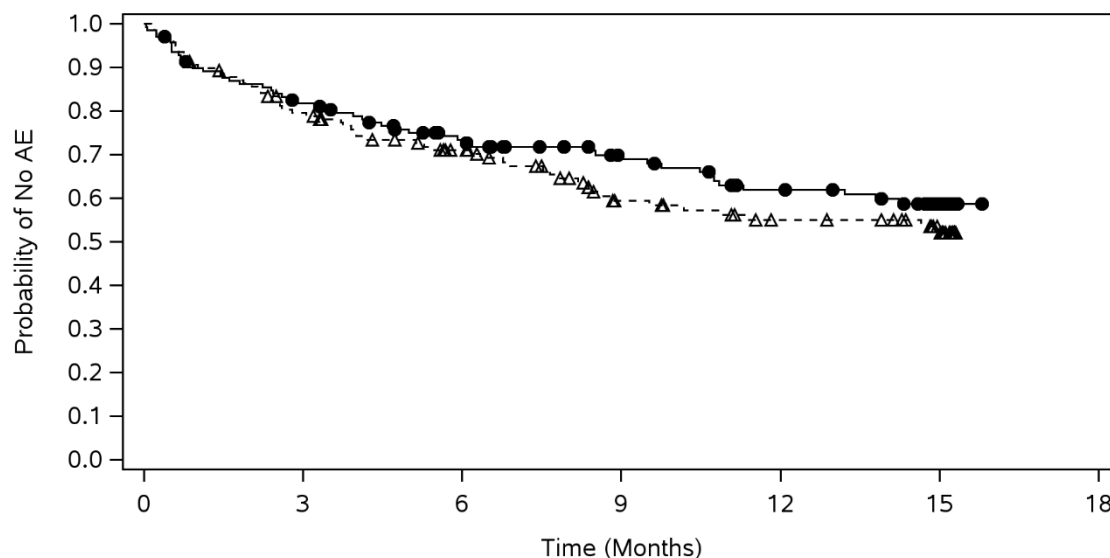
Program Path: /projects/bms214671/stats/market/ma274_202502/prog/figures

Program Name: rg-ae-ae-ebr45.sas

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Figure 11.3

Kaplan-Meier Plot of Time to any Serious Adverse Events - Excluding Progression Terms - SAF



Number of Subjects at Risk

(Number of Censored Subjects)

Placebo

139	107	83	55	45	35	0
(0)	(4)	(17)	(33)	(39)	(48)	(82)

Nivolumab

139	111	91	72	60	34	0
(0)	(3)	(12)	(27)	(31)	(54)	(88)

--△-- Placebo (events: 57/139), median and 95% CI: N.A. (9.53, N.A.)

—●— Nivolumab (events: 51/139), median and 95% CI: N.A. (14.23, N.A.)

Hazard Ratio (Nivolumab vs Placebo) and 95% CI: 0.827 (0.566, 1.209)

FEB2025 DBL.

Includes events reported between first dose and 100 days after last dose of study therapy.

Stratified Cox proportional hazard model.

Symbols represent censored observations.

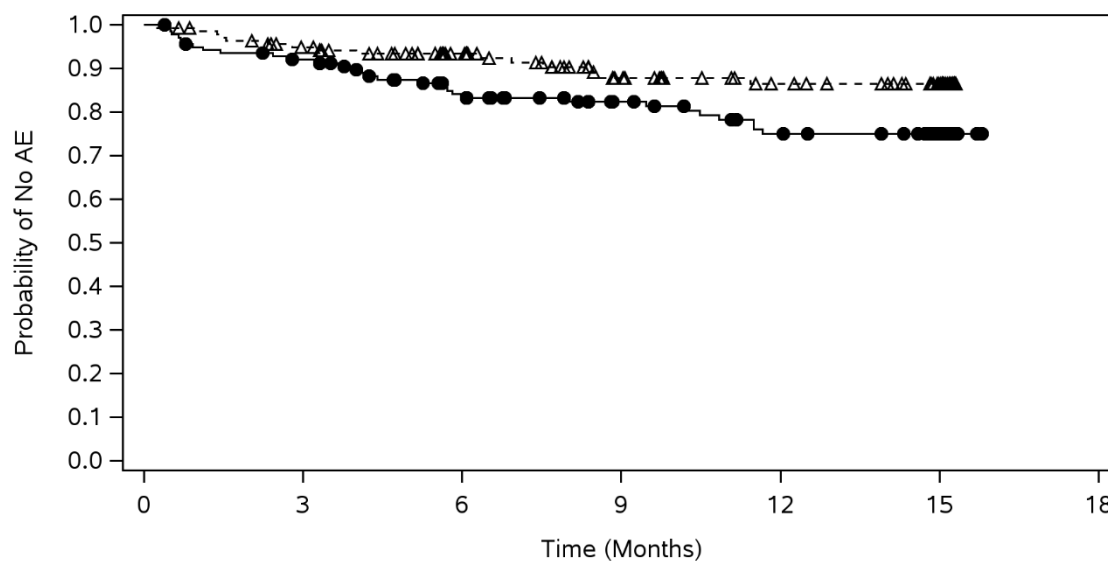
Program Path: /projects/bms214671/stats/market/ma274_202502/prog/figures

Program Name: rg-ae-ae-ebr45.sas

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Figure 11.4

Kaplan-Meier Plot of Time to any Adverse Events Leading to Discontinuation of Study Treatment
- Excluding Progression Terms - SAF



Number of Subjects at Risk

(Number of Censored Subjects)

Placebo

139	125	101	71	58	43	0
(0)	(7)	(29)	(54)	(66)	(81)	(124)

Nivolumab

139	124	100	82	70	44	0
(0)	(4)	(17)	(34)	(39)	(65)	(109)

--△-- Placebo (events: 15/139), median and 95% CI: N.A. (N.A., N.A.)

—●— Nivolumab (events: 30/139), median and 95% CI: N.A. (N.A., N.A.)

Hazard Ratio (Nivolumab vs Placebo) and 95% CI: 1.943 (1.045, 3.616)

FEB2025 DBL.

Includes events reported between first dose and 100 days after last dose of study therapy.

Stratified Cox proportional hazard model.

Symbols represent censored observations.

Program Path: /projects/bms214671/stats/market/ma274_202502/prog/figures

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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

5.1.2 Subgruppenanalysen**5.1.2.1 Schwere UE (CTCAE ≥ 3)**

Table 6.1
Subgroup Time-Adjusted Analyses
for Adverse Events with CTCAE Grade ≥ 3 on Hazard Ratio
Excluding Progression Terms
SAF

Adverse Events with CTCAE Grade 3-4-5 Subgroup	Placebo			Nivolumab			Nivolumab vs. Placebo	
	N	Subjects with Event n (%)	KME [95%CI] (mon) (1)	N	Subjects with Event n (%)	KME [95%CI] (mon) (1)	HR	Test for
							[95%CI] P-value (2) (3)	Interaction P-value (4) (5)
OVERALL	139	61 (43.9)	15.01 (8.41, N.A.)	139	74 (53.2)	9.49 (6.11, N.A.)	1.242 (0.885, 1.744) 0.2086	
PRIOR NEO-ADJUVANT CISPLATIN THERAPY								0.9128
YES	61	25 (41.0)	14.65 (8.38, N.A.)	57	30 (52.6)	9.00 (5.82, N.A.)	1.261 (0.741, 2.144) 0.3918	
NO	78	36 (46.2)	15.01 (6.18, N.A.)	82	44 (53.7)	10.84 (5.45, N.A.)	1.222 (0.786, 1.899) 0.3713	

FEB2025 DBL. Includes events reported between first dose and 100 days after last dose of the study therapy.

MedDRA Version: 27.1; CTCAE Version 4.0. HR = hazard ratio; KME = Kaplan-Meier estimate; N.M.E. = Not meaningful estimate.

(1) KME of median time to first AE. (2) Unstratified log-rank test.

(3) Unstratified Cox proportional hazard model. HR is Nivolumab over Placebo.

(4) Unstratified Cox proportional hazard model with treatment, subgroup and treatment*subgroup interaction is to assess the significance of the interaction between treatment and the subgroup.

(5) A p-value of <0.05 is indicated by 1 asterisk (indicates potential effect modification).

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Program Name: rt-ae-tsubaehr-ebr45.sas

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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

Table 6.1
Subgroup Time-Adjusted Analyses
for Adverse Events with CTCAE Grade ≥ 3 on Hazard Ratio
Excluding Progression Terms
SAF

Adverse Events with CTCAE Grade 3-4-5 Subgroup	Placebo		Nivolumab		Nivolumab vs. Placebo		Test for Interaction P-value (4) (5)
	N	Subjects with Event n (%)	KME [95%CI] (mon) (1)	N	Subjects with Event n (%)	KME [95%CI] (mon) (1)	HR [95%CI] P-value (2) (3)
PRIOR CISPLATIN STATUS							
RECEIVED NEO-ADJUVANT	61	25 (41.0)	14.65 (8.38, N.A.)	57	30 (52.6)	9.00 (5.82, N.A.)	1.261 (0.741, 2.144) 0.3918
UNWILLING TO RECEIVE NEO-ADJUVANT	45	22 (48.9)	15.01 (4.37, N.A.)	50	27 (54.0)	9.26 (3.75, N.A.)	1.240 (0.706, 2.179) 0.4561
NOT ELIGIBLE TO RECEIVE NEO-ADJUVANT	32	13 (40.6)	N.A. (5.42, N.A.)	27	13 (48.1)	13.80 (4.50, N.A.)	1.107 (0.512, 2.393) 0.7890
USE OF ANY PRIOR NEO-ADJUVANT SYSTEMIC THERAPY							
YES	62	26 (41.9)	14.65 (8.38, N.A.)	61	31 (50.8)	10.74 (5.82, N.A.)	1.192 (0.707, 2.008) 0.5106
NO	77	35 (45.5)	N.A. (6.34, N.A.)	78	43 (55.1)	9.49 (5.45, N.A.)	1.277 (0.817, 1.995) 0.2820

FEB2025 DBL. Includes events reported between first dose and 100 days after last dose of the study therapy.

MedDRA Version: 27.1; CTCAE Version 4.0. HR = hazard ratio; KME = Kaplan-Meier estimate; N.M.E. = Not meaningful estimate.

(1) KME of median time to first AE. (2) Unstratified log-rank test.

(3) Unstratified Cox proportional hazard model. HR is Nivolumab over Placebo.

(4) Unstratified Cox proportional hazard model with treatment, subgroup and treatment*subgroup interaction is to assess the significance of the interaction between treatment and the subgroup.

(5) A p-value of <0.05 is indicated by 1 asterisk (indicates potential effect modification).

Program Path: /projects/bms214671/stats/market/ma274_202502/prog/tables

Program Name: rt-ae-tsubaehr-ebr45.sas

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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

Table 6.1
Subgroup Time-Adjusted Analyses
for Adverse Events with CTCAE Grade ≥ 3 on Hazard Ratio
Excluding Progression Terms
SAF

Adverse Events with CTCAE Grade 3-4-5 Subgroup	Placebo			Nivolumab			Nivolumab vs. Placebo	
	N	Subjects with Event n (%)	KME [95%CI] (mon) (1)	N	Subjects with Event n (%)	KME [95%CI] (mon) (1)	HR [95%CI] P-value (2) (3)	Test for Interaction P-value (4) (5)
PATHOLOGICAL LYMPH NODE STATUS								0.7420
N+	64	31 (48.4)	9.20 (5.42, N.A.)	60	34 (56.7)	8.77 (4.24, N.A.)	1.141 (0.701, 1.858)	
N0/X WITH <10 NODES REMOVED	38	18 (47.4)	14.65 (4.37, N.A.)	38	20 (52.6)	9.49 (3.75, N.A.)	0.5974 1.170 (0.619, 2.212)	
N0 WITH $\geq$ 10 NODES REMOVED	37	12 (32.4)	N.A. (15.01, N.A.)	41	20 (48.8)	12.06 (5.59, N.A.)	0.6318 1.589 (0.776, 3.254)	

FEB2025 DBL. Includes events reported between first dose and 100 days after last dose of the study therapy.
MedDRA Version: 27.1; CTCAE Version 4.0. HR = hazard ratio; KME = Kaplan-Meier estimate; N.M.E. = Not meaningful estimate.

(1) KME of median time to first AE. (2) Unstratified log-rank test.

(3) Unstratified Cox proportional hazard model. HR is Nivolumab over Placebo.

(4) Unstratified Cox proportional hazard model with treatment, subgroup and treatment*subgroup interaction is to assess the significance of the interaction between treatment and the subgroup.

(5) A p-value of <0.05 is indicated by 1 asterisk (indicates potential effect modification).

Program Path: /projects/bms214671/stats/market/ma274_202502/prog/tables

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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

Table 6.1
Subgroup Time-Adjusted Analyses
for Adverse Events with CTCAE Grade ≥ 3 on Hazard Ratio
Excluding Progression Terms
SAF

Adverse Events with CTCAE Grade 3-4-5 Subgroup	Placebo			Nivolumab			Nivolumab vs. Placebo	
	N	Subjects with Event n (%)	KME [95%CI] (mon) (1)	N	Subjects with Event n (%)	KME [95%CI] (mon) (1)	HR [95%CI] P-value (2) (3)	Test for Interaction P-value (4) (5)
PATHOLOGICAL STATUS								0.3324
PT0-2	31	18 (58.1)	8.54 (4.14, N.A.)	26	13 (50.0)	10.74 (4.24, N.A.)	0.801 (0.392, 1.635)	
PT3	80	30 (37.5)	N.A. (7.75, N.A.)	86	42 (48.8)	11.24 (8.21, N.A.)	0.5407 1.289 (0.807, 2.060)	
PT4A	27	13 (48.1)	14.13 (3.71, N.A.)	23	16 (69.6)	5.45 (2.60, 12.85)	0.2864 1.794 (0.861, 3.736)	
AGE CATEGORY I								0.8415
< 65	59	25 (42.4)	15.01 (7.75, N.A.)	67	33 (49.3)	13.21 (5.03, N.A.)	1.214 (0.722, 2.042)	
≥ 65	80	36 (45.0)	N.A. (6.34, N.A.)	72	41 (56.9)	9.49 (5.82, 12.85)	0.4648 1.287 (0.822, 2.014)	

FEB2025 DBL. Includes events reported between first dose and 100 days after last dose of the study therapy.

MedDRA Version: 27.1; CTCAE Version 4.0. HR = hazard ratio; KME = Kaplan-Meier estimate; N.M.E. = Not meaningful estimate.

(1) KME of median time to first AE. (2) Unstratified log-rank test.

(3) Unstratified Cox proportional hazard model. HR is Nivolumab over Placebo.

(4) Unstratified Cox proportional hazard model with treatment, subgroup and treatment*subgroup interaction is to assess the significance of the interaction between treatment and the subgroup.

(5) A p-value of <0.05 is indicated by 1 asterisk (indicates potential effect modification).

Program Path: /projects/bms214671/stats/market/ma274_202502/prog/tables

Program Name: rt-ae-tsubaehr-ebr45.sas

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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

Table 6.1
Subgroup Time-Adjusted Analyses
for Adverse Events with CTCAE Grade ≥ 3 on Hazard Ratio
Excluding Progression Terms
SAF

Adverse Events with CTCAE Grade 3-4-5 Subgroup	Placebo			Nivolumab			Nivolumab vs. Placebo	
	N	Subjects with Event n (%)	KME [95%CI] (mon) (1)	N	Subjects with Event n (%)	KME [95%CI] (mon) (1)	HR [95%CI] P-value (2) (3)	Test for Interaction P-value (4) (5)
AGE CATEGORY II								0.8788
< 65	59	25 (42.4)	15.01 (7.75, N.A.)	67	33 (49.3)	13.21 (5.03, N.A.)	1.214 (0.722, 2.042)	
≥ 65 AND < 75	59	27 (45.8)	14.13 (6.18, N.A.)	49	27 (55.1)	9.26 (4.50, N.A.)	1.184 (0.694, 2.020)	
≥ 75	21	9 (42.9)	N.A. (4.07, N.A.)	23	14 (60.9)	10.84 (3.68, N.A.)	0.5336 1.507 (0.652, 3.485)	

FEB2025 DBL. Includes events reported between first dose and 100 days after last dose of the study therapy.

MedDRA Version: 27.1; CTCAE Version 4.0. HR = hazard ratio; KME = Kaplan-Meier estimate; N.M.E. = Not meaningful estimate.

(1) KME of median time to first AE. (2) Unstratified log-rank test.

(3) Unstratified Cox proportional hazard model. HR is Nivolumab over Placebo.

(4) Unstratified Cox proportional hazard model with treatment, subgroup and treatment*subgroup interaction is to assess the significance of the interaction between treatment and the subgroup.

(5) A p-value of <0.05 is indicated by 1 asterisk (indicates potential effect modification).

Program Path: /projects/bms214671/stats/market/ma274_202502/prog/tables

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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

Table 6.1
Subgroup Time-Adjusted Analyses
for Adverse Events with CTCAE Grade ≥ 3 on Hazard Ratio
Excluding Progression Terms
SAF

Adverse Events with CTCAE Grade 3-4-5 Subgroup	Placebo			Nivolumab			Nivolumab vs. Placebo	
	N	Subjects with Event n (%)	KME [95%CI] (mon) (1)	N	Subjects with Event n (%)	KME [95%CI] (mon) (1)	HR [95%CI] P-value (2) (3)	Test for Interaction P-value (4) (5)
REGION								0.5859
US	23	13 (56.5)	7.52 (2.04, N.A.)	17	10 (58.8)	3.94 (0.85, N.A.)	1.047 (0.458, 2.390)	
EUROPE	68	26 (38.2)	N.A. (9.89, N.A.)	72	35 (48.6)	12.06 (7.36, N.A.)	0.9192 1.291 (0.777, 2.144)	
ASIA	28	11 (39.3)	N.A. (5.42, N.A.)	33	21 (63.6)	8.77 (2.63, 12.85)	0.3221 1.838 (0.885, 3.817)	
REST OF WORLD	20	11 (55.0)	6.90 (2.53, N.A.)	17	8 (47.1)	N.A. (1.38, N.A.)	0.0973 0.907 (0.364, 2.262)	

FEB2025 DBL. Includes events reported between first dose and 100 days after last dose of the study therapy.

MedDRA Version: 27.1; CTCAE Version 4.0. HR = hazard ratio; KME = Kaplan-Meier estimate; N.M.E. = Not meaningful estimate.

(1) KME of median time to first AE. (2) Unstratified log-rank test.

(3) Unstratified Cox proportional hazard model. HR is Nivolumab over Placebo.

(4) Unstratified Cox proportional hazard model with treatment, subgroup and treatment*subgroup interaction is to assess the significance of the interaction between treatment and the subgroup.

(5) A p-value of <0.05 is indicated by 1 asterisk (indicates potential effect modification).

Program Path: /projects/bms214671/stats/market/ma274_202502/prog/tables

Program Name: rt-ae-tsubaehr-ebr45.sas

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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

Table 6.1
Subgroup Time-Adjusted Analyses
for Adverse Events with CTCAE Grade ≥ 3 on Hazard Ratio
Excluding Progression Terms
SAF

Adverse Events with CTCAE Grade 3-4-5 Subgroup	Placebo			Nivolumab			Nivolumab vs. Placebo	
	N	Subjects with Event n (%)	KME [95%CI] (mon) (1)	N	Subjects with Event n (%)	KME [95%CI] (mon) (1)	HR [95%CI] P-value (2) (3)	Test for Interaction P-value (4) (5)
GENDER								0.5038
MALE	109	47 (43.1)	15.01 (8.54, N.A.)	101	54 (53.5)	10.74 (5.59, N.A.)	1.316 (0.890, 1.946)	
FEMALE	30	14 (46.7)	N.A. (2.14, N.A.)	38	20 (52.6)	9.00 (5.82, N.A.)	0.1674 0.988 (0.498, 1.960)	
RACE								0.2109
WHITE	106	48 (45.3)	15.01 (8.41, N.A.)	103	51 (49.5)	11.24 (7.33, N.A.)	1.087 (0.733, 1.613)	
ASIAN	28	11 (39.3)	N.A. (5.42, N.A.)	33	21 (63.6)	8.77 (2.63, 12.85)	0.6780 1.838 (0.885, 3.817)	

FEB2025 DBL. Includes events reported between first dose and 100 days after last dose of the study therapy.

MedDRA Version: 27.1; CTCAE Version 4.0. HR = hazard ratio; KME = Kaplan-Meier estimate; N.M.E. = Not meaningful estimate.

(1) KME of median time to first AE. (2) Unstratified log-rank test.

(3) Unstratified Cox proportional hazard model. HR is Nivolumab over Placebo.

(4) Unstratified Cox proportional hazard model with treatment, subgroup and treatment*subgroup interaction is to assess the significance of the interaction between treatment and the subgroup.

(5) A p-value of <0.05 is indicated by 1 asterisk (indicates potential effect modification).

Program Path: /projects/bms214671/stats/market/ma274_202502/prog/tables

Program Name: rt-ae-tsubaehr-ebr45.sas

23JUN2025:09:49:52

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

Table 6.1
Subgroup Time-Adjusted Analyses
for Adverse Events with CTCAE Grade ≥ 3 on Hazard Ratio
Excluding Progression Terms
SAF

Adverse Events with CTCAE Grade 3-4-5 Subgroup	Placebo			Nivolumab			Nivolumab vs. Placebo	
	N	Subjects with Event n (%)	KME [95%CI] (mon) (1)	N	Subjects with Event n (%)	KME [95%CI] (mon) (1)	HR [95%CI] P-value (2) (3)	Test for Interaction P-value (4) (5)
BASELINE ECOG STATUS								0.5377
0	83	33 (39.8)	N.A. (8.54, N.A.)	85	45 (52.9)	10.84 (5.91, N.A.)	1.386 (0.884, 2.173) 0.1528	
1	52	26 (50.0)	9.20 (4.14, N.A.)	51	28 (54.9)	9.49 (3.61, N.A.)	1.116 (0.654, 1.904) 0.6860	
SMOKING STATUS								0.5209
NEVER SMOKED	39	19 (48.7)	7.66 (2.60, N.A.)	41	22 (53.7)	9.26 (3.45, N.A.)	1.004 (0.543, 1.856) 0.9878	
CURRENT/FORMER	99	42 (42.4)	15.01 (8.54, N.A.)	96	50 (52.1)	10.84 (6.11, N.A.)	1.282 (0.850, 1.932) 0.2341	

FEB2025 DBL. Includes events reported between first dose and 100 days after last dose of the study therapy.

MedDRA Version: 27.1; CTCAE Version 4.0. HR = hazard ratio; KME = Kaplan-Meier estimate; N.M.E. = Not meaningful estimate.

(1) KME of median time to first AE. (2) Unstratified log-rank test.

(3) Unstratified Cox proportional hazard model. HR is Nivolumab over Placebo.

(4) Unstratified Cox proportional hazard model with treatment, subgroup and treatment*subgroup interaction is to assess the significance of the interaction between treatment and the subgroup.

(5) A p-value of <0.05 is indicated by 1 asterisk (indicates potential effect modification).

Program Path: /projects/bms214671/stats/market/ma274_202502/prog/tables

Program Name: rt-ae-tsubaehr-ebr45.sas

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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

Table 6.1
Subgroup Time-Adjusted Analyses
for Adverse Events with CTCAE Grade ≥ 3 on Hazard Ratio
Excluding Progression Terms
SAF

Adverse Events with CTCAE Grade 3-4-5 Subgroup	Placebo			Nivolumab			Nivolumab vs. Placebo	
	N	Subjects with Event n (%)	KME [95%CI] (mon) (1)	N	Subjects with Event n (%)	KME [95%CI] (mon) (1)	HR [95%CI] P-value (2) (3)	Test for Interaction P-value (4) (5)
BASELINE HEMOGLOBIN								0.3623
<10 G/DL	14	9 (64.3)	4.58 (1.38, N.A.)	7	6 (85.7)	0.92 (0.56, 11.43)	2.155 (0.754, 6.159)	
							0.1428	
≥ 10 G/DL	125	52 (41.6)	N.A. (8.54, N.A.)	132	68 (51.5)	10.74 (7.33, N.A.)	1.253 (0.873, 1.797)	
							0.2214	
BASELINE CREATININE CLEARANCE								0.1466
<60 ML/MIN	60	31 (51.7)	9.20 (4.37, N.A.)	54	27 (50.0)	11.43 (5.45, N.A.)	0.930 (0.555, 1.558)	
							0.7814	
≥ 60 ML/MIN	79	30 (38.0)	N.A. (8.41, N.A.)	84	46 (54.8)	9.00 (5.03, N.A.)	1.546 (0.976, 2.450)	
							0.0614	

FEB2025 DBL. Includes events reported between first dose and 100 days after last dose of the study therapy.

MedDRA Version: 27.1; CTCAE Version 4.0. HR = hazard ratio; KME = Kaplan-Meier estimate; N.M.E. = Not meaningful estimate.

(1) KME of median time to first AE. (2) Unstratified log-rank test.

(3) Unstratified Cox proportional hazard model. HR is Nivolumab over Placebo.

(4) Unstratified Cox proportional hazard model with treatment, subgroup and treatment*subgroup interaction is to assess the significance of the interaction between treatment and the subgroup.

(5) A p-value of <0.05 is indicated by 1 asterisk (indicates potential effect modification).

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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

Table 6.1
Subgroup Time-Adjusted Analyses
for Adverse Events with CTCAE Grade ≥ 3 on Hazard Ratio
Excluding Progression Terms
SAF

Adverse Events with CTCAE Grade 3-4-5 Subgroup	Placebo			Nivolumab			Nivolumab vs. Placebo	
	N	Subjects with Event n (%)	KME [95%CI] (mon) (1)	N	Subjects with Event n (%)	KME [95%CI] (mon) (1)	HR [95%CI] P-value (2) (3)	Test for Interaction P-value (4) (5)
TIME FROM IUC SURGERY TO RANDOMIZATION (DAYS)								0.2042
>30-60	28	11 (39.3)	N.A. (4.37, N.A.)	34	23 (67.6)	5.59 (1.87, 8.51)	2.185 (1.064, 4.488) 0.0288	
>60-90	65	29 (44.6)	15.01 (7.75, N.A.)	57	29 (50.9)	12.85 (5.98, N.A.)	1.094 (0.653, 1.830) 0.7374	
>90-120	41	19 (46.3)	9.89 (5.42, N.A.)	46	22 (47.8)	12.06 (5.45, N.A.)	1.044 (0.565, 1.930) 0.8936	

FEB2025 DBL. Includes events reported between first dose and 100 days after last dose of the study therapy.

MedDRA Version: 27.1; CTCAE Version 4.0. HR = hazard ratio; KME = Kaplan-Meier estimate; N.M.E. = Not meaningful estimate.

(1) KME of median time to first AE. (2) Unstratified log-rank test.

(3) Unstratified Cox proportional hazard model. HR is Nivolumab over Placebo.

(4) Unstratified Cox proportional hazard model with treatment, subgroup and treatment*subgroup interaction is to assess the significance of the interaction between treatment and the subgroup.

(5) A p-value of <0.05 is indicated by 1 asterisk (indicates potential effect modification).

Program Path: /projects/bms214671/stats/market/ma274_202502/prog/tables

Program Name: rt-ae-tsubaehr-ebr45.sas

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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

Table 6.1
Subgroup Time-Adjusted Analyses
for Adverse Events with CTCAE Grade ≥ 3 on Hazard Ratio
Excluding Progression Terms
SAF

Adverse Events with CTCAE Grade 3-4-5 Subgroup	Placebo			Nivolumab			Nivolumab vs. Placebo	
	N	Subjects with Event n (%)	KME [95%CI] (mon) (1)	N	Subjects with Event n (%)	KME [95%CI] (mon) (1)	HR [95%CI] P-value (2) (3)	Test for Interaction P-value (4) (5)
INITIAL TUMOR ORIGIN								0.9146
URINARY BLADDER	115	51 (44.3)	15.01 (8.38, N.A.)	112	58 (51.8)	10.74 (6.01, N.A.)	1.194 (0.819, 1.739)	
RENAL PELVIS	13	5 (38.5)	N.A. (1.38, N.A.)	19	12 (63.2)	9.49 (2.76, N.A.)	0.3558 1.482 (0.520, 4.222)	
URETER	11	5 (45.5)	N.A. (2.30, N.A.)	8	4 (50.0)	5.45 (0.69, N.A.)	0.4581 1.688 (0.447, 6.379)	
MINOR HISTOLOGICAL VARIANTS								0.7915
PRESENCE	60	21 (35.0)	N.A. (9.89, N.A.)	61	27 (44.3)	13.21 (8.51, N.A.)	1.317 (0.745, 2.330)	
ABSENCE	79	40 (50.6)	9.20 (5.42, N.A.)	78	47 (60.3)	6.01 (3.94, 12.85)	0.3423 1.203 (0.789, 1.835)	

FEB2025 DBL. Includes events reported between first dose and 100 days after last dose of the study therapy.

MedDRA Version: 27.1; CTCAE Version 4.0. HR = hazard ratio; KME = Kaplan-Meier estimate; N.M.E. = Not meaningful estimate.

(1) KME of median time to first AE. (2) Unstratified log-rank test.

(3) Unstratified Cox proportional hazard model. HR is Nivolumab over Placebo.

(4) Unstratified Cox proportional hazard model with treatment, subgroup and treatment*subgroup interaction is to assess the significance of the interaction between treatment and the subgroup.

(5) A p-value of <0.05 is indicated by 1 asterisk (indicates potential effect modification).

Program Path: /projects/bms214671/stats/market/ma274_202502/prog/tables

Program Name: rt-ae-tsubaehr-ebr45.sas

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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

5.1.2.2 SUE

Table 6.2
Subgroup Time-Adjusted Analyses
for Serious Adverse Events on Hazard Ratio
Excluding Progression Terms
SAF

Serious Adverse Events Subgroup	Placebo			Nivolumab			Nivolumab vs. Placebo	
	N	Subjects with Event n (%)	KME [95%CI] (mon) (1)	N	Subjects with Event n (%)	KME [95%CI] (mon) (1)	HR [95%CI] P-value (2) (3)	Test for Interaction P-value (4) (5)
OVERALL	139	57 (41.0)	N.A. (9.53, N.A.)	139	51 (36.7)	N.A. (14.23, N.A.)	0.830 (0.569, 1.212) 0.3331	
PRIOR NEO-ADJUVANT CISPLATIN THERAPY								0.6825
YES	61	25 (41.0)	14.65 (8.41, N.A.)	57	24 (42.1)	N.A. (9.76, N.A.)	0.884 (0.504, 1.550) 0.6675	
NO	78	32 (41.0)	N.A. (8.18, N.A.)	82	27 (32.9)	N.A.	0.787 (0.471, 1.314) 0.3582	

FEB2025 DBL. Includes events reported between first dose and 100 days after last dose of the study therapy.

MedDRA Version: 27.1; CTCAE Version 4.0. HR = hazard ratio; KME = Kaplan-Meier estimate; N.M.E. = Not meaningful estimate.

(1) KME of median time to first AE. (2) Unstratified log-rank test.

(3) Unstratified Cox proportional hazard model. HR is Nivolumab over Placebo.

(4) Unstratified Cox proportional hazard model with treatment, subgroup and treatment*subgroup interaction is to assess the significance of the interaction between treatment and the subgroup.

(5) A p-value of <0.05 is indicated by 1 asterisk (indicates potential effect modification).

Program Path: /projects/bms214671/stats/market/ma274_202502/prog/tables

Program Name: rt-ae-tsubaehr-ebr45.sas

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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

Table 6.2
Subgroup Time-Adjusted Analyses
for Serious Adverse Events on Hazard Ratio
Excluding Progression Terms
SAF

Serious Adverse Events Subgroup	Placebo			Nivolumab			Nivolumab vs. Placebo		Test for Interaction P-value (4) (5)
	N	Subjects with Event n (%)	KME [95%CI] (mon) (1)	N	Subjects with Event n (%)	KME [95%CI] (mon) (1)	HR [95%CI] P-value (2) (3)		
PRIOR CISPLATIN STATUS RECEIVED NEO-ADJUVANT	61	25 (41.0)	14.65 (8.41, N.A.)	57	24 (42.1)	N.A. (9.76, N.A.)	0.884 (0.504, 1.550)	0.4438	
UNWILLING TO RECEIVE NEO-ADJUVANT	45	20 (44.4)	N.A. (6.34, N.A.)	50	13 (26.0)	N.A.	0.6675 0.588 (0.292, 1.183)		
NOT ELIGIBLE TO RECEIVE NEO-ADJUVANT	32	12 (37.5)	N.A. (6.24, N.A.)	27	12 (44.4)	N.A. (4.47, N.A.)	0.1321 1.121 (0.502, 2.503)		
USE OF ANY PRIOR NEO-ADJUVANT SYSTEMIC THERAPY YES	62	25 (40.3)	14.65 (8.41, N.A.)	61	24 (39.3)	N.A. (10.68, N.A.)	0.7843 0.828 (0.472, 1.453)	0.9034	
NO	77	32 (41.6)	N.A. (7.66, N.A.)	78	27 (34.6)	N.A. (13.80, N.A.)	0.5105 0.825 (0.494, 1.378)		
							0.4606		

FEB2025 DBL. Includes events reported between first dose and 100 days after last dose of the study therapy.

MedDRA Version: 27.1; CTCAE Version 4.0. HR = hazard ratio; KME = Kaplan-Meier estimate; N.M.E. = Not meaningful estimate.

(1) KME of median time to first AE. (2) Unstratified log-rank test.

(3) Unstratified Cox proportional hazard model. HR is Nivolumab over Placebo.

(4) Unstratified Cox proportional hazard model with treatment, subgroup and treatment*subgroup interaction is to assess the significance of the interaction between treatment and the subgroup.

(5) A p-value of <0.05 is indicated by 1 asterisk (indicates potential effect modification).

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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

Table 6.2
Subgroup Time-Adjusted Analyses
for Serious Adverse Events on Hazard Ratio
Excluding Progression Terms
SAF

Serious Adverse Events Subgroup	Placebo			Nivolumab			Nivolumab vs. Placebo	
	N	Subjects with Event n (%)	KME [95%CI] (mon) (1)	N	Subjects with Event n (%)	KME [95%CI] (mon) (1)	HR [95%CI] P-value (2) (3)	Test for Interaction P-value (4) (5)
PATHOLOGICAL LYMPH NODE STATUS								0.9929
N+	64	28 (43.8)	10.18 (7.52, N.A.)	60	25 (41.7)	N.A. (9.76, N.A.)	0.837 (0.487, 1.438)	
N0/X WITH <10 NODES REMOVED	38	15 (39.5)	N.A. (7.66, N.A.)	38	12 (31.6)	N.A. (10.48, N.A.)	0.5192 0.793 (0.371, 1.695)	
N0 WITH >= 10 NODES REMOVED	37	14 (37.8)	N.A. (7.75, N.A.)	41	14 (34.1)	N.A. (10.68, N.A.)	0.5460 0.850 (0.405, 1.785)	

FEB2025 DBL. Includes events reported between first dose and 100 days after last dose of the study therapy.

MedDRA Version: 27.1; CTCAE Version 4.0. HR = hazard ratio; KME = Kaplan-Meier estimate; N.M.E. = Not meaningful estimate.

(1) KME of median time to first AE. (2) Unstratified log-rank test.

(3) Unstratified Cox proportional hazard model. HR is Nivolumab over Placebo.

(4) Unstratified Cox proportional hazard model with treatment, subgroup and treatment*subgroup interaction is to assess the significance of the interaction between treatment and the subgroup.

(5) A p-value of <0.05 is indicated by 1 asterisk (indicates potential effect modification).

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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

Table 6.2
Subgroup Time-Adjusted Analyses
for Serious Adverse Events on Hazard Ratio
Excluding Progression Terms
SAF

Serious Adverse Events Subgroup	Placebo			Nivolumab			Nivolumab vs. Placebo	
	N	Subjects with Event n (%)	KME [95%CI] (mon) (1)	N	Subjects with Event n (%)	KME [95%CI] (mon) (1)	HR [95%CI] P-value (2) (3)	Test for Interaction P-value (4) (5)
PATHOLOGICAL STATUS								0.4079
PT0-2	31	18 (58.1)	8.54 (4.17, N.A.)	26	11 (42.3)	N.A. (4.99, N.A.)	0.633 (0.299, 1.341)	
PT3	80	27 (33.8)	N.A. (10.18, N.A.)	86	31 (36.0)	N.A. (11.30, N.A.)	0.2285 0.999 (0.596, 1.675)	
PT4A	27	12 (44.4)	N.A. (3.71, N.A.)	23	6 (26.1)	N.A. (5.91, N.A.)	0.9954 0.521 (0.195, 1.392)	
AGE CATEGORY I								0.6707
< 65	59	22 (37.3)	N.A. (10.91, N.A.)	67	21 (31.3)	N.A.	0.774 (0.425, 1.409)	
>= 65	80	35 (43.8)	10.18 (7.66, N.A.)	72	30 (41.7)	N.A. (9.76, N.A.)	0.4019 0.901 (0.553, 1.468)	

FEB2025 DBL. Includes events reported between first dose and 100 days after last dose of the study therapy.

MedDRA Version: 27.1; CTCAE Version 4.0. HR = hazard ratio; KME = Kaplan-Meier estimate; N.M.E. = Not meaningful estimate.

(1) KME of median time to first AE. (2) Unstratified log-rank test.

(3) Unstratified Cox proportional hazard model. HR is Nivolumab over Placebo.

(4) Unstratified Cox proportional hazard model with treatment, subgroup and treatment*subgroup interaction is to assess the significance of the interaction between treatment and the subgroup.

(5) A p-value of <0.05 is indicated by 1 asterisk (indicates potential effect modification).

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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

Table 6.2
Subgroup Time-Adjusted Analyses
for Serious Adverse Events on Hazard Ratio
Excluding Progression Terms
SAF

Serious Adverse Events Subgroup	Placebo			Nivolumab			Nivolumab vs. Placebo	
	N	Subjects with Event n (%)	KME [95%CI] (mon) (1)	N	Subjects with Event n (%)	KME [95%CI] (mon) (1)	HR	Test for
							[95%CI] P-value (2) (3)	Interaction P-value (4) (5)
AGE CATEGORY II								0.9047
< 65	59	22 (37.3)	N.A. (10.91, N.A.)	67	21 (31.3)	N.A.	0.774 (0.425, 1.409)	
>= 65 AND < 75	59	26 (44.1)	10.18 (7.66, N.A.)	49	20 (40.8)	N.A. (9.00, N.A.)	0.4019 0.873 (0.487, 1.565)	
>= 75	21	9 (42.9)	N.A. (3.91, N.A.)	23	10 (43.5)	13.80 (4.47, N.A.)	0.6483 0.961 (0.390, 2.370)	
							0.9267	

FEB2025 DBL. Includes events reported between first dose and 100 days after last dose of the study therapy.

MedDRA Version: 27.1; CTCAE Version 4.0. HR = hazard ratio; KME = Kaplan-Meier estimate; N.M.E. = Not meaningful estimate.

(1) KME of median time to first AE. (2) Unstratified log-rank test.

(3) Unstratified Cox proportional hazard model. HR is Nivolumab over Placebo.

(4) Unstratified Cox proportional hazard model with treatment, subgroup and treatment*subgroup interaction is to assess the significance of the interaction between treatment and the subgroup.

(5) A p-value of <0.05 is indicated by 1 asterisk (indicates potential effect modification).

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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

Table 6.2
Subgroup Time-Adjusted Analyses
for Serious Adverse Events on Hazard Ratio
Excluding Progression Terms
SAF

Serious Adverse Events Subgroup	Placebo			Nivolumab			Nivolumab vs. Placebo	
	N	Subjects with Event n (%)	KME [95%CI] (mon) (1)	N	Subjects with Event n (%)	KME [95%CI] (mon) (1)	HR [95%CI] P-value (2) (3)	Test for Interaction P-value (4) (5)
REGION								0.2460
US	23	13 (56.5)	8.38 (2.20, N.A.)	17	7 (41.2)	10.68 (3.94, N.A.)	0.597 (0.238, 1.500)	
EUROPE	68	26 (38.2)	N.A. (9.53, N.A.)	72	27 (37.5)	N.A. (10.84, N.A.)	0.2671 0.933 (0.545, 1.600)	
ASIA	28	8 (28.6)	N.A. (6.34, N.A.)	33	13 (39.4)	N.A. (4.47, N.A.)	0.8019 1.437 (0.595, 3.470)	
REST OF WORLD	20	10 (50.0)	14.65 (2.53, N.A.)	17	4 (23.5)	N.A. (14.23, N.A.)	0.4173 0.383 (0.119, 1.237)	

FEB2025 DBL. Includes events reported between first dose and 100 days after last dose of the study therapy.

MedDRA Version: 27.1; CTCAE Version 4.0. HR = hazard ratio; KME = Kaplan-Meier estimate; N.M.E. = Not meaningful estimate.

(1) KME of median time to first AE. (2) Unstratified log-rank test.

(3) Unstratified Cox proportional hazard model. HR is Nivolumab over Placebo.

(4) Unstratified Cox proportional hazard model with treatment, subgroup and treatment*subgroup interaction is to assess the significance of the interaction between treatment and the subgroup.

(5) A p-value of <0.05 is indicated by 1 asterisk (indicates potential effect modification).

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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

Table 6.2
Subgroup Time-Adjusted Analyses
for Serious Adverse Events on Hazard Ratio
Excluding Progression Terms
SAF

Serious Adverse Events Subgroup	Placebo			Nivolumab			Nivolumab vs. Placebo	
	N	Subjects with Event n (%)	KME [95%CI] (mon) (1)	N	Subjects with Event n (%)	KME [95%CI] (mon) (1)	HR [95%CI] P-value (2) (3)	Test for Interaction P-value (4) (5)
GENDER								
MALE	109	45 (41.3)	N.A. (8.54, N.A.)	101	37 (36.6)	N.A. (13.80, N.A.)	0.823 (0.532, 1.272) 0.3779	0.9623
FEMALE	30	12 (40.0)	N.A. (5.29, N.A.)	38	14 (36.8)	N.A. (8.51, N.A.)	0.849 (0.393, 1.837) 0.6757	
RACE								
WHITE	106	47 (44.3)	15.01 (8.54, N.A.)	103	36 (35.0)	N.A. (14.23, N.A.)	0.702 (0.455, 1.085) 0.1092	0.1527
ASIAN	28	8 (28.6)	N.A. (6.34, N.A.)	33	13 (39.4)	N.A. (4.47, N.A.)	1.437 (0.595, 3.470) 0.4173	

FEB2025 DBL. Includes events reported between first dose and 100 days after last dose of the study therapy.

MedDRA Version: 27.1; CTCAE Version 4.0. HR = hazard ratio; KME = Kaplan-Meier estimate; N.M.E. = Not meaningful estimate.

(1) KME of median time to first AE. (2) Unstratified log-rank test.

(3) Unstratified Cox proportional hazard model. HR is Nivolumab over Placebo.

(4) Unstratified Cox proportional hazard model with treatment, subgroup and treatment*subgroup interaction is to assess the significance of the interaction between treatment and the subgroup.

(5) A p-value of <0.05 is indicated by 1 asterisk (indicates potential effect modification).

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Table 6.2
Subgroup Time-Adjusted Analyses
for Serious Adverse Events on Hazard Ratio
Excluding Progression Terms
SAF

Serious Adverse Events Subgroup	Placebo			Nivolumab			Nivolumab vs. Placebo	
	N	Subjects with Event n (%)	KME [95%CI] (mon) (1)	N	Subjects with Event n (%)	KME [95%CI] (mon) (1)	HR [95%CI] P-value (2) (3)	Test for Interaction P-value (4) (5)
BASELINE ECOG STATUS								
0	83	30 (36.1)	N.A. (10.18, N.A.)	85	34 (40.0)	N.A. (11.30, N.A.)	1.038 (0.634, 1.699) 0.8826	0.1310
1	52	25 (48.1)	15.01 (3.91, N.A.)	51	16 (31.4)	N.A. (10.74, N.A.)	0.577 (0.308, 1.082) 0.0829	
SMOKING STATUS								
NEVER SMOKED	39	15 (38.5)	N.A. (5.42, N.A.)	41	16 (39.0)	N.A. (9.76, N.A.)	0.936 (0.462, 1.895) 0.8543	0.6470
CURRENT/FORMER	99	42 (42.4)	15.01 (8.54, N.A.)	96	34 (35.4)	N.A. (13.80, N.A.)	0.770 (0.490, 1.211) 0.2560	

FEB2025 DBL. Includes events reported between first dose and 100 days after last dose of the study therapy.

MedDRA Version: 27.1; CTCAE Version 4.0. HR = hazard ratio; KME = Kaplan-Meier estimate; N.M.E. = Not meaningful estimate.

(1) KME of median time to first AE. (2) Unstratified log-rank test.

(3) Unstratified Cox proportional hazard model. HR is Nivolumab over Placebo.

(4) Unstratified Cox proportional hazard model with treatment, subgroup and treatment*subgroup interaction is to assess the significance of the interaction between treatment and the subgroup.

(5) A p-value of <0.05 is indicated by 1 asterisk (indicates potential effect modification).

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Table 6.2
Subgroup Time-Adjusted Analyses
for Serious Adverse Events on Hazard Ratio
Excluding Progression Terms
SAF

Serious Adverse Events Subgroup	Placebo			Nivolumab			Nivolumab vs. Placebo	
	N	Subjects with Event n (%)	KME [95%CI] (mon) (1)	N	Subjects with Event n (%)	KME [95%CI] (mon) (1)	HR [95%CI] P-value (2) (3)	Test for Interaction P-value (4) (5)
BASELINE HEMOGLOBIN <10 G/DL	14	8 (57.1)	8.77 (1.48, N.A.)	7	4 (57.1)	10.68 (0.53, N.A.)	1.031 (0.307, 3.456) 0.9659	0.7642
>=10 G/DL	125	49 (39.2)	N.A. (9.53, N.A.)	132	47 (35.6)	N.A. (14.23, N.A.)	0.839 (0.562, 1.253) 0.3909	
BASELINE CREATININE CLEARANCE <60 ML/MIN	60	29 (48.3)	9.53 (6.34, N.A.)	54	19 (35.2)	N.A. (10.68, N.A.)	0.672 (0.377, 1.200) 0.1754	0.3366
>=60 ML/MIN	79	28 (35.4)	N.A. (10.91, N.A.)	84	31 (36.9)	N.A. (11.30, N.A.)	0.972 (0.582, 1.621) 0.9131	

FEB2025 DBL. Includes events reported between first dose and 100 days after last dose of the study therapy.

MedDRA Version: 27.1; CTCAE Version 4.0. HR = hazard ratio; KME = Kaplan-Meier estimate; N.M.E. = Not meaningful estimate.

(1) KME of median time to first AE. (2) Unstratified log-rank test.

(3) Unstratified Cox proportional hazard model. HR is Nivolumab over Placebo.

(4) Unstratified Cox proportional hazard model with treatment, subgroup and treatment*subgroup interaction is to assess the significance of the interaction between treatment and the subgroup.

(5) A p-value of <0.05 is indicated by 1 asterisk (indicates potential effect modification).

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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

Table 6.2
Subgroup Time-Adjusted Analyses
for Serious Adverse Events on Hazard Ratio
Excluding Progression Terms
SAF

Serious Adverse Events Subgroup	Placebo			Nivolumab			Nivolumab vs. Placebo	
	N	Subjects with Event n (%)	KME [95%CI] (mon) (1)	N	Subjects with Event n (%)	KME [95%CI] (mon) (1)	HR [95%CI] P-value (2) (3)	Test for Interaction P-value (4) (5)
TIME FROM IUC SURGERY TO RANDOMIZATION (DAYS)								0.0753
>30-60	28	7 (25.0)	N.A.	34	16 (47.1)	10.48 (4.99, N.A.)	2.081 (0.855, 5.064)	
>60-90	65	25 (38.5)	N.A. (9.53, N.A.)	57	16 (28.1)	N.A.	0.0981 0.627 (0.334, 1.175)	
>90-120	41	22 (53.7)	8.38 (4.01, N.A.)	46	19 (41.3)	N.A. (6.01, N.A.)	0.1416 0.720 (0.389, 1.333)	

FEB2025 DBL. Includes events reported between first dose and 100 days after last dose of the study therapy.

MedDRA Version: 27.1; CTCAE Version 4.0. HR = hazard ratio; KME = Kaplan-Meier estimate; N.M.E. = Not meaningful estimate.

(1) KME of median time to first AE. (2) Unstratified log-rank test.

(3) Unstratified Cox proportional hazard model. HR is Nivolumab over Placebo.

(4) Unstratified Cox proportional hazard model with treatment, subgroup and treatment*subgroup interaction is to assess the significance of the interaction between treatment and the subgroup.

(5) A p-value of <0.05 is indicated by 1 asterisk (indicates potential effect modification).

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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

Table 6.2
Subgroup Time-Adjusted Analyses
for Serious Adverse Events on Hazard Ratio
Excluding Progression Terms
SAF

Serious Adverse Events Subgroup	Placebo			Nivolumab			Nivolumab vs. Placebo	
	N	Subjects with Event n (%)	KME [95%CI] (mon) (1)	N	Subjects with Event n (%)	KME [95%CI] (mon) (1)	HR [95%CI] P-value (2) (3)	Test for Interaction P-value (4) (5)
INITIAL TUMOR ORIGIN								
URINARY BLADDER	115	51 (44.3)	15.01 (8.38, N.A.)	112	42 (37.5)	N.A. (13.21, N.A.)	0.771 (0.512, 1.160) 0.2097	0.4325
RENAL PELVIS	13	2 (15.4)	N.A. (6.34, N.A.)	19	7 (36.8)	N.A. (9.49, N.A.)	2.215 (0.459, 10.687) 0.3096	
URETER	11	4 (36.4)	N.A. (2.30, N.A.)	8	2 (25.0)	N.A. (0.69, N.A.)	0.957 (0.175, 5.241) 0.9595	
MINOR HISTOLOGICAL VARIANTS								
PRESENCE	60	21 (35.0)	N.A. (10.18, N.A.)	61	18 (29.5)	N.A. (13.21, N.A.)	0.801 (0.427, 1.503) 0.4883	0.8989
ABSENCE	79	36 (45.6)	14.65 (7.75, N.A.)	78	33 (42.3)	N.A. (9.00, N.A.)	0.847 (0.527, 1.359) 0.4902	

FEB2025 DBL. Includes events reported between first dose and 100 days after last dose of the study therapy.

MedDRA Version: 27.1; CTCAE Version 4.0. HR = hazard ratio; KME = Kaplan-Meier estimate; N.M.E. = Not meaningful estimate.

(1) KME of median time to first AE. (2) Unstratified log-rank test.

(3) Unstratified Cox proportional hazard model. HR is Nivolumab over Placebo.

(4) Unstratified Cox proportional hazard model with treatment, subgroup and treatment*subgroup interaction is to assess the significance of the interaction between treatment and the subgroup.

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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

5.1.2.3 Zum Therapieabbruch führende UE

Table 6.3
Subgroup Time-Adjusted Analyses
for Adverse Events Leading to Discontinuation of Study Treatment on Hazard Ratio
Excluding Progression Terms
SAF

AEs Leading to Discontinuation of Study Treatment Subgroup	Placebo			Nivolumab			Nivolumab vs. Placebo	
	N	Subjects with Event n (%)	KME [95%CI] (mon) (1)	N	Subjects with Event n (%)	KME [95%CI] (mon) (1)	HR [95%CI] P-value (2) (3)	Test for Interaction P-value (4) (5)
OVERALL	139	15 (10.8)	N.A.	139	30 (21.6)	N.A.	1.944 (1.046, 3.614) 0.0324	
PRIOR NEO-ADJUVANT CISPLATIN THERAPY								0.7425
YES	61	6 (9.8)	N.A.	57	13 (22.8)	N.A.	2.192 (0.833, 5.770) 0.1029	
NO	78	9 (11.5)	N.A.	82	17 (20.7)	N.A.	1.771 (0.789, 3.975) 0.1604	

FEB2025 DBL. Includes events reported between first dose and 100 days after last dose of the study therapy.

MedDRA Version: 27.1; CTCAE Version 4.0. HR = hazard ratio; KME = Kaplan-Meier estimate; N.M.E. = Not meaningful estimate.

(1) KME of median time to first AE. (2) Unstratified log-rank test.

(3) Unstratified Cox proportional hazard model. HR is Nivolumab over Placebo.

(4) Unstratified Cox proportional hazard model with treatment, subgroup and treatment*subgroup interaction is to assess the significance of the interaction between treatment and the subgroup.

(5) A p-value of <0.05 is indicated by 1 asterisk (indicates potential effect modification).

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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

Table 6.3
Subgroup Time-Adjusted Analyses
for Adverse Events Leading to Discontinuation of Study Treatment on Hazard Ratio
Excluding Progression Terms
SAF

AEs Leading to Discontinuation of Study Treatment Subgroup	Placebo			Nivolumab			Nivolumab vs. Placebo	
	N	Subjects with Event n (%)	KME [95%CI] (mon) (1)	N	Subjects with Event n (%)	KME [95%CI] (mon) (1)	HR [95%CI] P-value (2) (3)	Test for Interaction P-value (4) (5)
PRIOR CISPLATIN STATUS								
RECEIVED NEO-ADJUVANT	61	6 (9.8)	N.A.	57	13 (22.8)	N.A.	2.192 (0.833, 5.770)	0.9365
UNWILLING TO RECEIVE NEO-ADJUVANT	45	5 (11.1)	N.A.	50	10 (20.0)	N.A.	0.1029 1.781 (0.608, 5.215)	
NOT ELIGIBLE TO RECEIVE NEO-ADJUVANT	32	4 (12.5)	N.A.	27	6 (22.2)	N.A.	0.2856 1.727 (0.487, 6.130)	
USE OF ANY PRIOR NEO-ADJUVANT SYSTEMIC THERAPY								
YES	62	6 (9.7)	N.A.	61	13 (21.3)	N.A.	0.3920 2.075 (0.788, 5.461)	0.8637
NO	77	9 (11.7)	N.A.	78	17 (21.8)	N.A.	0.1308 1.851 (0.824, 4.154)	
							0.1296	

FEB2025 DBL. Includes events reported between first dose and 100 days after last dose of the study therapy.

MedDRA Version: 27.1; CTCAE Version 4.0. HR = hazard ratio; KME = Kaplan-Meier estimate; N.M.E. = Not meaningful estimate.

(1) KME of median time to first AE. (2) Unstratified log-rank test.

(3) Unstratified Cox proportional hazard model. HR is Nivolumab over Placebo.

(4) Unstratified Cox proportional hazard model with treatment, subgroup and treatment*subgroup interaction is to assess the significance of the interaction between treatment and the subgroup.

(5) A p-value of <0.05 is indicated by 1 asterisk (indicates potential effect modification).

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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

Table 6.3
Subgroup Time-Adjusted Analyses
for Adverse Events Leading to Discontinuation of Study Treatment on Hazard Ratio
Excluding Progression Terms
SAF

AEs Leading to Discontinuation of Study Treatment Subgroup	Placebo			Nivolumab			Nivolumab vs. Placebo	
	N	Subjects with Event n (%)	KME [95%CI] (mon) (1)	N	Subjects with Event n (%)	KME [95%CI] (mon) (1)	HR [95%CI] P-value (2) (3)	Test for Interaction P-value (4) (5)
PATHOLOGICAL LYMPH NODE STATUS								0.9262
N+	64	7 (10.9)	N.A.	60	12 (20.0)	N.A.	1.674 (0.658, 4.259)	
N0/X WITH <10 NODES REMOVED	38	8 (21.1)	N.A.	38	10 (26.3)	N.A.	0.2742 1.300 (0.513, 3.296)	
N0 WITH >= 10 NODES REMOVED	37	0	N.A.	41	8 (19.5)	N.A.	0.5791 N.M.E. 0.0083	

FEB2025 DBL. Includes events reported between first dose and 100 days after last dose of the study therapy.

MedDRA Version: 27.1; CTCAE Version 4.0. HR = hazard ratio; KME = Kaplan-Meier estimate; N.M.E. = Not meaningful estimate.

(1) KME of median time to first AE. (2) Unstratified log-rank test.

(3) Unstratified Cox proportional hazard model. HR is Nivolumab over Placebo.

(4) Unstratified Cox proportional hazard model with treatment, subgroup and treatment*subgroup interaction is to assess the significance of the interaction between treatment and the subgroup.

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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

Table 6.3
Subgroup Time-Adjusted Analyses
for Adverse Events Leading to Discontinuation of Study Treatment on Hazard Ratio
Excluding Progression Terms
SAF

AEs Leading to Discontinuation of Study Treatment Subgroup	Placebo			Nivolumab			Nivolumab vs. Placebo	
	N	Subjects with Event n (%)	KME [95%CI] (mon) (1)	N	Subjects with Event n (%)	KME [95%CI] (mon) (1)	HR [95%CI] P-value (2) (3)	Test for Interaction P-value (4) (5)
PATHOLOGICAL STATUS								0.9828
PT0-2	31	5 (16.1)	N.A.	26	7 (26.9)	N.A. (9.46, N.A.)	1.815 (0.575, 5.730)	
PT3	80	7 (8.8)	N.A.	86	16 (18.6)	N.A.	0.3022 1.947 (0.800, 4.741)	
PT4A	27	3 (11.1)	N.A.	23	5 (21.7)	N.A.	0.1350 2.194 (0.524, 9.183)	
AGE CATEGORY I							0.2698	0.6762
< 65	59	4 (6.8)	N.A.	67	8 (11.9)	N.A.	1.651 (0.496, 5.491)	
>= 65	80	11 (13.8)	N.A.	72	22 (30.6)	N.A.	0.4086 2.241 (1.087, 4.624)	
							0.0248	

FEB2025 DBL. Includes events reported between first dose and 100 days after last dose of the study therapy.

MedDRA Version: 27.1; CTCAE Version 4.0. HR = hazard ratio; KME = Kaplan-Meier estimate; N.M.E. = Not meaningful estimate.

(1) KME of median time to first AE. (2) Unstratified log-rank test.

(3) Unstratified Cox proportional hazard model. HR is Nivolumab over Placebo.

(4) Unstratified Cox proportional hazard model with treatment, subgroup and treatment*subgroup interaction is to assess the significance of the interaction between treatment and the subgroup.

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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

Table 6.3
Subgroup Time-Adjusted Analyses
for Adverse Events Leading to Discontinuation of Study Treatment on Hazard Ratio
Excluding Progression Terms
SAF

AEs Leading to Discontinuation of Study Treatment Subgroup	Placebo			Nivolumab			Nivolumab vs. Placebo	
	N	Subjects with Event n (%)	KME [95%CI] (mon) (1)	N	Subjects with Event n (%)	KME [95%CI] (mon) (1)	HR [95%CI] P-value (2) (3)	Test for Interaction P-value (4) (5)
AGE CATEGORY II								0.8930
< 65	59	4 (6.8)	N.A.	67	8 (11.9)	N.A.	1.651 (0.496, 5.491)	
>= 65 AND < 75	59	9 (15.3)	N.A.	49	16 (32.7)	N.A. (10.22, N.A.)	0.4086 2.214 (0.978, 5.011)	
>= 75	21	2 (9.5)	N.A.	23	6 (26.1)	N.A. (10.48, N.A.)	0.0503 2.537 (0.510, 12.632)	

FEB2025 DBL. Includes events reported between first dose and 100 days after last dose of the study therapy.

MedDRA Version: 27.1; CTCAE Version 4.0. HR = hazard ratio; KME = Kaplan-Meier estimate; N.M.E. = Not meaningful estimate.

(1) KME of median time to first AE. (2) Unstratified log-rank test.

(3) Unstratified Cox proportional hazard model. HR is Nivolumab over Placebo.

(4) Unstratified Cox proportional hazard model with treatment, subgroup and treatment*subgroup interaction is to assess the significance of the interaction between treatment and the subgroup.

(5) A p-value of <0.05 is indicated by 1 asterisk (indicates potential effect modification).

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Excluding Progression Terms
SAF

AEs Leading to Discontinuation of Study Treatment Subgroup	Placebo			Nivolumab			Nivolumab vs. Placebo	
	N	Subjects with Event n (%)	KME [95%CI] (mon) (1)	N	Subjects with Event n (%)	KME [95%CI] (mon) (1)	HR [95%CI] P-value (2) (3)	Test for Interaction P-value (4) (5)
REGION								0.6265
US	23	1 (4.3)	N.A.	17	3 (17.6)	N.A.	4.395 (0.456, 42.359)	
EUROPE	68	9 (13.2)	N.A.	72	14 (19.4)	N.A.	0.1615 1.306 (0.565, 3.020)	
ASIA	28	3 (10.7)	N.A.	33	7 (21.2)	N.A.	0.5330 2.142 (0.553, 8.295)	
REST OF WORLD	20	2 (10.0)	N.A.	17	6 (35.3)	N.A. (4.17, N.A.)	0.2583 3.500 (0.705, 17.370)	
							0.1023	

FEB2025 DBL. Includes events reported between first dose and 100 days after last dose of the study therapy.

MedDRA Version: 27.1; CTCAE Version 4.0. HR = hazard ratio; KME = Kaplan-Meier estimate; N.M.E. = Not meaningful estimate.

(1) KME of median time to first AE. (2) Unstratified log-rank test.

(3) Unstratified Cox proportional hazard model. HR is Nivolumab over Placebo.

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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

Table 6.3
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for Adverse Events Leading to Discontinuation of Study Treatment on Hazard Ratio
Excluding Progression Terms
SAF

AEs Leading to Discontinuation of Study Treatment Subgroup	Placebo			Nivolumab			Nivolumab vs. Placebo	
	N	Subjects with Event n (%)	KME [95%CI] (mon) (1)	N	Subjects with Event n (%)	KME [95%CI] (mon) (1)	HR [95%CI] P-value (2) (3)	Test for Interaction P-value (4) (5)
GENDER								0.8294
MALE	109	13 (11.9)	N.A.	101	24 (23.8)	N.A.	1.911 (0.972, 3.757) 0.0561	
FEMALE	30	2 (6.7)	N.A.	38	6 (15.8)	N.A.	2.256 (0.455, 11.188) 0.3060	
RACE								0.9904
WHITE	106	10 (9.4)	N.A.	103	22 (21.4)	N.A.	2.113 (1.000, 4.464) 0.0449	
ASIAN	28	3 (10.7)	N.A.	33	7 (21.2)	N.A.	2.142 (0.553, 8.295) 0.2583	

FEB2025 DBL. Includes events reported between first dose and 100 days after last dose of the study therapy.

MedDRA Version: 27.1; CTCAE Version 4.0. HR = hazard ratio; KME = Kaplan-Meier estimate; N.M.E. = Not meaningful estimate.

(1) KME of median time to first AE. (2) Unstratified log-rank test.

(3) Unstratified Cox proportional hazard model. HR is Nivolumab over Placebo.

(4) Unstratified Cox proportional hazard model with treatment, subgroup and treatment*subgroup interaction is to assess the significance of the interaction between treatment and the subgroup.

(5) A p-value of <0.05 is indicated by 1 asterisk (indicates potential effect modification).

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Excluding Progression Terms
SAF

AEs Leading to Discontinuation of Study Treatment Subgroup	Placebo			Nivolumab			Nivolumab vs. Placebo	
	N	Subjects with Event n (%)	KME [95%CI] (mon) (1)	N	Subjects with Event n (%)	KME [95%CI] (mon) (1)	HR [95%CI] P-value (2) (3)	Test for Interaction P-value (4) (5)
BASELINE ECOG STATUS								
0	83	9 (10.8)	N.A.	85	19 (22.4)	N.A.	2.014 (0.910, 4.456) 0.0780	0.7409
1	52	6 (11.5)	N.A.	51	10 (19.6)	N.A.	1.638 (0.595, 4.507) 0.3346	
SMOKING STATUS								
NEVER SMOKED	39	2 (5.1)	N.A.	41	10 (24.4)	N.A. (11.50, N.A.)	4.905 (1.074, 22.396) 0.0229	0.1385
CURRENT/FORMER	99	13 (13.1)	N.A.	96	19 (19.8)	N.A.	1.413 (0.697, 2.863) 0.3356	

FEB2025 DBL. Includes events reported between first dose and 100 days after last dose of the study therapy.

MedDRA Version: 27.1; CTCAE Version 4.0. HR = hazard ratio; KME = Kaplan-Meier estimate; N.M.E. = Not meaningful estimate.

(1) KME of median time to first AE. (2) Unstratified log-rank test.

(3) Unstratified Cox proportional hazard model. HR is Nivolumab over Placebo.

(4) Unstratified Cox proportional hazard model with treatment, subgroup and treatment*subgroup interaction is to assess the significance of the interaction between treatment and the subgroup.

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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

Table 6.3
Subgroup Time-Adjusted Analyses
for Adverse Events Leading to Discontinuation of Study Treatment on Hazard Ratio
Excluding Progression Terms
SAF

AEs Leading to Discontinuation of Study Treatment Subgroup	Placebo			Nivolumab			Nivolumab vs. Placebo	
	N	Subjects with Event n (%)	KME [95%CI] (mon) (1)	N	Subjects with Event n (%)	KME [95%CI] (mon) (1)	HR [95%CI] P-value (2) (3)	Test for Interaction P-value (4) (5)
BASELINE HEMOGLOBIN <10 G/DL	14	1 (7.1)	N.A.	7	2 (28.6)	N.A. (0.66, N.A.)	4.492 (0.406, 49.706)	0.5155
>=10 G/DL	125	14 (11.2)	N.A.	132	28 (21.2)	N.A.	0.1794 1.824 (0.960, 3.467)	
BASELINE CREATININE CLEARANCE <60 ML/MIN	60	10 (16.7)	N.A.	54	11 (20.4)	N.A.	1.200 (0.510, 2.827)	0.1051
>=60 ML/MIN	79	5 (6.3)	N.A.	84	19 (22.6)	N.A.	0.6761 3.426 (1.278, 9.181)	
							0.0092	

FEB2025 DBL. Includes events reported between first dose and 100 days after last dose of the study therapy.

MedDRA Version: 27.1; CTCAE Version 4.0. HR = hazard ratio; KME = Kaplan-Meier estimate; N.M.E. = Not meaningful estimate.

(1) KME of median time to first AE. (2) Unstratified log-rank test.

(3) Unstratified Cox proportional hazard model. HR is Nivolumab over Placebo.

(4) Unstratified Cox proportional hazard model with treatment, subgroup and treatment*subgroup interaction is to assess the significance of the interaction between treatment and the subgroup.

(5) A p-value of <0.05 is indicated by 1 asterisk (indicates potential effect modification).

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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

Table 6.3
Subgroup Time-Adjusted Analyses
for Adverse Events Leading to Discontinuation of Study Treatment on Hazard Ratio
Excluding Progression Terms
SAF

AEs Leading to Discontinuation of Study Treatment Subgroup	Placebo			Nivolumab			Nivolumab vs. Placebo	
	N	Subjects with Event n (%)	KME [95%CI] (mon) (1)	N	Subjects with Event n (%)	KME [95%CI] (mon) (1)	HR [95%CI] P-value (2) (3)	Test for Interaction P-value (4) (5)
TIME FROM IUC SURGERY TO RANDOMIZATION (DAYS)								0.7166
>30-60	28	2 (7.1)	N.A.	34	8 (23.5)	N.A. (11.50, N.A.)	3.300 (0.700, 15.566) 0.1098	
>60-90	65	7 (10.8)	N.A.	57	11 (19.3)	N.A.	1.660 (0.643, 4.284) 0.2896	
>90-120	41	6 (14.6)	N.A.	46	11 (23.9)	N.A.	1.676 (0.619, 4.534) 0.3042	

FEB2025 DBL. Includes events reported between first dose and 100 days after last dose of the study therapy.

MedDRA Version: 27.1; CTCAE Version 4.0. HR = hazard ratio; KME = Kaplan-Meier estimate; N.M.E. = Not meaningful estimate.

(1) KME of median time to first AE. (2) Unstratified log-rank test.

(3) Unstratified Cox proportional hazard model. HR is Nivolumab over Placebo.

(4) Unstratified Cox proportional hazard model with treatment, subgroup and treatment*subgroup interaction is to assess the significance of the interaction between treatment and the subgroup.

(5) A p-value of <0.05 is indicated by 1 asterisk (indicates potential effect modification).

Program Path: /projects/bms214671/stats/market/ma274_202502/prog/tables

Program Name: rt-ae-tsubaehr-ebr45.sas

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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

Table 6.3
Subgroup Time-Adjusted Analyses
for Adverse Events Leading to Discontinuation of Study Treatment on Hazard Ratio
Excluding Progression Terms
SAF

AEs Leading to Discontinuation of Study Treatment Subgroup	Placebo			Nivolumab			Nivolumab vs. Placebo	
	N	Subjects with Event n (%)	KME [95%CI] (mon) (1)	N	Subjects with Event n (%)	KME [95%CI] (mon) (1)	HR [95%CI] P-value (2) (3)	Test for Interaction P-value (4) (5)
INITIAL TUMOR ORIGIN								
URINARY BLADDER	115	10 (8.7)	N.A.	112	24 (21.4)	N.A.	2.356 (1.126, 4.930) 0.0190	0.3573
RENAL PELVIS	13	4 (30.8)	N.A. (2.33, N.A.)	19	5 (26.3)	N.A. (10.48, N.A.)	0.776 (0.208, 2.896) 0.7050	
URETER	11	1 (9.1)	N.A. (8.54, N.A.)	8	1 (12.5)	N.A. (0.69, N.A.)	1.658 (0.104, 26.539) 0.7178	
MINOR HISTOLOGICAL VARIANTS								
PRESENCE	60	5 (8.3)	N.A.	61	14 (23.0)	N.A.	2.753 (0.991, 7.645) 0.0428	0.3361
ABSENCE	79	10 (12.7)	N.A.	78	16 (20.5)	N.A.	1.560 (0.707, 3.439) 0.2666	

FEB2025 DBL. Includes events reported between first dose and 100 days after last dose of the study therapy.

MedDRA Version: 27.1; CTCAE Version 4.0. HR = hazard ratio; KME = Kaplan-Meier estimate; N.M.E. = Not meaningful estimate.

(1) KME of median time to first AE. (2) Unstratified log-rank test.

(3) Unstratified Cox proportional hazard model. HR is Nivolumab over Placebo.

(4) Unstratified Cox proportional hazard model with treatment, subgroup and treatment*subgroup interaction is to assess the significance of the interaction between treatment and the subgroup.

(5) A p-value of <0.05 is indicated by 1 asterisk (indicates potential effect modification).

Program Path: /projects/bms214671/stats/market/ma274_202502/prog/tables

Program Name: rt-ae-tsubaehr-ebr45.sas

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5.1.3 Kaplan-Meier Kurven für Subgruppen mit statistisch signifikantem Interaktionsterm

5.1.3.1 Schwere UE (CTCAE ≥ 3)

Nicht zutreffend.

5.1.3.2 SUE

Nicht zutreffend.

5.1.3.3 Zum Therapieabbruch führende UE

Nicht zutreffend.

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

5.2 Häufige UE nach SOC und PT

5.2.1 UE-Hauptkategorien

5.2.1.1 Jegliche UE

Table 12.1
Time-Adjusted Analyses for
Adverse Events
by SOC/PT on Hazard Ratio
SAF

System Organ Class (%) Preferred Term (%)	Placebo				Nivolumab				Nivolumab vs. Placebo	
	N	Subjects with Event n (%)	Censored Subjects n (%)	KME [95%CI] (mon) (1)	N	Subjects with Event n (%)	Censored Subjects n (%)	KME [95%CI] (mon) (1)	HR [95%CI] (2)	P-value (3)
TOTAL SUBJECTS WITH AN EVENT	139	133 (95.7)	6 (4.3)	0.59 (0.49, 0.85)	139	138 (99.3)	1 (0.7)	0.49 (0.33, 0.49)	1.466 (1.143, 1.881)	0.0031
GASTROINTESTINAL DISORDERS	139	81 (58.3)	58 (41.7)	4.93 (3.45, 8.77)	139	85 (61.2)	54 (38.8)	4.37 (2.79, 8.67)	1.068 (0.786, 1.450)	0.6766
DIARRHOEA	139	35 (25.2)	104 (74.8)	N.A. (N.A., N.A.)	139	44 (31.7)	95 (68.3)	N.A. (N.A., N.A.)	1.171 (0.750, 1.828)	0.4815
NAUSEA	139	21 (15.1)	118 (84.9)	N.A. (N.A., N.A.)	139	27 (19.4)	112 (80.6)	N.A. (N.A., N.A.)	1.221 (0.689, 2.162)	0.4933
CONSTIPATION	139	25 (18.0)	114 (82.0)	N.A. (N.A., N.A.)	139	21 (15.1)	118 (84.9)	N.A. (N.A., N.A.)	0.813 (0.455, 1.454)	0.4847
ABDOMINAL PAIN	139	17 (12.2)	122 (87.8)	N.A. (N.A., N.A.)	139	13 (9.4)	126 (90.6)	N.A. (N.A., N.A.)	0.723 (0.351, 1.491)	0.3783
VOMITING	139	16 (11.5)	123 (88.5)	N.A. (N.A., N.A.)	139	11 (7.9)	128 (92.1)	N.A. (N.A., N.A.)	0.661 (0.306, 1.426)	0.2876

FEB2025 DBL. Includes events reported between first dose and 100 days after last dose of the study therapy.

MedDRA Version: 27.1; CTC Version 4.0.

HR = hazard ratio; KME = Kaplan-Meier estimate; N.M.E. = Not meaningful estimate.

(1) KME of median time to first AE.

(2) Stratified Cox proportional hazard model. HR is Nivolumab over Placebo.

(3) Log-rank test stratified by prior neo-adjuvant cisplatin, pathological nodal status, as entered in IRT.

Program Path: /projects/bms214671/stats/market/ma274_202502/prog/tables

Program Name: rt-ae-taesocpth-ebr45.sas

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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

Table 12.1
Time-Adjusted Analyses for
Adverse Events
by SOC/PT on Hazard Ratio
SAF

System Organ Class (%) Preferred Term (%)	Placebo				Nivolumab				Nivolumab vs. Placebo	
	N	Subjects with Event n (%)	Censored Subjects n (%)	KME [95%CI] (mon) (1)	N	Subjects with Event n (%)	Censored Subjects n (%)	KME [95%CI] (mon) (1)	HR [95%CI] (2)	P-value (3)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	139	64 (46.0)	75 (54.0)	9.66 (5.75, N.A.)	139	77 (55.4)	62 (44.6)	7.82 (4.53, 10.58)	1.193 (0.855, 1.665)	0.3032
FATIGUE	139	32 (23.0)	107 (77.0)	N.A. (N.A., N.A.)	139	37 (26.6)	102 (73.4)	N.A. (N.A., N.A.)	1.067 (0.663, 1.719)	0.7884
ASTHENIA	139	5 (3.6)	134 (96.4)	N.A. (N.A., N.A.)	139	19 (13.7)	120 (86.3)	N.A. (N.A., N.A.)	3.956 (1.477, 10.600)	0.0031
OEDEMA PERIPHERAL	139	9 (6.5)	130 (93.5)	N.A. (N.A., N.A.)	139	14 (10.1)	125 (89.9)	N.A. (N.A., N.A.)	1.487 (0.643, 3.439)	0.3500
PYREXIA	139	16 (11.5)	123 (88.5)	N.A. (N.A., N.A.)	139	11 (7.9)	128 (92.1)	N.A. (N.A., N.A.)	0.643 (0.298, 1.387)	0.2561
INFLUENZA LIKE ILLNESS	139	5 (3.6)	134 (96.4)	N.A. (N.A., N.A.)	139	10 (7.2)	129 (92.8)	N.A. (N.A., N.A.)	1.874 (0.639, 5.502)	0.2451
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	139	45 (32.4)	94 (67.6)	N.A. (N.A., N.A.)	139	77 (55.4)	62 (44.6)	5.22 (2.50, 10.35)	1.951 (1.347, 2.826)	0.0003
PRURITUS	139	19 (13.7)	120 (86.3)	N.A. (N.A., N.A.)	139	39 (28.1)	100 (71.9)	N.A. (N.A., N.A.)	2.141 (1.236, 3.708)	0.0054

FEB2025 DBL. Includes events reported between first dose and 100 days after last dose of the study therapy.

MedDRA Version: 27.1; CTC Version 4.0.

HR = hazard ratio; KME = Kaplan-Meier estimate; N.M.E. = Not meaningful estimate.

(1) KME of median time to first AE.

(2) Stratified Cox proportional hazard model. HR is Nivolumab over Placebo.

(3) Log-rank test stratified by prior neo-adjuvant cisplatin, pathological nodal status, as entered in IRT.

Program Path: /projects/bms214671/stats/market/ma274_202502/prog/tables

Program Name: rt-ae-taesocpth-eb45.sas

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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

Table 12.1
Time-Adjusted Analyses for
Adverse Events
by SOC/PT on Hazard Ratio
SAF

System Organ Class (%) Preferred Term (%)	Placebo				Nivolumab				Nivolumab vs. Placebo	
	N	Subjects with Event n (%)	Censored Subjects n (%)	KME [95%CI] (mon) (1)	N	Subjects with Event n (%)	Censored Subjects n (%)	KME [95%CI] (mon) (1)	HR [95%CI] (2)	P-value (3)
RASH	139	16 (11.5)	123 (88.5)	N.A. (N.A., N.A.)	139	23 (16.5)	116 (83.5)	N.A. (N.A., N.A.)	1.436 (0.757, 2.723)	0.2648
DRY SKIN	139	8 (5.8)	131 (94.2)	N.A. (N.A., N.A.)	139	13 (9.4)	126 (90.6)	N.A. (N.A., N.A.)	1.526 (0.631, 3.692)	0.3448
INVESTIGATIONS	139	52 (37.4)	87 (62.6)	N.A. (9.89, N.A.)	139	67 (48.2)	72 (51.8)	10.64 (6.01, N.A.)	1.267 (0.881, 1.823)	0.1992
BLOOD CREATININE INCREASED	139	20 (14.4)	119 (85.6)	N.A. (N.A., N.A.)	139	19 (13.7)	120 (86.3)	N.A. (N.A., N.A.)	0.920 (0.490, 1.727)	0.7953
LIPASE INCREASED	139	10 (7.2)	129 (92.8)	N.A. (N.A., N.A.)	139	19 (13.7)	120 (86.3)	N.A. (N.A., N.A.)	1.845 (0.857, 3.973)	0.1125
AMYLASE INCREASED	139	12 (8.6)	127 (91.4)	N.A. (N.A., N.A.)	139	12 (8.6)	127 (91.4)	N.A. (N.A., N.A.)	0.935 (0.420, 2.084)	0.8673
ALANINE AMINOTRANSFERASE INCREASED	139	8 (5.8)	131 (94.2)	N.A. (N.A., N.A.)	139	11 (7.9)	128 (92.1)	N.A. (N.A., N.A.)	1.336 (0.537, 3.326)	0.5304

FEB2025 DBL. Includes events reported between first dose and 100 days after last dose of the study therapy.

MedDRA Version: 27.1; CTC Version 4.0.

HR = hazard ratio; KME = Kaplan-Meier estimate; N.M.E. = Not meaningful estimate.

(1) KME of median time to first AE.

(2) Stratified Cox proportional hazard model. HR is Nivolumab over Placebo.

(3) Log-rank test stratified by prior neo-adjuvant cisplatin, pathological nodal status, as entered in IRT.

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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

Table 12.1
Time-Adjusted Analyses for
Adverse Events
by SOC/PT on Hazard Ratio
SAF

System Organ Class (%) Preferred Term (%)	Placebo				Nivolumab				Nivolumab vs. Placebo	
	N	Subjects with Event n (%)	Censored Subjects n (%)	KME [95%CI] (mon) (1)	N	Subjects with Event n (%)	Censored Subjects n (%)	KME [95%CI] (mon) (1)	HR [95%CI] (2)	P-value (3)
ASPARTATE AMINOTRANSFERASE INCREASED	139	10 (7.2)	129 (92.8)	N.A. (N.A., N.A.)	139	8 (5.8)	131 (94.2)	N.A. (N.A., N.A.)	0.769 (0.303, 1.954)	0.5805
INFECTIONS AND INFESTATIONS	139	72 (51.8)	67 (48.2)	9.40 (5.82, 15.01)	139	66 (47.5)	73 (52.5)	10.74 (6.34, N.A.)	0.890 (0.636, 1.244)	0.4948
URINARY TRACT INFECTION	139	32 (23.0)	107 (77.0)	N.A. (N.A., N.A.)	139	34 (24.5)	105 (75.5)	N.A. (N.A., N.A.)	0.999 (0.616, 1.620)	0.9974
NASOPHARYNGITIS	139	11 (7.9)	128 (92.1)	N.A. (N.A., N.A.)	139	12 (8.6)	127 (91.4)	N.A. (N.A., N.A.)	0.985 (0.434, 2.238)	0.9714
UPPER RESPIRATORY TRACT INFECTION	139	10 (7.2)	129 (92.8)	N.A. (N.A., N.A.)	139	11 (7.9)	128 (92.1)	N.A. (N.A., N.A.)	1.079 (0.457, 2.545)	0.8595
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	139	56 (40.3)	83 (59.7)	N.A. (9.49, N.A.)	139	58 (41.7)	81 (58.3)	N.A. (9.33, N.A.)	0.989 (0.684, 1.429)	0.9562
BACK PAIN	139	18 (12.9)	121 (87.1)	N.A. (N.A., N.A.)	139	20 (14.4)	119 (85.6)	N.A. (N.A., N.A.)	1.059 (0.560, 2.004)	0.8603

FEB2025 DBL. Includes events reported between first dose and 100 days after last dose of the study therapy.

MedDRA Version: 27.1; CTC Version 4.0.

HR = hazard ratio; KME = Kaplan-Meier estimate; N.M.E. = Not meaningful estimate.

(1) KME of median time to first AE.

(2) Stratified Cox proportional hazard model. HR is Nivolumab over Placebo.

(3) Log-rank test stratified by prior neo-adjuvant cisplatin, pathological nodal status, as entered in IRT.

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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

Table 12.1
Time-Adjusted Analyses for
Adverse Events
by SOC/PT on Hazard Ratio
SAF

System Organ Class (%) Preferred Term (%)	Placebo				Nivolumab				Nivolumab vs. Placebo	
	N	Subjects with Event n (%)	Censored Subjects n (%)	KME [95%CI] (mon) (1)	N	Subjects with Event n (%)	Censored Subjects n (%)	KME [95%CI] (mon) (1)	HR [95%CI] (2)	P-value (3)
ARTHRALGIA	139	21 (15.1)	118 (84.9)	N.A. (N.A., N.A.)	139	16 (11.5)	123 (88.5)	N.A. (N.A., N.A.)	0.733 (0.382, 1.406)	0.3476
METABOLISM AND NUTRITION DISORDERS	139	48 (34.5)	91 (65.5)	N.A. (N.A., N.A.)	139	52 (37.4)	87 (62.6)	N.A. (N.A., N.A.)	1.076 (0.726, 1.594)	0.7135
DECREASED APPETITE	139	14 (10.1)	125 (89.9)	N.A. (N.A., N.A.)	139	16 (11.5)	123 (88.5)	N.A. (N.A., N.A.)	1.126 (0.550, 2.309)	0.7467
HYPERGLYCAEMIA	139	13 (9.4)	126 (90.6)	N.A. (N.A., N.A.)	139	9 (6.5)	130 (93.5)	N.A. (N.A., N.A.)	0.666 (0.284, 1.558)	0.3468
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	139	36 (25.9)	103 (74.1)	N.A. (N.A., N.A.)	139	45 (32.4)	94 (67.6)	N.A. (N.A., N.A.)	1.229 (0.792, 1.906)	0.3559
COUGH	139	13 (9.4)	126 (90.6)	N.A. (N.A., N.A.)	139	17 (12.2)	122 (87.8)	N.A. (N.A., N.A.)	1.271 (0.616, 2.621)	0.5153
DYSPNOEA	139	10 (7.2)	129 (92.8)	N.A. (N.A., N.A.)	139	13 (9.4)	126 (90.6)	N.A. (N.A., N.A.)	1.193 (0.522, 2.728)	0.6750

FEB2025 DBL. Includes events reported between first dose and 100 days after last dose of the study therapy.

MedDRA Version: 27.1; CTC Version 4.0.

HR = hazard ratio; KME = Kaplan-Meier estimate; N.M.E. = Not meaningful estimate.

(1) KME of median time to first AE.

(2) Stratified Cox proportional hazard model. HR is Nivolumab over Placebo.

(3) Log-rank test stratified by prior neo-adjuvant cisplatin, pathological nodal status, as entered in IRT.

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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

Table 12.1
Time-Adjusted Analyses for
Adverse Events
by SOC/PT on Hazard Ratio
SAF

System Organ Class (%) Preferred Term (%)	Placebo				Nivolumab				Nivolumab vs. Placebo	
	N	Subjects with Event n (%)	Censored Subjects n (%)	KME [95%CI] (mon) (1)	N	Subjects with Event n (%)	Censored Subjects n (%)	KME [95%CI] (mon) (1)	HR [95%CI] (2)	P-value (3)
NERVOUS SYSTEM DISORDERS	139	44 (31.7)	95 (68.3)	N.A. (N.A., N.A.)	139	41 (29.5)	98 (70.5)	N.A. (N.A., N.A.)	0.910 (0.594, 1.396)	0.6636
DIZZINESS	139	15 (10.8)	124 (89.2)	N.A. (N.A., N.A.)	139	14 (10.1)	125 (89.9)	N.A. (N.A., N.A.)	0.894 (0.431, 1.855)	0.7639
HEADACHE	139	13 (9.4)	126 (90.6)	N.A. (N.A., N.A.)	139	13 (9.4)	126 (90.6)	N.A. (N.A., N.A.)	0.970 (0.449, 2.096)	0.9380
ENDOCRINE DISORDERS	139	7 (5.0)	132 (95.0)	N.A. (N.A., N.A.)	139	31 (22.3)	108 (77.7)	N.A. (N.A., N.A.)	4.841 (2.129, 11.006)	<0.0001
HYPOTHYROIDISM	139	4 (2.9)	135 (97.1)	N.A. (N.A., N.A.)	139	20 (14.4)	119 (85.6)	N.A. (N.A., N.A.)	5.150 (1.759, 15.079)	0.0009
HYPERTHYROIDISM	139	3 (2.2)	136 (97.8)	N.A. (N.A., N.A.)	139	14 (10.1)	125 (89.9)	N.A. (N.A., N.A.)	4.918 (1.412, 17.125)	0.0056
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	139	20 (14.4)	119 (85.6)	N.A. (N.A., N.A.)	139	30 (21.6)	109 (78.4)	N.A. (N.A., N.A.)	1.532 (0.869, 2.701)	0.1378

FEB2025 DBL. Includes events reported between first dose and 100 days after last dose of the study therapy.

MedDRA Version: 27.1; CTC Version 4.0.

HR = hazard ratio; KME = Kaplan-Meier estimate; N.M.E. = Not meaningful estimate.

(1) KME of median time to first AE.

(2) Stratified Cox proportional hazard model. HR is Nivolumab over Placebo.

(3) Log-rank test stratified by prior neo-adjuvant cisplatin, pathological nodal status, as entered in IRT.

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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

Table 12.1
Time-Adjusted Analyses for
Adverse Events
by SOC/PT on Hazard Ratio
SAF

System Organ Class (%) Preferred Term (%)	Placebo				Nivolumab				Nivolumab vs. Placebo	
	N	Subjects with Event n (%)	Censored Subjects n (%)	KME [95%CI] (mon) (1)	N	Subjects with Event n (%)	Censored Subjects n (%)	KME [95%CI] (mon) (1)	HR [95%CI] (2)	P-value (3)
BLOOD AND LYMPHATIC SYSTEM DISORDERS	139	26 (18.7)	113 (81.3)	N.A. (N.A., N.A.)	139	26 (18.7)	113 (81.3)	N.A. (N.A., N.A.)	0.937 (0.543, 1.616)	0.8179
ANAEMIA	139	21 (15.1)	118 (84.9)	N.A. (N.A., N.A.)	139	19 (13.7)	120 (86.3)	N.A. (N.A., N.A.)	0.852 (0.458, 1.587)	0.6162
RENAL AND URINARY DISORDERS	139	25 (18.0)	114 (82.0)	N.A. (N.A., N.A.)	139	23 (16.5)	116 (83.5)	N.A. (N.A., N.A.)	0.887 (0.503, 1.564)	0.6783
VASCULAR DISORDERS	139	16 (11.5)	123 (88.5)	N.A. (N.A., N.A.)	139	20 (14.4)	119 (85.6)	N.A. (N.A., N.A.)	1.185 (0.613, 2.291)	0.6123
PSYCHIATRIC DISORDERS	139	15 (10.8)	124 (89.2)	N.A. (N.A., N.A.)	139	15 (10.8)	124 (89.2)	N.A. (N.A., N.A.)	0.983 (0.480, 2.013)	0.9627
REPRODUCTIVE SYSTEM AND BREAST DISORDERS	139	9 (6.5)	130 (93.5)	N.A. (N.A., N.A.)	139	14 (10.1)	125 (89.9)	N.A. (N.A., N.A.)	1.544 (0.666, 3.579)	0.3074

FEB2025 DBL. Includes events reported between first dose and 100 days after last dose of the study therapy.

MedDRA Version: 27.1; CTC Version 4.0.

HR = hazard ratio; KME = Kaplan-Meier estimate; N.M.E. = Not meaningful estimate.

(1) KME of median time to first AE.

(2) Stratified Cox proportional hazard model. HR is Nivolumab over Placebo.

(3) Log-rank test stratified by prior neo-adjuvant cisplatin, pathological nodal status, as entered in IRT.

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Table 12.1
Time-Adjusted Analyses for
Adverse Events
by SOC/PT on Hazard Ratio
SAF

System Organ Class (%) Preferred Term (%)	Placebo				Nivolumab				Nivolumab vs. Placebo	
	N	Subjects with Event n (%)	Censored Subjects n (%)	KME [95%CI] (mon) (1)	N	Subjects with Event n (%)	Censored Subjects n (%)	KME [95%CI] (mon) (1)	HR [95%CI] (2)	P-value (3)
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	139	23 (16.5)	116 (83.5)	N.A. (N.A., N.A.)	139	13 (9.4)	126 (90.6)	N.A. (N.A., N.A.)	0.532 (0.269, 1.051)	0.0646
MALIGNANT NEOPLASM PROGRESSION	139	16 (11.5)	123 (88.5)	N.A. (N.A., N.A.)	139	4 (2.9)	135 (97.1)	N.A. (N.A., N.A.)	0.247 (0.082, 0.739)	0.0067
EYE DISORDERS	139	8 (5.8)	131 (94.2)	N.A. (N.A., N.A.)	139	10 (7.2)	129 (92.8)	N.A. (N.A., N.A.)	1.210 (0.477, 3.069)	0.6874
CARDIAC DISORDERS	139	18 (12.9)	121 (87.1)	N.A. (N.A., N.A.)	139	8 (5.8)	131 (94.2)	N.A. (N.A., N.A.)	0.414 (0.180, 0.955)	0.0328

FEB2025 DBL. Includes events reported between first dose and 100 days after last dose of the study therapy.

MedDRA Version: 27.1; CTC Version 4.0.

HR = hazard ratio; KME = Kaplan-Meier estimate; N.M.E. = Not meaningful estimate.

(1) KME of median time to first AE.

(2) Stratified Cox proportional hazard model. HR is Nivolumab over Placebo.

(3) Log-rank test stratified by prior neo-adjuvant cisplatin, pathological nodal status, as entered in IRT.

Program Path: /projects/bms214671/stats/market/ma274_202502/prog/tables

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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

5.2.1.2 Schwere UE (CTCAE ≥ 3)

Table 12.2
Time-Adjusted Analyses for
Adverse Events with CTCAE Grade ≥ 3
by SOC/PT on Hazard Ratio
SAF

System Organ Class (%) Preferred Term (%)	Placebo				Nivolumab				Nivolumab vs. Placebo	
	N	Subjects with Event n (%)	Censored Subjects n (%)	KME [95%CI] (mon) (1)	N	Subjects with Event n (%)	Censored Subjects n (%)	KME [95%CI] (mon) (1)	HR [95%CI] (2)	P-value (3)
TOTAL SUBJECTS WITH AN EVENT	139	67 (48.2)	72 (51.8)	11.43 (6.90, N.A.)	139	76 (54.7)	63 (45.3)	9.26 (5.98, 13.80)	1.148 (0.826, 1.597)	0.4104
INVESTIGATIONS	139	8 (5.8)	131 (94.2)	N.A. (N.A., N.A.)	139	20 (14.4)	119 (85.6)	N.A. (N.A., N.A.)	2.432 (1.069, 5.532)	0.0286
LIPASE INCREASED	139	1 (0.7)	138 (99.3)	N.A. (N.A., N.A.)	139	11 (7.9)	128 (92.1)	N.A. (N.A., N.A.)	10.449 (1.348, 81.026)	0.0052
INFECTIONS AND INFESTATIONS	139	29 (20.9)	110 (79.1)	N.A. (N.A., N.A.)	139	17 (12.2)	122 (87.8)	N.A. (N.A., N.A.)	0.562 (0.309, 1.025)	0.0567
URINARY TRACT INFECTION	139	15 (10.8)	124 (89.2)	N.A. (N.A., N.A.)	139	11 (7.9)	128 (92.1)	N.A. (N.A., N.A.)	0.708 (0.325, 1.542)	0.3825
METABOLISM AND NUTRITION DISORDERS	139	8 (5.8)	131 (94.2)	N.A. (N.A., N.A.)	139	10 (7.2)	129 (92.8)	N.A. (N.A., N.A.)	1.232 (0.486, 3.125)	0.6593

FEB2025 DBL. Includes events reported between first dose and 100 days after last dose of the study therapy.

MedDRA Version: 27.1; CTC Version 4.0.

HR = hazard ratio; KME = Kaplan-Meier estimate; N.M.E. = Not meaningful estimate.

(1) KME of median time to first AE.

(2) Stratified Cox proportional hazard model. HR is Nivolumab over Placebo.

(3) Log-rank test stratified by prior neo-adjuvant cisplatin, pathological nodal status, as entered in IRT.

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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

Table 12.2
Time-Adjusted Analyses for
Adverse Events with CTCAE Grade ≥ 3
by SOC/PT on Hazard Ratio
SAF

System Organ Class (%) Preferred Term (%)	Placebo				Nivolumab				Nivolumab vs. Placebo	
	N	Subjects with Event n (%)	Censored Subjects n (%)	KME [95%CI] (mon) (1)	N	Subjects with Event n (%)	Censored Subjects n (%)	KME [95%CI] (mon) (1)	HR [95%CI] (2)	P-value (3)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	139	3 (2.2)	136 (97.8)	N.A. (N.A., N.A.)	139	10 (7.2)	129 (92.8)	N.A. (N.A., N.A.)	3.004 (0.824, 10.952)	0.0801
GASTROINTESTINAL DISORDERS	139	17 (12.2)	122 (87.8)	N.A. (N.A., N.A.)	139	8 (5.8)	131 (94.2)	N.A. (N.A., N.A.)	0.435 (0.187, 1.011)	0.0467
RENAL AND URINARY DISORDERS	139	9 (6.5)	130 (93.5)	N.A. (N.A., N.A.)	139	8 (5.8)	131 (94.2)	N.A. (N.A., N.A.)	0.792 (0.304, 2.064)	0.6322
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	139	19 (13.7)	120 (86.3)	N.A. (N.A., N.A.)	139	7 (5.0)	132 (95.0)	N.A. (N.A., N.A.)	0.354 (0.149, 0.843)	0.0142
MALIGNANT NEOPLASM PROGRESSION	139	15 (10.8)	124 (89.2)	N.A. (N.A., N.A.)	139	3 (2.2)	136 (97.8)	N.A. (N.A., N.A.)	0.198 (0.057, 0.685)	0.0044

FEB2025 DBL. Includes events reported between first dose and 100 days after last dose of the study therapy.

MedDRA Version: 27.1; CTC Version 4.0.

HR = hazard ratio; KME = Kaplan-Meier estimate; N.M.E. = Not meaningful estimate.

(1) KME of median time to first AE.

(2) Stratified Cox proportional hazard model. HR is Nivolumab over Placebo.

(3) Log-rank test stratified by prior neo-adjuvant cisplatin, pathological nodal status, as entered in IRT.

Program Path: /projects/bms214671/stats/market/ma274_202502/prog/tables

Program Name: rt-ae-taesocpth-ebr45.sas

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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

5.2.1.3 SUE

Table 12.3
Time-Adjusted Analyses for
Serious Adverse Events
by SOC/PT on Hazard Ratio
SAF

System Organ Class (%) Preferred Term (%)	Placebo				Nivolumab				Nivolumab vs. Placebo	
	N	Subjects with Event n (%)	Censored Subjects n (%)	KME [95%CI] (mon) (1)	N	Subjects with Event n (%)	Censored Subjects n (%)	KME [95%CI] (mon) (1)	HR [95%CI] (2)	P-value (3)
TOTAL SUBJECTS WITH AN EVENT	139	63 (45.3)	76 (54.7)	14.65 (8.41, N.A.)	139	56 (40.3)	83 (59.7)	N.A. (11.30, N.A.)	0.832 (0.580, 1.194)	0.3211
INFECTIONS AND INFESTATIONS	139	28 (20.1)	111 (79.9)	N.A. (N.A., N.A.)	139	14 (10.1)	125 (89.9)	N.A. (N.A., N.A.)	0.466 (0.245, 0.887)	0.0172
URINARY TRACT INFECTION	139	14 (10.1)	125 (89.9)	N.A. (N.A., N.A.)	139	8 (5.8)	131 (94.2)	N.A. (N.A., N.A.)	0.549 (0.230, 1.312)	0.1708
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	139	20 (14.4)	119 (85.6)	N.A. (N.A., N.A.)	139	9 (6.5)	130 (93.5)	N.A. (N.A., N.A.)	0.432 (0.196, 0.949)	0.0313
MALIGNANT NEOPLASM PROGRESSION	139	16 (11.5)	123 (88.5)	N.A. (N.A., N.A.)	139	4 (2.9)	135 (97.1)	N.A. (N.A., N.A.)	0.247 (0.082, 0.739)	0.0067
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	139	1 (0.7)	138 (99.3)	N.A. (N.A., N.A.)	139	9 (6.5)	130 (93.5)	N.A. (N.A., N.A.)	8.297 (1.050, 65.589)	0.0164

FEB2025 DBL. Includes events reported between first dose and 100 days after last dose of the study therapy.

MedDRA Version: 27.1; CTC Version 4.0.

HR = hazard ratio; KME = Kaplan-Meier estimate; N.M.E. = Not meaningful estimate.

(1) KME of median time to first AE.

(2) Stratified Cox proportional hazard model. HR is Nivolumab over Placebo.

(3) Log-rank test stratified by prior neo-adjuvant cisplatin, pathological nodal status, as entered in IRT.

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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

Table 12.3
Time-Adjusted Analyses for
Serious Adverse Events
by SOC/PT on Hazard Ratio
SAF

System Organ Class (%) Preferred Term (%)	Placebo				Nivolumab				Nivolumab vs. Placebo	
	N	Subjects with Event n (%)	Censored Subjects n (%)	KME [95%CI] (mon) (1)	N	Subjects with Event n (%)	Censored Subjects n (%)	KME [95%CI] (mon) (1)	HR [95%CI] (2)	P-value (3)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	139	5 (3.6)	134 (96.4)	N.A. (N.A., N.A.)	139	7 (5.0)	132 (95.0)	N.A. (N.A., N.A.)	1.337 (0.422, 4.236)	0.6209
GASTROINTESTINAL DISORDERS	139	12 (8.6)	127 (91.4)	N.A. (N.A., N.A.)	139	6 (4.3)	133 (95.7)	N.A. (N.A., N.A.)	0.495 (0.185, 1.323)	0.1524
RENAL AND URINARY DISORDERS	139	8 (5.8)	131 (94.2)	N.A. (N.A., N.A.)	139	5 (3.6)	134 (96.4)	N.A. (N.A., N.A.)	0.552 (0.180, 1.694)	0.2917

FEB2025 DBL. Includes events reported between first dose and 100 days after last dose of the study therapy.

MedDRA Version: 27.1; CTC Version 4.0.

HR = hazard ratio; KME = Kaplan-Meier estimate; N.M.E. = Not meaningful estimate.

(1) KME of median time to first AE.

(2) Stratified Cox proportional hazard model. HR is Nivolumab over Placebo.

(3) Log-rank test stratified by prior neo-adjuvant cisplatin, pathological nodal status, as entered in IRT.

Program Path: /projects/bms214671/stats/market/ma274_202502/prog/tables

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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

5.2.1.4 Zum Therapieabbruch führende UE (deskriptive Darstellung)

Table 7.1
Adverse Events Leading to Discontinuation of Study Treatment Summary
by SOC/PT and Worst CTCAE Grade (Any Grade, Grade 3-4, Grade 5)
SAF

System Organ Class (%) Preferred Term (%)	Placebo N = 139			Nivolumab N = 139		
	Any Grade	Grade 3-4	Grade 5	Any Grade	Grade 3-4	Grade 5
TOTAL SUBJECTS WITH AN EVENT	18 (12.9)	11 (7.9)	2 (1.4)	32 (23.0)	21 (15.1)	0
Respiratory, thoracic and mediastinal disorders	1 (0.7)	0	0	7 (5.0)	4 (2.9)	0
Pneumonitis	1 (0.7)	0	0	5 (3.6)	2 (1.4)	0
Immune-mediated lung disease	0	0	0	1 (0.7)	1 (0.7)	0
Interstitial lung disease	0	0	0	1 (0.7)	1 (0.7)	0
Gastrointestinal disorders	4 (2.9)	4 (2.9)	0	4 (2.9)	3 (2.2)	0
Colitis	2 (1.4)	2 (1.4)	0	1 (0.7)	1 (0.7)	0
Diarrhoea	0	0	0	1 (0.7)	0	0
Intestinal obstruction	0	0	0	1 (0.7)	0	0
Nausea	0	0	0	1 (0.7)	1 (0.7)	0
Pancreatitis	1 (0.7)	1 (0.7)	0	1 (0.7)	1 (0.7)	0
Abdominal pain	1 (0.7)	1 (0.7)	0	0	0	0
Necrotising oesophagitis	1 (0.7)	1 (0.7)	0	0	0	0
Skin and subcutaneous tissue disorders	0	0	0	4 (2.9)	1 (0.7)	0
Granuloma annulare	0	0	0	1 (0.7)	0	0
Pemphigoid	0	0	0	1 (0.7)	1 (0.7)	0
Rash	0	0	0	1 (0.7)	0	0
Urticaria	0	0	0	1 (0.7)	0	0

FEB2025 DBL.

Includes events reported between the first dose and 100 days after the last dose of the study therapy.

MedDRA Version: 27.1; CTCAE Version: 4.0.

Program Path: /projects/bms214671/stats/market/ma274_202502/prog/tables

Program Name: rt-ae-aeltdcat-ebr45.sas

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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

Table 7.1
Adverse Events Leading to Discontinuation of Study Treatment Summary
by SOC/PT and Worst CTCAE Grade (Any Grade, Grade 3-4, Grade 5)
SAF

System Organ Class (%) Preferred Term (%)	Placebo N = 139			Nivolumab N = 139		
	Any Grade	Grade 3-4	Grade 5	Any Grade	Grade 3-4	Grade 5
Investigations	2 (1.4)	1 (0.7)	0	3 (2.2)	2 (1.4)	0
Alanine aminotransferase increased	0	0	0	1 (0.7)	1 (0.7)	0
Aspartate aminotransferase increased	0	0	0	1 (0.7)	1 (0.7)	0
Blood alkaline phosphatase increased	0	0	0	1 (0.7)	0	0
Blood creatinine increased	1 (0.7)	0	0	1 (0.7)	0	0
Transaminases increased	0	0	0	1 (0.7)	1 (0.7)	0
Amylase increased	1 (0.7)	1 (0.7)	0	0	0	0
Blood urea increased	1 (0.7)	0	0	0	0	0
Lipase increased	1 (0.7)	1 (0.7)	0	0	0	0
Musculoskeletal and connective tissue disorders	0	0	0	3 (2.2)	0	0
Autoimmune myositis	0	0	0	1 (0.7)	0	0
Myositis	0	0	0	1 (0.7)	0	0
Sacroiliitis	0	0	0	1 (0.7)	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	4 (2.9)	2 (1.4)	1 (0.7)	3 (2.2)	3 (2.2)	0
Colon cancer	0	0	0	1 (0.7)	1 (0.7)	0
Malignant neoplasm progression	2 (1.4)	0	1 (0.7)	1 (0.7)	1 (0.7)	0
Recurrent cancer	0	0	0	1 (0.7)	1 (0.7)	0
Metastases to central nervous system	1 (0.7)	1 (0.7)	0	0	0	0
Rectal cancer	1 (0.7)	1 (0.7)	0	0	0	0
Nervous system disorders	1 (0.7)	1 (0.7)	0	3 (2.2)	2 (1.4)	0
Balance disorder	0	0	0	1 (0.7)	0	0
Demyelination	0	0	0	1 (0.7)	1 (0.7)	0
Headache	0	0	0	1 (0.7)	0	0
Myasthenia gravis	0	0	0	1 (0.7)	1 (0.7)	0
Neurotoxicity	0	0	0	1 (0.7)	0	0
Ischaemic cerebral infarction	1 (0.7)	1 (0.7)	0	0	0	0

FEB2025 DBL.

Includes events reported between the first dose and 100 days after the last dose of the study therapy.

MedDRA Version: 27.1; CTCAE Version: 4.0.

Program Path: /projects/bms214671/stats/market/ma274_202502/prog/tables

Program Name: rt-ae-aeltdcat-ebr45.sas

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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

Table 7.1
Adverse Events Leading to Discontinuation of Study Treatment Summary
by SOC/PT and Worst CTCAE Grade (Any Grade, Grade 3-4, Grade 5)
SAF

System Organ Class (%) Preferred Term (%)	Placebo N = 139			Nivolumab N = 139		
	Any Grade	Grade 3-4	Grade 5	Any Grade	Grade 3-4	Grade 5
General disorders and administration site conditions	1 (0.7)	0	0	2 (1.4)	1 (0.7)	0
Fatigue	1 (0.7)	0	0	1 (0.7)	1 (0.7)	0
Granuloma	0	0	0	1 (0.7)	0	0
Hepatobiliary disorders	0	0	0	2 (1.4)	2 (1.4)	0
Hepatic failure	0	0	0	1 (0.7)	1 (0.7)	0
Liver injury	0	0	0	1 (0.7)	1 (0.7)	0
Infections and infestations	2 (1.4)	0	1 (0.7)	2 (1.4)	2 (1.4)	0
Skin infection	0	0	0	1 (0.7)	1 (0.7)	0
Urinary tract infection	0	0	0	1 (0.7)	1 (0.7)	0
Sepsis	1 (0.7)	0	1 (0.7)	0	0	0
Septic shock	1 (0.7)	0	0	0	0	0
Renal and urinary disorders	2 (1.4)	2 (1.4)	0	2 (1.4)	1 (0.7)	0
Acute kidney injury	1 (0.7)	1 (0.7)	0	1 (0.7)	1 (0.7)	0
Immune-mediated nephritis	0	0	0	1 (0.7)	0	0
Chronic kidney disease	1 (0.7)	1 (0.7)	0	0	0	0
Cardiac disorders	1 (0.7)	1 (0.7)	0	1 (0.7)	1 (0.7)	0
Immune-mediated myocarditis	0	0	0	1 (0.7)	1 (0.7)	0
Atrioventricular block complete	1 (0.7)	1 (0.7)	0	0	0	0
Eye disorders	0	0	0	1 (0.7)	0	0
Uveitis	0	0	0	1 (0.7)	0	0
Metabolism and nutrition disorders	1 (0.7)	1 (0.7)	0	1 (0.7)	0	0
Diabetes mellitus	0	0	0	1 (0.7)	0	0
Hyperglycaemia	1 (0.7)	1 (0.7)	0	0	0	0

FEB2025 DBL.

Includes events reported between the first dose and 100 days after the last dose of the study therapy.

MedDRA Version: 27.1; CTCAE Version: 4.0.

Program Path: /projects/bms214671/stats/market/ma274_202502/prog/tables

Program Name: rt-ae-aeltcat-ebr45.sas

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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

5.2.2 Subgruppenanalysen

5.2.2.1 Jegliche UE

Table 8.1
Subgroup Time-Adjusted Analyses
of Adverse Events
by Significant SOC/PT on Hazard Ratio
SAF

SOC: General Disorders and Administration Site Conditions. PT: Asthenia

Adverse Events Subgroups	Placebo			Nivolumab			Nivolumab vs. Placebo	
	N	Patients with Event n (%)	KME [95%CI] (mon) (1)	N	Patients with Event n (%)	KME [95%CI] (mon) (1)	HR [95%CI] P-value (2) (3)	Test for Interaction P-value (4) (5)
OVERALL	139	5 (3.6)	N.A.	139	19 (13.7)	N.A.	3.917 (1.462, 10.492) 0.0034	0.9912
PRIOR NEO-ADJUVANT CISPLATIN THERAPY								
YES	61	0	N.A.	57	9 (15.8)	N.A.	N.M.E. 0.0017	
NO	78	5 (6.4)	N.A.	82	10 (12.2)	N.A.	1.992 (0.681, 5.831) 0.1993	

FEB2025 DBL. Includes events reported between first dose and 100 days after last dose of the study therapy.

MedDRA Version: 27.1; CTC Version 4.0. HR = hazard ratio; KME = Kaplan-Meier estimate; N.M.E. = Not meaningful estimate.

(1) KME of median time to first AE. (2) Unstratified log-rank test.

(3) Unstratified Cox proportional hazard model. HR is Nivolumab over Placebo

(4) Unstratified Cox proportional hazard model with treatment, subgroup and treatment*subgroup interaction is to assess the significance of the interaction between treatment and the subgroup.

(5) A p-value of <0.05 needs to be indicated by 1 asterisk (indicates potential effect modification).

IUC = invasive urothelial carcinoma.

Program Path: /projects/bms214671/stats/market/ma274_202502/prog/tables

Program Name: rt-ae-tsubsocae-hr-ebr45.sas

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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

Table 8.1
Subgroup Time-Adjusted Analyses
of Adverse Events
by Significant SOC/PT on Hazard Ratio
SAF

SOC: General Disorders and Administration Site Conditions. PT: Asthenia

Adverse Events Subgroups	Placebo			Nivolumab			Nivolumab vs. Placebo	
	N	Patients with Event n (%)	KME [95%CI] (mon) (1)	N	Patients with Event n (%)	KME [95%CI] (mon) (1)	HR [95%CI] P-value (2) (3)	Test for Interaction P-value (4) (5)
PRIOR CISPLATIN STATUS								0.9873
RECEIVED NEO-ADJUVANT	61	0	N.A.	57	9 (15.8)	N.A.	N.M.E. 0.0017	
UNWILLING TO RECEIVE NEO-ADJUVANT	45	3 (6.7)	N.A.	50	7 (14.0)	N.A.	2.230 (0.576, 8.626)	
NOT ELIGIBLE TO RECEIVE NEO-ADJUVANT	32	2 (6.3)	N.A.	27	3 (11.1)	N.A.	0.2326 1.908 (0.319, 11.422)	
							0.4715	

FEB2025 DBL. Includes events reported between first dose and 100 days after last dose of the study therapy.

MedDRA Version: 27.1; CTC Version 4.0. HR = hazard ratio; KME = Kaplan-Meier estimate; N.M.E. = Not meaningful estimate.

(1) KME of median time to first AE. (2) Unstratified log-rank test.

(3) Unstratified Cox proportional hazard model. HR is Nivolumab over Placebo

(4) Unstratified Cox proportional hazard model with treatment, subgroup and treatment*subgroup interaction is to assess the significance of the interaction between treatment and the subgroup.

(5) A p-value of <0.05 needs to be indicated by 1 asterisk (indicates potential effect modification).

IUC = invasive urothelial carcinoma.

Program Path: /projects/bms214671/stats/market/ma274_202502/prog/tables

Program Name: rt-ae-tsubsocaehr-ebr45.sas

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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

Table 8.1
Subgroup Time-Adjusted Analyses
of Adverse Events
by Significant SOC/PT on Hazard Ratio
SAF

SOC: General Disorders and Administration Site Conditions. PT: Asthenia

Adverse Events Subgroups	Placebo			Nivolumab			Nivolumab vs. Placebo	
	N	Patients with Event n (%)	KME [95%CI] (mon) (1)	N	Patients with Event n (%)	KME [95%CI] (mon) (1)	HR [95%CI] P-value (2) (3)	Test for Interaction P-value (4) (5)
USE OF ANY PRIOR NEO-ADJUVANT SYSTEMIC THERAPY								0.9911
YES	62	0	N.A.	61	9 (14.8)	N.A.	N.M.E. 0.0023	
NO	77	5 (6.5)	N.A.	78	10 (12.8)	N.A.	2.069 (0.707, 6.056) 0.1747	

FEB2025 DBL. Includes events reported between first dose and 100 days after last dose of the study therapy.

MedDRA Version: 27.1; CTC Version 4.0. HR = hazard ratio; KME = Kaplan-Meier estimate; N.M.E. = Not meaningful estimate.

(1) KME of median time to first AE. (2) Unstratified log-rank test.

(3) Unstratified Cox proportional hazard model. HR is Nivolumab over Placebo

(4) Unstratified Cox proportional hazard model with treatment, subgroup and treatment*subgroup interaction is to assess the significance of the interaction between treatment and the subgroup.

(5) A p-value of <0.05 needs to be indicated by 1 asterisk (indicates potential effect modification).

IUC = invasive urothelial carcinoma.

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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

Table 8.1
Subgroup Time-Adjusted Analyses
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by Significant SOC/PT on Hazard Ratio
SAF

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Adverse Events Subgroups	Placebo			Nivolumab			Nivolumab vs. Placebo	
	N	Patients with Event n (%)	KME [95%CI] (mon) (1)	N	Patients with Event n (%)	KME [95%CI] (mon) (1)	HR [95%CI] P-value (2) (3)	Test for Interaction P-value (4) (5)
PATHOLOGICAL LYMPH NODE STATUS								0.3826
N+	64	1 (1.6)	N.A.	60	9 (15.0)	N.A.	10.017 (1.269, 79.072)	
N0/X WITH <10 NODES REMOVED	38	3 (7.9)	N.A.	38	5 (13.2)	N.A.	0.0069 1.784 (0.426, 7.468)	
N0 WITH >= 10 NODES REMOVED	37	1 (2.7)	N.A.	41	5 (12.2)	N.A.	0.4215 4.496 (0.525, 38.485)	
							0.1323	

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	N	Patients with Event n (%)	KME [95%CI] (mon) (1)	N	Patients with Event n (%)	KME [95%CI] (mon) (1)	HR [95%CI] P-value (2) (3)	Test for Interaction P-value (4) (5)
PATHOLOGICAL STATUS								0.7118
PT0-2	31	2 (6.5)	N.A.	26	4 (15.4)	N.A.	2.472 (0.453, 13.499)	
PT3	80	2 (2.5)	N.A.	86	13 (15.1)	N.A.	0.2820 5.991 (1.351, 26.558)	
PT4A	27	1 (3.7)	N.A.	23	2 (8.7)	N.A.	0.0073 2.562 (0.232, 28.285)	
							0.4259	

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	N	Patients with Event n (%)	KME [95%CI] (mon) (1)	N	Patients with Event n (%)	KME [95%CI] (mon) (1)	HR [95%CI] P-value (2) (3)	Test for Interaction P-value (4) (5)
AGE CATEGORY I								0.9032
< 65	59	2 (3.4)	N.A.	67	8 (11.9)	N.A.	3.714 (0.789, 17.490) 0.0749	
>= 65	80	3 (3.8)	N.A.	72	11 (15.3)	N.A.	4.166 (1.162, 14.934) 0.0173	

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	N	Patients with Event n (%)	KME [95%CI] (mon) (1)	N	Patients with Event n (%)	KME [95%CI] (mon) (1)	HR [95%CI] P-value (2) (3)	Test for Interaction P-value (4) (5)
AGE CATEGORY II < 65	59	2 (3.4)	N.A.	67	8 (11.9)	N.A.	3.714 (0.789, 17.490)	0.7111
>= 65 AND < 75	59	1 (1.7)	N.A.	49	6 (12.2)	N.A.	0.0749 7.282 (0.877, 60.466)	
>= 75	21	2 (9.5)	N.A.	23	5 (21.7)	N.A.	0.0311 2.471 (0.479, 12.740)	
							0.2636	

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	N	Patients with Event n (%)	KME [95%CI] (mon) (1)	N	Patients with Event n (%)	KME [95%CI] (mon) (1)	HR [95%CI] P-value (2) (3)	Test for Interaction P-value (4) (5)
REGION								0.8939
US	23	0	N.A.	17	0	N.A.	N.M.E. N.A.	
EUROPE	68	3 (4.4)	N.A.	72	15 (20.8)	N.A.	4.772 (1.381, 16.486)	
ASIA	28	1 (3.6)	N.A.	33	2 (6.1)	N.A.	0.0063 1.811 (0.164, 19.981)	
REST OF WORLD	20	1 (5.0)	N.A.	17	2 (11.8)	N.A.	0.6225 2.519 (0.228, 27.810)	
							0.4346	

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	N	Patients with Event n (%)	KME [95%CI] (mon) (1)	N	Patients with Event n (%)	KME [95%CI] (mon) (1)	HR [95%CI] P-value (2) (3)	Test for Interaction P-value (4) (5)
GENDER								0.8159
MALE	109	4 (3.7)	N.A.	101	15 (14.9)	N.A.	4.180 (1.387, 12.598)	
FEMALE	30	1 (3.3)	N.A.	38	4 (10.5)	N.A.	0.0057 3.105 (0.347, 27.781)	
RACE								0.5430
WHITE	106	4 (3.8)	N.A.	103	16 (15.5)	N.A.	4.129 (1.380, 12.352)	
ASIAN	28	1 (3.6)	N.A.	33	2 (6.1)	N.A.	0.0059 1.811 (0.164, 19.981)	
							0.6225	

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	N	Patients with Event n (%)	KME [95%CI] (mon) (1)	N	Patients with Event n (%)	KME [95%CI] (mon) (1)	HR [95%CI] P-value (2) (3)	Test for Interaction P-value (4) (5)
BASELINE ECOG STATUS								
0	83	2 (2.4)	N.A.	85	12 (14.1)	N.A.	6.149 (1.376, 27.477) 0.0065	0.3422
1	52	3 (5.8)	N.A.	51	7 (13.7)	N.A.	2.321 (0.600, 8.976) 0.2087	
SMOKING STATUS								
NEVER SMOKED	39	2 (5.1)	N.A.	41	4 (9.8)	N.A.	1.862 (0.341, 10.168) 0.4658	0.3719
CURRENT/FORMER	99	3 (3.0)	N.A.	96	14 (14.6)	N.A.	4.912 (1.411, 17.098) 0.0056	

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	N	Patients with Event n (%)	KME [95%CI] (mon) (1)	N	Patients with Event n (%)	KME [95%CI] (mon) (1)	HR [95%CI] P-value (2) (3)	Test for Interaction P-value (4) (5)
BASELINE HEMOGLOBIN								0.9448
<10 G/DL	14	1 (7.1)	N.A.	7	2 (28.6)	N.A. (0.03, N.A.)	4.492 (0.406, 49.706)	
							0.1794	
>=10 G/DL	125	4 (3.2)	N.A.	132	17 (12.9)	N.A.	4.139 (1.392, 12.301)	
							0.0055	
BASELINE CREATININE CLEARANCE								0.5836
<60 ML/MIN	60	4 (6.7)	N.A.	54	11 (20.4)	N.A.	3.420 (1.088, 10.744)	
							0.0252	
>=60 ML/MIN	79	1 (1.3)	N.A.	84	7 (8.3)	N.A.	6.486 (0.797, 52.758)	
							0.0441	

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	N	Patients with Event n (%)	KME [95%CI] (mon) (1)	N	Patients with Event n (%)	KME [95%CI] (mon) (1)	HR [95%CI] P-value (2) (3)	Test for Interaction P-value (4) (5)
TIME FROM IUC SURGERY TO RANDOMIZATION (DAYS)								0.8374
>30-60	28	1 (3.6)	N.A.	34	4 (11.8)	N.A.	3.471 (0.388, 31.083)	
>60-90	65	2 (3.1)	N.A.	57	9 (15.8)	N.A.	0.2357 5.334 (1.152, 24.689)	
>90-120	41	2 (4.9)	N.A.	46	6 (13.0)	N.A.	0.0164 2.674 (0.539, 13.260)	
							0.2101	

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	N	Patients with Event n (%)	KME [95%CI] (mon) (1)	N	Patients with Event n (%)	KME [95%CI] (mon) (1)	HR [95%CI] P-value (2) (3)	Test for Interaction P-value (4) (5)
INITIAL TUMOR ORIGIN								0.9867
URINARY BLADDER	115	4 (3.5)	N.A.	112	16 (14.3)	N.A.	4.183 (1.398, 12.514) 0.0054	
RENAL PELVIS	13	0	N.A.	19	1 (5.3)	N.A.	N.M.E. 0.4497	
URETER	11	1 (9.1)	N.A.	8	2 (25.0)	N.A. (2.30, N.A.)	3.713 (0.335, 41.154) 0.2518	

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	N	Patients with Event n (%)	KME [95%CI] (mon) (1)	N	Patients with Event n (%)	KME [95%CI] (mon) (1)	HR [95%CI] P-value (2) (3)	Test for Interaction P-value (4) (5)
MINOR HISTOLOGICAL VARIANTS								0.1364
PRESENCE	60	2 (3.3)	N.A.	61	14 (23.0)	N.A.	7.674 (1.743, 33.775) 0.0014	
ABSENCE	79	3 (3.8)	N.A.	78	5 (6.4)	N.A.	1.610 (0.384, 6.743) 0.5106	

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SOC: Skin and Subcutaneous Tissue Disorders

Adverse Events Subgroups	Placebo			Nivolumab			Nivolumab vs. Placebo	
	N	Patients with Event n (%)	KME [95%CI] (mon) (1)	N	Patients with Event n (%)	KME [95%CI] (mon) (1)	HR [95%CI] P-value (2) (3)	Test for Interaction P-value (4) (5)
OVERALL	139	45 (32.4)	N.A.	139	77 (55.4)	5.22 (2.50, 10.35)	2.027 (1.402, 2.929) 0.0001	
PRIOR NEO-ADJUVANT CISPLATIN THERAPY								0.1140
YES	61	25 (41.0)	N.A. (4.24, N.A.)	57	33 (57.9)	5.09 (2.14, N.A.)	1.497 (0.890, 2.518) 0.1264	
NO	78	20 (25.6)	N.A.	82	44 (53.7)	5.39 (2.30, N.A.)	2.675 (1.575, 4.544) 0.0002	

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SOC: Skin and Subcutaneous Tissue Disorders

Adverse Events Subgroups	Placebo			Nivolumab			Nivolumab vs. Placebo	
	N	Patients with Event n (%)	KME [95%CI] (mon) (1)	N	Patients with Event n (%)	KME [95%CI] (mon) (1)	HR [95%CI] P-value (2) (3)	Test for Interaction P-value (4) (5)
PRIOR CISPLATIN STATUS								0.2555
RECEIVED NEO-ADJUVANT	61	25 (41.0)	N.A. (4.24, N.A.)	57	33 (57.9)	5.09 (2.14, N.A.)	1.497 (0.890, 2.518) 0.1264	
UNWILLING TO RECEIVE NEO-ADJUVANT	45	10 (22.2)	N.A.	50	26 (52.0)	5.39 (2.10, N.A.)	3.050 (1.468, 6.338) 0.0017	
NOT ELIGIBLE TO RECEIVE NEO-ADJUVANT	32	10 (31.3)	N.A. (7.56, N.A.)	27	15 (55.6)	5.32 (1.12, N.A.)	2.073 (0.930, 4.621) 0.0677	

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(1) KME of median time to first AE. (2) Unstratified log-rank test.

(3) Unstratified Cox proportional hazard model. HR is Nivolumab over Placebo

(4) Unstratified Cox proportional hazard model with treatment, subgroup and treatment*subgroup interaction is to assess the significance of the interaction between treatment and the subgroup.

(5) A p-value of <0.05 needs to be indicated by 1 asterisk (indicates potential effect modification).

IUC = invasive urothelial carcinoma.

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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

Table 8.1
Subgroup Time-Adjusted Analyses
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by Significant SOC/PT on Hazard Ratio
SAF

SOC: Skin and Subcutaneous Tissue Disorders

Adverse Events Subgroups	Placebo			Nivolumab			Nivolumab vs. Placebo	
	N	Patients with Event n (%)	KME [95%CI] (mon) (1)	N	Patients with Event n (%)	KME [95%CI] (mon) (1)	HR [95%CI] P-value (2) (3)	Test for Interaction P-value (4) (5)
USE OF ANY PRIOR NEO-ADJUVANT SYSTEMIC THERAPY								0.0522
YES	62	25 (40.3)	N.A. (4.99, N.A.)	61	33 (54.1)	5.22 (2.33, N.A.)	1.387 (0.825, 2.333)	
NO	77	20 (26.0)	N.A.	78	44 (56.4)	4.27 (2.10, N.A.)	0.2165 2.845 (1.675, 4.833) <0.0001	

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PATHOLOGICAL LYMPH NODE STATUS								0.2134
N+	64	18 (28.1)	N.A.	60	33 (55.0)	5.03 (1.81, N.A.)	2.371 (1.334, 4.217) 0.0024	
N0/X WITH <10 NODES REMOVED	38	10 (26.3)	N.A.	38	21 (55.3)	5.39 (1.94, N.A.)	2.683 (1.260, 5.714) 0.0076	
N0 WITH >= 10 NODES REMOVED	37	17 (45.9)	8.05 (3.25, N.A.)	41	23 (56.1)	7.03 (2.04, N.A.)	1.263 (0.675, 2.365) 0.4634	

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	N	Patients with Event n (%)	KME [95%CI] (mon) (1)	N	Patients with Event n (%)	KME [95%CI] (mon) (1)	HR [95%CI] P-value (2) (3)	Test for Interaction P-value (4) (5)
PATHOLOGICAL STATUS								0.6433
PT0-2	31	11 (35.5)	N.A. (5.13, N.A.)	26	17 (65.4)	3.55 (0.89, N.A.)	2.342 (1.095, 5.013) 0.0237	
PT3	80	28 (35.0)	N.A. (7.56, N.A.)	86	48 (55.8)	6.90 (2.50, 10.48)	1.752 (1.099, 2.792) 0.0171	
PT4A	27	6 (22.2)	N.A. (8.05, N.A.)	23	10 (43.5)	N.A. (1.38, N.A.)	2.384 (0.864, 6.579) 0.0833	

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	N	Patients with Event n (%)	KME [95%CI] (mon) (1)	N	Patients with Event n (%)	KME [95%CI] (mon) (1)	HR [95%CI] P-value (2) (3)	Test for Interaction P-value (4) (5)
AGE CATEGORY I								0.2505
< 65	59	20 (33.9)	N.A. (6.21, N.A.)	67	33 (49.3)	6.90 (3.78, N.A.)	1.602 (0.919, 2.793) 0.0943	
>= 65	80	25 (31.3)	N.A.	72	44 (61.1)	4.27 (1.91, 8.84)	2.506 (1.531, 4.101) 0.0002	

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	N	Patients with Event n (%)	KME [95%CI] (mon) (1)	N	Patients with Event n (%)	KME [95%CI] (mon) (1)	HR [95%CI] P-value (2) (3)	Test for Interaction P-value (4) (5)
AGE CATEGORY II								0.5275
< 65	59	20 (33.9)	N.A. (6.21, N.A.)	67	33 (49.3)	6.90 (3.78, N.A.)	1.602 (0.919, 2.793) 0.0943	
>= 65 AND < 75	59	18 (30.5)	N.A. (12.16, N.A.)	49	29 (59.2)	5.03 (2.10, 8.84)	2.467 (1.365, 4.456) 0.0020	
>= 75	21	7 (33.3)	N.A. (3.91, N.A.)	23	15 (65.2)	2.79 (0.59, 10.48)	2.457 (0.999, 6.041) 0.0429	

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	N	Patients with Event n (%)	KME [95%CI] (mon) (1)	N	Patients with Event n (%)	KME [95%CI] (mon) (1)	HR [95%CI] P-value (2) (3)	Test for Interaction P-value (4) (5)
REGION								0.3708
US	23	9 (39.1)	N.A. (3.02, N.A.)	17	8 (47.1)	7.29 (0.95, N.A.)	1.167 (0.447, 3.043)	
EUROPE	68	20 (29.4)	N.A.	72	37 (51.4)	8.84 (4.63, N.A.)	0.7472 1.889 (1.096, 3.255)	
ASIA	28	8 (28.6)	N.A. (4.67, N.A.)	33	20 (60.6)	2.33 (1.12, N.A.)	0.0198 2.876 (1.260, 6.564)	
REST OF WORLD	20	8 (40.0)	N.A. (3.09, N.A.)	17	12 (70.6)	0.95 (0.13, N.A.)	0.0087 2.790 (1.133, 6.874)	
							0.0204	

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	N	Patients with Event n (%)	KME [95%CI] (mon) (1)	N	Patients with Event n (%)	KME [95%CI] (mon) (1)	HR [95%CI] P-value (2) (3)	Test for Interaction P-value (4) (5)
GENDER								0.1623
MALE	109	33 (30.3)	N.A.	101	57 (56.4)	4.93 (2.30, N.A.)	2.315 (1.507, 3.557) <0.0001	
FEMALE	30	12 (40.0)	N.A. (2.89, N.A.)	38	20 (52.6)	7.03 (2.14, N.A.)	1.251 (0.611, 2.562) 0.5372	
RACE								0.1940
WHITE	106	35 (33.0)	N.A.	103	54 (52.4)	7.16 (4.63, N.A.)	1.749 (1.143, 2.676) 0.0091	
ASIAN	28	8 (28.6)	N.A. (4.67, N.A.)	33	20 (60.6)	2.33 (1.12, N.A.)	2.876 (1.260, 6.564) 0.0087	

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	N	Patients with Event n (%)	KME [95%CI] (mon) (1)	N	Patients with Event n (%)	KME [95%CI] (mon) (1)	HR [95%CI] P-value (2) (3)	Test for Interaction P-value (4) (5)
BASELINE ECOG STATUS								
0	83	25 (30.1)	N.A.	85	42 (49.4)	8.84 (2.99, N.A.)	1.907 (1.162, 3.131) 0.0094	0.7915
1	52	19 (36.5)	N.A. (3.91, N.A.)	51	33 (64.7)	4.21 (1.41, 5.32)	2.080 (1.181, 3.662) 0.0095	
SMOKING STATUS								
NEVER SMOKED	39	14 (35.9)	N.A. (4.67, N.A.)	41	22 (53.7)	7.03 (1.68, N.A.)	1.756 (0.892, 3.457) 0.0997	0.5619
CURRENT/FORMER	99	31 (31.3)	N.A.	96	54 (56.3)	5.09 (2.46, N.A.)	2.155 (1.385, 3.354) 0.0005	

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BASELINE HEMOGLOBIN								
<10 G/DL	14	3 (21.4)	N.A. (4.99, N.A.)	7	6 (85.7)	0.92 (0.16, 2.33)	8.165 (1.900, 35.079) 0.0012	0.0308*
>=10 G/DL	125	42 (33.6)	N.A.	132	71 (53.8)	5.39 (3.78, N.A.)	1.841 (1.256, 2.696) 0.0015	
BASELINE CREATININE CLEARANCE								
<60 ML/MIN	60	18 (30.0)	N.A. (12.16, N.A.)	54	35 (64.8)	2.33 (1.61, 7.03)	3.055 (1.725, 5.413) <0.0001	0.0694
>=60 ML/MIN	79	27 (34.2)	N.A. (8.05, N.A.)	84	41 (48.8)	8.84 (4.93, N.A.)	1.507 (0.927, 2.451) 0.0951	

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	N	Patients with Event n (%)	KME [95%CI] (mon) (1)	N	Patients with Event n (%)	KME [95%CI] (mon) (1)	HR [95%CI] P-value (2) (3)	Test for Interaction P-value (4) (5)
TIME FROM IUC SURGERY TO RANDOMIZATION (DAYS)								0.9334
>30-60	28	8 (28.6)	N.A. (4.24, N.A.)	34	16 (47.1)	10.48 (1.12, N.A.)	1.947 (0.832, 4.560)	
>60-90	65	23 (35.4)	N.A. (4.99, N.A.)	57	36 (63.2)	4.63 (2.14, 7.29)	0.1181 1.994 (1.181, 3.366)	
>90-120	41	12 (29.3)	N.A. (12.16, N.A.)	46	24 (52.2)	6.90 (1.91, N.A.)	0.0085 2.313 (1.155, 4.635)	

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	N	Patients with Event n (%)	KME [95%CI] (mon) (1)	N	Patients with Event n (%)	KME [95%CI] (mon) (1)	HR [95%CI] P-value (2) (3)	Test for Interaction P-value (4) (5)
INITIAL TUMOR ORIGIN								0.4321
URINARY BLADDER	115	37 (32.2)	N.A.	112	60 (53.6)	5.22 (2.50, N.A.)	1.920 (1.274, 2.893) 0.0015	
RENAL PELVIS	13	4 (30.8)	N.A. (4.67, N.A.)	19	10 (52.6)	10.35 (1.84, N.A.)	2.094 (0.650, 6.743) 0.2059	
URETER	11	4 (36.4)	N.A. (3.29, N.A.)	8	7 (87.5)	1.76 (0.20, N.A.)	6.632 (1.614, 27.247) 0.0033	

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Adverse Events Subgroups	Placebo			Nivolumab			Nivolumab vs. Placebo	
	N	Patients with Event n (%)	KME [95%CI] (mon) (1)	N	Patients with Event n (%)	KME [95%CI] (mon) (1)	HR [95%CI] P-value (2) (3)	Test for Interaction P-value (4) (5)
MINOR HISTOLOGICAL VARIANTS								0.4169
PRESENCE	60	21 (35.0)	N.A. (7.56, N.A.)	61	32 (52.5)	7.16 (2.50, N.A.)	1.744 (1.005, 3.028) 0.0452	
ABSENCE	79	24 (30.4)	N.A.	78	45 (57.7)	4.27 (2.04, N.A.)	2.321 (1.413, 3.814) 0.0006	

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(1) KME of median time to first AE. (2) Unstratified log-rank test.

(3) Unstratified Cox proportional hazard model. HR is Nivolumab over Placebo

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(5) A p-value of <0.05 needs to be indicated by 1 asterisk (indicates potential effect modification).

IUC = invasive urothelial carcinoma.

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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

Table 8.1
Subgroup Time-Adjusted Analyses
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SAF

SOC: Skin and Subcutaneous Tissue Disorders. PT: Pruritus

Adverse Events Subgroups	Placebo			Nivolumab			Nivolumab vs. Placebo	
	N	Patients with Event n (%)	KME [95%CI] (mon) (1)	N	Patients with Event n (%)	KME [95%CI] (mon) (1)	HR [95%CI] P-value (2) (3)	Test for Interaction P-value (4) (5)
OVERALL	139	19 (13.7)	N.A.	139	39 (28.1)	N.A.	2.156 (1.246, 3.731) 0.0049	
PRIOR NEO-ADJUVANT CISPLATIN THERAPY								0.5179
YES	61	9 (14.8)	N.A.	57	15 (26.3)	N.A.	1.773 (0.776, 4.052) 0.1682	
NO	78	10 (12.8)	N.A.	82	24 (29.3)	N.A.	2.542 (1.215, 5.317) 0.0103	

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PRIOR CISPLATIN STATUS								0.3542
RECEIVED NEO-ADJUVANT	61	9 (14.8)	N.A.	57	15 (26.3)	N.A.	1.773 (0.776, 4.052)	
UNWILLING TO RECEIVE NEO-ADJUVANT	45	5 (11.1)	N.A.	50	18 (36.0)	N.A. (4.60, N.A.)	0.1682 3.828 (1.419, 10.321)	
NOT ELIGIBLE TO RECEIVE NEO-ADJUVANT	32	5 (15.6)	N.A.	27	6 (22.2)	N.A. (10.48, N.A.)	0.0043 1.350 (0.410, 4.450)	
							0.6211	

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	N	Patients with Event n (%)	KME [95%CI] (mon) (1)	N	Patients with Event n (%)	KME [95%CI] (mon) (1)	HR [95%CI] P-value (2) (3)	Test for Interaction P-value (4) (5)
USE OF ANY PRIOR NEO-ADJUVANT SYSTEMIC THERAPY								0.4001
YES	62	9 (14.5)	N.A.	61	15 (24.6)	N.A.	1.663 (0.727, 3.800)	
NO	77	10 (13.0)	N.A.	78	24 (30.8)	N.A.	0.2224 2.665 (1.274, 5.576) 0.0068	

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	N	Patients with Event n (%)	KME [95%CI] (mon) (1)	N	Patients with Event n (%)	KME [95%CI] (mon) (1)	HR [95%CI] P-value (2) (3)	Test for Interaction P-value (4) (5)
PATHOLOGICAL LYMPH NODE STATUS								0.3833
N+	64	7 (10.9)	N.A.	60	14 (23.3)	N.A.	2.184 (0.881, 5.411)	
N0/X WITH <10 NODES REMOVED	38	4 (10.5)	N.A.	38	13 (34.2)	N.A. (10.35, N.A.)	0.0838 3.684 (1.201, 11.303)	
N0 WITH >= 10 NODES REMOVED	37	8 (21.6)	N.A.	41	12 (29.3)	N.A.	0.0145 1.368 (0.559, 3.347)	
							0.4920	

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	N	Patients with Event n (%)	KME [95%CI] (mon) (1)	N	Patients with Event n (%)	KME [95%CI] (mon) (1)	HR [95%CI] P-value (2) (3)	Test for Interaction P-value (4) (5)
PATHOLOGICAL STATUS								0.8780
PT0-2	31	6 (19.4)	N.A.	26	9 (34.6)	N.A. (6.97, N.A.)	1.933 (0.687, 5.435) 0.2009	
PT3	80	10 (12.5)	N.A.	86	26 (30.2)	N.A.	2.474 (1.193, 5.131) 0.0118	
PT4A	27	3 (11.1)	N.A.	23	4 (17.4)	N.A.	1.663 (0.372, 7.439) 0.5009	

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	N	Patients with Event n (%)	KME [95%CI] (mon) (1)	N	Patients with Event n (%)	KME [95%CI] (mon) (1)	HR [95%CI] P-value (2) (3)	Test for Interaction P-value (4) (5)
AGE CATEGORY I								0.7693
< 65	59	7 (11.9)	N.A.	67	18 (26.9)	N.A.	2.413 (1.008, 5.779) 0.0412	
>= 65	80	12 (15.0)	N.A.	72	21 (29.2)	N.A.	2.047 (1.007, 4.161) 0.0432	

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	N	Patients with Event n (%)	KME [95%CI] (mon) (1)	N	Patients with Event n (%)	KME [95%CI] (mon) (1)	HR [95%CI] P-value (2) (3)	Test for Interaction P-value (4) (5)
AGE CATEGORY II < 65	59	7 (11.9)	N.A.	67	18 (26.9)	N.A.	2.413 (1.008, 5.779)	0.9173
>= 65 AND < 75	59	8 (13.6)	N.A.	49	13 (26.5)	N.A.	0.0412 2.129 (0.882, 5.139)	
>= 75	21	4 (19.0)	N.A.	23	8 (34.8)	N.A. (4.60, N.A.)	0.0853 1.797 (0.538, 5.995) 0.3337	

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REGION								0.4660
US	23	4 (17.4)	N.A.	17	2 (11.8)	N.A. (7.29, N.A.)	0.667 (0.122, 3.652)	
EUROPE	68	8 (11.8)	N.A.	72	20 (27.8)	N.A.	0.6439 2.355 (1.037, 5.347)	
ASIA	28	4 (14.3)	N.A.	33	10 (30.3)	N.A. (4.60, N.A.)	0.0348 2.365 (0.741, 7.546)	
REST OF WORLD	20	3 (15.0)	N.A.	17	7 (41.2)	N.A. (0.89, N.A.)	0.1332 3.201 (0.826, 12.404)	
							0.0755	

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GENDER								
MALE	109	14 (12.8)	N.A.	101	28 (27.7)	N.A.	2.307 (1.214, 4.382)	0.6152
FEMALE	30	5 (16.7)	N.A.	38	11 (28.9)	N.A. (10.12, N.A.)	0.0086 1.668 (0.579, 4.807)	
RACE								
WHITE	106	14 (13.2)	N.A.	103	28 (27.2)	N.A.	2.063 (1.086, 3.920)	0.7559
ASIAN	28	4 (14.3)	N.A.	33	10 (30.3)	N.A. (4.60, N.A.)	0.0237 2.365 (0.741, 7.546)	

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BASELINE ECOG STATUS								
0	83	9 (10.8)	N.A.	85	21 (24.7)	N.A.	2.438 (1.116, 5.325)	0.5631
1	52	10 (19.2)	N.A.	51	17 (33.3)	N.A. (10.48, N.A.)	0.0208 1.771 (0.811, 3.870)	
SMOKING STATUS								
NEVER SMOKED	39	7 (17.9)	N.A.	41	12 (29.3)	N.A. (7.29, N.A.)	1.722 (0.677, 4.379)	0.6153
CURRENT/FORMER	99	12 (12.1)	N.A.	96	26 (27.1)	N.A.	0.2474 2.326 (1.173, 4.610)	
							0.0128	

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BASELINE HEMOGLOBIN <10 G/DL	14	1 (7.1)	N.A.	7	2 (28.6)	N.A. (0.46, N.A.)	4.242 (0.384, 46.803) 0.1988	0.5584
>=10 G/DL	125	18 (14.4)	N.A.	132	37 (28.0)	N.A.	2.039 (1.161, 3.582) 0.0113	
BASELINE CREATININE CLEARANCE <60 ML/MIN	60	8 (13.3)	N.A.	54	19 (35.2)	N.A. (10.12, N.A.)	2.966 (1.298, 6.778) 0.0068	0.3385
>=60 ML/MIN	79	11 (13.9)	N.A.	84	20 (23.8)	N.A.	1.734 (0.831, 3.619) 0.1372	

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TIME FROM IUC SURGERY TO RANDOMIZATION (DAYS)								0.5830
>30-60	28	4 (14.3)	N.A.	34	9 (26.5)	N.A. (10.48, N.A.)	1.919 (0.591, 6.233)	
>60-90	65	9 (13.8)	N.A.	57	22 (38.6)	N.A. (7.16, N.A.)	0.2695 3.005 (1.384, 6.527)	
>90-120	41	5 (12.2)	N.A.	46	8 (17.4)	N.A.	0.0035 1.484 (0.485, 4.537) 0.4856	

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Program Path: /projects/bms214671/stats/market/ma274_202502/prog/tables

Program Name: rt-ae-tsubsocae-hr-ebr45.sas

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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

Table 8.1
Subgroup Time-Adjusted Analyses
of Adverse Events
by Significant SOC/PT on Hazard Ratio
SAF

SOC: Skin and Subcutaneous Tissue Disorders. PT: Pruritus

Adverse Events Subgroups	Placebo			Nivolumab			Nivolumab vs. Placebo	
	N	Patients with Event n (%)	KME [95%CI] (mon) (1)	N	Patients with Event n (%)	KME [95%CI] (mon) (1)	HR [95%CI] P-value (2) (3)	Test for Interaction P-value (4) (5)
INITIAL TUMOR ORIGIN								0.8722
URINARY BLADDER	115	17 (14.8)	N.A.	112	27 (24.1)	N.A.	1.651 (0.900, 3.030)	
RENAL PELVIS	13	2 (15.4)	N.A. (6.54, N.A.)	19	7 (36.8)	N.A. (7.29, N.A.)	0.1021 2.491 (0.516, 12.017)	
URETER	11	0	N.A.	8	5 (62.5)	2.81 (0.20, N.A.)	0.2396 N.M.E. 0.0021	

FEB2025 DBL. Includes events reported between first dose and 100 days after last dose of the study therapy.

MedDRA Version: 27.1; CTC Version 4.0. HR = hazard ratio; KME = Kaplan-Meier estimate; N.M.E. = Not meaningful estimate.

(1) KME of median time to first AE. (2) Unstratified log-rank test.

(3) Unstratified Cox proportional hazard model. HR is Nivolumab over Placebo

(4) Unstratified Cox proportional hazard model with treatment, subgroup and treatment*subgroup interaction is to assess the significance of the interaction between treatment and the subgroup.

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MINOR HISTOLOGICAL VARIANTS								0.6097
PRESENCE	60	8 (13.3)	N.A.	61	19 (31.1)	N.A. (10.48, N.A.)	2.550 (1.116, 5.826) 0.0213	
ABSENCE	79	11 (13.9)	N.A.	78	20 (25.6)	N.A.	1.914 (0.917, 3.994) 0.0789	

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SOC: Endocrine Disorders

Adverse Events Subgroups	Placebo			Nivolumab			Nivolumab vs. Placebo	
	N	Patients with Event n (%)	KME [95%CI] (mon) (1)	N	Patients with Event n (%)	KME [95%CI] (mon) (1)	HR [95%CI] P-value (2) (3)	Test for Interaction P-value (4) (5)
OVERALL	139	7 (5.0)	N.A.	139	31 (22.3)	N.A.	4.773 (2.101, 10.841) <0.0001	0.7519
PRIOR NEO-ADJUVANT CISPLATIN THERAPY								
YES	61	3 (4.9)	N.A.	57	11 (19.3)	N.A.	4.075 (1.137, 14.614) 0.0196	
NO	78	4 (5.1)	N.A.	82	20 (24.4)	N.A.	5.343 (1.825, 15.636) 0.0006	

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PRIOR CISPLATIN STATUS								
RECEIVED NEO-ADJUVANT	61	3 (4.9)	N.A.	57	11 (19.3)	N.A.	4.075 (1.137, 14.614)	0.6339
UNWILLING TO RECEIVE NEO-ADJUVANT	45	4 (8.9)	N.A.	50	7 (14.0)	N.A.	0.0196 1.703 (0.498, 5.822)	
NOT ELIGIBLE TO RECEIVE NEO-ADJUVANT	32	0	N.A.	27	10 (37.0)	N.A. (6.01, N.A.)	0.3917 N.M.E. 0.0002	

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USE OF ANY PRIOR NEO-ADJUVANT SYSTEMIC THERAPY								0.8152
YES	62	3 (4.8)	N.A.	61	12 (19.7)	N.A.	4.268 (1.204, 15.132)	
NO	77	4 (5.2)	N.A.	78	19 (24.4)	N.A.	0.0145 5.250 (1.785, 15.440) 0.0008	

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(1) KME of median time to first AE. (2) Unstratified log-rank test.

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PATHOLOGICAL LYMPH NODE STATUS								0.3716
N+	64	3 (4.7)	N.A.	60	15 (25.0)	N.A.	5.395 (1.560, 18.655)	
N0/X WITH <10 NODES REMOVED	38	0	N.A.	38	9 (23.7)	N.A.	0.0028 N.M.E.	
N0 WITH >= 10 NODES REMOVED	37	4 (10.8)	N.A.	41	7 (17.1)	N.A.	0.0010 1.624 (0.475, 5.547)	
							0.4385	

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PATHOLOGICAL STATUS								0.8485
PT0-2	31	1 (3.2)	N.A.	26	6 (23.1)	N.A.	7.551 (0.909, 62.712)	
PT3	80	5 (6.3)	N.A.	86	21 (24.4)	N.A.	0.0273 3.989 (1.503, 10.584)	
PT4A	27	1 (3.7)	N.A.	23	3 (13.0)	N.A.	0.0027 3.970 (0.413, 38.193)	
							0.1969	

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AGE CATEGORY I								0.2309
< 65	59	4 (6.8)	N.A.	67	12 (17.9)	N.A.	2.764 (0.890, 8.577)	
>= 65	80	3 (3.8)	N.A.	72	19 (26.4)	N.A.	0.0667 7.870 (2.328, 26.605) <0.0001	

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AGE CATEGORY II < 65	59	4 (6.8)	N.A.	67	12 (17.9)	N.A.	2.764 (0.890, 8.577)	0.6381
>= 65 AND < 75	59	3 (5.1)	N.A.	49	14 (28.6)	N.A. (14.00, N.A.)	0.0667 6.330 (1.818, 22.042)	
>= 75	21	0	N.A.	23	5 (21.7)	N.A. (7.82, N.A.)	0.0009 N.M.E. 0.0283	

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REGION								0.4171
US	23	1 (4.3)	N.A.	17	4 (23.5)	N.A. (2.76, N.A.)	6.297 (0.700, 56.653) 0.0603	
EUROPE	68	4 (5.9)	N.A.	72	19 (26.4)	N.A.	4.753 (1.617, 13.974) 0.0018	
ASIA	28	0	N.A.	33	7 (21.2)	N.A. (14.00, N.A.)	N.M.E. 0.0071	
REST OF WORLD	20	2 (10.0)	N.A. (10.28, N.A.)	17	1 (5.9)	N.A.	0.503 (0.045, 5.660) 0.5709	

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GENDER								
MALE	109	6 (5.5)	N.A.	101	22 (21.8)	N.A.	4.253 (1.723, 10.495) 0.0006	0.6112
FEMALE	30	1 (3.3)	N.A.	38	9 (23.7)	N.A.	7.476 (0.947, 59.014) 0.0247	
RACE								
WHITE	106	6 (5.7)	N.A.	103	24 (23.3)	N.A.	4.349 (1.777, 10.641) 0.0004	0.9889
ASIAN	28	0	N.A.	33	7 (21.2)	N.A. (14.00, N.A.)	N.M.E. 0.0071	

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BASELINE ECOG STATUS								
0	83	6 (7.2)	N.A.	85	23 (27.1)	N.A.	4.246 (1.728, 10.433) 0.0006	0.5706
1	52	1 (1.9)	N.A.	51	8 (15.7)	N.A.	8.357 (1.045, 66.829) 0.0165	
SMOKING STATUS								
NEVER SMOKED	39	2 (5.1)	N.A.	41	11 (26.8)	N.A. (7.82, N.A.)	5.901 (1.307, 26.632) 0.0087	0.6845
CURRENT/FORMER	99	5 (5.1)	N.A.	96	19 (19.8)	N.A.	4.070 (1.519, 10.908) 0.0025	

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BASILINE HEMOGLOBIN								
<10 G/DL	14	1 (7.1)	N.A. (8.31, N.A.)	7	1 (14.3)	N.A. (0.49, N.A.)	2.449 (0.151, 39.712)	0.6055
>=10 G/DL	125	6 (4.8)	N.A.	132	30 (22.7)	N.A.	0.5151 5.078 (2.113, 12.202) <0.0001	
BASILINE CREATININE CLEARANCE								
<60 ML/MIN	60	1 (1.7)	N.A.	54	14 (25.9)	N.A. (14.00, N.A.)	17.492 (2.300, >99.999)	0.1091
>=60 ML/MIN	79	6 (7.6)	N.A.	84	17 (20.2)	N.A.	0.0001 2.828 (1.115, 7.175) 0.0223	

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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

Table 8.1
Subgroup Time-Adjusted Analyses
of Adverse Events
by Significant SOC/PT on Hazard Ratio
SAF

SOC: Endocrine Disorders

Adverse Events Subgroups	Placebo			Nivolumab			Nivolumab vs. Placebo	
	N	Patients with Event n (%)	KME [95%CI] (mon) (1)	N	Patients with Event n (%)	KME [95%CI] (mon) (1)	HR [95%CI] P-value (2) (3)	Test for Interaction P-value (4) (5)
TIME FROM IUC SURGERY TO RANDOMIZATION (DAYS)								0.4415
>30-60	28	2 (7.1)	N.A.	34	5 (14.7)	N.A.	2.018 (0.391, 10.414)	
>60-90	65	2 (3.1)	N.A.	57	14 (24.6)	N.A.	0.3920 8.590 (1.952, 37.804)	
>90-120	41	3 (7.3)	N.A.	46	11 (23.9)	N.A.	0.0006 3.549 (0.989, 12.733)	
							0.0379	

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(1) KME of median time to first AE. (2) Unstratified log-rank test.

(3) Unstratified Cox proportional hazard model. HR is Nivolumab over Placebo

(4) Unstratified Cox proportional hazard model with treatment, subgroup and treatment*subgroup interaction is to assess the significance of the interaction between treatment and the subgroup.

(5) A p-value of <0.05 needs to be indicated by 1 asterisk (indicates potential effect modification).

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INITIAL TUMOR ORIGIN								
URINARY BLADDER	115	7 (6.1)	N.A.	112	24 (21.4)	N.A.	3.689 (1.589, 8.565)	>0.9999
RENAL PELVIS	13	0	N.A.	19	6 (31.6)	N.A.	0.0011 N.M.E.	
URETER	11	0	N.A.	8	1 (12.5)	(5.52, N.A.) N.A. (7.79, N.A.)	0.0354 N.M.E. 0.1336	

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MINOR HISTOLOGICAL VARIANTS								0.5118
PRESENCE	60	4 (6.7)	N.A.	61	13 (21.3)	N.A.	3.579 (1.166, 10.984)	
ABSENCE	79	3 (3.8)	N.A.	78	18 (23.1)	N.A.	0.0172 6.222 (1.832, 21.130) 0.0008	

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SOC: Endocrine Disorders. PT: Hypothyroidism

Adverse Events Subgroups	Placebo			Nivolumab			Nivolumab vs. Placebo	
	N	Patients with Event n (%)	KME [95%CI] (mon) (1)	N	Patients with Event n (%)	KME [95%CI] (mon) (1)	HR [95%CI] P-value (2) (3)	Test for Interaction P-value (4) (5)
OVERALL	139	4 (2.9)	N.A.	139	20 (14.4)	N.A.	5.136 (1.755, 15.027) 0.0009	0.5903
PRIOR NEO-ADJUVANT CISPLATIN THERAPY								
YES	61	2 (3.3)	N.A.	57	7 (12.3)	N.A.	3.633 (0.754, 17.496) 0.0851	
NO	78	2 (2.6)	N.A.	82	13 (15.9)	N.A.	6.626 (1.495, 29.368) 0.0040	

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PRIOR CISPLATIN STATUS								N.M.E.
RECEIVED NEO-ADJUVANT	61	2 (3.3)	N.M.E.	57	7 (12.3)	N.M.E.	N.M.E.	
UNWILLING TO RECEIVE NEO-ADJUVANT	45	2 (4.4)	N.M.E.	50	4 (8.0)	N.M.E.	N.M.E.	
NOT ELIGIBLE TO RECEIVE NEO-ADJUVANT	32	0	N.M.E.	27	8 (29.6)	N.M.E.	N.M.E.	

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	N	Patients with Event n (%)	KME [95%CI] (mon) (1)	N	Patients with Event n (%)	KME [95%CI] (mon) (1)	HR [95%CI] P-value (2) (3)	Test for Interaction P-value (4) (5)
USE OF ANY PRIOR NEO-ADJUVANT SYSTEMIC THERAPY								0.6872
YES	62	2 (3.2)	N.A.	61	8 (13.1)	N.A.	4.013 (0.852, 18.906)	
NO	77	2 (2.6)	N.A.	78	12 (15.4)	N.A.	0.0572 6.302 (1.410, 28.157) 0.0057	

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PATHOLOGICAL LYMPH NODE STATUS								0.8099
N+	64	2 (3.1)	N.A.	60	9 (15.0)	N.A.	4.567 (0.986, 21.162)	
N0/X WITH <10 NODES REMOVED	38	0	N.A.	38	6 (15.8)	N.A.	0.0329 N.M.E.	
N0 WITH >= 10 NODES REMOVED	37	2 (5.4)	N.A.	41	5 (12.2)	N.A.	0.0090 2.228 (0.432, 11.487)	
							0.3255	

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PATHOLOGICAL STATUS								0.9348
PT0-2	31	0	N.A.	26	3 (11.5)	N.A.	N.M.E. 0.0591	
PT3	80	3 (3.8)	N.A.	86	14 (16.3)	N.A.	4.228 (1.214, 14.720)	
PT4A	27	1 (3.7)	N.A.	23	2 (8.7)	N.A.	0.0137 2.691 (0.244, 29.687)	
							0.4000	

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AGE CATEGORY I								0.4244
< 65	59	2 (3.4)	N.A.	67	7 (10.4)	N.A.	3.034 (0.629, 14.622)	
>= 65	80	2 (2.5)	N.A.	72	13 (18.1)	N.A.	0.1458 7.637 (1.723, 33.851) 0.0016	

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AGE CATEGORY II < 65	59	2 (3.4)	N.A.	67	7 (10.4)	N.A.	3.034 (0.629, 14.622)	0.8662
>= 65 AND < 75	59	2 (3.4)	N.A.	49	9 (18.4)	N.A.	0.1458 5.641 (1.218, 26.115)	
>= 75	21	0	N.A.	23	4 (17.4)	N.A.	0.0124 N.M.E. 0.0540	

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REGION								0.3183
US	23	1 (4.3)	N.A.	17	4 (23.5)	N.A. (2.76, N.A.)	6.194 (0.688, 55.777) 0.0643	
EUROPE	68	1 (1.5)	N.A.	72	11 (15.3)	N.A.	10.120 (1.306, 78.397) 0.0061	
ASIA	28	0	N.A.	33	4 (12.1)	N.A.	N.M.E. 0.0456	
REST OF WORLD	20	2 (10.0)	N.A. (10.28, N.A.)	17	1 (5.9)	N.A.	0.503 (0.045, 5.660) 0.5709	

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GENDER								0.5945
MALE	109	3 (2.8)	N.A.	101	16 (15.8)	N.A.	6.003 (1.748, 20.612)	
FEMALE	30	1 (3.3)	N.A.	38	4 (10.5)	N.A.	0.0012 2.993 (0.335, 26.780)	
RACE								0.9917
WHITE	106	3 (2.8)	N.A.	103	16 (15.5)	N.A.	5.450 (1.588, 18.705)	
ASIAN	28	0	N.A.	33	4 (12.1)	N.A.	0.0024 N.M.E. 0.0456	

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BASELINE ECOG STATUS								
0	83	3 (3.6)	N.A.	85	15 (17.6)	N.A.	5.195 (1.503, 17.954) 0.0036	0.9496
1	52	1 (1.9)	N.A.	51	5 (9.8)	N.A.	4.971 (0.581, 42.555) 0.1041	
SMOKING STATUS								
NEVER SMOKED	39	2 (5.1)	N.A.	41	8 (19.5)	N.A.	4.058 (0.861, 19.114) 0.0548	0.6926
CURRENT/FORMER	99	2 (2.0)	N.A.	96	12 (12.5)	N.A.	6.207 (1.389, 27.744) 0.0063	

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	N	Patients with Event n (%)	KME [95%CI] (mon) (1)	N	Patients with Event n (%)	KME [95%CI] (mon) (1)	HR [95%CI] P-value (2) (3)	Test for Interaction P-value (4) (5)
BASELINE HEMOGLOBIN								0.9904
<10 G/DL	14	0	N.A.	7	1 (14.3)	N.A. (1.38, N.A.)	N.M.E. 0.1730	
>=10 G/DL	125	4 (3.2)	N.A.	132	19 (14.4)	N.A.	4.586 (1.560, 13.482) 0.0023	
BASELINE CREATININE CLEARANCE								0.3664
<60 ML/MIN	60	1 (1.7)	N.A.	54	9 (16.7)	N.A.	10.616 (1.345, 83.805) 0.0051	
>=60 ML/MIN	79	3 (3.8)	N.A.	84	11 (13.1)	N.A.	3.452 (0.963, 12.378) 0.0428	

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MedDRA Version: 27.1; CTC Version 4.0. HR = hazard ratio; KME = Kaplan-Meier estimate; N.M.E. = Not meaningful estimate.

(1) KME of median time to first AE. (2) Unstratified log-rank test.

(3) Unstratified Cox proportional hazard model. HR is Nivolumab over Placebo

(4) Unstratified Cox proportional hazard model with treatment, subgroup and treatment*subgroup interaction is to assess the significance of the interaction between treatment and the subgroup.

(5) A p-value of <0.05 needs to be indicated by 1 asterisk (indicates potential effect modification).

IUC = invasive urothelial carcinoma.

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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

Table 8.1
Subgroup Time-Adjusted Analyses
of Adverse Events
by Significant SOC/PT on Hazard Ratio
SAF

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TIME FROM IUC SURGERY TO RANDOMIZATION (DAYS)								0.8165
>30-60	28	2 (7.1)	N.A.	34	3 (8.8)	N.A.	1.216 (0.203, 7.293)	
>60-90	65	0	N.A.	57	10 (17.5)	N.A.	0.8307 N.M.E.	
>90-120	41	2 (4.9)	N.A.	46	6 (13.0)	N.A.	0.0006 2.671 (0.539, 13.248)	
							0.2101	

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INITIAL TUMOR ORIGIN								>0.9999
URINARY BLADDER	115	4 (3.5)	N.A.	112	14 (12.5)	N.A.	3.562 (1.172, 10.826)	
RENAL PELVIS	13	0	N.A.	19	5 (26.3)	N.A.	0.0167 N.M.E.	
URETER	11	0	N.A.	8	1 (12.5)	(5.52, N.A.) N.A. (7.79, N.A.)	0.0576 N.M.E. 0.1336	

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MINOR HISTOLOGICAL VARIANTS								0.9902
PRESENCE	60	4 (6.7)	N.A.	61	8 (13.1)	N.A.	2.066 (0.622, 6.864)	
ABSENCE	79	0	N.A.	78	12 (15.4)	N.A.	0.2260 N.M.E. 0.0005	

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OVERALL	139	3 (2.2)	N.A.	139	14 (10.1)	N.A.	4.869 (1.399, 16.943) 0.0059	
PRIOR NEO-ADJUVANT CISPLATIN THERAPY								N.M.E.
YES	61	1 (1.6)	N.M.E.	57	8 (14.0)	N.M.E.	N.M.E.	
NO	78	2 (2.6)	N.M.E.	82	6 (7.3)	N.M.E.	N.M.E.	

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PRIOR CISPLATIN STATUS								N.M.E.
RECEIVED NEO-ADJUVANT	61	1 (1.6)	N.M.E.	57	8 (14.0)	N.M.E.	N.M.E.	
UNWILLING TO RECEIVE NEO-ADJUVANT	45	2 (4.4)	N.M.E.	50	5 (10.0)	N.M.E.	N.M.E.	
NOT ELIGIBLE TO RECEIVE NEO-ADJUVANT	32	0	N.M.E.	27	1 (3.7)	N.M.E.	N.M.E.	

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	N	Patients with Event n (%)	KME [95%CI] (mon) (1)	N	Patients with Event n (%)	KME [95%CI] (mon) (1)	HR [95%CI] P-value (2) (3)	Test for Interaction P-value (4) (5)
USE OF ANY PRIOR NEO-ADJUVANT SYSTEMIC THERAPY								N.M.E.
YES	62	1 (1.6)	N.M.E.	61	8 (13.1)	N.M.E.	N.M.E.	
NO	77	2 (2.6)	N.M.E.	78	6 (7.7)	N.M.E.	N.M.E.	

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PATHOLOGICAL LYMPH NODE STATUS								N.M.E.
N+	64	1 (1.6)	N.M.E.	60	5 (8.3)	N.M.E.	N.M.E.	
N0/X WITH <10 NODES REMOVED	38	0	N.M.E.	38	4 (10.5)	N.M.E.	N.M.E.	
N0 WITH >= 10 NODES REMOVED	37	2 (5.4)	N.M.E.	41	5 (12.2)	N.M.E.	N.M.E.	

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PATHOLOGICAL STATUS								0.9998
PT0-2	31	1 (3.2)	N.A.	26	3 (11.5)	N.A.	3.677 (0.382, 35.352)	
PT3	80	2 (2.5)	N.A.	86	8 (9.3)	N.A.	0.2267 3.753 (0.797, 17.676)	
PT4A	27	0	N.A.	23	3 (13.0)	N.A.	0.0726 N.M.E. 0.0475	

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AGE CATEGORY I								
< 65	59	2 (3.4)	N.M.E.	67	6 (9.0)	N.M.E.	N.M.E.	N.M.E.
>= 65	80	1 (1.3)	N.M.E.	72	8 (11.1)	N.M.E.	N.M.E.	

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AGE CATEGORY II								N.M.E.
< 65	59	2 (3.4)	N.M.E.	67	6 (9.0)	N.M.E.	N.M.E.	
>= 65 AND < 75	59	1 (1.7)	N.M.E.	49	8 (16.3)	N.M.E.	N.M.E.	
>= 75	21	0	N.M.E.	23	0	N.M.E.	N.M.E.	

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REGION								>0.9999
US	23	0	N.A.	17	2 (11.8)	N.A.	N.M.E. 0.0949	
EUROPE	68	3 (4.4)	N.A.	72	10 (13.9)	N.A.	3.234 (0.890, 11.752)	
ASIA	28	0	N.A.	33	2 (6.1)	N.A.	0.0595 N.M.E.	
REST OF WORLD	20	0	N.A.	17	0	N.A.	0.1682 N.M.E. N.A.	

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GENDER								
MALE	109	3 (2.8)	N.A.	101	8 (7.9)	N.A.	2.993 (0.794, 11.285)	0.9928
FEMALE	30	0	N.A.	38	6 (15.8)	N.A.	0.0893 N.M.E. 0.0275	
RACE								
WHITE	106	3 (2.8)	N.A.	103	12 (11.7)	N.A.	4.189 (1.182, 14.844)	0.9928
ASIAN	28	0	N.A.	33	2 (6.1)	N.A.	0.0159 N.M.E. 0.1682	

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BASELINE ECOG STATUS								
0	83	3 (3.6)	N.A.	85	10 (11.8)	N.A.	3.506 (0.965, 12.743)	0.9903
1	52	0	N.A.	51	4 (7.8)	N.A.	0.0421 N.M.E. 0.0449	
SMOKING STATUS								
NEVER SMOKED	39	0	N.A.	41	6 (14.6)	N.A.	N.M.E. 0.0132	0.9920
CURRENT/FORMER	99	3 (3.0)	N.A.	96	7 (7.3)	N.A.	2.446 (0.632, 9.459) 0.1809	

FEB2025 DBL. Includes events reported between first dose and 100 days after last dose of the study therapy.

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(1) KME of median time to first AE. (2) Unstratified log-rank test.

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IUC = invasive urothelial carcinoma.

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Program Name: rt-ae-tsubsocaehr-ebr45.sas

23JUN2025:09:50:18

Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

Table 8.1
Subgroup Time-Adjusted Analyses
of Adverse Events
by Significant SOC/PT on Hazard Ratio
SAF

SOC: Endocrine Disorders. PT: Hyperthyroidism

Adverse Events Subgroups	Placebo			Nivolumab			Nivolumab vs. Placebo	
	N	Patients with Event n (%)	KME [95%CI] (mon) (1)	N	Patients with Event n (%)	KME [95%CI] (mon) (1)	HR [95%CI] P-value (2) (3)	Test for Interaction P-value (4) (5)
BASELINE HEMOGLOBIN								0.5339
<10 G/DL	14	1 (7.1)	N.A. (8.31, N.A.)	7	1 (14.3)	N.A. (0.49, N.A.)	2.449 (0.151, 39.712)	
>=10 G/DL	125	2 (1.6)	N.A.	132	13 (9.8)	N.A.	0.5151 6.423 (1.449, 28.464) 0.0049	
BASELINE CREATININE CLEARANCE								0.9929
<60 ML/MIN	60	0	N.A.	54	5 (9.3)	N.A.	N.M.E. 0.0157	
>=60 ML/MIN	79	3 (3.8)	N.A.	84	9 (10.7)	N.A.	2.915 (0.789, 10.767) 0.0929	

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TIME FROM IUC SURGERY TO RANDOMIZATION (DAYS)								N.M.E.
>30-60	28	0	N.M.E.	34	1 (2.9)	N.M.E.	N.M.E.	
>60-90	65	2 (3.1)	N.M.E.	57	7 (12.3)	N.M.E.	N.M.E.	
>90-120	41	1 (2.4)	N.M.E.	46	6 (13.0)	N.M.E.	N.M.E.	

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INITIAL TUMOR ORIGIN								>0.9999
URINARY BLADDER	115	3 (2.6)	N.A.	112	12 (10.7)	N.A.	4.210 (1.188, 14.920)	
RENAL PELVIS	13	0	N.A.	19	2 (10.5)	N.A.	0.0154 N.M.E.	
URETER	11	0	N.A.	8	0	N.A.	0.2215 N.M.E. N.A.	

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	Patients with Event		KME	Patients with Event		KME	HR	Test for
	N	n (%)	[95%CI] (mon) (1)	N	n (%)	[95%CI] (mon) (1)	[95%CI] P-value (2) (3)	Interaction P-value (4) (5)
MINOR HISTOLOGICAL VARIANTS								0.9928
PRESENCE	60	0	N.A.	61	7 (11.5)	N.A.	N.M.E. 0.0068	
ABSENCE	79	3 (3.8)	N.A.	78	7 (9.0)	N.A.	2.392 (0.618, 9.252) 0.1926	

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SAF

SOC: Neoplasms Benign, Malignant and Unspecified (Incl Cysts and Polyps). PT: Malignant Neoplasm Progression

Adverse Events Subgroups	Placebo			Nivolumab			Nivolumab vs. Placebo	
	N	Patients with Event n (%)	KME [95%CI] (mon) (1)	N	Patients with Event n (%)	KME [95%CI] (mon) (1)	HR [95%CI] P-value (2) (3)	Test for Interaction P-value (4) (5)
OVERALL	139	16 (11.5)	N.A.	139	4 (2.9)	N.A.	0.237 (0.079, 0.710) 0.0051	
PRIOR NEO-ADJUVANT CISPLATIN THERAPY								0.4896
YES	61	5 (8.2)	N.A.	57	2 (3.5)	N.A.	0.391 (0.076, 2.015) 0.2442	
NO	78	11 (14.1)	N.A.	82	2 (2.4)	N.A.	0.173 (0.038, 0.780) 0.0097	

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	N	Patients with Event n (%)	KME [95%CI] (mon) (1)	N	Patients with Event n (%)	KME [95%CI] (mon) (1)	HR [95%CI] P-value (2) (3)	Test for Interaction P-value (4) (5)
PRIOR CISPLATIN STATUS								N.M.E.
RECEIVED NEO-ADJUVANT	61	5 (8.2)	N.M.E.	57	2 (3.5)	N.M.E.	N.M.E.	
UNWILLING TO RECEIVE NEO-ADJUVANT	45	2 (4.4)	N.M.E.	50	2 (4.0)	N.M.E.	N.M.E.	
NOT ELIGIBLE TO RECEIVE NEO-ADJUVANT	32	9 (28.1)	N.M.E.	27	0	N.M.E.	N.M.E.	

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USE OF ANY PRIOR NEO-ADJUVANT SYSTEMIC THERAPY								0.5391
YES	62	5 (8.1)	N.A.	61	2 (3.3)	N.A.	0.373 (0.072, 1.925)	
NO	77	11 (14.3)	N.A.	78	2 (2.6)	N.A.	0.2203 0.180 (0.040, 0.812) 0.0119	

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PATHOLOGICAL LYMPH NODE STATUS								>0.9999
N+	64	10 (15.6)	N.A.	60	4 (6.7)	N.A.	0.389 (0.122, 1.243)	
N0/X WITH <10 NODES REMOVED	38	2 (5.3)	N.A.	38	0	N.A.	0.0984 N.M.E.	
N0 WITH >= 10 NODES REMOVED	37	4 (10.8)	N.A.	41	0	N.A.	0.1801 N.M.E. 0.0273	

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PATHOLOGICAL STATUS								>0.9999
PT0-2	31	0	N.A.	26	1 (3.8)	N.A.	N.M.E. 0.2909	
PT3	80	13 (16.3)	N.A.	86	3 (3.5)	N.A.	0.192 (0.055, 0.674)	
PT4A	27	3 (11.1)	N.A.	23	0	N.A.	0.0040 N.M.E. 0.1228	

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AGE CATEGORY I								
< 65	59	4 (6.8)	N.A.	67	2 (3.0)	N.A.	0.433 (0.079, 2.364)	0.4600
>= 65	80	12 (15.0)	N.A.	72	2 (2.8)	N.A.	0.3197 0.178 (0.040, 0.795) 0.0107	

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AGE CATEGORY II < 65	59	4 (6.8)	N.A.	67	2 (3.0)	N.A.	0.433 (0.079, 2.364)	0.6766
>= 65 AND < 75	59	9 (15.3)	N.A.	49	1 (2.0)	N.A.	0.3197 (0.016, 0.998)	
>= 75	21	3 (14.3)	N.A.	23	1 (4.3)	N.A.	0.126 (0.016, 0.998) 0.0197 0.330 (0.034, 3.170) 0.3120	

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REGION								0.9990
US	23	2 (8.7)	N.A.	17	0	N.A.	N.M.E. 0.2098	
EUROPE	68	9 (13.2)	N.A.	72	2 (2.8)	N.A.	0.186 (0.040, 0.862)	
ASIA	28	0	N.A.	33	1 (3.0)	N.A.	0.0159 N.M.E.	
REST OF WORLD	20	5 (25.0)	N.A. (9.63, N.A.)	17	1 (5.9)	N.A.	0.3276 0.228 (0.027, 1.959)	
							0.1412	

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GENDER								
MALE	109	15 (13.8)	N.A.	101	2 (2.0)	N.A.	0.137 (0.031, 0.600)	0.1038
FEMALE	30	1 (3.3)	N.A.	38	2 (5.3)	N.A.	0.0020 1.418 (0.128, 15.651) 0.7744	
RACE								
WHITE	106	15 (14.2)	N.A.	103	3 (2.9)	N.A.	0.187 (0.054, 0.645)	0.9918
ASIAN	28	0	N.A.	33	1 (3.0)	N.A.	0.0029 N.M.E. 0.3276	

FEB2025 DBL. Includes events reported between first dose and 100 days after last dose of the study therapy.

MedDRA Version: 27.1; CTC Version 4.0. HR = hazard ratio; KME = Kaplan-Meier estimate; N.M.E. = Not meaningful estimate.

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IUC = invasive urothelial carcinoma.

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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

Table 8.1
Subgroup Time-Adjusted Analyses
of Adverse Events
by Significant SOC/PT on Hazard Ratio
SAF

SOC: Neoplasms Benign, Malignant and Unspecified (Incl Cysts and Polyps). PT: Malignant Neoplasm Progression

Adverse Events Subgroups	Placebo			Nivolumab			Nivolumab vs. Placebo	
	N	Patients with Event n (%)	KME [95%CI] (mon) (1)	N	Patients with Event n (%)	KME [95%CI] (mon) (1)	HR [95%CI] P-value (2) (3)	Test for Interaction P-value (4) (5)
BASELINE ECOG STATUS								
0	83	8 (9.6)	N.A.	85	4 (4.7)	N.A.	0.493 (0.148, 1.636)	0.9892
1	52	5 (9.6)	N.A.	51	0	N.A.	0.2378 N.M.E. 0.0199	
SMOKING STATUS								
NEVER SMOKED	39	4 (10.3)	N.A.	41	1 (2.4)	N.A.	0.222 (0.025, 1.984)	0.9589
CURRENT/FORMER	99	12 (12.1)	N.A.	96	3 (3.1)	N.A.	0.1394 0.240 (0.068, 0.850) 0.0162	

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BASELINE HEMOGLOBIN								0.9995
<10 G/DL	14	0	N.A.	7	0	N.A.	N.M.E. N.A.	
>=10 G/DL	125	16 (12.8)	N.A.	132	4 (3.0)	N.A.	0.223 (0.075, 0.667) 0.0033	
BASELINE CREATININE CLEARANCE								0.4734
<60 ML/MIN	60	8 (13.3)	N.A.	54	1 (1.9)	N.A.	0.137 (0.017, 1.097) 0.0281	
>=60 ML/MIN	79	8 (10.1)	N.A.	84	3 (3.6)	N.A.	0.337 (0.089, 1.272) 0.0921	

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	N	Patients with Event n (%)	KME [95%CI] (mon) (1)	N	Patients with Event n (%)	KME [95%CI] (mon) (1)	HR [95%CI] P-value (2) (3)	Test for Interaction P-value (4) (5)
TIME FROM IUC SURGERY TO RANDOMIZATION (DAYS)								0.8617
>30-60	28	1 (3.6)	N.A.	34	1 (2.9)	N.A.	0.796 (0.050, 12.733)	
>60-90	65	9 (13.8)	N.A.	57	3 (5.3)	N.A.	0.8715 0.351 (0.095, 1.295)	
>90-120	41	5 (12.2)	N.A.	46	0	N.A.	0.1000 N.M.E. 0.0179	

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	N	Patients with Event n (%)	KME [95%CI] (mon) (1)	N	Patients with Event n (%)	KME [95%CI] (mon) (1)	HR [95%CI] P-value (2) (3)	Test for Interaction P-value (4) (5)
INITIAL TUMOR ORIGIN								>0.9999
URINARY BLADDER	115	14 (12.2)	N.A.	112	4 (3.6)	N.A.	0.272 (0.090, 0.827)	
RENAL PELVIS	13	1 (7.7)	N.A.	19	0	N.A.	0.0139 N.M.E.	
URETER	11	1 (9.1)	N.A. (4.67, N.A.)	8	0	N.A.	0.2340 N.M.E. 0.4795	

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	N	Patients with Event n (%)	KME [95%CI] (mon) (1)	N	Patients with Event n (%)	KME [95%CI] (mon) (1)	HR [95%CI] P-value (2) (3)	Test for Interaction P-value (4) (5)
MINOR HISTOLOGICAL VARIANTS								0.8365
PRESENCE	60	5 (8.3)	N.A.	61	1 (1.6)	N.A.	0.198 (0.023, 1.696)	
ABSENCE	79	11 (13.9)	N.A.	78	3 (3.8)	N.A.	0.1001 0.252 (0.070, 0.906) 0.0225	

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Adverse Events Subgroups	Placebo			Nivolumab			Nivolumab vs. Placebo	
	N	Patients with Event n (%)	KME [95%CI] (mon) (1)	N	Patients with Event n (%)	KME [95%CI] (mon) (1)	HR [95%CI] P-value (2) (3)	Test for Interaction P-value (4) (5)
OVERALL	139	18 (12.9)	N.A.	139	8 (5.8)	N.A.	0.413 (0.179, 0.951) 0.0316	
PRIOR NEO-ADJUVANT CISPLATIN THERAPY								0.7019
YES	61	6 (9.8)	N.A.	57	2 (3.5)	N.A.	0.300 (0.060, 1.488) 0.1179	
NO	78	12 (15.4)	N.A.	82	6 (7.3)	N.A.	0.463 (0.174, 1.233) 0.1141	

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	N	Patients with Event n (%)	KME [95%CI] (mon) (1)	N	Patients with Event n (%)	KME [95%CI] (mon) (1)	HR [95%CI] P-value (2) (3)	Test for Interaction P-value (4) (5)
PRIOR CISPLATIN STATUS								N.M.E.
RECEIVED NEO-ADJUVANT	61	6 (9.8)	N.M.E.	57	2 (3.5)	N.M.E.	N.M.E.	
UNWILLING TO RECEIVE NEO-ADJUVANT	45	7 (15.6)	N.M.E.	50	2 (4.0)	N.M.E.	N.M.E.	
NOT ELIGIBLE TO RECEIVE NEO-ADJUVANT	32	5 (15.6)	N.M.E.	27	4 (14.8)	N.M.E.	N.M.E.	

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	N	Patients with Event n (%)	KME [95%CI] (mon) (1)	N	Patients with Event n (%)	KME [95%CI] (mon) (1)	HR [95%CI] P-value (2) (3)	Test for Interaction P-value (4) (5)
USE OF ANY PRIOR NEO-ADJUVANT SYSTEMIC THERAPY								0.4505
YES	62	7 (11.3)	N.A.	61	2 (3.3)	N.A.	0.243 (0.050, 1.175)	
NO	77	11 (14.3)	N.A.	78	6 (7.7)	N.A.	0.0564 0.527 (0.195, 1.425) 0.1990	

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PATHOLOGICAL LYMPH NODE STATUS								0.6953
N+	64	7 (10.9)	N.A.	60	4 (6.7)	N.A.	0.546 (0.160, 1.869)	
N0/X WITH <10 NODES REMOVED	38	8 (21.1)	N.A.	38	2 (5.3)	N.A.	0.3278 0.245 (0.052, 1.153)	
N0 WITH >= 10 NODES REMOVED	37	3 (8.1)	N.A.	41	2 (4.9)	N.A.	0.0536 0.585 (0.098, 3.501) 0.5519	

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PATHOLOGICAL STATUS								0.7236
PT0-2	31	6 (19.4)	N.A.	26	2 (7.7)	N.A.	0.386 (0.078, 1.915)	
PT3	80	7 (8.8)	N.A.	86	5 (5.8)	N.A.	0.2268 0.611 (0.194, 1.928)	
PT4A	27	5 (18.5)	N.A.	23	1 (4.3)	N.A.	0.3961 0.246 (0.029, 2.107) 0.1653	

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AGE CATEGORY I								0.9695
< 65	59	4 (6.8)	N.A.	67	2 (3.0)	N.A.	0.391 (0.071, 2.140)	
>= 65	80	14 (17.5)	N.A.	72	6 (8.3)	N.A.	0.2614 0.439 (0.169, 1.143) 0.0827	

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AGE CATEGORY II								0.9969
< 65	59	4 (6.8)	N.A.	67	2 (3.0)	N.A.	0.391 (0.071, 2.140)	
>= 65 AND < 75	59	10 (16.9)	N.A.	49	4 (8.2)	N.A.	0.2614 0.442 (0.138, 1.411)	
>= 75	21	4 (19.0)	N.A. (6.41, N.A.)	23	2 (8.7)	N.A.	0.1565 0.426 (0.078, 2.327)	
							0.3099	

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REGION								0.6682
US	23	3 (13.0)	N.A.	17	1 (5.9)	N.A.	0.451 (0.047, 4.338)	
EUROPE	68	6 (8.8)	N.A.	72	4 (5.6)	N.A.	0.4792 0.566 (0.159, 2.009)	
ASIA	28	8 (28.6)	N.A. (6.41, N.A.)	33	2 (6.1)	N.A.	0.3720 0.207 (0.044, 0.975)	
REST OF WORLD	20	1 (5.0)	N.A.	17	1 (5.9)	N.A.	0.0275 1.224 (0.076, 19.569)	
							0.8864	

FEB2025 DBL. Includes events reported between first dose and 100 days after last dose of the study therapy.

MedDRA Version: 27.1; CTC Version 4.0. HR = hazard ratio; KME = Kaplan-Meier estimate; N.M.E. = Not meaningful estimate.

(1) KME of median time to first AE. (2) Unstratified log-rank test.

(3) Unstratified Cox proportional hazard model. HR is Nivolumab over Placebo

(4) Unstratified Cox proportional hazard model with treatment, subgroup and treatment*subgroup interaction is to assess the significance of the interaction between treatment and the subgroup.

(5) A p-value of <0.05 needs to be indicated by 1 asterisk (indicates potential effect modification).

IUC = invasive urothelial carcinoma.

Program Path: /projects/bms214671/stats/market/ma274_202502/prog/tables

Program Name: rt-ae-tsubsocaehr-ebr45.sas

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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

Table 8.1
Subgroup Time-Adjusted Analyses
of Adverse Events
by Significant SOC/PT on Hazard Ratio
SAF

SOC: Cardiac Disorders

Adverse Events Subgroups	Placebo			Nivolumab			Nivolumab vs. Placebo	
	N	Patients with Event n (%)	KME [95%CI] (mon) (1)	N	Patients with Event n (%)	KME [95%CI] (mon) (1)	HR [95%CI] P-value (2) (3)	Test for Interaction P-value (4) (5)
GENDER								
MALE	109	14 (12.8)	N.A.	101	4 (4.0)	N.A.	0.277 (0.091, 0.842)	0.2799
FEMALE	30	4 (13.3)	N.A.	38	4 (10.5)	N.A.	0.0155 0.785 (0.196, 3.142)	
RACE								
WHITE	106	9 (8.5)	N.A.	103	6 (5.8)	N.A.	0.626 (0.223, 1.762)	0.2293
ASIAN	28	8 (28.6)	N.A. (6.41, N.A.)	33	2 (6.1)	N.A.	0.3711 0.207 (0.044, 0.975)	
							0.7279 0.0275	

FEB2025 DBL. Includes events reported between first dose and 100 days after last dose of the study therapy.

MedDRA Version: 27.1; CTC Version 4.0. HR = hazard ratio; KME = Kaplan-Meier estimate; N.M.E. = Not meaningful estimate.

(1) KME of median time to first AE. (2) Unstratified log-rank test.

(3) Unstratified Cox proportional hazard model. HR is Nivolumab over Placebo

(4) Unstratified Cox proportional hazard model with treatment, subgroup and treatment*subgroup interaction is to assess the significance of the interaction between treatment and the subgroup.

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SAF

SOC: Cardiac Disorders

Adverse Events Subgroups	Placebo			Nivolumab			Nivolumab vs. Placebo	
	N	Patients with Event n (%)	KME [95%CI] (mon) (1)	N	Patients with Event n (%)	KME [95%CI] (mon) (1)	HR [95%CI] P-value (2) (3)	Test for Interaction P-value (4) (5)
BASELINE ECOG STATUS								
0	83	8 (9.6)	N.A.	85	5 (5.9)	N.A.	0.601 (0.196, 1.838)	0.5425
1	52	8 (15.4)	N.A.	51	3 (5.9)	N.A.	0.3655 0.342 (0.091, 1.290)	
SMOKING STATUS								
NEVER SMOKED	39	8 (20.5)	N.A.	41	5 (12.2)	N.A.	0.571 (0.186, 1.747)	0.2369
CURRENT/FORMER	99	10 (10.1)	N.A.	96	2 (2.1)	N.A.	0.3194 0.183 (0.040, 0.837)	
							0.0139	

FEB2025 DBL. Includes events reported between first dose and 100 days after last dose of the study therapy.

MedDRA Version: 27.1; CTC Version 4.0. HR = hazard ratio; KME = Kaplan-Meier estimate; N.M.E. = Not meaningful estimate.

(1) KME of median time to first AE. (2) Unstratified log-rank test.

(3) Unstratified Cox proportional hazard model. HR is Nivolumab over Placebo

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by Significant SOC/PT on Hazard Ratio
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SOC: Cardiac Disorders

Adverse Events Subgroups	Placebo			Nivolumab			Nivolumab vs. Placebo	
	N	Patients with Event n (%)	KME [95%CI] (mon) (1)	N	Patients with Event n (%)	KME [95%CI] (mon) (1)	HR [95%CI] P-value (2) (3)	Test for Interaction P-value (4) (5)
BASELINE HEMOGLOBIN <10 G/DL	14	2 (14.3)	N.A. (10.71, N.A.)	7	1 (14.3)	N.A. (2.00, N.A.)	0.957 (0.087, 10.579)	0.4754
>=10 G/DL	125	16 (12.8)	N.A.	132	7 (5.3)	N.A.	0.9714 0.384 (0.158, 0.934) 0.0284	
BASELINE CREATININE CLEARANCE <60 ML/MIN	60	10 (16.7)	N.A.	54	5 (9.3)	N.A.	0.533 (0.182, 1.561) 0.2421	0.5527
>=60 ML/MIN	79	8 (10.1)	N.A.	84	3 (3.6)	N.A.	0.310 (0.082, 1.172) 0.0680	

FEB2025 DBL. Includes events reported between first dose and 100 days after last dose of the study therapy.

MedDRA Version: 27.1; CTC Version 4.0. HR = hazard ratio; KME = Kaplan-Meier estimate; N.M.E. = Not meaningful estimate.

(1) KME of median time to first AE. (2) Unstratified log-rank test.

(3) Unstratified Cox proportional hazard model. HR is Nivolumab over Placebo

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SAF

SOC: Cardiac Disorders

Adverse Events Subgroups	Placebo			Nivolumab			Nivolumab vs. Placebo	
	N	Patients with Event n (%)	KME [95%CI] (mon) (1)	N	Patients with Event n (%)	KME [95%CI] (mon) (1)	HR [95%CI] P-value (2) (3)	Test for Interaction P-value (4) (5)
TIME FROM IUC SURGERY TO RANDOMIZATION (DAYS)								N.M.E.
>30-60	28	4 (14.3)	N.M.E.	34	4 (11.8)	N.M.E.	N.M.E.	
>60-90	65	6 (9.2)	N.M.E.	57	1 (1.8)	N.M.E.	N.M.E.	
>90-120	41	5 (12.2)	N.M.E.	46	3 (6.5)	N.M.E.	N.M.E.	

FEB2025 DBL. Includes events reported between first dose and 100 days after last dose of the study therapy.

MedDRA Version: 27.1; CTC Version 4.0. HR = hazard ratio; KME = Kaplan-Meier estimate; N.M.E. = Not meaningful estimate.

(1) KME of median time to first AE. (2) Unstratified log-rank test.

(3) Unstratified Cox proportional hazard model. HR is Nivolumab over Placebo

(4) Unstratified Cox proportional hazard model with treatment, subgroup and treatment*subgroup interaction is to assess the significance of the interaction between treatment and the subgroup.

(5) A p-value of <0.05 needs to be indicated by 1 asterisk (indicates potential effect modification).

IUC = invasive urothelial carcinoma.

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SOC: Cardiac Disorders

Adverse Events Subgroups	Placebo			Nivolumab			Nivolumab vs. Placebo	
	N	Patients with Event n (%)	KME [95%CI] (mon) (1)	N	Patients with Event n (%)	KME [95%CI] (mon) (1)	HR [95%CI] P-value (2) (3)	Test for Interaction P-value (4) (5)
INITIAL TUMOR ORIGIN								0.4815
URINARY BLADDER	115	14 (12.2)	N.A.	112	6 (5.4)	N.A.	0.400 (0.153, 1.041)	
RENAL PELVIS	13	3 (23.1)	N.A. (3.81, N.A.)	19	1 (5.3)	N.A.	0.0517 0.191 (0.020, 1.846)	
URETER	11	1 (9.1)	N.A.	8	1 (12.5)	N.A. (0.85, N.A.)	0.1104 1.697 (0.106, 27.192)	
							0.7053	

FEB2025 DBL. Includes events reported between first dose and 100 days after last dose of the study therapy.

MedDRA Version: 27.1; CTC Version 4.0. HR = hazard ratio; KME = Kaplan-Meier estimate; N.M.E. = Not meaningful estimate.

(1) KME of median time to first AE. (2) Unstratified log-rank test.

(3) Unstratified Cox proportional hazard model. HR is Nivolumab over Placebo

(4) Unstratified Cox proportional hazard model with treatment, subgroup and treatment*subgroup interaction is to assess the significance of the interaction between treatment and the subgroup.

(5) A p-value of <0.05 needs to be indicated by 1 asterisk (indicates potential effect modification).

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by Significant SOC/PT on Hazard Ratio
SAF

SOC: Cardiac Disorders

Adverse Events Subgroups	Placebo			Nivolumab			Nivolumab vs. Placebo	
	N	Patients with Event n (%)	KME [95%CI] (mon) (1)	N	Patients with Event n (%)	KME [95%CI] (mon) (1)	HR [95%CI] P-value (2) (3)	Test for Interaction P-value (4) (5)
MINOR HISTOLOGICAL VARIANTS								0.5634
PRESENCE	60	5 (8.3)	N.A.	61	3 (4.9)	N.A.	0.574 (0.137, 2.404)	
ABSENCE	79	13 (16.5)	N.A.	78	5 (6.4)	N.A.	0.4396 0.352 (0.125, 0.988) 0.0380	

FEB2025 DBL. Includes events reported between first dose and 100 days after last dose of the study therapy.

MedDRA Version: 27.1; CTC Version 4.0. HR = hazard ratio; KME = Kaplan-Meier estimate; N.M.E. = Not meaningful estimate.

(1) KME of median time to first AE. (2) Unstratified log-rank test.

(3) Unstratified Cox proportional hazard model. HR is Nivolumab over Placebo

(4) Unstratified Cox proportional hazard model with treatment, subgroup and treatment*subgroup interaction is to assess the significance of the interaction between treatment and the subgroup.

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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

5.2.2.2 Schwere UE (CTCAE ≥ 3)

Table 8.2
Subgroup Time-Adjusted Analyses
of Adverse Events with CTCAE Grade ≥ 3
by Significant SOC/PT on Hazard Ratio
SAF

SOC: Investigations

Adverse Events with CTCAE Grade 3-4-5 Subgroups	Placebo			Nivolumab			Nivolumab vs. Placebo	
	N	Patients with Event n (%)	KME [95%CI] (mon) (1)	N	Patients with Event n (%)	KME [95%CI] (mon) (1)	HR [95%CI] P-value (2) (3)	Test for Interaction P-value (4) (5)
OVERALL	139	8 (5.8)	N.A.	139	20 (14.4)	N.A.	2.528 (1.114, 5.740) 0.0216	
PRIOR NEO-ADJUVANT CISPLATIN THERAPY								0.8300
YES	61	4 (6.6)	N.A.	57	9 (15.8)	N.A.	2.288 (0.704, 7.429) 0.1565	
NO	78	4 (5.1)	N.A.	82	11 (13.4)	N.A.	2.752 (0.876, 8.644) 0.0705	

FEB2025 DBL. Includes events reported between first dose and 100 days after last dose of the study therapy.

MedDRA Version: 27.1; CTC Version 4.0. HR = hazard ratio; KME = Kaplan-Meier estimate; N.M.E. = Not meaningful estimate.

(1) KME of median time to first AE. (2) Unstratified log-rank test.

(3) Unstratified Cox proportional hazard model. HR is Nivolumab over Placebo

(4) Unstratified Cox proportional hazard model with treatment, subgroup and treatment*subgroup interaction is to assess the significance of the interaction between treatment and the subgroup.

(5) A p-value of <0.05 needs to be indicated by 1 asterisk (indicates potential effect modification).

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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

Table 8.2
Subgroup Time-Adjusted Analyses
of Adverse Events with CTCAE Grade ≥ 3
by Significant SOC/PT on Hazard Ratio
SAF

SOC: Investigations

Adverse Events with CTCAE Grade 3-4-5 Subgroups	Placebo			Nivolumab			Nivolumab vs. Placebo	
	N	Patients with Event n (%)	KME [95%CI] (mon) (1)	N	Patients with Event n (%)	KME [95%CI] (mon) (1)	HR [95%CI] P-value (2) (3)	Test for Interaction P-value (4) (5)
PRIOR CISPLATIN STATUS								0.7318
RECEIVED NEO-ADJUVANT	61	4 (6.6)	N.A.	57	9 (15.8)	N.A.	2.288 (0.704, 7.429)	
UNWILLING TO RECEIVE NEO-ADJUVANT	45	1 (2.2)	N.A.	50	5 (10.0)	N.A.	0.1565 4.613 (0.539, 39.491)	
NOT ELIGIBLE TO RECEIVE NEO-ADJUVANT	32	3 (9.4)	N.A.	27	4 (14.8)	N.A.	0.1246 1.634 (0.366, 7.304)	
							0.5161	

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MedDRA Version: 27.1; CTC Version 4.0. HR = hazard ratio; KME = Kaplan-Meier estimate; N.M.E. = Not meaningful estimate.

(1) KME of median time to first AE. (2) Unstratified log-rank test.

(3) Unstratified Cox proportional hazard model. HR is Nivolumab over Placebo

(4) Unstratified Cox proportional hazard model with treatment, subgroup and treatment*subgroup interaction is to assess the significance of the interaction between treatment and the subgroup.

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Table 8.2
Subgroup Time-Adjusted Analyses
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by Significant SOC/PT on Hazard Ratio
SAF

SOC: Investigations

Adverse Events with CTCAE Grade 3-4-5 Subgroups	Placebo			Nivolumab			Nivolumab vs. Placebo	
	N	Patients with Event n (%)	KME [95%CI] (mon) (1)	N	Patients with Event n (%)	KME [95%CI] (mon) (1)	HR [95%CI] P-value (2) (3)	Test for Interaction P-value (4) (5)
USE OF ANY PRIOR NEO-ADJUVANT SYSTEMIC THERAPY								0.5116
YES	62	5 (8.1)	N.A.	61	10 (16.4)	N.A.	1.958 (0.669, 5.729)	
NO	77	3 (3.9)	N.A.	78	10 (12.8)	N.A.	0.2114 3.438 (0.946, 12.493) 0.0458	

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(1) KME of median time to first AE. (2) Unstratified log-rank test.

(3) Unstratified Cox proportional hazard model. HR is Nivolumab over Placebo

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SAF

SOC: Investigations

Adverse Events with CTCAE Grade 3-4-5 Subgroups	Placebo			Nivolumab			Nivolumab vs. Placebo	
	N	Patients with Event n (%)	KME [95%CI] (mon) (1)	N	Patients with Event n (%)	KME [95%CI] (mon) (1)	HR [95%CI] P-value (2) (3)	Test for Interaction P-value (4) (5)
PATHOLOGICAL LYMPH NODE STATUS								0.9194
N+	64	3 (4.7)	N.A.	60	8 (13.3)	N.A.	2.766 (0.734, 10.432)	
N0/X WITH <10 NODES REMOVED	38	4 (10.5)	N.A.	38	8 (21.1)	N.A.	0.1169 2.167 (0.652, 7.200)	
N0 WITH ≥ 10 NODES REMOVED	37	1 (2.7)	N.A.	41	4 (9.8)	N.A.	0.1956 3.574 (0.399, 31.988)	
							0.2234	

FEB2025 DBL. Includes events reported between first dose and 100 days after last dose of the study therapy.

MedDRA Version: 27.1; CTC Version 4.0. HR = hazard ratio; KME = Kaplan-Meier estimate; N.M.E. = Not meaningful estimate.

(1) KME of median time to first AE. (2) Unstratified log-rank test.

(3) Unstratified Cox proportional hazard model. HR is Nivolumab over Placebo

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Table 8.2
Subgroup Time-Adjusted Analyses
of Adverse Events with CTCAE Grade ≥ 3
by Significant SOC/PT on Hazard Ratio
SAF

SOC: Investigations

Adverse Events with CTCAE Grade 3-4-5 Subgroups	Placebo			Nivolumab			Nivolumab vs. Placebo	
	N	Patients with Event n (%)	KME [95%CI] (mon) (1)	N	Patients with Event n (%)	KME [95%CI] (mon) (1)	HR [95%CI] P-value (2) (3)	Test for Interaction P-value (4) (5)
PATHOLOGICAL STATUS								0.2053
PT0-2	31	2 (6.5)	N.A.	26	3 (11.5)	N.A.	1.820 (0.304, 10.897)	
PT3	80	5 (6.3)	N.A.	86	8 (9.3)	N.A.	0.5055 1.362 (0.445, 4.166)	
PT4A	27	1 (3.7)	N.A.	23	8 (34.8)	N.A. (5.45, N.A.)	0.5868 11.511 (1.438, 92.115)	
							0.0035	

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MedDRA Version: 27.1; CTC Version 4.0. HR = hazard ratio; KME = Kaplan-Meier estimate; N.M.E. = Not meaningful estimate.

(1) KME of median time to first AE. (2) Unstratified log-rank test.

(3) Unstratified Cox proportional hazard model. HR is Nivolumab over Placebo

(4) Unstratified Cox proportional hazard model with treatment, subgroup and treatment*subgroup interaction is to assess the significance of the interaction between treatment and the subgroup.

(5) A p-value of <0.05 needs to be indicated by 1 asterisk (indicates potential effect modification).

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Subgroup Time-Adjusted Analyses
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SAF

SOC: Investigations

Adverse Events with CTCAE Grade 3-4-5 Subgroups	Placebo			Nivolumab			Nivolumab vs. Placebo	
	N	Patients with Event n (%)	KME [95%CI] (mon) (1)	N	Patients with Event n (%)	KME [95%CI] (mon) (1)	HR [95%CI] P-value (2) (3)	Test for Interaction P-value (4) (5)
AGE CATEGORY I								0.5766
< 65	59	3 (5.1)	N.A.	67	11 (16.4)	N.A.	3.236 (0.903, 11.603)	
							0.0564	
≥ 65	80	5 (6.3)	N.A.	72	9 (12.5)	N.A.	2.023 (0.678, 6.036)	
							0.1974	

FEB2025 DBL. Includes events reported between first dose and 100 days after last dose of the study therapy.

MedDRA Version: 27.1; CTC Version 4.0. HR = hazard ratio; KME = Kaplan-Meier estimate; N.M.E. = Not meaningful estimate.

(1) KME of median time to first AE. (2) Unstratified log-rank test.

(3) Unstratified Cox proportional hazard model. HR is Nivolumab over Placebo

(4) Unstratified Cox proportional hazard model with treatment, subgroup and treatment*subgroup interaction is to assess the significance of the interaction between treatment and the subgroup.

(5) A p-value of <0.05 needs to be indicated by 1 asterisk (indicates potential effect modification).

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Subgroup Time-Adjusted Analyses
of Adverse Events with CTCAE Grade ≥ 3
by Significant SOC/PT on Hazard Ratio
SAF

SOC: Investigations

Adverse Events with CTCAE Grade 3-4-5 Subgroups	Placebo			Nivolumab			Nivolumab vs. Placebo	
	N	Patients with Event n (%)	KME [95%CI] (mon) (1)	N	Patients with Event n (%)	KME [95%CI] (mon) (1)	HR [95%CI] P-value (2) (3)	Test for Interaction P-value (4) (5)
AGE CATEGORY II								0.6383
< 65	59	3 (5.1)	N.A.	67	11 (16.4)	N.A.	3.236 (0.903, 11.603)	
>= 65 AND < 75	59	4 (6.8)	N.A.	49	5 (10.2)	N.A.	0.0564 1.515 (0.407, 5.642)	
>= 75	21	1 (4.8)	N.A.	23	4 (17.4)	N.A.	0.5329 3.775 (0.422, 33.781)	
							0.2015	

FEB2025 DBL. Includes events reported between first dose and 100 days after last dose of the study therapy.

MedDRA Version: 27.1; CTC Version 4.0. HR = hazard ratio; KME = Kaplan-Meier estimate; N.M.E. = Not meaningful estimate.

(1) KME of median time to first AE. (2) Unstratified log-rank test.

(3) Unstratified Cox proportional hazard model. HR is Nivolumab over Placebo

(4) Unstratified Cox proportional hazard model with treatment, subgroup and treatment*subgroup interaction is to assess the significance of the interaction between treatment and the subgroup.

(5) A p-value of <0.05 needs to be indicated by 1 asterisk (indicates potential effect modification).

IUC = invasive urothelial carcinoma.

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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

Table 8.2
Subgroup Time-Adjusted Analyses
of Adverse Events with CTCAE Grade ≥ 3
by Significant SOC/PT on Hazard Ratio
SAF

SOC: Investigations

Adverse Events with CTCAE Grade 3-4-5 Subgroups	Placebo			Nivolumab			Nivolumab vs. Placebo	
	N	Patients with Event n (%)	KME [95%CI] (mon) (1)	N	Patients with Event n (%)	KME [95%CI] (mon) (1)	HR [95%CI] P-value (2) (3)	Test for Interaction P-value (4) (5)
REGION								0.9934
US	23	0	N.A.	17	5 (29.4)	N.A. (5.91, N.A.)	N.M.E. 0.0056	
EUROPE	68	3 (4.4)	N.A.	72	7 (9.7)	N.A.	2.066 (0.534, 7.994)	
ASIA	28	3 (10.7)	N.A.	33	5 (15.2)	N.A.	0.2824 1.530 (0.366, 6.408)	
REST OF WORLD	20	2 (10.0)	N.A.	17	3 (17.6)	N.A. (8.21, N.A.)	0.5573 1.802 (0.301, 10.807)	
							0.5132	

FEB2025 DBL. Includes events reported between first dose and 100 days after last dose of the study therapy.

MedDRA Version: 27.1; CTC Version 4.0. HR = hazard ratio; KME = Kaplan-Meier estimate; N.M.E. = Not meaningful estimate.

(1) KME of median time to first AE. (2) Unstratified log-rank test.

(3) Unstratified Cox proportional hazard model. HR is Nivolumab over Placebo

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by Significant SOC/PT on Hazard Ratio
SAF

SOC: Investigations

Adverse Events with CTCAE Grade 3-4-5 Subgroups	Placebo			Nivolumab			Nivolumab vs. Placebo	
	N	Patients with Event n (%)	KME [95%CI] (mon) (1)	N	Patients with Event n (%)	KME [95%CI] (mon) (1)	HR [95%CI] P-value (2) (3)	Test for Interaction P-value (4) (5)
GENDER								0.6188
MALE	109	7 (6.4)	N.A.	101	18 (17.8)	N.A.	2.858 (1.194, 6.844)	
FEMALE	30	1 (3.3)	N.A.	38	2 (5.3)	N.A.	0.0136 1.491 (0.135, 16.453)	
RACE								0.4497
WHITE	106	5 (4.7)	N.A.	103	15 (14.6)	N.A.	3.036 (1.103, 8.353)	
ASIAN	28	3 (10.7)	N.A.	33	5 (15.2)	N.A.	0.0237 1.530 (0.366, 6.408)	
							0.5573	

FEB2025 DBL. Includes events reported between first dose and 100 days after last dose of the study therapy.

MedDRA Version: 27.1; CTC Version 4.0. HR = hazard ratio; KME = Kaplan-Meier estimate; N.M.E. = Not meaningful estimate.

(1) KME of median time to first AE. (2) Unstratified log-rank test.

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SAF

SOC: Investigations

Adverse Events with CTCAE Grade 3-4-5 Subgroups	Placebo			Nivolumab			Nivolumab vs. Placebo	
	N	Patients with Event n (%)	KME [95%CI] (mon) (1)	N	Patients with Event n (%)	KME [95%CI] (mon) (1)	HR [95%CI] P-value (2) (3)	Test for Interaction P-value (4) (5)
BASELINE ECOG STATUS								
0	83	5 (6.0)	N.A.	85	14 (16.5)	N.A.	2.799 (1.008, 7.772) 0.0391	0.7097
1	52	3 (5.8)	N.A.	51	6 (11.8)	N.A.	2.021 (0.505, 8.082) 0.3099	
SMOKING STATUS								
NEVER SMOKED	39	2 (5.1)	N.A.	41	4 (9.8)	N.A.	1.899 (0.347, 10.382) 0.4515	0.7007
CURRENT/FORMER	99	6 (6.1)	N.A.	96	16 (16.7)	N.A.	2.791 (1.092, 7.136) 0.0252	

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MedDRA Version: 27.1; CTC Version 4.0. HR = hazard ratio; KME = Kaplan-Meier estimate; N.M.E. = Not meaningful estimate.

(1) KME of median time to first AE. (2) Unstratified log-rank test.

(3) Unstratified Cox proportional hazard model. HR is Nivolumab over Placebo

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SAF

SOC: Investigations

Adverse Events with CTCAE Grade 3-4-5 Subgroups	Placebo			Nivolumab			Nivolumab vs. Placebo	
	N	Patients with Event n (%)	KME [95%CI] (mon) (1)	N	Patients with Event n (%)	KME [95%CI] (mon) (1)	HR [95%CI] P-value (2) (3)	Test for Interaction P-value (4) (5)
BASILINE HEMOGLOBIN								
<10 G/DL	14	1 (7.1)	N.A.	7	3 (42.9)	8.31 (0.85, N.A.)	7.440 (0.767, 72.163) 0.0426	0.3215
≥ 10 G/DL	125	7 (5.6)	N.A.	132	17 (12.9)	N.A.	2.288 (0.949, 5.518) 0.0579	
BASILINE CREATININE CLEARANCE								
<60 ML/MIN	60	4 (6.7)	N.A.	54	9 (16.7)	N.A.	2.645 (0.814, 8.589) 0.0924	0.8904
≥ 60 ML/MIN	79	4 (5.1)	N.A.	84	10 (11.9)	N.A.	2.348 (0.736, 7.488) 0.1371	

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(1) KME of median time to first AE. (2) Unstratified log-rank test.

(3) Unstratified Cox proportional hazard model. HR is Nivolumab over Placebo

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Table 8.2
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SAF

SOC: Investigations

Adverse Events with CTCAE Grade 3-4-5 Subgroups	Placebo			Nivolumab			Nivolumab vs. Placebo	
	N	Patients with Event n (%)	KME [95%CI] (mon) (1)	N	Patients with Event n (%)	KME [95%CI] (mon) (1)	HR [95%CI] P-value (2) (3)	Test for Interaction P-value (4) (5)
TIME FROM IUC SURGERY TO RANDOMIZATION (DAYS)								0.7713
>30-60	28	2 (7.1)	N.A.	34	7 (20.6)	N.A.	3.105 (0.645, 14.950)	
>60-90	65	4 (6.2)	N.A.	57	10 (17.5)	N.A.	0.1363 2.809 (0.881, 8.958)	
>90-120	41	2 (4.9)	N.A.	46	3 (6.5)	N.A.	0.0681 1.381 (0.231, 8.266)	
							0.7226	

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MedDRA Version: 27.1; CTC Version 4.0. HR = hazard ratio; KME = Kaplan-Meier estimate; N.M.E. = Not meaningful estimate.

(1) KME of median time to first AE. (2) Unstratified log-rank test.

(3) Unstratified Cox proportional hazard model. HR is Nivolumab over Placebo

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SOC: Investigations

Adverse Events with CTCAE Grade 3-4-5 Subgroups	Placebo			Nivolumab			Nivolumab vs. Placebo	
	N	Patients with Event n (%)	KME [95%CI] (mon) (1)	N	Patients with Event n (%)	KME [95%CI] (mon) (1)	HR [95%CI] P-value (2) (3)	Test for Interaction P-value (4) (5)
INITIAL TUMOR ORIGIN								0.6532
URINARY BLADDER	115	5 (4.3)	N.A.	112	15 (13.4)	N.A.	3.068 (1.115, 8.443) 0.0222	
RENAL PELVIS	13	2 (15.4)	N.A.	19	4 (21.1)	N.A. (9.26, N.A.)	1.337 (0.244, 7.317) 0.7371	
URETER	11	1 (9.1)	N.A.	8	1 (12.5)	N.A. (5.45, N.A.)	1.880 (0.116, 30.399) 0.6513	

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MedDRA Version: 27.1; CTC Version 4.0. HR = hazard ratio; KME = Kaplan-Meier estimate; N.M.E. = Not meaningful estimate.

(1) KME of median time to first AE. (2) Unstratified log-rank test.

(3) Unstratified Cox proportional hazard model. HR is Nivolumab over Placebo

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SAF

SOC: Investigations

Adverse Events with CTCAE Grade 3-4-5 Subgroups	Placebo			Nivolumab			Nivolumab vs. Placebo	
	N	Patients with Event n (%)	KME [95%CI] (mon) (1)	N	Patients with Event n (%)	KME [95%CI] (mon) (1)	HR [95%CI] P-value (2) (3)	Test for Interaction P-value (4) (5)
MINOR HISTOLOGICAL VARIANTS								0.6876
PRESENCE	60	3 (5.0)	N.A.	61	9 (14.8)	N.A.	3.129 (0.847, 11.562)	
ABSENCE	79	5 (6.3)	N.A.	78	11 (14.1)	N.A.	0.0711 2.216 (0.770, 6.380) 0.1299	

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MedDRA Version: 27.1; CTC Version 4.0. HR = hazard ratio; KME = Kaplan-Meier estimate; N.M.E. = Not meaningful estimate.

(1) KME of median time to first AE. (2) Unstratified log-rank test.

(3) Unstratified Cox proportional hazard model. HR is Nivolumab over Placebo

(4) Unstratified Cox proportional hazard model with treatment, subgroup and treatment*subgroup interaction is to assess the significance of the interaction between treatment and the subgroup.

(5) A p-value of <0.05 needs to be indicated by 1 asterisk (indicates potential effect modification).

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Table 8.2
Subgroup Time-Adjusted Analyses
of Adverse Events with CTCAE Grade ≥ 3
by Significant SOC/PT on Hazard Ratio
SAF

SOC: Investigations. PT: Lipase Increased

Adverse Events with CTCAE Grade 3-4-5 Subgroups	Placebo			Nivolumab			Nivolumab vs. Placebo	
	N	Patients with Event n (%)	KME [95%CI] (mon) (1)	N	Patients with Event n (%)	KME [95%CI] (mon) (1)	HR [95%CI] P-value (2) (3)	Test for Interaction P-value (4) (5)
OVERALL	139	1 (0.7)	N.A.	139	11 (7.9)	N.A.	10.815 (1.396, 83.774) 0.0043	N.M.E.
PRIOR NEO-ADJUVANT CISPLATIN THERAPY								
YES	61	1 (1.6)	N.M.E.	57	4 (7.0)	N.M.E.	N.M.E.	
NO	78	0	N.M.E.	82	7 (8.5)	N.M.E.	N.M.E.	

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MedDRA Version: 27.1; CTC Version 4.0. HR = hazard ratio; KME = Kaplan-Meier estimate; N.M.E. = Not meaningful estimate.

(1) KME of median time to first AE. (2) Unstratified log-rank test.

(3) Unstratified Cox proportional hazard model. HR is Nivolumab over Placebo

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SOC: Investigations. PT: Lipase Increased

Adverse Events with CTCAE Grade 3-4-5 Subgroups	Placebo			Nivolumab			Nivolumab vs. Placebo	
	N	Patients with Event n (%)	KME [95%CI] (mon) (1)	N	Patients with Event n (%)	KME [95%CI] (mon) (1)	HR [95%CI] P-value (2) (3)	Test for Interaction P-value (4) (5)
PRIOR CISPLATIN STATUS								N.M.E.
RECEIVED NEO-ADJUVANT	61	1 (1.6)	N.M.E.	57	4 (7.0)	N.M.E.	N.M.E.	
UNWILLING TO RECEIVE NEO-ADJUVANT	45	0	N.M.E.	50	3 (6.0)	N.M.E.	N.M.E.	
NOT ELIGIBLE TO RECEIVE NEO-ADJUVANT	32	0	N.M.E.	27	3 (11.1)	N.M.E.	N.M.E.	

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SAF

SOC: Investigations. PT: Lipase Increased

Adverse Events with CTCAE Grade 3-4-5 Subgroups	Placebo			Nivolumab			Nivolumab vs. Placebo	
	N	Patients with Event n (%)	KME [95%CI] (mon) (1)	N	Patients with Event n (%)	KME [95%CI] (mon) (1)	HR [95%CI] P-value (2) (3)	Test for Interaction P-value (4) (5)
USE OF ANY PRIOR NEO-ADJUVANT SYSTEMIC THERAPY								N.M.E.
YES	62	1 (1.6)	N.M.E.	61	5 (8.2)	N.M.E.	N.M.E.	
NO	77	0	N.M.E.	78	6 (7.7)	N.M.E.	N.M.E.	

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	N	Patients with Event n (%)	KME [95%CI] (mon) (1)	N	Patients with Event n (%)	KME [95%CI] (mon) (1)	HR [95%CI] P-value (2) (3)	Test for Interaction P-value (4) (5)
PATHOLOGICAL LYMPH NODE STATUS								N.M.E.
N+	64	0	N.M.E.	60	5 (8.3)	N.M.E.	N.M.E.	
N0/X WITH <10 NODES REMOVED	38	1 (2.6)	N.M.E.	38	3 (7.9)	N.M.E.	N.M.E.	
N0 WITH ≥ 10 NODES REMOVED	37	0	N.M.E.	41	3 (7.3)	N.M.E.	N.M.E.	

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MedDRA Version: 27.1; CTC Version 4.0. HR = hazard ratio; KME = Kaplan-Meier estimate; N.M.E. = Not meaningful estimate.

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Adverse Events with CTCAE Grade 3-4-5 Subgroups	Placebo			Nivolumab			Nivolumab vs. Placebo	
	N	Patients with Event n (%)	KME [95%CI] (mon) (1)	N	Patients with Event n (%)	KME [95%CI] (mon) (1)	HR [95%CI] P-value (2) (3)	Test for Interaction P-value (4) (5)
PATHOLOGICAL STATUS								N.M.E.
PT0-2	31	0	N.M.E.	26	2 (7.7)	N.M.E.	N.M.E.	
PT3	80	1 (1.3)	N.M.E.	86	5 (5.8)	N.M.E.	N.M.E.	
PT4A	27	0	N.M.E.	23	4 (17.4)	N.M.E.	N.M.E.	

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(1) KME of median time to first AE. (2) Unstratified log-rank test.

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SAF

SOC: Investigations. PT: Lipase Increased

Adverse Events with CTCAE Grade 3-4-5 Subgroups	Placebo			Nivolumab			Nivolumab vs. Placebo	
	N	Patients with Event n (%)	KME [95%CI] (mon) (1)	N	Patients with Event n (%)	KME [95%CI] (mon) (1)	HR [95%CI] P-value (2) (3)	Test for Interaction P-value (4) (5)
AGE CATEGORY I								
< 65	59	0	N.M.E.	67	8 (11.9)	N.M.E.	N.M.E.	N.M.E.
≥ 65	80	1 (1.3)	N.M.E.	72	3 (4.2)	N.M.E.	N.M.E.	

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MedDRA Version: 27.1; CTC Version 4.0. HR = hazard ratio; KME = Kaplan-Meier estimate; N.M.E. = Not meaningful estimate.

(1) KME of median time to first AE. (2) Unstratified log-rank test.

(3) Unstratified Cox proportional hazard model. HR is Nivolumab over Placebo

(4) Unstratified Cox proportional hazard model with treatment, subgroup and treatment*subgroup interaction is to assess the significance of the interaction between treatment and the subgroup.

(5) A p-value of <0.05 needs to be indicated by 1 asterisk (indicates potential effect modification).

IUC = invasive urothelial carcinoma.

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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

Table 8.2
Subgroup Time-Adjusted Analyses
of Adverse Events with CTCAE Grade ≥ 3
by Significant SOC/PT on Hazard Ratio
SAF

SOC: Investigations. PT: Lipase Increased

Adverse Events with CTCAE Grade 3-4-5 Subgroups	Placebo			Nivolumab			Nivolumab vs. Placebo	
	N	Patients with Event n (%)	KME [95%CI] (mon) (1)	N	Patients with Event n (%)	KME [95%CI] (mon) (1)	HR [95%CI] P-value (2) (3)	Test for Interaction P-value (4) (5)
AGE CATEGORY II								N.M.E.
< 65	59	0	N.M.E.	67	8 (11.9)	N.M.E.	N.M.E.	
≥ 65 AND < 75	59	1 (1.7)	N.M.E.	49	0	N.M.E.	N.M.E.	
≥ 75	21	0	N.M.E.	23	3 (13.0)	N.M.E.	N.M.E.	

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Adverse Events with CTCAE Grade 3-4-5 Subgroups	Placebo			Nivolumab			Nivolumab vs. Placebo	
	N	Patients with Event n (%)	KME [95%CI] (mon) (1)	N	Patients with Event n (%)	KME [95%CI] (mon) (1)	HR [95%CI] P-value (2) (3)	Test for Interaction P-value (4) (5)
REGION								N.M.E.
US	23	0	N.M.E.	17	3 (17.6)	N.M.E.	N.M.E.	
EUROPE	68	0	N.M.E.	72	2 (2.8)	N.M.E.	N.M.E.	
ASIA	28	0	N.M.E.	33	3 (9.1)	N.M.E.	N.M.E.	
REST OF WORLD	20	1 (5.0)	N.M.E.	17	3 (17.6)	N.M.E.	N.M.E.	

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Adverse Events with CTCAE Grade 3-4-5 Subgroups	Placebo			Nivolumab			Nivolumab vs. Placebo	
	N	Patients with Event n (%)	KME [95%CI] (mon) (1)	N	Patients with Event n (%)	KME [95%CI] (mon) (1)	HR [95%CI] P-value (2) (3)	Test for Interaction P-value (4) (5)
GENDER								
MALE	109	1 (0.9)	N.A.	101	10 (9.9)	N.A.	10.738 (1.374, 83.917)	0.9953
FEMALE	30	0	N.A.	38	1 (2.6)	N.A.	0.0046 N.M.E. 0.3743	
RACE								
WHITE	106	1 (0.9)	N.M.E.	103	8 (7.8)	N.M.E.	N.M.E.	N.M.E.
ASIAN	28	0	N.M.E.	33	3 (9.1)	N.M.E.	N.M.E.	

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(1) KME of median time to first AE. (2) Unstratified log-rank test.

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Adverse Events with CTCAE Grade 3-4-5 Subgroups	Placebo			Nivolumab			Nivolumab vs. Placebo	
	N	Patients with Event n (%)	KME [95%CI] (mon) (1)	N	Patients with Event n (%)	KME [95%CI] (mon) (1)	HR [95%CI] P-value (2) (3)	Test for Interaction P-value (4) (5)
BASELINE ECOG STATUS								N.M.E.
0	83	1 (1.2)	N.M.E.	85	8 (9.4)	N.M.E.	N.M.E.	
1	52	0	N.M.E.	51	3 (5.9)	N.M.E.	N.M.E.	
SMOKING STATUS								0.9939
NEVER SMOKED	39	0	N.A.	41	2 (4.9)	N.A.	N.M.E. 0.1750	
CURRENT/FORMER	99	1 (1.0)	N.A.	96	9 (9.4)	N.A.	8.880 (1.124, 70.134) 0.0122	

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MedDRA Version: 27.1; CTC Version 4.0. HR = hazard ratio; KME = Kaplan-Meier estimate; N.M.E. = Not meaningful estimate.

(1) KME of median time to first AE. (2) Unstratified log-rank test.

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Adverse Events with CTCAE Grade 3-4-5 Subgroups	Placebo			Nivolumab			Nivolumab vs. Placebo	
	N	Patients with Event n (%)	KME [95%CI] (mon) (1)	N	Patients with Event n (%)	KME [95%CI] (mon) (1)	HR [95%CI] P-value (2) (3)	Test for Interaction P-value (4) (5)
BASELINE HEMOGLOBIN								0.9940
<10 G/DL	14	0	N.A.	7	1 (14.3)	N.A.	N.M.E.	
						(6.14, N.A.)	0.1797	
≥ 10 G/DL	125	1 (0.8)	N.A.	132	10 (7.6)	N.A.	9.291	
							(1.189, 72.595)	
							0.0095	
BASELINE CREATININE CLEARANCE								N.M.E.
<60 ML/MIN	60	0	N.M.E.	54	5 (9.3)	N.M.E.	N.M.E.	
≥ 60 ML/MIN	79	1 (1.3)	N.M.E.	84	6 (7.1)	N.M.E.	N.M.E.	

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MedDRA Version: 27.1; CTC Version 4.0. HR = hazard ratio; KME = Kaplan-Meier estimate; N.M.E. = Not meaningful estimate.

(1) KME of median time to first AE. (2) Unstratified log-rank test.

(3) Unstratified Cox proportional hazard model. HR is Nivolumab over Placebo

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Adverse Events with CTCAE Grade 3-4-5 Subgroups	Placebo			Nivolumab			Nivolumab vs. Placebo	
	N	Patients with Event n (%)	KME [95%CI] (mon) (1)	N	Patients with Event n (%)	KME [95%CI] (mon) (1)	HR [95%CI] P-value (2) (3)	Test for Interaction P-value (4) (5)
TIME FROM IUC SURGERY TO RANDOMIZATION (DAYS)								N.M.E.
>30-60	28	0	N.M.E.	34	3 (8.8)	N.M.E.	N.M.E.	
>60-90	65	0	N.M.E.	57	5 (8.8)	N.M.E.	N.M.E.	
>90-120	41	1 (2.4)	N.M.E.	46	3 (6.5)	N.M.E.	N.M.E.	

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(1) KME of median time to first AE. (2) Unstratified log-rank test.

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	N	Patients with Event n (%)	KME [95%CI] (mon) (1)	N	Patients with Event n (%)	KME [95%CI] (mon) (1)	HR [95%CI] P-value (2) (3)	Test for Interaction P-value (4) (5)
INITIAL TUMOR ORIGIN								N.M.E.
URINARY BLADDER	115	1 (0.9)	N.M.E.	112	7 (6.3)	N.M.E.	N.M.E.	
RENAL PELVIS	13	0	N.M.E.	19	3 (15.8)	N.M.E.	N.M.E.	
URETER	11	0	N.M.E.	8	1 (12.5)	N.M.E.	N.M.E.	

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MedDRA Version: 27.1; CTC Version 4.0. HR = hazard ratio; KME = Kaplan-Meier estimate; N.M.E. = Not meaningful estimate.

(1) KME of median time to first AE. (2) Unstratified log-rank test.

(3) Unstratified Cox proportional hazard model. HR is Nivolumab over Placebo

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Adverse Events with CTCAE Grade 3-4-5 Subgroups	Placebo			Nivolumab			Nivolumab vs. Placebo	
	Patients with Event		KME	Patients with Event		KME	HR	Test for
	N	n (%)	[95%CI] (mon) (1)	N	n (%)	[95%CI] (mon) (1)	P-value [95%CI] (2) (3)	Interaction P-value (4) (5)
MINOR HISTOLOGICAL VARIANTS								N.M.E.
PRESENCE	60	0	N.M.E.	61	3 (4.9)	N.M.E.	N.M.E.	
ABSENCE	79	1 (1.3)	N.M.E.	78	8 (10.3)	N.M.E.	N.M.E.	

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MedDRA Version: 27.1; CTC Version 4.0. HR = hazard ratio; KME = Kaplan-Meier estimate; N.M.E. = Not meaningful estimate.

(1) KME of median time to first AE. (2) Unstratified log-rank test.

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SAF

SOC: Gastrointestinal Disorders

Adverse Events with CTCAE Grade 3-4-5 Subgroups	Placebo			Nivolumab			Nivolumab vs. Placebo	
	N	Patients with Event n (%)	KME [95%CI] (mon) (1)	N	Patients with Event n (%)	KME [95%CI] (mon) (1)	HR [95%CI] P-value (2) (3)	Test for Interaction P-value (4) (5)
OVERALL	139	17 (12.2)	N.A.	139	8 (5.8)	N.A.	0.427 (0.184, 0.991) 0.0412	
PRIOR NEO-ADJUVANT CISPLATIN THERAPY								0.6112
YES	61	6 (9.8)	N.A.	57	2 (3.5)	N.A.	0.298 (0.060, 1.477) 0.1154	
NO	78	11 (14.1)	N.A.	82	6 (7.3)	N.A.	0.500 (0.185, 1.353) 0.1639	

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(1) KME of median time to first AE. (2) Unstratified log-rank test.

(3) Unstratified Cox proportional hazard model. HR is Nivolumab over Placebo

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SAF

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	N	Patients with Event n (%)	KME [95%CI] (mon) (1)	N	Patients with Event n (%)	KME [95%CI] (mon) (1)	HR [95%CI] P-value (2) (3)	Test for Interaction P-value (4) (5)
PRIOR CISPLATIN STATUS								0.5926
RECEIVED NEO-ADJUVANT	61	6 (9.8)	N.A.	57	2 (3.5)	N.A.	0.298 (0.060, 1.477)	
UNWILLING TO RECEIVE NEO-ADJUVANT	45	9 (20.0)	N.A.	50	4 (8.0)	N.A.	0.1154 0.396 (0.122, 1.286)	
NOT ELIGIBLE TO RECEIVE NEO-ADJUVANT	32	2 (6.3)	N.A.	27	2 (7.4)	N.A.	0.1101 1.136 (0.160, 8.075) 0.8990	

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(1) KME of median time to first AE. (2) Unstratified log-rank test.

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Adverse Events with CTCAE Grade 3-4-5 Subgroups	Placebo			Nivolumab			Nivolumab vs. Placebo	
	N	Patients with Event n (%)	KME [95%CI] (mon) (1)	N	Patients with Event n (%)	KME [95%CI] (mon) (1)	HR [95%CI] P-value (2) (3)	Test for Interaction P-value (4) (5)
USE OF ANY PRIOR NEO-ADJUVANT SYSTEMIC THERAPY								0.9894
YES	62	6 (9.7)	N.A.	61	3 (4.9)	N.A.	0.423 (0.106, 1.695)	
NO	77	11 (14.3)	N.A.	78	5 (6.4)	N.A.	0.2103 0.433 (0.150, 1.248) 0.1106	

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	N	Patients with Event n (%)	KME [95%CI] (mon) (1)	N	Patients with Event n (%)	KME [95%CI] (mon) (1)	HR [95%CI] P-value (2) (3)	Test for Interaction P-value (4) (5)
PATHOLOGICAL LYMPH NODE STATUS								0.2601
N+	64	10 (15.6)	N.A.	60	2 (3.3)	N.A.	0.177 (0.039, 0.809)	
N0/X WITH <10 NODES REMOVED	38	3 (7.9)	N.A.	38	3 (7.9)	N.A.	0.0118 1.035 (0.209, 5.130)	
N0 WITH ≥ 10 NODES REMOVED	37	4 (10.8)	N.A.	41	3 (7.3)	N.A.	0.9662 0.662 (0.147, 2.976) 0.5884	

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SOC: Gastrointestinal Disorders

Adverse Events with CTCAE Grade 3-4-5 Subgroups	Placebo			Nivolumab			Nivolumab vs. Placebo	
	N	Patients with Event n (%)	KME [95%CI] (mon) (1)	N	Patients with Event n (%)	KME [95%CI] (mon) (1)	HR [95%CI] P-value (2) (3)	Test for Interaction P-value (4) (5)
PATHOLOGICAL STATUS								0.8792
PT0-2	31	4 (12.9)	N.A.	26	1 (3.8)	N.A.	0.291 (0.032, 2.604)	
PT3	80	6 (7.5)	N.A.	86	4 (4.7)	N.A.	0.2397 0.546 (0.154, 1.941)	
PT4A	27	7 (25.9)	N.A.	23	3 (13.0)	N.A.	0.3425 0.473 (0.122, 1.835) 0.2678	

FEB2025 DBL. Includes events reported between first dose and 100 days after last dose of the study therapy.

MedDRA Version: 27.1; CTC Version 4.0. HR = hazard ratio; KME = Kaplan-Meier estimate; N.M.E. = Not meaningful estimate.

(1) KME of median time to first AE. (2) Unstratified log-rank test.

(3) Unstratified Cox proportional hazard model. HR is Nivolumab over Placebo

(4) Unstratified Cox proportional hazard model with treatment, subgroup and treatment*subgroup interaction is to assess the significance of the interaction between treatment and the subgroup.

(5) A p-value of <0.05 needs to be indicated by 1 asterisk (indicates potential effect modification).

IUC = invasive urothelial carcinoma.

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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

Table 8.2
Subgroup Time-Adjusted Analyses
of Adverse Events with CTCAE Grade ≥ 3
by Significant SOC/PT on Hazard Ratio
SAF

SOC: Gastrointestinal Disorders

Adverse Events with CTCAE Grade 3-4-5 Subgroups	Placebo			Nivolumab			Nivolumab vs. Placebo	
	N	Patients with Event n (%)	KME [95%CI] (mon) (1)	N	Patients with Event n (%)	KME [95%CI] (mon) (1)	HR [95%CI] P-value (2) (3)	Test for Interaction P-value (4) (5)
AGE CATEGORY I								0.3289
< 65	59	6 (10.2)	N.A.	67	5 (7.5)	N.A.	0.702 (0.214, 2.304)	
							0.5579	
≥ 65	80	11 (13.8)	N.A.	72	3 (4.2)	N.A.	0.271 (0.076, 0.974)	
							0.0319	

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MedDRA Version: 27.1; CTC Version 4.0. HR = hazard ratio; KME = Kaplan-Meier estimate; N.M.E. = Not meaningful estimate.

(1) KME of median time to first AE. (2) Unstratified log-rank test.

(3) Unstratified Cox proportional hazard model. HR is Nivolumab over Placebo

(4) Unstratified Cox proportional hazard model with treatment, subgroup and treatment*subgroup interaction is to assess the significance of the interaction between treatment and the subgroup.

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SAF

SOC: Gastrointestinal Disorders

Adverse Events with CTCAE Grade 3-4-5 Subgroups	Placebo			Nivolumab			Nivolumab vs. Placebo	
	N	Patients with Event n (%)	KME [95%CI] (mon) (1)	N	Patients with Event n (%)	KME [95%CI] (mon) (1)	HR [95%CI] P-value (2) (3)	Test for Interaction P-value (4) (5)
AGE CATEGORY II								0.7429
< 65	59	6 (10.2)	N.A.	67	5 (7.5)	N.A.	0.702 (0.214, 2.304)	
≥ 65 AND < 75	59	10 (16.9)	N.A.	49	3 (6.1)	N.A.	0.5579 0.324 (0.089, 1.178)	
≥ 75	21	1 (4.8)	N.A.	23	0	N.A.	0.0714 N.M.E. 0.3049	

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MedDRA Version: 27.1; CTC Version 4.0. HR = hazard ratio; KME = Kaplan-Meier estimate; N.M.E. = Not meaningful estimate.

(1) KME of median time to first AE. (2) Unstratified log-rank test.

(3) Unstratified Cox proportional hazard model. HR is Nivolumab over Placebo

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Table 8.2
Subgroup Time-Adjusted Analyses
of Adverse Events with CTCAE Grade ≥ 3
by Significant SOC/PT on Hazard Ratio
SAF

SOC: Gastrointestinal Disorders

Adverse Events with CTCAE Grade 3-4-5 Subgroups	Placebo			Nivolumab			Nivolumab vs. Placebo	
	N	Patients with Event n (%)	KME [95%CI] (mon) (1)	N	Patients with Event n (%)	KME [95%CI] (mon) (1)	HR [95%CI] P-value (2) (3)	Test for Interaction P-value (4) (5)
REGION								0.2942
US	23	4 (17.4)	N.A. (8.77, N.A.)	17	1 (5.9)	N.A.	0.309 (0.035, 2.771)	
EUROPE	68	8 (11.8)	N.A.	72	3 (4.2)	N.A.	0.2670 0.308 (0.082, 1.165)	
ASIA	28	1 (3.6)	N.A.	33	4 (12.1)	N.A.	0.0664 3.732 (0.417, 33.409)	
REST OF WORLD	20	4 (20.0)	N.A.	17	0	N.A.	0.2062 N.M.E. 0.0506	

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MedDRA Version: 27.1; CTC Version 4.0. HR = hazard ratio; KME = Kaplan-Meier estimate; N.M.E. = Not meaningful estimate.

(1) KME of median time to first AE. (2) Unstratified log-rank test.

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SAF

SOC: Gastrointestinal Disorders

Adverse Events with CTCAE Grade 3-4-5 Subgroups	Placebo			Nivolumab			Nivolumab vs. Placebo	
	N	Patients with Event n (%)	KME [95%CI] (mon) (1)	N	Patients with Event n (%)	KME [95%CI] (mon) (1)	HR [95%CI] P-value (2) (3)	Test for Interaction P-value (4) (5)
GENDER								
MALE	109	14 (12.8)	N.A.	101	7 (6.9)	N.A.	0.492 (0.198, 1.221)	0.6010
FEMALE	30	3 (10.0)	N.A.	38	1 (2.6)	N.A.	0.1187 0.250 (0.026, 2.402)	
RACE								
WHITE	106	15 (14.2)	N.A.	103	4 (3.9)	N.A.	0.236 (0.078, 0.713)	0.0318*
ASIAN	28	1 (3.6)	N.A.	33	4 (12.1)	N.A.	0.0054 3.732 (0.417, 33.409)	
							0.2062	

FEB2025 DBL. Includes events reported between first dose and 100 days after last dose of the study therapy.

MedDRA Version: 27.1; CTC Version 4.0. HR = hazard ratio; KME = Kaplan-Meier estimate; N.M.E. = Not meaningful estimate.

(1) KME of median time to first AE. (2) Unstratified log-rank test.

(3) Unstratified Cox proportional hazard model. HR is Nivolumab over Placebo

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SAF

SOC: Gastrointestinal Disorders

Adverse Events with CTCAE Grade 3-4-5 Subgroups	Placebo			Nivolumab			Nivolumab vs. Placebo	
	N	Patients with Event n (%)	KME [95%CI] (mon) (1)	N	Patients with Event n (%)	KME [95%CI] (mon) (1)	HR [95%CI] P-value (2) (3)	Test for Interaction P-value (4) (5)
BASELINE ECOG STATUS								
0	83	11 (13.3)	N.A.	85	3 (3.5)	N.A.	0.234 (0.065, 0.840)	0.2445
1	52	5 (9.6)	N.A.	51	4 (7.8)	N.A.	0.0152 0.730 (0.196, 2.720)	
SMOKING STATUS								
NEVER SMOKED	39	2 (5.1)	N.A.	41	4 (9.8)	N.A.	1.883 (0.345, 10.284)	0.0305*
CURRENT/FORMER	99	15 (15.2)	N.A.	96	3 (3.1)	N.A.	0.4575 0.183 (0.053, 0.631)	
							0.0025	

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(1) KME of median time to first AE. (2) Unstratified log-rank test.

(3) Unstratified Cox proportional hazard model. HR is Nivolumab over Placebo

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SAF

SOC: Gastrointestinal Disorders

Adverse Events with CTCAE Grade 3-4-5 Subgroups	Placebo			Nivolumab			Nivolumab vs. Placebo	
	N	Patients with Event n (%)	KME [95%CI] (mon) (1)	N	Patients with Event n (%)	KME [95%CI] (mon) (1)	HR [95%CI] P-value (2) (3)	Test for Interaction P-value (4) (5)
BASELINE HEMOGLOBIN								0.9922
<10 G/DL	14	2 (14.3)	N.A.	7	0	N.A.	N.M.E.	
			(8.77, N.A.)				0.3217	
≥ 10 G/DL	125	15 (12.0)	N.A.	132	8 (6.1)	N.A.	0.456	
							(0.193, 1.077)	
							0.0663	
BASELINE CREATININE CLEARANCE								0.9691
<60 ML/MIN	60	5 (8.3)	N.A.	54	2 (3.7)	N.A.	0.423	
							(0.082, 2.180)	
							0.2888	
≥ 60 ML/MIN	79	12 (15.2)	N.A.	84	6 (7.1)	N.A.	0.413	
							(0.155, 1.102)	
							0.0683	

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MedDRA Version: 27.1; CTC Version 4.0. HR = hazard ratio; KME = Kaplan-Meier estimate; N.M.E. = Not meaningful estimate.

(1) KME of median time to first AE. (2) Unstratified log-rank test.

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SAF

SOC: Gastrointestinal Disorders

Adverse Events with CTCAE Grade 3-4-5 Subgroups	Placebo			Nivolumab			Nivolumab vs. Placebo	
	N	Patients with Event n (%)	KME [95%CI] (mon) (1)	N	Patients with Event n (%)	KME [95%CI] (mon) (1)	HR [95%CI] P-value (2) (3)	Test for Interaction P-value (4) (5)
TIME FROM IUC SURGERY TO RANDOMIZATION (DAYS)								0.1084
>30-60	28	1 (3.6)	N.A.	34	3 (8.8)	N.A.	2.459 (0.256, 23.649)	
>60-90	65	10 (15.4)	N.A.	57	1 (1.8)	N.A.	0.4204 (0.013, 0.795)	
>90-120	41	5 (12.2)	N.A.	46	4 (8.7)	N.A.	0.102 (0.0073, 0.653) (0.175, 2.438) 0.5232	

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MedDRA Version: 27.1; CTC Version 4.0. HR = hazard ratio; KME = Kaplan-Meier estimate; N.M.E. = Not meaningful estimate.

(1) KME of median time to first AE. (2) Unstratified log-rank test.

(3) Unstratified Cox proportional hazard model. HR is Nivolumab over Placebo

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SAF

SOC: Gastrointestinal Disorders

Adverse Events with CTCAE Grade 3-4-5 Subgroups	Placebo			Nivolumab			Nivolumab vs. Placebo	
	N	Patients with Event n (%)	KME [95%CI] (mon) (1)	N	Patients with Event n (%)	KME [95%CI] (mon) (1)	HR [95%CI] P-value (2) (3)	Test for Interaction P-value (4) (5)
INITIAL TUMOR ORIGIN								0.9999
URINARY BLADDER	115	16 (13.9)	N.A.	112	5 (4.5)	N.A.	0.281 (0.103, 0.768)	
RENAL PELVIS	13	0	N.A.	19	3 (15.8)	N.A.	0.0083 N.M.E.	
URETER	11	1 (9.1)	N.A. (9.03, N.A.)	8	0	N.A.	0.1530 N.M.E. 0.4142	

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(1) KME of median time to first AE. (2) Unstratified log-rank test.

(3) Unstratified Cox proportional hazard model. HR is Nivolumab over Placebo

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Adverse Events with CTCAE Grade 3-4-5 Subgroups	Placebo			Nivolumab			Nivolumab vs. Placebo	
	N	Patients with Event n (%)	KME [95%CI] (mon) (1)	N	Patients with Event n (%)	KME [95%CI] (mon) (1)	HR [95%CI] P-value (2) (3)	Test for Interaction P-value (4) (5)
MINOR HISTOLOGICAL VARIANTS								0.4666
PRESENCE	60	6 (10.0)	N.A.	61	4 (6.6)	N.A.	0.604 (0.170, 2.143)	
ABSENCE	79	11 (13.9)	N.A.	78	4 (5.1)	N.A.	0.4305 0.328 (0.104, 1.031) 0.0447	

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(1) KME of median time to first AE. (2) Unstratified log-rank test.

(3) Unstratified Cox proportional hazard model. HR is Nivolumab over Placebo

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Table 8.2
Subgroup Time-Adjusted Analyses
of Adverse Events with CTCAE Grade ≥ 3
by Significant SOC/PT on Hazard Ratio
SAF

SOC: Neoplasms Benign, Malignant and Unspecified (Incl Cysts and Polyps)

Adverse Events with CTCAE Grade 3-4-5 Subgroups	Placebo			Nivolumab			Nivolumab vs. Placebo	
	N	Patients with Event n (%)	KME [95%CI] (mon) (1)	N	Patients with Event n (%)	KME [95%CI] (mon) (1)	HR [95%CI] P-value (2) (3)	Test for Interaction P-value (4) (5)
OVERALL	139	19 (13.7)	N.A.	139	7 (5.0)	N.A.	0.347 (0.146, 0.826) 0.0122	
PRIOR NEO-ADJUVANT CISPLATIN THERAPY								0.8963
YES	61	6 (9.8)	N.A.	57	2 (3.5)	N.A.	0.324 (0.065, 1.604) 0.1455	
NO	78	13 (16.7)	N.A.	82	5 (6.1)	N.A.	0.358 (0.127, 1.004) 0.0415	

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MedDRA Version: 27.1; CTC Version 4.0. HR = hazard ratio; KME = Kaplan-Meier estimate; N.M.E. = Not meaningful estimate.

(1) KME of median time to first AE. (2) Unstratified log-rank test.

(3) Unstratified Cox proportional hazard model. HR is Nivolumab over Placebo

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of Adverse Events with CTCAE Grade ≥ 3
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SAF

SOC: Neoplasms Benign, Malignant and Unspecified (Incl Cysts and Polyps)

Adverse Events with CTCAE Grade 3-4-5 Subgroups	Placebo			Nivolumab			Nivolumab vs. Placebo	
	N	Patients with Event n (%)	KME [95%CI] (mon) (1)	N	Patients with Event n (%)	KME [95%CI] (mon) (1)	HR [95%CI] P-value (2) (3)	Test for Interaction P-value (4) (5)
PRIOR CISPLATIN STATUS								0.1494
RECEIVED NEO-ADJUVANT	61	6 (9.8)	N.A.	57	2 (3.5)	N.A.	0.324 (0.065, 1.604)	
UNWILLING TO RECEIVE NEO-ADJUVANT	45	3 (6.7)	N.A.	50	4 (8.0)	N.A.	0.1455 1.259 (0.282, 5.627)	
NOT ELIGIBLE TO RECEIVE NEO-ADJUVANT	32	10 (31.3)	N.A. (9.20, N.A.)	27	1 (3.7)	N.A.	0.7626 0.103 (0.013, 0.804) 0.0078	

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SAF

SOC: Neoplasms Benign, Malignant and Unspecified (Incl Cysts and Polyps)

Adverse Events with CTCAE Grade 3-4-5 Subgroups	Placebo			Nivolumab			Nivolumab vs. Placebo	
	N	Patients with Event n (%)	KME [95%CI] (mon) (1)	N	Patients with Event n (%)	KME [95%CI] (mon) (1)	HR [95%CI] P-value (2) (3)	Test for Interaction P-value (4) (5)
USE OF ANY PRIOR NEO-ADJUVANT SYSTEMIC THERAPY								0.8234
YES	62	6 (9.7)	N.A.	61	2 (3.3)	N.A.	0.307 (0.062, 1.524)	
NO	77	13 (16.9)	N.A.	78	5 (6.4)	N.A.	0.1263 0.372 (0.133, 1.045) 0.0507	

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(1) KME of median time to first AE. (2) Unstratified log-rank test.

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IUC = invasive urothelial carcinoma.

Program Path: /projects/bms214671/stats/market/ma274_202502/prog/tables

Program Name: rt-ae-tsubsocae-hr-ebr45.sas

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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

Table 8.2
Subgroup Time-Adjusted Analyses
of Adverse Events with CTCAE Grade ≥ 3
by Significant SOC/PT on Hazard Ratio
SAF

SOC: Neoplasms Benign, Malignant and Unspecified (Incl Cysts and Polyps)

Adverse Events with CTCAE Grade 3-4-5 Subgroups	Placebo			Nivolumab			Nivolumab vs. Placebo	
	Patients with Event		KME	Patients with Event		KME	HR	Test for
	N	n (%)	[95%CI] (mon) (1)	N	n (%)	[95%CI] (mon) (1)	[95%CI] P-value (2) (3)	Interaction P-value (4) (5)
PATHOLOGICAL LYMPH NODE STATUS								0.7448
N+	64	11 (17.2)	N.A.	60	6 (10.0)	N.A.	0.525 (0.194, 1.423)	
N0/X WITH <10 NODES REMOVED	38	4 (10.5)	N.A.	38	0	N.A.	0.1979 N.M.E.	
N0 WITH ≥ 10 NODES REMOVED	37	4 (10.8)	N.A.	41	1 (2.4)	N.A.	0.0500 0.209 (0.023, 1.870)	
							0.1217	

FEB2025 DBL. Includes events reported between first dose and 100 days after last dose of the study therapy.

MedDRA Version: 27.1; CTC Version 4.0. HR = hazard ratio; KME = Kaplan-Meier estimate; N.M.E. = Not meaningful estimate.

(1) KME of median time to first AE. (2) Unstratified log-rank test.

(3) Unstratified Cox proportional hazard model. HR is Nivolumab over Placebo

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Adverse Events with CTCAE Grade 3-4-5 Subgroups	Placebo			Nivolumab			Nivolumab vs. Placebo	
	N	Patients with Event n (%)	KME [95%CI] (mon) (1)	N	Patients with Event n (%)	KME [95%CI] (mon) (1)	HR [95%CI] P-value (2) (3)	Test for Interaction P-value (4) (5)
PATHOLOGICAL STATUS								0.8942
PT0-2	31	2 (6.5)	N.A.	26	1 (3.8)	N.A.	0.573 (0.052, 6.320)	
PT3	80	13 (16.3)	N.A.	86	5 (5.8)	N.A.	0.6448 0.315 (0.112, 0.885)	
PT4A	27	4 (14.8)	N.A.	23	1 (4.3)	N.A.	0.0207 0.317 (0.035, 2.845) 0.2791	

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Adverse Events with CTCAE Grade 3-4-5 Subgroups	Placebo			Nivolumab			Nivolumab vs. Placebo	
	N	Patients with Event n (%)	KME [95%CI] (mon) (1)	N	Patients with Event n (%)	KME [95%CI] (mon) (1)	HR [95%CI] P-value (2) (3)	Test for Interaction P-value (4) (5)
AGE CATEGORY I								0.8901
< 65	59	4 (6.8)	N.A.	67	2 (3.0)	N.A.	0.432 (0.079, 2.360)	
							0.3188	
≥ 65	80	15 (18.8)	N.A.	72	5 (6.9)	N.A.	0.354 (0.129, 0.975)	
							0.0359	

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Adverse Events with CTCAE Grade 3-4-5 Subgroups	Placebo			Nivolumab			Nivolumab vs. Placebo	
	N	Patients with Event n (%)	KME [95%CI] (mon) (1)	N	Patients with Event n (%)	KME [95%CI] (mon) (1)	HR [95%CI] P-value (2) (3)	Test for Interaction P-value (4) (5)
AGE CATEGORY II < 65	59	4 (6.8)	N.A.	67	2 (3.0)	N.A.	0.432 (0.079, 2.360)	0.5387
>= 65 AND < 75	59	11 (18.6)	N.A.	49	2 (4.1)	N.A.	0.3188 0.204 (0.045, 0.918)	
>= 75	21	4 (19.0)	N.A.	23	3 (13.0)	N.A. (13.80, N.A.)	0.0217 0.704 (0.157, 3.156) 0.6445	

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	N	Patients with Event n (%)	KME [95%CI] (mon) (1)	N	Patients with Event n (%)	KME [95%CI] (mon) (1)	HR [95%CI] P-value (2) (3)	Test for Interaction P-value (4) (5)
REGION								0.1071
US	23	3 (13.0)	N.A.	17	0	N.A.	N.M.E. 0.1195	
EUROPE	68	10 (14.7)	N.A.	72	1 (1.4)	N.A.	0.082 (0.011, 0.642)	
ASIA	28	1 (3.6)	N.A.	33	4 (12.1)	N.A.	0.0023 3.654 (0.408, 32.727)	
REST OF WORLD	20	5 (25.0)	N.A. (8.41, N.A.)	17	2 (11.8)	N.A.	0.2147 0.443 (0.086, 2.294)	
							0.3191	

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	N	Patients with Event n (%)	KME [95%CI] (mon) (1)	N	Patients with Event n (%)	KME [95%CI] (mon) (1)	HR [95%CI] P-value (2) (3)	Test for Interaction P-value (4) (5)
GENDER								
MALE	109	18 (16.5)	N.A.	101	6 (5.9)	N.A.	0.342 (0.136, 0.862)	0.6332
FEMALE	30	1 (3.3)	N.A.	38	1 (2.6)	N.A.	0.0171 0.695 (0.043, 11.130)	
RACE								
WHITE	106	17 (16.0)	N.A.	103	3 (2.9)	N.A.	0.163 (0.048, 0.556)	0.0149*
ASIAN	28	1 (3.6)	N.A.	33	4 (12.1)	N.A.	0.0009 3.654 (0.408, 32.727)	
							0.2147	

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	N	Patients with Event n (%)	KME [95%CI] (mon) (1)	N	Patients with Event n (%)	KME [95%CI] (mon) (1)	HR [95%CI] P-value (2) (3)	Test for Interaction P-value (4) (5)
BASELINE ECOG STATUS								
0	83	10 (12.0)	N.A.	85	6 (7.1)	N.A.	0.578 (0.210, 1.593)	0.2600
1	52	6 (11.5)	N.A.	51	1 (2.0)	N.A.	0.2842 0.153 (0.018, 1.270)	
SMOKING STATUS								
NEVER SMOKED	39	5 (12.8)	N.A.	41	2 (4.9)	N.A.	0.360 (0.070, 1.857)	0.9446
CURRENT/FORMER	99	14 (14.1)	N.A.	96	5 (5.2)	N.A.	0.2027 0.335 (0.120, 0.931)	
							0.0277	

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	N	Patients with Event n (%)	KME [95%CI] (mon) (1)	N	Patients with Event n (%)	KME [95%CI] (mon) (1)	HR [95%CI] P-value (2) (3)	Test for Interaction P-value (4) (5)
BASELINE HEMOGLOBIN								
<10 G/DL	14	0	N.A.	7	0	N.A.	N.M.E. N.A.	0.9997
≥ 10 G/DL	125	19 (15.2)	N.A.	132	7 (5.3)	N.A.	0.325 (0.137, 0.775) 0.0076	
BASELINE CREATININE CLEARANCE								
<60 ML/MIN	60	9 (15.0)	N.A.	54	4 (7.4)	N.A.	0.477 (0.147, 1.550) 0.2078	0.5046
≥ 60 ML/MIN	79	10 (12.7)	N.A.	84	3 (3.6)	N.A.	0.266 (0.073, 0.966) 0.0307	

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	N	Patients with Event n (%)	KME [95%CI] (mon) (1)	N	Patients with Event n (%)	KME [95%CI] (mon) (1)	HR [95%CI] P-value (2) (3)	Test for Interaction P-value (4) (5)
TIME FROM IUC SURGERY TO RANDOMIZATION (DAYS)								0.3348
>30-60	28	1 (3.6)	N.A.	34	2 (5.9)	N.A.	1.670 (0.151, 18.417)	
>60-90	65	11 (16.9)	N.A.	57	4 (7.0)	N.A.	0.6720 (0.118, 1.168)	
>90-120	41	6 (14.6)	N.A.	46	1 (2.2)	N.A.	0.372 (0.0778, 0.146) (0.018, 1.213)	

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	N	Patients with Event n (%)	KME [95%CI] (mon) (1)	N	Patients with Event n (%)	KME [95%CI] (mon) (1)	HR [95%CI] P-value (2) (3)	Test for Interaction P-value (4) (5)
INITIAL TUMOR ORIGIN								0.5184
URINARY BLADDER	115	17 (14.8)	N.A.	112	5 (4.5)	N.A.	0.279 (0.103, 0.756)	
RENAL PELVIS	13	1 (7.7)	N.A.	19	2 (10.5)	N.A. (13.80, N.A.)	0.0073 1.493 (0.135, 16.509)	
URETER	11	1 (9.1)	N.A. (4.67, N.A.)	8	0	N.A.	0.7421 N.M.E. 0.4795	

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	N	Patients with Event n (%)	KME [95%CI] (mon) (1)	N	Patients with Event n (%)	KME [95%CI] (mon) (1)	HR [95%CI] P-value (2) (3)	Test for Interaction P-value (4) (5)
MINOR HISTOLOGICAL VARIANTS								0.7336
PRESENCE	60	4 (6.7)	N.A.	61	1 (1.6)	N.A.	0.246 (0.027, 2.201)	
ABSENCE	79	15 (19.0)	N.A.	78	6 (7.7)	N.A.	0.1739 0.364 (0.141, 0.940) 0.0295	

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Adverse Events with CTCAE Grade 3-4-5 Subgroups	Placebo			Nivolumab			Nivolumab vs. Placebo	
	N	Patients with Event n (%)	KME [95%CI] (mon) (1)	N	Patients with Event n (%)	KME [95%CI] (mon) (1)	HR [95%CI] P-value (2) (3)	Test for Interaction P-value (4) (5)
OVERALL	139	15 (10.8)	N.A.	139	3 (2.2)	N.A.	0.190 (0.055, 0.655) 0.0033	0.8211
PRIOR NEO-ADJUVANT CISPLATIN THERAPY								
YES	61	4 (6.6)	N.A.	57	1 (1.8)	N.A.	0.243 (0.027, 2.174) 0.1696	
NO	78	11 (14.1)	N.A.	82	2 (2.4)	N.A.	0.173 (0.038, 0.780) 0.0097	

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SAF

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Adverse Events with CTCAE Grade 3-4-5 Subgroups	Placebo			Nivolumab			Nivolumab vs. Placebo	
	Patients with Event		KME	Patients with Event		KME	HR	Test for
	N	n (%)	[95%CI] (mon) (1)	N	n (%)	[95%CI] (mon) (1)	P-value [95%CI] (2) (3)	Interaction P-value (4) (5)
PRIOR CISPLATIN STATUS								N.M.E.
RECEIVED NEO-ADJUVANT	61	4 (6.6)	N.M.E.	57	1 (1.8)	N.M.E.	N.M.E.	
UNWILLING TO RECEIVE NEO-ADJUVANT	45	2 (4.4)	N.M.E.	50	2 (4.0)	N.M.E.	N.M.E.	
NOT ELIGIBLE TO RECEIVE NEO-ADJUVANT	32	9 (28.1)	N.M.E.	27	0	N.M.E.	N.M.E.	

FEB2025 DBL. Includes events reported between first dose and 100 days after last dose of the study therapy.

MedDRA Version: 27.1; CTC Version 4.0. HR = hazard ratio; KME = Kaplan-Meier estimate; N.M.E. = Not meaningful estimate.

(1) KME of median time to first AE. (2) Unstratified log-rank test.

(3) Unstratified Cox proportional hazard model. HR is Nivolumab over Placebo

(4) Unstratified Cox proportional hazard model with treatment, subgroup and treatment*subgroup interaction is to assess the significance of the interaction between treatment and the subgroup.

(5) A p-value of <0.05 needs to be indicated by 1 asterisk (indicates potential effect modification).

IUC = invasive urothelial carcinoma.

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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

Table 8.2
Subgroup Time-Adjusted Analyses
of Adverse Events with CTCAE Grade ≥ 3
by Significant SOC/PT on Hazard Ratio
SAF

SOC: Neoplasms Benign, Malignant and Unspecified (Incl Cysts and Polyps). PT: Malignant Neoplasm Progression

Adverse Events with CTCAE Grade 3-4-5 Subgroups	Placebo			Nivolumab			Nivolumab vs. Placebo	
	N	Patients with Event n (%)	KME [95%CI] (mon) (1)	N	Patients with Event n (%)	KME [95%CI] (mon) (1)	HR [95%CI] P-value (2) (3)	Test for Interaction P-value (4) (5)
USE OF ANY PRIOR NEO-ADJUVANT SYSTEMIC THERAPY								0.8716
YES	62	4 (6.5)	N.A.	61	1 (1.6)	N.A.	0.232 (0.026, 2.077)	
NO	77	11 (14.3)	N.A.	78	2 (2.6)	N.A.	0.1541 0.180 (0.040, 0.812) 0.0119	

FEB2025 DBL. Includes events reported between first dose and 100 days after last dose of the study therapy.

MedDRA Version: 27.1; CTC Version 4.0. HR = hazard ratio; KME = Kaplan-Meier estimate; N.M.E. = Not meaningful estimate.

(1) KME of median time to first AE. (2) Unstratified log-rank test.

(3) Unstratified Cox proportional hazard model. HR is Nivolumab over Placebo

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Table 8.2
Subgroup Time-Adjusted Analyses
of Adverse Events with CTCAE Grade ≥ 3
by Significant SOC/PT on Hazard Ratio
SAF

SOC: Neoplasms Benign, Malignant and Unspecified (Incl Cysts and Polyps). PT: Malignant Neoplasm Progression

Adverse Events with CTCAE Grade 3-4-5 Subgroups	Placebo			Nivolumab			Nivolumab vs. Placebo	
	N	Patients with Event n (%)	KME [95%CI] (mon) (1)	N	Patients with Event n (%)	KME [95%CI] (mon) (1)	HR [95%CI] P-value (2) (3)	Test for Interaction P-value (4) (5)
PATHOLOGICAL LYMPH NODE STATUS								>0.9999
N+	64	9 (14.1)	N.A.	60	3 (5.0)	N.A.	0.323 (0.087, 1.194)	
N0/X WITH <10 NODES REMOVED	38	2 (5.3)	N.A.	38	0	N.A.	0.0742 N.M.E.	
N0 WITH ≥ 10 NODES REMOVED	37	4 (10.8)	N.A.	41	0	N.A.	0.1801 N.M.E. 0.0273	

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MedDRA Version: 27.1; CTC Version 4.0. HR = hazard ratio; KME = Kaplan-Meier estimate; N.M.E. = Not meaningful estimate.

(1) KME of median time to first AE. (2) Unstratified log-rank test.

(3) Unstratified Cox proportional hazard model. HR is Nivolumab over Placebo

(4) Unstratified Cox proportional hazard model with treatment, subgroup and treatment*subgroup interaction is to assess the significance of the interaction between treatment and the subgroup.

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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

Table 8.2
Subgroup Time-Adjusted Analyses
of Adverse Events with CTCAE Grade ≥ 3
by Significant SOC/PT on Hazard Ratio
SAF

SOC: Neoplasms Benign, Malignant and Unspecified (Incl Cysts and Polyps). PT: Malignant Neoplasm Progression

Adverse Events with CTCAE Grade 3-4-5 Subgroups	Placebo			Nivolumab			Nivolumab vs. Placebo	
	N	Patients with Event n (%)	KME [95%CI] (mon) (1)	N	Patients with Event n (%)	KME [95%CI] (mon) (1)	HR [95%CI] P-value (2) (3)	Test for Interaction P-value (4) (5)
PATHOLOGICAL STATUS								>0.9999
PT0-2	31	0	N.A.	26	1 (3.8)	N.A.	N.M.E. 0.2909	
PT3	80	12 (15.0)	N.A.	86	2 (2.3)	N.A.	0.137 (0.031, 0.614)	
PT4A	27	3 (11.1)	N.A.	23	0	N.A.	0.0023 N.M.E. 0.1228	

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MedDRA Version: 27.1; CTC Version 4.0. HR = hazard ratio; KME = Kaplan-Meier estimate; N.M.E. = Not meaningful estimate.

(1) KME of median time to first AE. (2) Unstratified log-rank test.

(3) Unstratified Cox proportional hazard model. HR is Nivolumab over Placebo

(4) Unstratified Cox proportional hazard model with treatment, subgroup and treatment*subgroup interaction is to assess the significance of the interaction between treatment and the subgroup.

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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

Table 8.2
Subgroup Time-Adjusted Analyses
of Adverse Events with CTCAE Grade ≥ 3
by Significant SOC/PT on Hazard Ratio
SAF

SOC: Neoplasms Benign, Malignant and Unspecified (Incl Cysts and Polyps). PT: Malignant Neoplasm Progression

Adverse Events with CTCAE Grade 3-4-5 Subgroups	Placebo			Nivolumab			Nivolumab vs. Placebo	
	Patients with Event		KME	Patients with Event		KME	HR	Test for
	N	n (%)	[95%CI] (mon) (1)	N	n (%)	[95%CI] (mon) (1)	P-value [95%CI] (2) (3)	Interaction P-value (4) (5)
AGE CATEGORY I								0.7515
< 65	59	3 (5.1)	N.A.	67	1 (1.5)	N.A.	0.286 (0.030, 2.751)	
							0.2478	
≥ 65	80	12 (15.0)	N.A.	72	2 (2.8)	N.A.	0.178 (0.040, 0.795)	
							0.0107	

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MedDRA Version: 27.1; CTC Version 4.0. HR = hazard ratio; KME = Kaplan-Meier estimate; N.M.E. = Not meaningful estimate.

(1) KME of median time to first AE. (2) Unstratified log-rank test.

(3) Unstratified Cox proportional hazard model. HR is Nivolumab over Placebo

(4) Unstratified Cox proportional hazard model with treatment, subgroup and treatment*subgroup interaction is to assess the significance of the interaction between treatment and the subgroup.

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Table 8.2
Subgroup Time-Adjusted Analyses
of Adverse Events with CTCAE Grade ≥ 3
by Significant SOC/PT on Hazard Ratio
SAF

SOC: Neoplasms Benign, Malignant and Unspecified (Incl Cysts and Polyps). PT: Malignant Neoplasm Progression

Adverse Events with CTCAE Grade 3-4-5 Subgroups	Placebo			Nivolumab			Nivolumab vs. Placebo	
	N	Patients with Event n (%)	KME [95%CI] (mon) (1)	N	Patients with Event n (%)	KME [95%CI] (mon) (1)	HR [95%CI] P-value (2) (3)	Test for Interaction P-value (4) (5)
AGE CATEGORY II								0.8233
< 65	59	3 (5.1)	N.A.	67	1 (1.5)	N.A.	0.286 (0.030, 2.751)	
>= 65 AND < 75	59	9 (15.3)	N.A.	49	1 (2.0)	N.A.	0.2478 0.126 (0.016, 0.998)	
>= 75	21	3 (14.3)	N.A.	23	1 (4.3)	N.A.	0.0197 0.330 (0.034, 3.170)	
							0.3120	

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MedDRA Version: 27.1; CTC Version 4.0. HR = hazard ratio; KME = Kaplan-Meier estimate; N.M.E. = Not meaningful estimate.

(1) KME of median time to first AE. (2) Unstratified log-rank test.

(3) Unstratified Cox proportional hazard model. HR is Nivolumab over Placebo

(4) Unstratified Cox proportional hazard model with treatment, subgroup and treatment*subgroup interaction is to assess the significance of the interaction between treatment and the subgroup.

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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

Table 8.2
Subgroup Time-Adjusted Analyses
of Adverse Events with CTCAE Grade ≥ 3
by Significant SOC/PT on Hazard Ratio
SAF

SOC: Neoplasms Benign, Malignant and Unspecified (Incl Cysts and Polyps). PT: Malignant Neoplasm Progression

Adverse Events with CTCAE Grade 3-4-5 Subgroups	Placebo			Nivolumab			Nivolumab vs. Placebo	
	N	Patients with Event n (%)	KME [95%CI] (mon) (1)	N	Patients with Event n (%)	KME [95%CI] (mon) (1)	HR [95%CI] P-value (2) (3)	Test for Interaction P-value (4) (5)
REGION								0.9076
US	23	2 (8.7)	N.A.	17	0	N.A.	N.M.E. 0.2098	
EUROPE	68	9 (13.2)	N.A.	72	1 (1.4)	N.A.	0.093 (0.012, 0.735)	
ASIA	28	0	N.A.	33	1 (3.0)	N.A.	0.0048 N.M.E.	
REST OF WORLD	20	4 (20.0)	N.A. (9.63, N.A.)	17	1 (5.9)	N.A.	0.3276 0.284 (0.032, 2.549)	

FEB2025 DBL. Includes events reported between first dose and 100 days after last dose of the study therapy.

MedDRA Version: 27.1; CTC Version 4.0. HR = hazard ratio; KME = Kaplan-Meier estimate; N.M.E. = Not meaningful estimate.

(1) KME of median time to first AE. (2) Unstratified log-rank test.

(3) Unstratified Cox proportional hazard model. HR is Nivolumab over Placebo

(4) Unstratified Cox proportional hazard model with treatment, subgroup and treatment*subgroup interaction is to assess the significance of the interaction between treatment and the subgroup.

(5) A p-value of <0.05 needs to be indicated by 1 asterisk (indicates potential effect modification).

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Table 8.2
Subgroup Time-Adjusted Analyses
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SAF

SOC: Neoplasms Benign, Malignant and Unspecified (Incl Cysts and Polyps). PT: Malignant Neoplasm Progression

Adverse Events with CTCAE Grade 3-4-5 Subgroups	Placebo			Nivolumab			Nivolumab vs. Placebo	
	N	Patients with Event n (%)	KME [95%CI] (mon) (1)	N	Patients with Event n (%)	KME [95%CI] (mon) (1)	HR [95%CI] P-value (2) (3)	Test for Interaction P-value (4) (5)
GENDER								0.9923
MALE	109	15 (13.8)	N.A.	101	2 (2.0)	N.A.	0.137 (0.031, 0.600)	
FEMALE	30	0	N.A.	38	1 (2.6)	N.A.	0.0020 N.M.E. 0.4070	
RACE								0.9923
WHITE	106	14 (13.2)	N.A.	103	2 (1.9)	N.A.	0.133 (0.030, 0.585)	
ASIAN	28	0	N.A.	33	1 (3.0)	N.A.	0.0017 N.M.E. 0.3276	

FEB2025 DBL. Includes events reported between first dose and 100 days after last dose of the study therapy.

MedDRA Version: 27.1; CTC Version 4.0. HR = hazard ratio; KME = Kaplan-Meier estimate; N.M.E. = Not meaningful estimate.

(1) KME of median time to first AE. (2) Unstratified log-rank test.

(3) Unstratified Cox proportional hazard model. HR is Nivolumab over Placebo

(4) Unstratified Cox proportional hazard model with treatment, subgroup and treatment*subgroup interaction is to assess the significance of the interaction between treatment and the subgroup.

(5) A p-value of <0.05 needs to be indicated by 1 asterisk (indicates potential effect modification).

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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

Table 8.2
Subgroup Time-Adjusted Analyses
of Adverse Events with CTCAE Grade ≥ 3
by Significant SOC/PT on Hazard Ratio
SAF

SOC: Neoplasms Benign, Malignant and Unspecified (Incl Cysts and Polyps). PT: Malignant Neoplasm Progression

Adverse Events with CTCAE Grade 3-4-5 Subgroups	Placebo			Nivolumab			Nivolumab vs. Placebo	
	N	Patients with Event n (%)	KME [95%CI] (mon) (1)	N	Patients with Event n (%)	KME [95%CI] (mon) (1)	HR [95%CI] P-value (2) (3)	Test for Interaction P-value (4) (5)
BASELINE ECOG STATUS								
0	83	8 (9.6)	N.A.	85	3 (3.5)	N.A.	0.369 (0.098, 1.390)	0.9903
1	52	4 (7.7)	N.A.	51	0	N.A.	0.1246 N.M.E. 0.0364	
SMOKING STATUS								
NEVER SMOKED	39	4 (10.3)	N.A.	41	1 (2.4)	N.A.	0.222 (0.025, 1.984)	0.8523
CURRENT/FORMER	99	11 (11.1)	N.A.	96	2 (2.1)	N.A.	0.1394 0.173 (0.038, 0.782) 0.0098	

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MedDRA Version: 27.1; CTC Version 4.0. HR = hazard ratio; KME = Kaplan-Meier estimate; N.M.E. = Not meaningful estimate.

(1) KME of median time to first AE. (2) Unstratified log-rank test.

(3) Unstratified Cox proportional hazard model. HR is Nivolumab over Placebo

(4) Unstratified Cox proportional hazard model with treatment, subgroup and treatment*subgroup interaction is to assess the significance of the interaction between treatment and the subgroup.

(5) A p-value of <0.05 needs to be indicated by 1 asterisk (indicates potential effect modification).

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Table 8.2
Subgroup Time-Adjusted Analyses
of Adverse Events with CTCAE Grade ≥ 3
by Significant SOC/PT on Hazard Ratio
SAF

SOC: Neoplasms Benign, Malignant and Unspecified (Incl Cysts and Polyps). PT: Malignant Neoplasm Progression

Adverse Events with CTCAE Grade 3-4-5 Subgroups	Placebo			Nivolumab			Nivolumab vs. Placebo	
	N	Patients with Event n (%)	KME [95%CI] (mon) (1)	N	Patients with Event n (%)	KME [95%CI] (mon) (1)	HR [95%CI] P-value (2) (3)	Test for Interaction P-value (4) (5)
BASELINE HEMOGLOBIN								0.9994
<10 G/DL	14	0	N.A.	7	0	N.A.	N.M.E.	
>=10 G/DL	125	15 (12.0)	N.A.	132	3 (2.3)	N.A.	N.A. 0.178 (0.051, 0.614) 0.0021	
BASELINE CREATININE CLEARANCE								N.M.E.
<60 ML/MIN	60	8 (13.3)	N.M.E.	54	1 (1.9)	N.M.E.	N.M.E.	
>=60 ML/MIN	79	7 (8.9)	N.M.E.	84	2 (2.4)	N.M.E.	N.M.E.	

FEB2025 DBL. Includes events reported between first dose and 100 days after last dose of the study therapy.

MedDRA Version: 27.1; CTC Version 4.0. HR = hazard ratio; KME = Kaplan-Meier estimate; N.M.E. = Not meaningful estimate.

(1) KME of median time to first AE. (2) Unstratified log-rank test.

(3) Unstratified Cox proportional hazard model. HR is Nivolumab over Placebo

(4) Unstratified Cox proportional hazard model with treatment, subgroup and treatment*subgroup interaction is to assess the significance of the interaction between treatment and the subgroup.

(5) A p-value of <0.05 needs to be indicated by 1 asterisk (indicates potential effect modification).

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Table 8.2
Subgroup Time-Adjusted Analyses
of Adverse Events with CTCAE Grade ≥ 3
by Significant SOC/PT on Hazard Ratio
SAF

SOC: Neoplasms Benign, Malignant and Unspecified (Incl Cysts and Polyps). PT: Malignant Neoplasm Progression

Adverse Events with CTCAE Grade 3-4-5 Subgroups	Placebo			Nivolumab			Nivolumab vs. Placebo	
	N	Patients with Event n (%)	KME [95%CI] (mon) (1)	N	Patients with Event n (%)	KME [95%CI] (mon) (1)	HR [95%CI] P-value (2) (3)	Test for Interaction P-value (4) (5)
TIME FROM IUC SURGERY TO RANDOMIZATION (DAYS)								>0.9999
>30-60	28	1 (3.6)	N.A.	34	0	N.A.	N.M.E. 0.2733	
>60-90	65	9 (13.8)	N.A.	57	3 (5.3)	N.A.	0.351 (0.095, 1.295)	
>90-120	41	4 (9.8)	N.A.	46	0	N.A.	0.1000 N.M.E. 0.0342	

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MedDRA Version: 27.1; CTC Version 4.0. HR = hazard ratio; KME = Kaplan-Meier estimate; N.M.E. = Not meaningful estimate.

(1) KME of median time to first AE. (2) Unstratified log-rank test.

(3) Unstratified Cox proportional hazard model. HR is Nivolumab over Placebo

(4) Unstratified Cox proportional hazard model with treatment, subgroup and treatment*subgroup interaction is to assess the significance of the interaction between treatment and the subgroup.

(5) A p-value of <0.05 needs to be indicated by 1 asterisk (indicates potential effect modification).

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Table 8.2
Subgroup Time-Adjusted Analyses
of Adverse Events with CTCAE Grade >=3
by Significant SOC/PT on Hazard Ratio
SAF

SOC: Neoplasms Benign, Malignant and Unspecified (Incl Cysts and Polyps). PT: Malignant Neoplasm Progression

Adverse Events with CTCAE Grade 3-4-5 Subgroups	Placebo			Nivolumab			Nivolumab vs. Placebo	
	N	Patients with Event n (%)	KME [95%CI] (mon) (1)	N	Patients with Event n (%)	KME [95%CI] (mon) (1)	HR [95%CI] P-value (2) (3)	Test for Interaction P-value (4) (5)
INITIAL TUMOR ORIGIN								
URINARY BLADDER	115	13 (11.3)	N.A.	112	3 (2.7)	N.A.	0.219 (0.062, 0.769)	>0.9999
RENAL PELVIS	13	1 (7.7)	N.A.	19	0	N.A.	0.0093 N.M.E.	
URETER	11	1 (9.1)	N.A. (4.67, N.A.)	8	0	N.A.	0.2340 N.M.E.	
							0.4795	

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MedDRA Version: 27.1; CTC Version 4.0. HR = hazard ratio; KME = Kaplan-Meier estimate; N.M.E. = Not meaningful estimate.
(1) KME of median time to first AE. (2) Unstratified log-rank test.
(3) Unstratified Cox proportional hazard model. HR is Nivolumab over Placebo
(4) Unstratified Cox proportional hazard model with treatment, subgroup and treatment*subgroup interaction is to assess the
significance of the interaction between treatment and the subgroup.
(5) A p-value of <0.05 needs to be indicated by 1 asterisk (indicates potential effect modification).
IUC = invasive urothelial carcinoma.
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Table 8.2
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of Adverse Events with CTCAE Grade ≥ 3
by Significant SOC/PT on Hazard Ratio
SAF

SOC: Neoplasms Benign, Malignant and Unspecified (Incl Cysts and Polyps). PT: Malignant Neoplasm Progression

Adverse Events with CTCAE Grade 3-4-5 Subgroups	Placebo			Nivolumab			Nivolumab vs. Placebo	
	N	Patients with Event n (%)	KME [95%CI] (mon) (1)	N	Patients with Event n (%)	KME [95%CI] (mon) (1)	HR [95%CI] P-value (2) (3)	Test for Interaction P-value (4) (5)
MINOR HISTOLOGICAL VARIANTS								0.9899
PRESENCE	60	4 (6.7)	N.A.	61	0	N.A.	N.M.E. 0.0438	
ABSENCE	79	11 (13.9)	N.A.	78	3 (3.8)	N.A.	0.252 (0.070, 0.906) 0.0225	

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MedDRA Version: 27.1; CTC Version 4.0. HR = hazard ratio; KME = Kaplan-Meier estimate; N.M.E. = Not meaningful estimate.

(1) KME of median time to first AE. (2) Unstratified log-rank test.

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(4) Unstratified Cox proportional hazard model with treatment, subgroup and treatment*subgroup interaction is to assess the significance of the interaction between treatment and the subgroup.

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IUC = invasive urothelial carcinoma.

Program Path: /projects/bms214671/stats/market/ma274_202502/prog/tables

Program Name: rt-ae-tsubsocaehr-ebr45.sas

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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

5.2.2.3 SUE

Table 8.3
Subgroup Time-Adjusted Analyses
of Serious Adverse Events
by Significant SOC/PT on Hazard Ratio
SAF

SOC: Infections and Infestations

Serious Adverse Events Subgroups	Placebo			Nivolumab			Nivolumab vs. Placebo	
	N	Patients with Event n (%)	KME [95%CI] (mon) (1)	N	Patients with Event n (%)	KME [95%CI] (mon) (1)	HR [95%CI] P-value (2) (3)	Test for Interaction P-value (4) (5)
OVERALL	139	28 (20.1)	N.A.	139	14 (10.1)	N.A.	0.465 (0.244, 0.883) 0.0165	
PRIOR NEO-ADJUVANT CISPLATIN THERAPY								0.4725
YES	61	15 (24.6)	N.A. (14.65, N.A.)	57	9 (15.8)	N.A.	0.559 (0.244, 1.280) 0.1632	
NO	78	13 (16.7)	N.A.	82	5 (6.1)	N.A.	0.359 (0.128, 1.007) 0.0419	

FEB2025 DBL. Includes events reported between first dose and 100 days after last dose of the study therapy.

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(1) KME of median time to first AE. (2) Unstratified log-rank test.

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Program Name: rt-ae-tsubsoae-hr-ebr45.sas

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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

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PRIOR CISPLATIN STATUS								0.5654
RECEIVED NEO-ADJUVANT	61	15 (24.6)	N.A. (14.65, N.A.)	57	9 (15.8)	N.A.	0.559 (0.244, 1.280)	
UNWILLING TO RECEIVE NEO-ADJUVANT	45	8 (17.8)	N.A.	50	2 (4.0)	N.A.	0.1632 0.226 (0.048, 1.066)	
NOT ELIGIBLE TO RECEIVE NEO-ADJUVANT	32	5 (15.6)	N.A.	27	2 (7.4)	N.A.	0.0397 0.467 (0.091, 2.408) 0.3513	

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(1) KME of median time to first AE. (2) Unstratified log-rank test.

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	N	Patients with Event n (%)	KME [95%CI] (mon) (1)	N	Patients with Event n (%)	KME [95%CI] (mon) (1)	HR [95%CI] P-value (2) (3)	Test for Interaction P-value (4) (5)
USE OF ANY PRIOR NEO-ADJUVANT SYSTEMIC THERAPY								0.5659
YES	62	15 (24.2)	N.A. (14.65, N.A.)	61	9 (14.8)	N.A.	0.527 (0.230, 1.207)	
NO	77	13 (16.9)	N.A.	78	5 (6.4)	N.A.	0.1237 0.373 (0.133, 1.047) 0.0511	

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(1) KME of median time to first AE. (2) Unstratified log-rank test.

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	N	Patients with Event n (%)	KME [95%CI] (mon) (1)	N	Patients with Event n (%)	KME [95%CI] (mon) (1)	HR [95%CI] P-value (2) (3)	Test for Interaction P-value (4) (5)
PATHOLOGICAL LYMPH NODE STATUS								0.4287
N+	64	14 (21.9)	N.A.	60	6 (10.0)	N.A.	0.429 (0.165, 1.117)	
N0/X WITH <10 NODES REMOVED	38	6 (15.8)	N.A.	38	1 (2.6)	N.A.	0.0742 0.164 (0.020, 1.364)	
N0 WITH >= 10 NODES REMOVED	37	8 (21.6)	N.A. (15.01, N.A.)	41	7 (17.1)	N.A.	0.0558 0.743 (0.269, 2.050) 0.5644	

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	N	Patients with Event n (%)	KME [95%CI] (mon) (1)	N	Patients with Event n (%)	KME [95%CI] (mon) (1)	HR [95%CI] P-value (2) (3)	Test for Interaction P-value (4) (5)
PATHOLOGICAL STATUS								0.6681
PT0-2	31	9 (29.0)	N.A. (11.33, N.A.)	26	3 (11.5)	N.A.	0.361 (0.098, 1.334)	
PT3	80	12 (15.0)	N.A.	86	9 (10.5)	N.A.	0.1107 0.638 (0.269, 1.516)	
PT4A	27	7 (25.9)	N.A. (9.53, N.A.)	23	2 (8.7)	N.A.	0.3047 0.342 (0.071, 1.646)	
							0.1605	

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	N	Patients with Event n (%)	KME [95%CI] (mon) (1)	N	Patients with Event n (%)	KME [95%CI] (mon) (1)	HR [95%CI] P-value (2) (3)	Test for Interaction P-value (4) (5)
AGE CATEGORY I								0.7809
< 65	59	13 (22.0)	N.A.	67	8 (11.9)	N.A.	0.496 (0.205, 1.198)	
							0.1123	
>= 65	80	15 (18.8)	N.A.	72	6 (8.3)	N.A.	0.422 (0.164, 1.088)	
							0.0656	

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	N	Patients with Event n (%)	KME [95%CI] (mon) (1)	N	Patients with Event n (%)	KME [95%CI] (mon) (1)	HR [95%CI] P-value (2) (3)	Test for Interaction P-value (4) (5)
AGE CATEGORY II								0.7334
< 65	59	13 (22.0)	N.A.	67	8 (11.9)	N.A.	0.496 (0.205, 1.198)	
>= 65 AND < 75	59	11 (18.6)	N.A.	49	3 (6.1)	N.A.	0.1123 0.306 (0.085, 1.097)	
>= 75	21	4 (19.0)	N.A.	23	3 (13.0)	N.A.	0.0542 0.681 (0.152, 3.044) 0.6131	

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REGION								0.4897
US	23	5 (21.7)	N.A.	17	1 (5.9)	N.A. (10.68, N.A.)	0.236 (0.028, 2.025)	
EUROPE	68	14 (20.6)	N.A.	72	11 (15.3)	N.A.	0.1519 0.693 (0.315, 1.528)	
ASIA	28	3 (10.7)	N.A.	33	1 (3.0)	N.A.	0.3612 0.298 (0.031, 2.866)	
REST OF WORLD	20	6 (30.0)	N.A. (9.66, N.A.)	17	1 (5.9)	N.A.	0.2653 0.155 (0.018, 1.310)	
							0.0505	

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GENDER								
MALE	109	23 (21.1)	N.A.	101	9 (8.9)	N.A.	0.384 (0.178, 0.832)	0.3660
FEMALE	30	5 (16.7)	N.A.	38	5 (13.2)	N.A.	0.0117 0.760 (0.220, 2.631)	
RACE								
WHITE	106	25 (23.6)	N.A.	103	12 (11.7)	N.A.	0.443 (0.223, 0.883)	0.7115
ASIAN	28	3 (10.7)	N.A.	33	1 (3.0)	N.A.	0.0174 0.298 (0.031, 2.866)	
							0.6643 0.2653	

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BASELINE ECOG STATUS								
0	83	13 (15.7)	N.A.	85	10 (11.8)	N.A.	0.721 (0.316, 1.647)	0.1366
1	52	14 (26.9)	N.A. (15.01, N.A.)	51	4 (7.8)	N.A.	0.4363 0.257 (0.085, 0.782)	
SMOKING STATUS								
NEVER SMOKED	39	5 (12.8)	N.A.	41	3 (7.3)	N.A.	0.552 (0.132, 2.312)	0.8041
CURRENT/FORMER	99	23 (23.2)	N.A.	96	11 (11.5)	N.A.	0.4098 0.448 (0.218, 0.919)	
							0.0245	

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BASELINE HEMOGLOBIN <10 G/DL	14	5 (35.7)	N.A. (3.75, N.A.)	7	3 (42.9)	N.A. (0.53, N.A.)	1.149 (0.272, 4.858)	0.2120
>=10 G/DL	125	23 (18.4)	N.A.	132	11 (8.3)	N.A.	0.8500 0.426 (0.207, 0.873)	
BASELINE CREATININE CLEARANCE <60 ML/MIN	60	15 (25.0)	N.A.	54	5 (9.3)	N.A.	0.350 (0.127, 0.962)	0.4163
>=60 ML/MIN	79	13 (16.5)	N.A.	84	9 (10.7)	N.A.	0.0331 0.607 (0.259, 1.422)	
							0.2461	

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TIME FROM IUC SURGERY TO RANDOMIZATION (DAYS)								0.4311
>30-60	28	2 (7.1)	N.A.	34	3 (8.8)	N.A.	1.267 (0.212, 7.583)	
>60-90	65	15 (23.1)	N.A. (15.01, N.A.)	57	5 (8.8)	N.A.	0.7952 0.323 (0.117, 0.890)	
>90-120	41	10 (24.4)	N.A.	46	6 (13.0)	N.A.	0.0213 0.511 (0.186, 1.407) 0.1864	

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	N	Patients with Event n (%)	KME [95%CI] (mon) (1)	N	Patients with Event n (%)	KME [95%CI] (mon) (1)	HR [95%CI] P-value (2) (3)	Test for Interaction P-value (4) (5)
INITIAL TUMOR ORIGIN								>0.9999
URINARY BLADDER	115	27 (23.5)	N.A.	112	14 (12.5)	N.A.	0.484 (0.254, 0.924)	
RENAL PELVIS	13	1 (7.7)	N.A.	19	0	N.A.	0.0246 N.M.E.	
URETER	11	0	N.A.	8	0	N.A.	0.2267 N.M.E. N.A.	

FEB2025 DBL. Includes events reported between first dose and 100 days after last dose of the study therapy.

MedDRA Version: 27.1; CTC Version 4.0. HR = hazard ratio; KME = Kaplan-Meier estimate; N.M.E. = Not meaningful estimate.

(1) KME of median time to first AE. (2) Unstratified log-rank test.

(3) Unstratified Cox proportional hazard model. HR is Nivolumab over Placebo

(4) Unstratified Cox proportional hazard model with treatment, subgroup and treatment*subgroup interaction is to assess the significance of the interaction between treatment and the subgroup.

(5) A p-value of <0.05 needs to be indicated by 1 asterisk (indicates potential effect modification).

IUC = invasive urothelial carcinoma.

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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

Table 8.3
Subgroup Time-Adjusted Analyses
of Serious Adverse Events
by Significant SOC/PT on Hazard Ratio
SAF

SOC: Infections and Infestations

Serious Adverse Events Subgroups	Placebo			Nivolumab			Nivolumab vs. Placebo	
	N	Patients with Event n (%)	KME [95%CI] (mon) (1)	N	Patients with Event n (%)	KME [95%CI] (mon) (1)	HR [95%CI] P-value (2) (3)	Test for Interaction P-value (4) (5)
MINOR HISTOLOGICAL VARIANTS								0.3089
PRESENCE	60	8 (13.3)	N.A.	61	6 (9.8)	N.A.	0.728 (0.252, 2.098)	
ABSENCE	79	20 (25.3)	N.A. (15.01, N.A.)	78	8 (10.3)	N.A.	0.5547 0.354 (0.156, 0.805) 0.0096	

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MedDRA Version: 27.1; CTC Version 4.0. HR = hazard ratio; KME = Kaplan-Meier estimate; N.M.E. = Not meaningful estimate.
(1) KME of median time to first AE. (2) Unstratified log-rank test.
(3) Unstratified Cox proportional hazard model. HR is Nivolumab over Placebo
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Table 8.3
Subgroup Time-Adjusted Analyses
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by Significant SOC/PT on Hazard Ratio
SAF

SOC: Neoplasms Benign, Malignant and Unspecified (Incl Cysts and Polyps)

Serious Adverse Events Subgroups	Placebo			Nivolumab			Nivolumab vs. Placebo	
	N	Patients with Event n (%)	KME [95%CI] (mon) (1)	N	Patients with Event n (%)	KME [95%CI] (mon) (1)	HR [95%CI] P-value (2) (3)	Test for Interaction P-value (4) (5)
OVERALL	139	20 (14.4)	N.A.	139	9 (6.5)	N.A.	0.425 (0.193, 0.933) 0.0280	
PRIOR NEO-ADJUVANT CISPLATIN THERAPY								0.9490
YES	61	7 (11.5)	N.A.	57	3 (5.3)	N.A.	0.419 (0.108, 1.621) 0.1934	
NO	78	13 (16.7)	N.A.	82	6 (7.3)	N.A.	0.429 (0.163, 1.130) 0.0776	

FEB2025 DBL. Includes events reported between first dose and 100 days after last dose of the study therapy.

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(1) KME of median time to first AE. (2) Unstratified log-rank test.

(3) Unstratified Cox proportional hazard model. HR is Nivolumab over Placebo

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SOC: Neoplasms Benign, Malignant and Unspecified (Incl Cysts and Polyps)

Serious Adverse Events Subgroups	Placebo			Nivolumab			Nivolumab vs. Placebo	
	N	Patients with Event n (%)	KME [95%CI] (mon) (1)	N	Patients with Event n (%)	KME [95%CI] (mon) (1)	HR [95%CI] P-value (2) (3)	Test for Interaction P-value (4) (5)
PRIOR CISPLATIN STATUS								0.2661
RECEIVED NEO-ADJUVANT	61	7 (11.5)	N.A.	57	3 (5.3)	N.A.	0.419 (0.108, 1.621)	
UNWILLING TO RECEIVE NEO-ADJUVANT	45	3 (6.7)	N.A.	50	4 (8.0)	N.A.	0.1934 1.259 (0.282, 5.627)	
NOT ELIGIBLE TO RECEIVE NEO-ADJUVANT	32	10 (31.3)	N.A. (9.20, N.A.)	27	2 (7.4)	N.A.	0.7626 0.206 (0.045, 0.941) 0.0242	

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MedDRA Version: 27.1; CTC Version 4.0. HR = hazard ratio; KME = Kaplan-Meier estimate; N.M.E. = Not meaningful estimate.

(1) KME of median time to first AE. (2) Unstratified log-rank test.

(3) Unstratified Cox proportional hazard model. HR is Nivolumab over Placebo

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SAF

SOC: Neoplasms Benign, Malignant and Unspecified (Incl Cysts and Polyps)

Serious Adverse Events Subgroups	Placebo			Nivolumab			Nivolumab vs. Placebo	
	N	Patients with Event n (%)	KME [95%CI] (mon) (1)	N	Patients with Event n (%)	KME [95%CI] (mon) (1)	HR [95%CI] P-value (2) (3)	Test for Interaction P-value (4) (5)
USE OF ANY PRIOR NEO-ADJUVANT SYSTEMIC THERAPY								0.8639
YES	62	7 (11.3)	N.A.	61	3 (4.9)	N.A.	0.398 (0.103, 1.541)	
NO	77	13 (16.9)	N.A.	78	6 (7.7)	N.A.	0.1672 0.447 (0.170, 1.176) 0.0937	

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MedDRA Version: 27.1; CTC Version 4.0. HR = hazard ratio; KME = Kaplan-Meier estimate; N.M.E. = Not meaningful estimate.

(1) KME of median time to first AE. (2) Unstratified log-rank test.

(3) Unstratified Cox proportional hazard model. HR is Nivolumab over Placebo

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Serious Adverse Events Subgroups	Placebo			Nivolumab			Nivolumab vs. Placebo	
	N	Patients with Event n (%)	KME [95%CI] (mon) (1)	N	Patients with Event n (%)	KME [95%CI] (mon) (1)	HR [95%CI] P-value (2) (3)	Test for Interaction P-value (4) (5)
PATHOLOGICAL LYMPH NODE STATUS								0.9496
N+	64	12 (18.8)	N.A.	60	7 (11.7)	N.A.	0.564 (0.222, 1.436)	
N0/X WITH <10 NODES REMOVED	38	4 (10.5)	N.A.	38	0	N.A.	0.2234 N.M.E.	
N0 WITH >= 10 NODES REMOVED	37	4 (10.8)	N.A.	41	2 (4.9)	N.A.	0.0500 0.414 (0.076, 2.262)	
							0.2932	

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MedDRA Version: 27.1; CTC Version 4.0. HR = hazard ratio; KME = Kaplan-Meier estimate; N.M.E. = Not meaningful estimate.

(1) KME of median time to first AE. (2) Unstratified log-rank test.

(3) Unstratified Cox proportional hazard model. HR is Nivolumab over Placebo

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Serious Adverse Events Subgroups	Placebo			Nivolumab			Nivolumab vs. Placebo	
	N	Patients with Event n (%)	KME [95%CI] (mon) (1)	N	Patients with Event n (%)	KME [95%CI] (mon) (1)	HR [95%CI] P-value (2) (3)	Test for Interaction P-value (4) (5)
PATHOLOGICAL STATUS								0.9269
PT0-2	31	2 (6.5)	N.A.	26	1 (3.8)	N.A.	0.573 (0.052, 6.320)	
PT3	80	14 (17.5)	N.A.	86	7 (8.1)	N.A.	0.6448 0.414 (0.167, 1.027)	
PT4A	27	4 (14.8)	N.A.	23	1 (4.3)	N.A.	0.0494 0.317 (0.035, 2.845)	
							0.2791	

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(1) KME of median time to first AE. (2) Unstratified log-rank test.

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SOC: Neoplasms Benign, Malignant and Unspecified (Incl Cysts and Polyps)

Serious Adverse Events Subgroups	Placebo			Nivolumab			Nivolumab vs. Placebo	
	N	Patients with Event n (%)	KME [95%CI] (mon) (1)	N	Patients with Event n (%)	KME [95%CI] (mon) (1)	HR [95%CI] P-value (2) (3)	Test for Interaction P-value (4) (5)
AGE CATEGORY I								0.8657
< 65	59	5 (8.5)	N.A.	67	3 (4.5)	N.A.	0.520 (0.124, 2.176)	
							0.3622	
>= 65	80	15 (18.8)	N.A.	72	6 (8.3)	N.A.	0.425 (0.165, 1.095)	
							0.0681	

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MedDRA Version: 27.1; CTC Version 4.0. HR = hazard ratio; KME = Kaplan-Meier estimate; N.M.E. = Not meaningful estimate.

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SAF

SOC: Neoplasms Benign, Malignant and Unspecified (Incl Cysts and Polyps)

Serious Adverse Events Subgroups	Placebo			Nivolumab			Nivolumab vs. Placebo	
	N	Patients with Event n (%)	KME [95%CI] (mon) (1)	N	Patients with Event n (%)	KME [95%CI] (mon) (1)	HR [95%CI] P-value (2) (3)	Test for Interaction P-value (4) (5)
AGE CATEGORY II								0.7274
< 65	59	5 (8.5)	N.A.	67	3 (4.5)	N.A.	0.520 (0.124, 2.176)	
>= 65 AND < 75	59	11 (18.6)	N.A.	49	3 (6.1)	N.A.	0.3622 0.307 (0.086, 1.100)	
>= 75	21	4 (19.0)	N.A.	23	3 (13.0)	N.A. (13.80, N.A.)	0.0549 0.704 (0.157, 3.156) 0.6445	

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(1) KME of median time to first AE. (2) Unstratified log-rank test.

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SAF

SOC: Neoplasms Benign, Malignant and Unspecified (Incl Cysts and Polyps)

Serious Adverse Events Subgroups	Placebo			Nivolumab			Nivolumab vs. Placebo	
	N	Patients with Event n (%)	KME [95%CI] (mon) (1)	N	Patients with Event n (%)	KME [95%CI] (mon) (1)	HR [95%CI] P-value (2) (3)	Test for Interaction P-value (4) (5)
REGION								0.2234
US	23	3 (13.0)	N.A.	17	0	N.A.	N.M.E. 0.1195	
EUROPE	68	10 (14.7)	N.A.	72	3 (4.2)	N.A.	0.247 (0.068, 0.898)	
ASIA	28	1 (3.6)	N.A.	33	4 (12.1)	N.A.	0.0215 3.654 (0.408, 32.727)	
REST OF WORLD	20	6 (30.0)	N.A. (8.41, N.A.)	17	2 (11.8)	N.A.	0.2147 0.372 (0.075, 1.851)	
							0.2089	

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SOC: Neoplasms Benign, Malignant and Unspecified (Incl Cysts and Polyps)

Serious Adverse Events Subgroups	Placebo			Nivolumab			Nivolumab vs. Placebo	
	N	Patients with Event n (%)	KME [95%CI] (mon) (1)	N	Patients with Event n (%)	KME [95%CI] (mon) (1)	HR [95%CI] P-value (2) (3)	Test for Interaction P-value (4) (5)
GENDER								
MALE	109	18 (16.5)	N.A.	101	6 (5.9)	N.A.	0.342 (0.136, 0.862)	0.2736
FEMALE	30	2 (6.7)	N.A.	38	3 (7.9)	N.A.	0.0171 1.022 (0.171, 6.121)	
RACE								
WHITE	106	18 (17.0)	N.A.	103	5 (4.9)	N.A.	0.257 (0.096, 0.693)	0.0299*
ASIAN	28	1 (3.6)	N.A.	33	4 (12.1)	N.A.	0.0038 3.654 (0.408, 32.727)	
							0.2147	

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Serious Adverse Events Subgroups	Placebo			Nivolumab			Nivolumab vs. Placebo	
	N	Patients with Event n (%)	KME [95%CI] (mon) (1)	N	Patients with Event n (%)	KME [95%CI] (mon) (1)	HR [95%CI] P-value (2) (3)	Test for Interaction P-value (4) (5)
BASELINE ECOG STATUS								
0	83	10 (12.0)	N.A.	85	8 (9.4)	N.A.	0.777 (0.306, 1.971)	0.1220
1	52	7 (13.5)	N.A.	51	1 (2.0)	N.A.	0.5961 0.131 (0.016, 1.065)	
SMOKING STATUS								
NEVER SMOKED	39	5 (12.8)	N.A.	41	3 (7.3)	N.A.	0.542 (0.129, 2.268)	0.6722
CURRENT/FORMER	99	15 (15.2)	N.A.	96	6 (6.3)	N.A.	0.3941 0.377 (0.146, 0.974)	
							0.0363	

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	N	Patients with Event n (%)	KME [95%CI] (mon) (1)	N	Patients with Event n (%)	KME [95%CI] (mon) (1)	HR [95%CI] P-value (2) (3)	Test for Interaction P-value (4) (5)
BASELINE HEMOGLOBIN								
<10 G/DL	14	0	N.A.	7	0	N.A.	N.M.E. N.A.	0.9997
>=10 G/DL	125	20 (16.0)	N.A.	132	9 (6.8)	N.A.	0.399 (0.182, 0.877) 0.0179	
BASELINE CREATININE CLEARANCE								
<60 ML/MIN	60	9 (15.0)	N.A.	54	5 (9.3)	N.A.	0.589 (0.197, 1.760) 0.3378	0.4488
>=60 ML/MIN	79	11 (13.9)	N.A.	84	4 (4.8)	N.A.	0.326 (0.104, 1.025) 0.0436	

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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

Table 8.3
Subgroup Time-Adjusted Analyses
of Serious Adverse Events
by Significant SOC/PT on Hazard Ratio
SAF

SOC: Neoplasms Benign, Malignant and Unspecified (Incl Cysts and Polyps)

Serious Adverse Events Subgroups	Placebo			Nivolumab			Nivolumab vs. Placebo	
	N	Patients with Event n (%)	KME [95%CI] (mon) (1)	N	Patients with Event n (%)	KME [95%CI] (mon) (1)	HR [95%CI] P-value (2) (3)	Test for Interaction P-value (4) (5)
TIME FROM IUC SURGERY TO RANDOMIZATION (DAYS)								0.1660
>30-60	28	1 (3.6)	N.A.	34	3 (8.8)	N.A.	2.448 (0.255, 23.542)	
>60-90	65	11 (16.9)	N.A.	57	5 (8.8)	N.A.	0.4230 0.466 (0.162, 1.343)	
>90-120	41	7 (17.1)	N.A.	46	1 (2.2)	N.A.	0.1475 0.125 (0.015, 1.019) 0.0210	

FEB2025 DBL. Includes events reported between first dose and 100 days after last dose of the study therapy.

MedDRA Version: 27.1; CTC Version 4.0. HR = hazard ratio; KME = Kaplan-Meier estimate; N.M.E. = Not meaningful estimate.

(1) KME of median time to first AE. (2) Unstratified log-rank test.

(3) Unstratified Cox proportional hazard model. HR is Nivolumab over Placebo

(4) Unstratified Cox proportional hazard model with treatment, subgroup and treatment*subgroup interaction is to assess the significance of the interaction between treatment and the subgroup.

(5) A p-value of <0.05 needs to be indicated by 1 asterisk (indicates potential effect modification).

IUC = invasive urothelial carcinoma.

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INITIAL TUMOR ORIGIN								0.3175
URINARY BLADDER	115	18 (15.7)	N.A.	112	6 (5.4)	N.A.	0.317 (0.126, 0.798)	
RENAL PELVIS	13	1 (7.7)	N.A.	19	2 (10.5)	N.A. (13.80, N.A.)	0.0101 1.493 (0.135, 16.509)	
URETER	11	1 (9.1)	N.A. (4.67, N.A.)	8	1 (12.5)	N.A. (6.21, N.A.)	0.7421 2.121 (0.133, 33.953)	
							0.5864	

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	N	Patients with Event n (%)	KME [95%CI] (mon) (1)	N	Patients with Event n (%)	KME [95%CI] (mon) (1)	HR [95%CI] P-value (2) (3)	Test for Interaction P-value (4) (5)
MINOR HISTOLOGICAL VARIANTS								0.9184
PRESENCE	60	5 (8.3)	N.A.	61	2 (3.3)	N.A.	0.396 (0.077, 2.040)	
ABSENCE	79	15 (19.0)	N.A.	78	7 (9.0)	N.A.	0.2511 0.425 (0.173, 1.045) 0.0546	

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SOC: Neoplasms Benign, Malignant and Unspecified (Incl Cysts and Polyps). PT: Malignant Neoplasm Progression

Serious Adverse Events Subgroups	Placebo			Nivolumab			Nivolumab vs. Placebo	
	N	Patients with Event n (%)	KME [95%CI] (mon) (1)	N	Patients with Event n (%)	KME [95%CI] (mon) (1)	HR [95%CI] P-value (2) (3)	Test for Interaction P-value (4) (5)
OVERALL	139	16 (11.5)	N.A.	139	4 (2.9)	N.A.	0.237 (0.079, 0.710) 0.0051	
PRIOR NEO-ADJUVANT CISPLATIN THERAPY								0.4896
YES	61	5 (8.2)	N.A.	57	2 (3.5)	N.A.	0.391 (0.076, 2.015) 0.2442	
NO	78	11 (14.1)	N.A.	82	2 (2.4)	N.A.	0.173 (0.038, 0.780) 0.0097	

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	N	Patients with Event n (%)	KME [95%CI] (mon) (1)	N	Patients with Event n (%)	KME [95%CI] (mon) (1)	HR [95%CI] P-value (2) (3)	Test for Interaction P-value (4) (5)
PRIOR CISPLATIN STATUS								N.M.E.
RECEIVED NEO-ADJUVANT	61	5 (8.2)	N.M.E.	57	2 (3.5)	N.M.E.	N.M.E.	
UNWILLING TO RECEIVE NEO-ADJUVANT	45	2 (4.4)	N.M.E.	50	2 (4.0)	N.M.E.	N.M.E.	
NOT ELIGIBLE TO RECEIVE NEO-ADJUVANT	32	9 (28.1)	N.M.E.	27	0	N.M.E.	N.M.E.	

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	N	Patients with Event n (%)	KME [95%CI] (mon) (1)	N	Patients with Event n (%)	KME [95%CI] (mon) (1)	HR [95%CI] P-value (2) (3)	Test for Interaction P-value (4) (5)
USE OF ANY PRIOR NEO-ADJUVANT SYSTEMIC THERAPY								0.5391
YES	62	5 (8.1)	N.A.	61	2 (3.3)	N.A.	0.373 (0.072, 1.925)	
NO	77	11 (14.3)	N.A.	78	2 (2.6)	N.A.	0.2203 0.180 (0.040, 0.812) 0.0119	

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	N	Patients with Event n (%)	KME [95%CI] (mon) (1)	N	Patients with Event n (%)	KME [95%CI] (mon) (1)	HR [95%CI] P-value (2) (3)	Test for Interaction P-value (4) (5)
PATHOLOGICAL LYMPH NODE STATUS								>0.9999
N+	64	10 (15.6)	N.A.	60	4 (6.7)	N.A.	0.389 (0.122, 1.243)	
N0/X WITH <10 NODES REMOVED	38	2 (5.3)	N.A.	38	0	N.A.	0.0984 N.M.E.	
N0 WITH >= 10 NODES REMOVED	37	4 (10.8)	N.A.	41	0	N.A.	0.1801 N.M.E. 0.0273	

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	N	Patients with Event n (%)	KME [95%CI] (mon) (1)	N	Patients with Event n (%)	KME [95%CI] (mon) (1)	HR [95%CI] P-value (2) (3)	Test for Interaction P-value (4) (5)
PATHOLOGICAL STATUS								>0.9999
PT0-2	31	0	N.A.	26	1 (3.8)	N.A.	N.M.E. 0.2909	
PT3	80	13 (16.3)	N.A.	86	3 (3.5)	N.A.	0.192 (0.055, 0.674)	
PT4A	27	3 (11.1)	N.A.	23	0	N.A.	0.0040 N.M.E. 0.1228	

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AGE CATEGORY I								
< 65	59	4 (6.8)	N.A.	67	2 (3.0)	N.A.	0.433 (0.079, 2.364)	0.4600
>= 65	80	12 (15.0)	N.A.	72	2 (2.8)	N.A.	0.3197 0.178 (0.040, 0.795) 0.0107	

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AGE CATEGORY II < 65	59	4 (6.8)	N.A.	67	2 (3.0)	N.A.	0.433 (0.079, 2.364)	0.6766
>= 65 AND < 75	59	9 (15.3)	N.A.	49	1 (2.0)	N.A.	0.3197 (0.016, 0.998)	
>= 75	21	3 (14.3)	N.A.	23	1 (4.3)	N.A.	0.126 (0.016, 0.998) 0.0197 0.330 (0.034, 3.170) 0.3120	

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REGION								0.9990
US	23	2 (8.7)	N.A.	17	0	N.A.	N.M.E. 0.2098	
EUROPE	68	9 (13.2)	N.A.	72	2 (2.8)	N.A.	0.186 (0.040, 0.862)	
ASIA	28	0	N.A.	33	1 (3.0)	N.A.	0.0159 N.M.E.	
REST OF WORLD	20	5 (25.0)	N.A.	17	1 (5.9)	N.A.	0.3276 0.228 (0.027, 1.959)	
			(9.63, N.A.)				0.1412	

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GENDER								
MALE	109	15 (13.8)	N.A.	101	2 (2.0)	N.A.	0.137 (0.031, 0.600)	0.1038
FEMALE	30	1 (3.3)	N.A.	38	2 (5.3)	N.A.	0.0020 1.418 (0.128, 15.651) 0.7744	
RACE								
WHITE	106	15 (14.2)	N.A.	103	3 (2.9)	N.A.	0.187 (0.054, 0.645)	0.9918
ASIAN	28	0	N.A.	33	1 (3.0)	N.A.	0.0029 N.M.E. 0.3276	

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	N	Patients with Event n (%)	KME [95%CI] (mon) (1)	N	Patients with Event n (%)	KME [95%CI] (mon) (1)	HR [95%CI] P-value (2) (3)	Test for Interaction P-value (4) (5)
BASELINE ECOG STATUS								
0	83	8 (9.6)	N.A.	85	4 (4.7)	N.A.	0.493 (0.148, 1.636)	0.9892
1	52	5 (9.6)	N.A.	51	0	N.A.	0.2378 N.M.E. 0.0199	
SMOKING STATUS								
NEVER SMOKED	39	4 (10.3)	N.A.	41	1 (2.4)	N.A.	0.222 (0.025, 1.984)	0.9589
CURRENT/FORMER	99	12 (12.1)	N.A.	96	3 (3.1)	N.A.	0.1394 0.240 (0.068, 0.850) 0.0162	

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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

Table 8.3
Subgroup Time-Adjusted Analyses
of Serious Adverse Events
by Significant SOC/PT on Hazard Ratio
SAF

SOC: Neoplasms Benign, Malignant and Unspecified (Incl Cysts and Polyps). PT: Malignant Neoplasm Progression

Serious Adverse Events Subgroups	Placebo			Nivolumab			Nivolumab vs. Placebo	
	N	Patients with Event n (%)	KME [95%CI] (mon) (1)	N	Patients with Event n (%)	KME [95%CI] (mon) (1)	HR [95%CI] P-value (2) (3)	Test for Interaction P-value (4) (5)
BASELINE HEMOGLOBIN								0.9995
<10 G/DL	14	0	N.A.	7	0	N.A.	N.M.E. N.A.	
>=10 G/DL	125	16 (12.8)	N.A.	132	4 (3.0)	N.A.	0.223 (0.075, 0.667) 0.0033	
BASELINE CREATININE CLEARANCE								0.4734
<60 ML/MIN	60	8 (13.3)	N.A.	54	1 (1.9)	N.A.	0.137 (0.017, 1.097) 0.0281	
>=60 ML/MIN	79	8 (10.1)	N.A.	84	3 (3.6)	N.A.	0.337 (0.089, 1.272) 0.0921	

FEB2025 DBL. Includes events reported between first dose and 100 days after last dose of the study therapy.

MedDRA Version: 27.1; CTC Version 4.0. HR = hazard ratio; KME = Kaplan-Meier estimate; N.M.E. = Not meaningful estimate.

(1) KME of median time to first AE. (2) Unstratified log-rank test.

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	N	Patients with Event n (%)	KME [95%CI] (mon) (1)	N	Patients with Event n (%)	KME [95%CI] (mon) (1)	HR [95%CI] P-value (2) (3)	Test for Interaction P-value (4) (5)
TIME FROM IUC SURGERY TO RANDOMIZATION (DAYS)								0.8617
>30-60	28	1 (3.6)	N.A.	34	1 (2.9)	N.A.	0.796 (0.050, 12.733)	
>60-90	65	9 (13.8)	N.A.	57	3 (5.3)	N.A.	0.8715 0.351 (0.095, 1.295)	
>90-120	41	5 (12.2)	N.A.	46	0	N.A.	0.1000 N.M.E. 0.0179	

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	N	Patients with Event n (%)	KME [95%CI] (mon) (1)	N	Patients with Event n (%)	KME [95%CI] (mon) (1)	HR [95%CI] P-value (2) (3)	Test for Interaction P-value (4) (5)
INITIAL TUMOR ORIGIN								>0.9999
URINARY BLADDER	115	14 (12.2)	N.A.	112	4 (3.6)	N.A.	0.272 (0.090, 0.827)	
RENAL PELVIS	13	1 (7.7)	N.A.	19	0	N.A.	0.0139 N.M.E.	
URETER	11	1 (9.1)	N.A. (4.67, N.A.)	8	0	N.A.	0.2340 N.M.E. 0.4795	

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	N	Patients with Event n (%)	KME [95%CI] (mon) (1)	N	Patients with Event n (%)	KME [95%CI] (mon) (1)	HR [95%CI] P-value (2) (3)	Test for Interaction P-value (4) (5)
MINOR HISTOLOGICAL VARIANTS								0.8365
PRESENCE	60	5 (8.3)	N.A.	61	1 (1.6)	N.A.	0.198 (0.023, 1.696)	
ABSENCE	79	11 (13.9)	N.A.	78	3 (3.8)	N.A.	0.1001 0.252 (0.070, 0.906) 0.0225	

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SOC: Respiratory, Thoracic and Mediastinal Disorders

Serious Adverse Events Subgroups	Placebo			Nivolumab			Nivolumab vs. Placebo	
	N	Patients with Event n (%)	KME [95%CI] (mon) (1)	N	Patients with Event n (%)	KME [95%CI] (mon) (1)	HR [95%CI] P-value (2) (3)	Test for Interaction P-value (4) (5)
OVERALL	139	1 (0.7)	N.A.	139	9 (6.5)	N.A.	8.334 (1.055, 65.824) 0.0160	N.M.E.
PRIOR NEO-ADJUVANT CISPLATIN THERAPY								
YES	61	1 (1.6)	N.M.E.	57	1 (1.8)	N.M.E.	N.M.E.	
NO	78	0	N.M.E.	82	8 (9.8)	N.M.E.	N.M.E.	

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PRIOR CISPLATIN STATUS								N.M.E.
RECEIVED NEO-ADJUVANT	61	1 (1.6)	N.M.E.	57	1 (1.8)	N.M.E.	N.M.E.	
UNWILLING TO RECEIVE NEO-ADJUVANT	45	0	N.M.E.	50	4 (8.0)	N.M.E.	N.M.E.	
NOT ELIGIBLE TO RECEIVE NEO-ADJUVANT	32	0	N.M.E.	27	4 (14.8)	N.M.E.	N.M.E.	

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	N	Patients with Event n (%)	KME [95%CI] (mon) (1)	N	Patients with Event n (%)	KME [95%CI] (mon) (1)	HR [95%CI] P-value (2) (3)	Test for Interaction P-value (4) (5)
USE OF ANY PRIOR NEO-ADJUVANT SYSTEMIC THERAPY								N.M.E.
YES	62	1 (1.6)	N.M.E.	61	1 (1.6)	N.M.E.	N.M.E.	
NO	77	0	N.M.E.	78	8 (10.3)	N.M.E.	N.M.E.	

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	N	Patients with Event n (%)	KME [95%CI] (mon) (1)	N	Patients with Event n (%)	KME [95%CI] (mon) (1)	HR [95%CI] P-value (2) (3)	Test for Interaction P-value (4) (5)
PATHOLOGICAL LYMPH NODE STATUS								N.M.E.
N+	64	1 (1.6)	N.M.E.	60	3 (5.0)	N.M.E.	N.M.E.	
N0/X WITH <10 NODES REMOVED	38	0	N.M.E.	38	5 (13.2)	N.M.E.	N.M.E.	
N0 WITH >= 10 NODES REMOVED	37	0	N.M.E.	41	1 (2.4)	N.M.E.	N.M.E.	

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PATHOLOGICAL STATUS								N.M.E.
PT0-2	31	1 (3.2)	N.M.E.	26	1 (3.8)	N.M.E.	N.M.E.	
PT3	80	0	N.M.E.	86	7 (8.1)	N.M.E.	N.M.E.	
PT4A	27	0	N.M.E.	23	1 (4.3)	N.M.E.	N.M.E.	

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AGE CATEGORY I								
< 65	59	1 (1.7)	N.M.E.	67	2 (3.0)	N.M.E.	N.M.E.	N.M.E.
>= 65	80	0	N.M.E.	72	7 (9.7)	N.M.E.	N.M.E.	

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AGE CATEGORY II								N.M.E.
< 65	59	1 (1.7)	N.M.E.	67	2 (3.0)	N.M.E.	N.M.E.	
>= 65 AND < 75	59	0	N.M.E.	49	3 (6.1)	N.M.E.	N.M.E.	
>= 75	21	0	N.M.E.	23	4 (17.4)	N.M.E.	N.M.E.	

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REGION								N.M.E.
US	23	0	N.M.E.	17	1 (5.9)	N.M.E.	N.M.E.	
EUROPE	68	0	N.M.E.	72	4 (5.6)	N.M.E.	N.M.E.	
ASIA	28	0	N.M.E.	33	3 (9.1)	N.M.E.	N.M.E.	
REST OF WORLD	20	1 (5.0)	N.M.E.	17	1 (5.9)	N.M.E.	N.M.E.	

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GENDER								N.M.E.
MALE	109	1 (0.9)	N.M.E.	101	7 (6.9)	N.M.E.	N.M.E.	
FEMALE	30	0	N.M.E.	38	2 (5.3)	N.M.E.	N.M.E.	
RACE								N.M.E.
WHITE	106	1 (0.9)	N.M.E.	103	5 (4.9)	N.M.E.	N.M.E.	
ASIAN	28	0	N.M.E.	33	3 (9.1)	N.M.E.	N.M.E.	

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by Significant SOC/PT on Hazard Ratio
SAF

SOC: Respiratory, Thoracic and Mediastinal Disorders

Serious Adverse Events Subgroups	Placebo			Nivolumab			Nivolumab vs. Placebo	
	N	Patients with Event n (%)	KME [95%CI] (mon) (1)	N	Patients with Event n (%)	KME [95%CI] (mon) (1)	HR [95%CI] P-value (2) (3)	Test for Interaction P-value (4) (5)
BASELINE ECOG STATUS								N.M.E.
0	83	1 (1.2)	N.M.E.	85	6 (7.1)	N.M.E.	N.M.E.	
1	52	0	N.M.E.	51	3 (5.9)	N.M.E.	N.M.E.	
SMOKING STATUS								N.M.E.
NEVER SMOKED	39	1 (2.6)	N.M.E.	41	3 (7.3)	N.M.E.	N.M.E.	
CURRENT/FORMER	99	0	N.M.E.	96	5 (5.2)	N.M.E.	N.M.E.	

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MedDRA Version: 27.1; CTC Version 4.0. HR = hazard ratio; KME = Kaplan-Meier estimate; N.M.E. = Not meaningful estimate.

(1) KME of median time to first AE. (2) Unstratified log-rank test.

(3) Unstratified Cox proportional hazard model. HR is Nivolumab over Placebo

(4) Unstratified Cox proportional hazard model with treatment, subgroup and treatment*subgroup interaction is to assess the significance of the interaction between treatment and the subgroup.

(5) A p-value of <0.05 needs to be indicated by 1 asterisk (indicates potential effect modification).

IUC = invasive urothelial carcinoma.

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Program Name: rt-ae-tsubsocaehr-ebr45.sas

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Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

Table 8.3
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BASELINE HEMOGLOBIN								
<10 G/DL	14	0	N.A.	7	0	N.A.	N.M.E.	0.9995
>=10 G/DL	125	1 (0.8)	N.A.	132	9 (6.8)	N.A.	N.A. 7.851 (0.994, 62.015) 0.0205	
BASELINE CREATININE CLEARANCE								
<60 ML/MIN	60	0	N.M.E.	54	5 (9.3)	N.M.E.	N.M.E.	N.M.E.
>=60 ML/MIN	79	1 (1.3)	N.M.E.	84	4 (4.8)	N.M.E.	N.M.E.	

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TIME FROM IUC SURGERY TO RANDOMIZATION (DAYS)								N.M.E.
>30-60	28	1 (3.6)	N.M.E.	34	3 (8.8)	N.M.E.	N.M.E.	
>60-90	65	0	N.M.E.	57	4 (7.0)	N.M.E.	N.M.E.	
>90-120	41	0	N.M.E.	46	2 (4.3)	N.M.E.	N.M.E.	

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INITIAL TUMOR ORIGIN								N.M.E.
URINARY BLADDER	115	1 (0.9)	N.M.E.	112	5 (4.5)	N.M.E.	N.M.E.	
RENAL PELVIS	13	0	N.M.E.	19	3 (15.8)	N.M.E.	N.M.E.	
URETER	11	0	N.M.E.	8	1 (12.5)	N.M.E.	N.M.E.	

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MINOR HISTOLOGICAL VARIANTS								N.M.E.
PRESENCE	60	0	N.M.E.	61	5 (8.2)	N.M.E.	N.M.E.	
ABSENCE	79	1 (1.3)	N.M.E.	78	4 (5.1)	N.M.E.	N.M.E.	

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