Dossier zur Nutzenbewertung gemäß § 35a SGB V

Pembrolizumab (KEYTRUDA®)

MSD Sharp & Dohme GmbH

Modul 4 A

Anhang 4-G: Weitere Ergebnisse

Behandlung des rezidivierenden oder refraktären klassischen Hodgkin-Lymphoms

Stand: 30.03.2021

Inhaltsverzeichnis

Seite

Tabellenverzeichnis

Abbildungsverzeichnis

Anhang 4-G1: Rücklaufquoten des EORTC QLQ-C30 und EQ-5D VAS der Studie KEYNOTE 204

Im Folgenden werden ergänzend zu Abschnitt 4.3.1.3.1.1.1. bzw. Abschnitt 4.3.1.3.1.2.1 die Rücklaufquoten des EORTC QLQ-C30 und die Rücklaufquoten des EQ-5D VAS dargestellt.

Alle Ergebnisse beziehen sich auf den Datenschnitt vom 16. Januar 2020 der Studie KEYNOTE 204.

Anhang 4-G1.1: Rücklaufquoten des EORTC QLQ-C30

Tabelle 4G-1: Gründe für das Fehlen von Werten im EORTC QLQ-C30 zu **Studienbeginn**

Study:KEYNOTE 204[a]	**Pembrolizumab N[b] = 146 n (%)**	**Brentuximab Vedotin N[b] = 150 n (%)**
Missing by Design[c]	0 (0.0)	0 (0.0)
Discontinued due to adverse event	0 (0.0)	0 (0.0)
Discontinued due to death	0 (0.0)	0 (0.0)
Discontinued due to physician decision	0 (0.0)	0 (0.0)
Discontinued due to progressive disease	0 (0.0)	0 (0.0)
Discontinued due to clinical progression	0 (0.0)	0 (0.0)
Discontinued due to withdrawal by subject	0 (0.0)	0 (0.0)
Discontinued due to other	0 (0.0)	0 (0.0)
Translation not available in subjects language	0 (0.0)	0 (0.0)
Subject died	0 (0.0)	0 (0.0)
No visit scheduled	0 (0.0)	0 (0.0)
Expected to Complete Questionnaires	146 (100.0)	150 (100.0)
Not Complete	12 (8.2)	12 (8.0)
Subject did not complete due to disease under study	0 (0.0)	0 (0.0)
Not completed due to site staff error	4 (2.7)	3 (2.0)
Subject in hospital or hospice	0 (0.0)	0 (0.0)
Subject was physically unable to complete	0 (0.0)	0 (0.0)
Subject lost to follow-up/unable to contact	0 (0.0)	0 (0.0)
Subject did not complete due to side effect of treatment	0 (0.0)	1 (0.7)
Subject refused for other reasons	0 (0.0)	0 (0.0)
Other	3 (2.1)	2 (1.3)
With visit, no record	5 (3.4)	6 (4.0)
Completed	134 (91.8)	138 (92.0)
Compliance (completed per protocol)[d]	134 (91.8)	138 (92.0)

a: Database Cutoff Date: 16JAN2020
b: Number of patients: full analysis set population
c: Includes death, discontinuation, translations not available, and no visit scheduled
d: Compliance is the proportion of subjects who completed the PRO questionnaire among these who are expected to complete at each time point, excluding these missing by design
PRO: Patient Reported Outcome.

Tabelle 4G-2: Gründe für das Fehlen von Werten im EORTC QLQ-C30 zu **Woche 6**

Study:KEYNOTE 204[a]	**Pembrolizumab N[b] = 146 n (%)**	**Brentuximab Vedotin N[b] = 150 n (%)**
Missing by Design[c]	0 (0.0)	1 (0.7)
Discontinued due to adverse event	0 (0.0)	0 (0.0)
Discontinued due to death	0 (0.0)	0 (0.0)
Discontinued due to physician decision	0 (0.0)	0 (0.0)
Discontinued due to progressive disease	0 (0.0)	0 (0.0)
Discontinued due to clinical progression	0 (0.0)	0 (0.0)

Study:KEYNOTE 204[a]	Pembrolizumab N[b] = 146 n (%)	Brentuximab Vedotin N[b] = 150 n (%)
Discontinued due to withdrawal by subject	0 (0.0)	0 (0.0)
Discontinued due to other	0 (0.0)	0 (0.0)
Translation not available in subjects language	0 (0.0)	1 (0.7)
Subject died	0 (0.0)	0 (0.0)
No visit scheduled	0 (0.0)	0 (0.0)
Expected to Complete Questionnaires	146 (100.0)	149 (99.3)
Not Complete	7 (4.8)	11 (7.3)
Subject did not complete due to disease under study	0 (0.0)	2 (1.3)
Not completed due to site staff error	3 (2.1)	2 (1.3)
Subject in hospital or hospice	0 (0.0)	1 (0.7)
Subject was physically unable to complete	0 (0.0)	0 (0.0)
Subject lost to follow-up/unable to contact	0 (0.0)	0 (0.0)
Subject did not complete due to side effect of treatment	0 (0.0)	0 (0.0)
Subject refused for other reasons	0 (0.0)	0 (0.0)
Other	0 (0.0)	3 (2.0)
With visit, no record	4 (2.7)	3 (2.0)
Completed	139 (95.2)	138 (92.0)
Compliance (completed per protocol)[d]	139 (95.2)	138 (92.6)

a: Database Cutoff Date: 16JAN2020
b: Number of patients: full analysis set population
c: Includes death, discontinuation, translations not available, and no visit scheduled
d: Compliance is the proportion of subjects who completed the PRO questionnaire among these who are expected to complete at each time point, excluding these missing by design
PRO: Patient Reported Outcome.

Tabelle 4G-3: Gründe für das Fehlen von Werten im EORTC QLQ-C30 zu **Woche 12**

Study:KEYNOTE 204[a]	Pembrolizumab N[b] = 146 n (%)	Brentuximab Vedotin N[b] = 150 n (%)
Missing by Design[c]	3 (2.1)	8 (5.3)
Discontinued due to adverse event	2 (1.4)	2 (1.3)
Discontinued due to death	0 (0.0)	0 (0.0)
Discontinued due to physician decision	0 (0.0)	0 (0.0)
Discontinued due to progressive disease	1 (0.7)	2 (1.3)
Discontinued due to clinical progression	0 (0.0)	2 (1.3)
Discontinued due to withdrawal by subject	0 (0.0)	1 (0.7)
Discontinued due to other	0 (0.0)	1 (0.7)
Translation not available in subjects language	0 (0.0)	0 (0.0)
Subject died	0 (0.0)	0 (0.0)
No visit scheduled	0 (0.0)	0 (0.0)
Expected to Complete Questionnaires	143 (97.9)	142 (94.7)
Not Complete	11 (7.5)	16 (10.7)
Subject did not complete due to disease under study	0 (0.0)	0 (0.0)
Not completed due to site staff error	3 (2.1)	7 (4.7)
Subject in hospital or hospice	0 (0.0)	0 (0.0)
Subject was physically unable to complete	0 (0.0)	0 (0.0)
Subject lost to follow-up/unable to contact	0 (0.0)	1 (0.7)
Subject did not complete due to side effect of treatment	0 (0.0)	1 (0.7)
Subject refused for other reasons	1 (0.7)	3 (2.0)
Other	4 (2.7)	2 (1.3)
With visit, no record	3 (2.1)	2 (1.3)
Completed	132 (90.4)	126 (84.0)
Compliance (completed per protocol)[d]	132 (92.3)	126 (88.7)

a: Database Cutoff Date: 16JAN2020
b: Number of patients: full analysis set population
c: Includes death, discontinuation, translations not available, and no visit scheduled

Study:KEYNOTE 204[a]	Pembrolizumab N[b] = 146 n (%)	Brentuximab Vedotin N[b] = 150 n (%)
d: Compliance is the proportion of subjects who completed the PRO questionnaire among these who are expected to complete at each time point, excluding these missing by design PRO: Patient Reported Outcome.		

Tabelle 4G-4: Gründe für das Fehlen von Werten im EORTC QLQ-C30 zu **Woche 18**

Study:KEYNOTE 204[a]	Pembrolizumab N[b] = 146 n (%)	Brentuximab Vedotin N[b] = 150 n (%)
Missing by Design[c]	17 (11.6)	39 (26.0)
Discontinued due to adverse event	5 (3.4)	10 (6.7)
Discontinued due to death	0 (0.0)	0 (0.0)
Discontinued due to physician decision	1 (0.7)	1 (0.7)
Discontinued due to progressive disease	4 (2.7)	16 (10.7)
Discontinued due to clinical progression	0 (0.0)	2 (1.3)
Discontinued due to withdrawal by subject	1 (0.7)	1 (0.7)
Discontinued due to other	6 (4.1)	9 (6.0)
Translation not available in subjects language	0 (0.0)	0 (0.0)
Subject died	0 (0.0)	0 (0.0)
No visit scheduled	0 (0.0)	0 (0.0)
Expected to Complete Questionnaires	129 (88.4)	111 (74.0)
Not Complete	14 (9.6)	21 (14.0)
Subject did not complete due to disease under study	0 (0.0)	0 (0.0)
Not completed due to site staff error	5 (3.4)	7 (4.7)
Subject in hospital or hospice	0 (0.0)	1 (0.7)
Subject was physically unable to complete	0 (0.0)	0 (0.0)
Subject lost to follow-up/unable to contact	0 (0.0)	0 (0.0)
Subject did not complete due to side effect of treatment	0 (0.0)	1 (0.7)
Subject refused for other reasons	1 (0.7)	0 (0.0)
Other	2 (1.4)	4 (2.7)
With visit, no record	6 (4.1)	8 (5.3)
Completed	115 (78.8)	90 (60.0)
Compliance (completed per protocol)[d]	115 (89.1)	90 (81.1)
a: Database Cutoff Date: 16JAN2020 b: Number of patients: full analysis set population c: Includes death, discontinuation, translations not available, and no visit scheduled d: Compliance is the proportion of subjects who completed the PRO questionnaire among these who are expected to complete at each time point, excluding these missing by design PRO: Patient Reported Outcome.		

Tabelle 4G-5: Gründe für das Fehlen von Werten im EORTC QLQ-C30 zu **Woche 24**

Study:KEYNOTE 204[a]	Pembrolizumab N[b] = 146 n (%)	Brentuximab Vedotin N[b] = 150 n (%)
Missing by Design[c]	26 (17.8)	65 (43.3)
Discontinued due to adverse event	4 (2.7)	10 (6.7)
Discontinued due to death	0 (0.0)	0 (0.0)
Discontinued due to physician decision	1 (0.7)	4 (2.7)
Discontinued due to progressive disease	11 (7.5)	26 (17.3)
Discontinued due to clinical progression	0 (0.0)	4 (2.7)
Discontinued due to withdrawal by subject	0 (0.0)	1 (0.7)
Discontinued due to other	10 (6.8)	19 (12.7)
Translation not available in subjects language	0 (0.0)	0 (0.0)
Subject died	0 (0.0)	1 (0.7)
No visit scheduled	0 (0.0)	0 (0.0)
Expected to Complete Questionnaires	120 (82.2)	85 (56.7)

Study:KEYNOTE 204[a]	Pembrolizumab N[b] = 146 n (%)	Brentuximab Vedotin N[b] = 150 n (%)
Not Complete	17 (11.6)	17 (11.3)
Subject did not complete due to disease under study	0 (0.0)	2 (1.3)
Not completed due to site staff error	7 (4.8)	7 (4.7)
Subject in hospital or hospice	0 (0.0)	1 (0.7)
Subject was physically unable to complete	0 (0.0)	0 (0.0)
Subject lost to follow-up/unable to contact	0 (0.0)	0 (0.0)
Subject did not complete due to side effect of treatment	0 (0.0)	2 (1.3)
Subject refused for other reasons	1 (0.7)	0 (0.0)
Other	5 (3.4)	4 (2.7)
With visit, no record	4 (2.7)	1 (0.7)
Completed	103 (70.5)	68 (45.3)
Compliance (completed per protocol)[d]	103 (85.8)	68 (80.0)

a: Database Cutoff Date: 16JAN2020
b: Number of patients: full analysis set population
c: Includes death, discontinuation, translations not available, and no visit scheduled
d: Compliance is the proportion of subjects who completed the PRO questionnaire among these who are expected to complete at each time point, excluding these missing by design
PRO: Patient Reported Outcome.

Tabelle 4G-6: Gründe für das Fehlen von Werten im EORTC QLQ-C30 zu **Woche 36**

Study:KEYNOTE 204[a]	Pembrolizumab N[b] = 146 n (%)	Brentuximab Vedotin N[b] = 150 n (%)
Missing by Design[c]	40 (27.4)	92 (61.3)
Discontinued due to adverse event	8 (5.5)	15 (10.0)
Discontinued due to death	0 (0.0)	0 (0.0)
Discontinued due to physician decision	1 (0.7)	4 (2.7)
Discontinued due to progressive disease	20 (13.7)	45 (30.0)
Discontinued due to clinical progression	0 (0.0)	5 (3.3)
Discontinued due to withdrawal by subject	0 (0.0)	2 (1.3)
Discontinued due to other	11 (7.5)	21 (14.0)
Translation not available in subjects language	0 (0.0)	0 (0.0)
Subject died	0 (0.0)	0 (0.0)
No visit scheduled	0 (0.0)	0 (0.0)
Expected to Complete Questionnaires	106 (72.6)	58 (38.7)
Not Complete	15 (10.3)	13 (8.7)
Subject did not complete due to disease under study	1 (0.7)	1 (0.7)
Not completed due to site staff error	5 (3.4)	4 (2.7)
Subject in hospital or hospice	0 (0.0)	1 (0.7)
Subject was physically unable to complete	0 (0.0)	0 (0.0)
Subject lost to follow-up/unable to contact	0 (0.0)	0 (0.0)
Subject did not complete due to side effect of treatment	0 (0.0)	0 (0.0)
Subject refused for other reasons	1 (0.7)	1 (0.7)
Other	3 (2.1)	1 (0.7)
With visit, no record	5 (3.4)	5 (3.3)
Completed	91 (62.3)	45 (30.0)
Compliance (completed per protocol)[d]	91 (85.8)	45 (77.6)

a: Database Cutoff Date: 16JAN2020
b: Number of patients: full analysis set population
c: Includes death, discontinuation, translations not available, and no visit scheduled
d: Compliance is the proportion of subjects who completed the PRO questionnaire among these who are expected to complete at each time point, excluding these missing by design
PRO: Patient Reported Outcome.

Tabelle 4G-7: Gründe für das Fehlen von Werten im EORTC QLQ-C30 zu **Woche 48**

Study:KEYNOTE 204[a]	**Pembrolizumab N[b] = 146 n (%)**	**Brentuximab Vedotin N[b] = 150 n (%)**
Missing by Design[c]	61 (41.8)	115 (76.7)
Discontinued due to adverse event	12 (8.2)	24 (16.0)
Discontinued due to death	0 (0.0)	0 (0.0)
Discontinued due to physician decision	2 (1.4)	4 (2.7)
Discontinued due to progressive disease	27 (18.5)	58 (38.7)
Discontinued due to clinical progression	1 (0.7)	5 (3.3)
Discontinued due to withdrawal by subject	0 (0.0)	2 (1.3)
Discontinued due to other	19 (13.0)	22 (14.7)
Translation not available in subjects language	0 (0.0)	0 (0.0)
Subject died	0 (0.0)	0 (0.0)
No visit scheduled	0 (0.0)	0 (0.0)
Expected to Complete Questionnaires	85 (58.2)	35 (23.3)
Not Complete	11 (7.5)	8 (5.3)
Subject did not complete due to disease under study	0 (0.0)	0 (0.0)
Not completed due to site staff error	6 (4.1)	3 (2.0)
Subject in hospital or hospice	1 (0.7)	0 (0.0)
Subject was physically unable to complete	0 (0.0)	0 (0.0)
Subject lost to follow-up/unable to contact	0 (0.0)	1 (0.7)
Subject did not complete due to side effect of treatment	0 (0.0)	0 (0.0)
Subject refused for other reasons	0 (0.0)	0 (0.0)
Other	2 (1.4)	1 (0.7)
With visit, no record	2 (1.4)	3 (2.0)
Completed	74 (50.7)	27 (18.0)
Compliance (completed per protocol)[d]	74 (87.1)	27 (77.1)

a: Database Cutoff Date: 16JAN2020
b: Number of patients: full analysis set population
c: Includes death, discontinuation, translations not available, and no visit scheduled
d: Compliance is the proportion of subjects who completed the PRO questionnaire among these who are expected to complete at each time point, excluding these missing by design
PRO: Patient Reported Outcome.

Anhang 4-G1.2: Rücklaufquoten des EQ-5D VAS

Tabelle 4G-8: Gründe für das Fehlen von Werten in der EQ-5D VAS zu **Studienbeginn**

Study:KEYNOTE 204[a]	**Pembrolizumab N[b] = 146 n (%)**	**Brentuximab Vedotin N[b] = 150 n (%)**
Missing by Design[c]	0 (0.0)	0 (0.0)
Discontinued due to adverse event	0 (0.0)	0 (0.0)
Discontinued due to death	0 (0.0)	0 (0.0)
Discontinued due to physician decision	0 (0.0)	0 (0.0)
Discontinued due to progressive disease	0 (0.0)	0 (0.0)
Discontinued due to clinical progression	0 (0.0)	0 (0.0)
Discontinued due to withdrawal by subject	0 (0.0)	0 (0.0)
Discontinued due to other	0 (0.0)	0 (0.0)
Translation not available in subjects language	0 (0.0)	0 (0.0)
Subject died	0 (0.0)	0 (0.0)
No visit scheduled	0 (0.0)	0 (0.0)
Expected to Complete Questionnaires	146 (100.0)	150 (100.0)
Not Complete	11 (7.5)	10 (6.7)
Subject did not complete due to disease under study	0 (0.0)	0 (0.0)
Not completed due to site staff error	4 (2.7)	2 (1.3)
Subject in hospital or hospice	0 (0.0)	0 (0.0)
Subject was physically unable to complete	0 (0.0)	0 (0.0)
Subject lost to follow-up/unable to contact	0 (0.0)	0 (0.0)
Subject did not complete due to side effect of treatment	0 (0.0)	0 (0.0)
Subject refused for other reasons	0 (0.0)	0 (0.0)
Other	2 (1.4)	1 (0.7)
With visit, no record	5 (3.4)	7 (4.7)
Completed	135 (92.5)	140 (93.3)
Compliance (completed per protocol)[d]	135 (92.5)	140 (93.3)

a: Database Cutoff Date: 16JAN2020
b: Number of patients: full analysis set population
c: Includes death, discontinuation, translations not available, and no visit scheduled
d: Compliance is the proportion of subjects who completed the PRO questionnaire among these who are expected to complete at each time point, excluding these missing by design
PRO: Patient Reported Outcome.

Tabelle 4G-9: Gründe für das Fehlen von Werten im EQ-5D VAS zu **Woche 6**

Study:KEYNOTE204[a]	**Pembrolizumab N[b] = 146 n (%)**	**Brentuximab Vedotin N[b] = 150 n (%)**
Missing by Design[c]	0 (0.0)	1 (0.7)
Discontinued due to adverse event	0 (0.0)	0 (0.0)
Discontinued due to death	0 (0.0)	0 (0.0)
Discontinued due to physician decision	0 (0.0)	0 (0.0)
Discontinued due to progressive disease	0 (0.0)	0 (0.0)
Discontinued due to clinical progression	0 (0.0)	0 (0.0)
Discontinued due to withdrawal by subject	0 (0.0)	0 (0.0)
Discontinued due to other	0 (0.0)	0 (0.0)
Translation not available in subjects language	0 (0.0)	1 (0.7)
Subject died	0 (0.0)	0 (0.0)
No visit scheduled	0 (0.0)	0 (0.0)
Expected to Complete Questionnaires	146 (100.0)	149 (99.3)
Not Complete	7 (4.8)	11 (7.3)
Subject did not complete due to disease under study	0 (0.0)	2 (1.3)
Not completed due to site staff error	3 (2.1)	2 (1.3)
Subject in hospital or hospice	0 (0.0)	1 (0.7)
Subject was physically unable to complete	0 (0.0)	0 (0.0)

Study:KEYNOTE204[a]	Pembrolizumab N[b] = 146 n (%)	Brentuximab Vedotin N[b] = 150 n (%)
Subject lost to follow-up/unable to contact	0 (0.0)	0 (0.0)
Subject did not complete due to side effect of treatment	0 (0.0)	0 (0.0)
Subject refused for other reasons	0 (0.0)	0 (0.0)
Other	0 (0.0)	3 (2.0)
With visit, no record	4 (2.7)	3 (2.0)
Completed	139 (95.2)	138 (92.0)
Compliance (completed per protocol)[d]	139 (95.2)	138 (92.6)

a: Database Cutoff Date: 16JAN2020
b: Number of patients: full analysis set population
c: Includes death, discontinuation, translations not available, and no visit scheduled
d: Compliance is the proportion of subjects who completed the PRO questionnaire among these who are expected to complete at each time point, excluding these missing by design
PRO: Patient Reported Outcome.

Tabelle 4G-10: Gründe für das Fehlen von Werten im EQ-5D VAS zu **Woche 12**

Study:KEYNOTE 204[a]	Pembrolizumab N[b] = 146 n (%)	Brentuximab Vedotin N[b] = 150 n (%)
Missing by Design[c]	3 (2.1)	8 (5.3)
Discontinued due to adverse event	2 (1.4)	2 (1.3)
Discontinued due to death	0 (0.0)	0 (0.0)
Discontinued due to physician decision	0 (0.0)	0 (0.0)
Discontinued due to progressive disease	1 (0.7)	2 (1.3)
Discontinued due to clinical progression	0 (0.0)	2 (1.3)
Discontinued due to withdrawal by subject	0 (0.0)	1 (0.7)
Discontinued due to other	0 (0.0)	1 (0.7)
Translation not available in subjects language	0 (0.0)	0 (0.0)
Subject died	0 (0.0)	0 (0.0)
No visit scheduled	0 (0.0)	0 (0.0)
Expected to Complete Questionnaires	143 (97.9)	142 (94.7)
Not Complete	10 (6.8)	16 (10.7)
Subject did not complete due to disease under study	0 (0.0)	0 (0.0)
Not completed due to site staff error	3 (2.1)	7 (4.7)
Subject in hospital or hospice	0 (0.0)	0 (0.0)
Subject was physically unable to complete	0 (0.0)	0 (0.0)
Subject lost to follow-up/unable to contact	0 (0.0)	1 (0.7)
Subject did not complete due to side effect of treatment	0 (0.0)	1 (0.7)
Subject refused for other reasons	1 (0.7)	3 (2.0)
Other	3 (2.1)	3 (2.0)
With visit, no record	3 (2.1)	1 (0.7)
Completed	133 (91.1)	126 (84.0)
Compliance (completed per protocol)[d]	133 (93.0)	126 (88.7)

a: Database Cutoff Date: 16JAN2020
b: Number of patients: full analysis set population
c: Includes death, discontinuation, translations not available, and no visit scheduled
d: Compliance is the proportion of subjects who completed the PRO questionnaire among these who are expected to complete at each time point, excluding these missing by design
PRO: Patient Reported Outcome.

Tabelle 4G-11: Gründe für das Fehlen von Werten im EQ-5D VAS zu **Woche 18**

Study:KEYNOTE 204[a]	Pembrolizumab N[b] = 146 n (%)	Brentuximab Vedotin N[b] = 150 n (%)
Missing by Design[c]	17 (11.6)	39 (26.0)

Study:KEYNOTE 204[a]	Pembrolizumab N[b] = 146 n (%)	Brentuximab Vedotin N[b] = 150 n (%)
Discontinued due to adverse event	5 (3.4)	10 (6.7)
Discontinued due to death	0 (0.0)	0 (0.0)
Discontinued due to physician decision	1 (0.7)	1 (0.7)
Discontinued due to progressive disease	4 (2.7)	16 (10.7)
Discontinued due to clinical progression	0 (0.0)	2 (1.3)
Discontinued due to withdrawal by subject	1 (0.7)	1 (0.7)
Discontinued due to other	6 (4.1)	9 (6.0)
Translation not available in subjects language	0 (0.0)	0 (0.0)
Subject died	0 (0.0)	0 (0.0)
No visit scheduled	0 (0.0)	0 (0.0)
Expected to Complete Questionnaires	129 (88.4)	111 (74.0)
Not Complete	14 (9.6)	21 (14.0)
Subject did not complete due to disease under study	0 (0.0)	0 (0.0)
Not completed due to site staff error	5 (3.4)	7 (4.7)
Subject in hospital or hospice	0 (0.0)	1 (0.7)
Subject was physically unable to complete	0 (0.0)	0 (0.0)
Subject lost to follow-up/unable to contact	0 (0.0)	0 (0.0)
Subject did not complete due to side effect of treatment	0 (0.0)	1 (0.7)
Subject refused for other reasons	1 (0.7)	0 (0.0)
Other	2 (1.4)	4 (2.7)
With visit, no record	6 (4.1)	8 (5.3)
Completed	115 (78.8)	90 (60.0)
Compliance (completed per protocol)[d]	115 (89.1)	90 (81.1)

a: Database Cutoff Date: 16JAN2020
b: Number of patients: full analysis set population
c: Includes death, discontinuation, translations not available, and no visit scheduled
d: Compliance is the proportion of subjects who completed the PRO questionnaire among these who are expected to complete at each time point, excluding these missing by design
PRO: Patient Reported Outcome.

Tabelle 4G-12: Gründe für das Fehlen von Werten im EQ-5D VAS zu **Woche 24**

Study:KEYNOTE 204[a]	Pembrolizumab N[b] = 146 n (%)	Brentuximab Vedotin N[b] = 150 n (%)
Missing by Design[c]	26 (17.8)	65 (43.3)
Discontinued due to adverse event	4 (2.7)	10 (6.7)
Discontinued due to death	0 (0.0)	0 (0.0)
Discontinued due to physician decision	1 (0.7)	4 (2.7)
Discontinued due to progressive disease	11 (7.5)	26 (17.3)
Discontinued due to clinical progression	0 (0.0)	4 (2.7)
Discontinued due to withdrawal by subject	0 (0.0)	1 (0.7)
Discontinued due to other	10 (6.8)	19 (12.7)
Translation not available in subjects language	0 (0.0)	0 (0.0)
Subject died	0 (0.0)	1 (0.7)
No visit scheduled	0 (0.0)	0 (0.0)
Expected to Complete Questionnaires	120 (82.2)	85 (56.7)
Not Complete	17 (11.6)	16 (10.7)
Subject did not complete due to disease under study	0 (0.0)	2 (1.3)
Not completed due to site staff error	7 (4.8)	6 (4.0)
Subject in hospital or hospice	0 (0.0)	1 (0.7)
Subject was physically unable to complete	0 (0.0)	0 (0.0)
Subject lost to follow-up/unable to contact	0 (0.0)	0 (0.0)
Subject did not complete due to side effect of treatment	0 (0.0)	2 (1.3)
Subject refused for other reasons	1 (0.7)	0 (0.0)
Other	5 (3.4)	4 (2.7)
With visit, no record	4 (2.7)	1 (0.7)

Study:KEYNOTE 204[a]	Pembrolizumab N[b] = 146 n (%)	Brentuximab Vedotin N[b] = 150 n (%)
Completed	103 (70.5)	69 (46.0)
Compliance (completed per protocol)[d]	103 (85.8)	69 (81.2)

a: Database Cutoff Date: 16JAN2020
b: Number of patients: full analysis set population
c: Includes death, discontinuation, translations not available, and no visit scheduled
d: Compliance is the proportion of subjects who completed the PRO questionnaire among these who are expected to complete at each time point, excluding these missing by design
PRO: Patient Reported Outcome.

Tabelle 4G-13: Gründe für das Fehlen von Werten im EQ-5D VAS zu **Woche 36**

Study:KEYNOTE 204[a]	Pembrolizumab N[b] = 146 n (%)	Brentuximab Vedotin N[b] = 150 n (%)
Missing by Design[c]	40 (27.4)	92 (61.3)
Discontinued due to adverse event	8 (5.5)	15 (10.0)
Discontinued due to death	0 (0.0)	0 (0.0)
Discontinued due to physician decision	1 (0.7)	4 (2.7)
Discontinued due to progressive disease	20 (13.7)	45 (30.0)
Discontinued due to clinical progression	0 (0.0)	5 (3.3)
Discontinued due to withdrawal by subject	0 (0.0)	2 (1.3)
Discontinued due to other	11 (7.5)	21 (14.0)
Translation not available in subjects language	0 (0.0)	0 (0.0)
Subject died	0 (0.0)	0 (0.0)
No visit scheduled	0 (0.0)	0 (0.0)
Expected to Complete Questionnaires	106 (72.6)	58 (38.7)
Not Complete	15 (10.3)	13 (8.7)
Subject did not complete due to disease under study	1 (0.7)	1 (0.7)
Not completed due to site staff error	5 (3.4)	4 (2.7)
Subject in hospital or hospice	0 (0.0)	1 (0.7)
Subject was physically unable to complete	0 (0.0)	0 (0.0)
Subject lost to follow-up/unable to contact	0 (0.0)	0 (0.0)
Subject did not complete due to side effect of treatment	0 (0.0)	0 (0.0)
Subject refused for other reasons	1 (0.7)	1 (0.7)
Other	3 (2.1)	1 (0.7)
With visit, no record	5 (3.4)	5 (3.3)
Completed	91 (62.3)	45 (30.0)
Compliance (completed per protocol)[d]	91 (85.8)	45 (77.6)

a: Database Cutoff Date: 16JAN2020
b: Number of patients: full analysis set population
c: Includes death, discontinuation, translations not available, and no visit scheduled
d: Compliance is the proportion of subjects who completed the PRO questionnaire among these who are expected to complete at each time point, excluding these missing by design
PRO: Patient Reported Outcome.

Tabelle 4G-14: Gründe für das Fehlen von Werten im EQ-5D VAS zu **Woche 48**

Study:KEYNOTE 204[a]	Pembrolizumab N[b] = 146 n (%)	Brentuximab Vedotin N[b] = 150 n (%)
Missing by Design[c]	61 (41.8)	115 (76.7)
Discontinued due to adverse event	12 (8.2)	24 (16.0)
Discontinued due to death	0 (0.0)	0 (0.0)
Discontinued due to physician decision	2 (1.4)	4 (2.7)
Discontinued due to progressive disease	27 (18.5)	58 (38.7)
Discontinued due to clinical progression	1 (0.7)	5 (3.3)

Study:KEYNOTE 204[a]	**Pembrolizumab N[b] = 146 n (%)**	**Brentuximab Vedotin N[b] = 150 n (%)**
Discontinued due to withdrawal by subject	0 (0.0)	2 (1.3)
Discontinued due to other	19 (13.0)	22 (14.7)
Translation not available in subjects language	0 (0.0)	0 (0.0)
Subject died	0 (0.0)	0 (0.0)
No visit scheduled	0 (0.0)	0 (0.0)
Expected to Complete Questionnaires	85 (58.2)	35 (23.3)
Not Complete	10 (6.8)	8 (5.3)
Subject did not complete due to disease under study	0 (0.0)	0 (0.0)
Not completed due to site staff error	5 (3.4)	3 (2.0)
Subject in hospital or hospice	1 (0.7)	0 (0.0)
Subject was physically unable to complete	0 (0.0)	0 (0.0)
Subject lost to follow-up/unable to contact	0 (0.0)	1 (0.7)
Subject did not complete due to side effect of treatment	0 (0.0)	0 (0.0)
Subject refused for other reasons	0 (0.0)	0 (0.0)
Other	2 (1.4)	1 (0.7)
With visit, no record	2 (1.4)	3 (2.0)
Completed	75 (51.4)	27 (18.0)
Compliance (completed per protocol)[d]	75 (88.2)	27 (77.1)

a: Database Cutoff Date: 16JAN2020

b: Number of patients: full analysis set population

c: Includes death, discontinuation, translations not available, and no visit scheduled

d: Compliance is the proportion of subjects who completed the PRO questionnaire among these who are expected to complete at each time point, excluding these missing by design

PRO: Patient Reported Outcome.

Anhang 4-G2: Ergänzende Analysen zur Studie KEYNOTE 204

Im Folgenden werden in Ergänzung zu Abschnitt 4.3.1.3.1 ergänzende Analysen zur Studie KEYNOTE 204 dargestellt.

Alle Ergebnisse beziehen sich auf den Datenschnitt vom 16. Januar 2020 der Studie KEYNOTE 204.

Anhang 4-G2.1: Ergänzende Analysen zum Endpunkt Objektive Ansprechrate und Komplette Remission

Tabelle 4G-15: Ergebnisse für den Endpunkt Objektive Ansprechrate (Lugano-Kriterien) aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE 204[a]	Pembrolizumab		Brentuximab Vedotin		Pembrolizumab vs. Brentuximab Vedotin		
	N[b]	Patients with Event n (%)	N[b]	Patients with Event n (%)	Risk Ratio/ Peto-Odds Ratio[c] [95 %-CI]	p-Value[d]	Adjusted Difference[e] [95 %-CI]
Objective Response [f]	151	110 (72.8)	153	103 (67.3)	1.08 [0.93; 1.25]	0.293	5.53 [-4.73; 15.75]

a: Database Cutoff Date: 16JAN2020

b: Number of patients: intention-to-treat population

c: Peto-Odds Ratio instead of Mantel-Haenszel Relative Risk if incidence is ≤ 1% or ≥ 99 % in at least one cell, stratified by prior auto-SCT (yes versus no) and HL status after frontline therapy (primary refractory versus relapsed less than 12 months after completion of frontline therapy versus relapse 12 months or more after completion of frontline therapy)

d: Two-sided p-value based on Wald test

e: Miettinen and Nurminen method stratified by prior auto-SCT (yes versus no) and HL status after frontline therapy (primary refractory versus relapsed less than 12 months after completion of frontline therapy versus relapse 12 months or more after completion of frontline therapy)

f: Responses are based on BICR assessments per Lugano Criterion and excludes data after auto-SCT or allo-SCT

allo-SCT: allogeneic Stem Cell Transplantation; auto-SCT: autologous Stem Cell Transplantation; BICR: Blinded Independent Central Review; CI: Confidence Interval; HL: Hodgkin Lymphoma

Tabelle 4G-16: Ergebnisse für den Endpunkt Komplette Remission (Lugano-Kriterien) aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE 204[a]	Pembrolizumab		Brentuximab Vedotin		Pembrolizumab vs. Brentuximab Vedotin		
	N[b]	Patients with Event n (%)	N[b]	Patients with Event n (%)	Risk Ratio/ Peto-Odds Ratio[c] [95 %-CI]	p-Value[d]	Adjusted Difference[e] [95 %-CI]
Complete Remission [f]	151	42 (27.8)	153	47 (30.7)	0.90 [0.64; 1.28]	0.570	-2.98 [-13.25; 7.32]

a: Database Cutoff Date: 16JAN2020

b: Number of patients: intention-to-treat population

c: Peto-Odds Ratio instead of Mantel-Haenszel Relative Risk if incidence is ≤ 1% or ≥ 99% in at least one cell, stratified by prior auto-SCT status and HL status after frontline therapy

d: Two-sided p-value based on Wald test

e: Miettinen and Nurminen method stratified by prior auto-SCT (yes, no) and HL status after frontline therapy (primary refractory versus relapsed less than 12 months after completion of frontline therapy versus relapse 12 months or more after completion of frontline therapy)

f: Complete remission includes patients who achieved complete response. Responses are based on BICR assessments per Lugano Criteria and excludes data after auto-SCT or allo-SCT

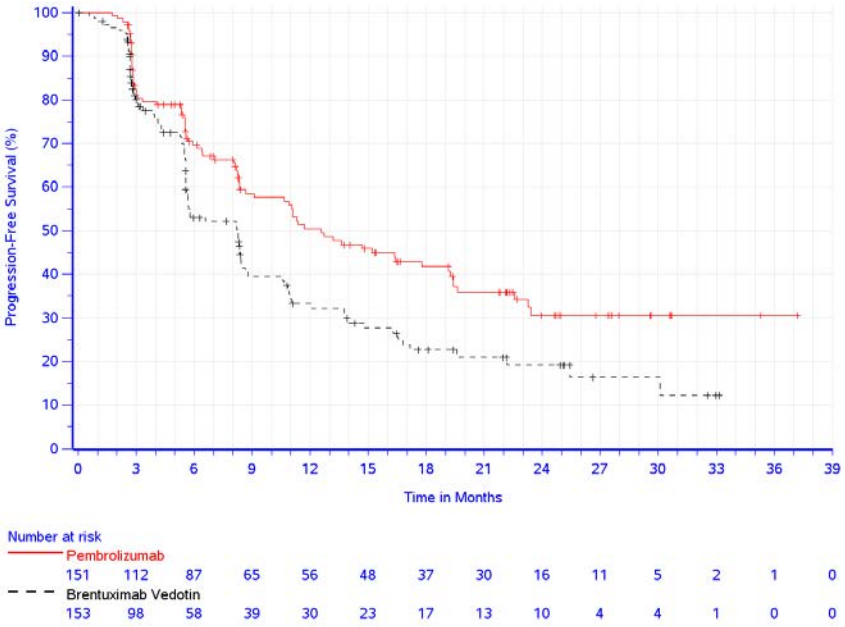
allo-SCT: allogeneic Stem Cell Transplantation; auto-SCT: autologous Stem Cell Transplantation;
BICR: Blinded Independent Central Review; CI: Confidence Interval; HL: Hodgkin Lymphoma

Anhang 4-G2.2: Ergänzende Analysen zum Endpunkt Ergänzende Morbiditätsendpunkte

Tabelle 4G-17: Ergebnisse für den Endpunkt Progressionsfreies Überleben (sekundäre Analyse) aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE 204[a]	Pembrolizumab			Brentuximab Vedotin			Pembrolizumab vs. Brentuximab Vedotin	
	N[b]	Patients with Event[c] n (%)	Median Time[d] in Months [95 %-CI]	N[b]	Patients with Event[c] n (%)	Median Time[d] in Months [95 %-CI]	Hazard Ratio[e] [95 %-CI]	p-Value[e,f]
Progression-Free Survival (BICR, Secondary Analysis[f])	151	81 (53.6)	12.6 [8.7; 19.2]	153	92 (60.1)	8.2 [5.6; 8.6]	0.62 [0.46; 0.85]	0.002

a: Database Cutoff Date: 16JAN2020
b: Number of patients: intention-to-treat population
c: From product-limit (Kaplan-Meier) method
d: Based on stratified Cox regression model with treatment as a covariate stratified by prior auto-SCT status (yes versus no) and HL status after frontline therapy (primary refractory versus relapsed less than 12 months after completion of frontline therapy versus relapse 12 months or more after completion of frontline therapy)
e: Two-sided p-value (Wald test)
f: The secondary Progression-Free Survival analysis is based on BICR assessments per IWG Criterion and excludes clinical and imaging data following auto-SCT or allo-SCT
allo-SCT: allogeneic Stem Cell Transplantation; auto-SCT: autologous Stem Cell Transplantation;
BICR: Blinded Independent Central Review; CI: Confidence Interval; HL: Hodgkin Lymphoma;
IWG: International Working Group



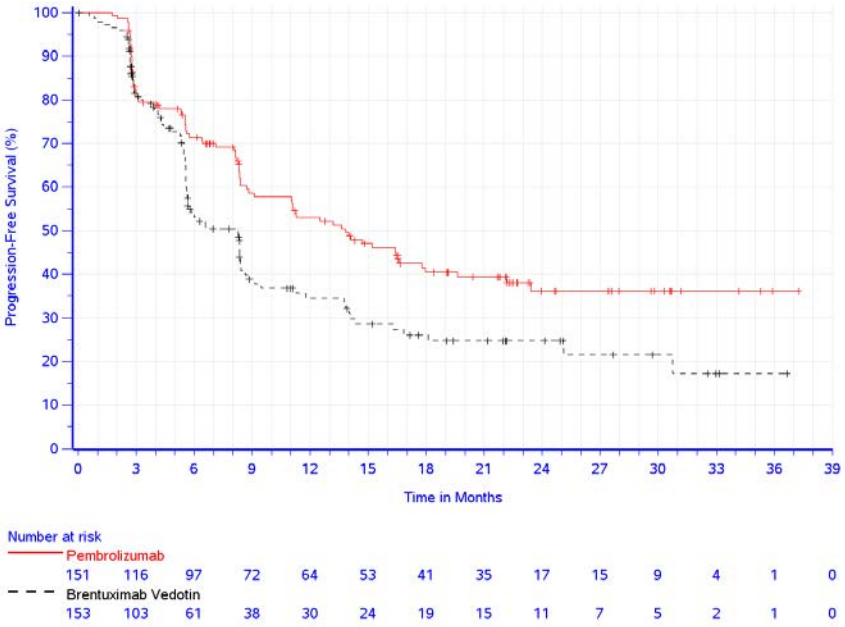
Database Cutoff Date: 16JAN2020

Abbildung 4G-1: Kaplan-Meier-Kurve für den Endpunkt Progressionsfreies Überleben (sekundäre Analyse) der Studie KEYNOTE 204

Tabelle 4G-18: Ergebnisse für den Endpunkt Progressionsfreies Überleben (Lugano-Kriterien) aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE 204[a]	Pembrolizumab			Brentuximab Vedotin			Pembrolizumab vs. Brentuximab Vedotin	
	N[b]	Patients with Event n (%)	Median Time[c] in Months [95 %-CI]	N[b]	Patients with Event n (%)	Median Time[c] in Months [95 %-CI]	Hazard Ratio[d] [95 %-CI]	p-Value[d,e]
Progression-Free Survival (BICR Primary Analysis[f]) (Lugano)	151	81 (53.6)	13.8 [8.8; 17.9]	153	89 (58.2)	8.3 [5.7; 8.4]	0.61 [0.45; 0.83]	0.002

a: Database Cutoff Date: 16JAN2020
b: Number of patients: intention-to-treat population
c: From product-limit (Kaplan-Meier) method
d: Based on stratified Cox regression model with treatment as a covariate stratified by prior auto-SCT (yes versus no) and HL status after frontline therapy (primary refractory versus relapsed less than 12 months after completion of frontline therapy versus relapse 12 months or more after completion of frontline therapy)
e: Two-sided p-value (Wald test)
f: The primary Progression-Free Survival analysis is based on BICR assessments per Lugano Criteria and includes clinical and imaging data following auto-SCT or allo-SCT
allo-SCT: allogeneic Stem Cell Transplantation; auto-SCT: autologous Stem Cell Transplantation;
BICR: Blinded Independent Central Review; CI: Confidence Interval; HL: Hodgkin Lymphoma



Database Cutoff Date: 16JAN2020

Abbildung 4G-2: Kaplan-Meier-Kurve für den Endpunkt Progressionsfreies Überleben (Lugano-Kriterien) der Studie KEYNOTE 204

Anhang 4-G2.3: Ergänzende Analysen zum Endpunkt Unerwünschte Ereignisse (gegliedert nach SOC und PT)

Tabelle 4G-19: Ergebnisse für Komplikationen nach einer allo-SZT (gegliedert nach PT) aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE 204[a]	**Patients with Event n (%)**	
Complications Post allo-SCT by PT[b,c]	**Pembrolizumab N[d]=14**	**Brentuximab Vedotin N[d]=13**
Patients with one or more complications	12 (85.7)	7 (53.8)
Acute graft versus host disease	8 (57.1)	5 (38.5)
Chronic graft versus host disease	3 (21.4)	3 (23.1)
Pyrexia	3 (21.4)	2 (15.4)
Febrile neutropenia	2 (14.3)	0 (0.0)
Acute kidney injury	1 (7.1)	0 (0.0)
Autoimmune haemolytic anaemia	1 (7.1)	0 (0.0)
Bacteraemia	1 (7.1)	0 (0.0)
Blood creatinine increased	1 (7.1)	0 (0.0)
Cytokine release syndrome	1 (7.1)	0 (0.0)
Engraftment syndrome	1 (7.1)	0 (0.0)
Hypovolaemic shock	1 (7.1)	0 (0.0)
Mucosal inflammation	1 (7.1)	1 (7.7)
Pneumonia	1 (7.1)	0 (0.0)
Pneumonia viral	1 (7.1)	0 (0.0)
Respiratory failure	1 (7.1)	0 (0.0)
Anaemia	0 (0.0)	1 (7.7)
Cystitis haemorrhagic	0 (0.0)	1 (7.7)
Cytomegalovirus infection	0 (0.0)	1 (7.7)
Diarrhoea	0 (0.0)	1 (7.7)
Nausea	0 (0.0)	1 (7.7)
Neutropenic sepsis	0 (0.0)	1 (7.7)
Obstructive airways disorder	0 (0.0)	1 (7.7)
Oropharyngeal pain	0 (0.0)	1 (7.7)
Pulmonary mycosis	0 (0.0)	1 (7.7)
Rash	0 (0.0)	1 (7.7)
Thrombocytopenia	0 (0.0)	1 (7.7)

a: Database Cutoff Date: 16JAN2020
b: Adverse events on and after receiving allo-SCT
c: A specific adverse event appears on this report only if its incidence is > 0% in one or more treatment groups
d: Number of patients: all-subjects-as-treated population who received allo-SCT after last dose
allo-SCT: allogeneic Stem Cell Transplantation; PT: Preferred Term

Anhang 4-G3: Kaplan-Meier-Kurven der Subgruppen mit signifikantem Interaktionstest (p < 0,05) der Studie KEYNOTE 204

Im Folgenden werden ergänzend zu Abschnitt 4.3.1.3.2.2 die Kaplan-Meier-Kurven der Subgruppenanalysen dargestellt, für die ein signifikanter Interaktionstest (p < 0,05) vorliegt.

Alle Ergebnisse beziehen sich auf den Datenschnitt vom 16. Januar 2020 der Studie KEYNOTE 204.

Anhang 4-G3.1: Morbidität

Krankheitssymptomatik und Gesundheitszustand

Im Folgenden werden die Kaplan-Meier-Kurven der Subgruppenanalysen für die Hauptanalyse der Endpunkte Krankheitssymptomatik und Gesundheitszustand (Zeit bis zur ersten Verschlechterung) dargestellt, für die ein signifikanter Interaktionstest (p < 0,05) vorliegt.

EORTC QLQ-C30: Symptomskala Übelkeit und Erbrechen

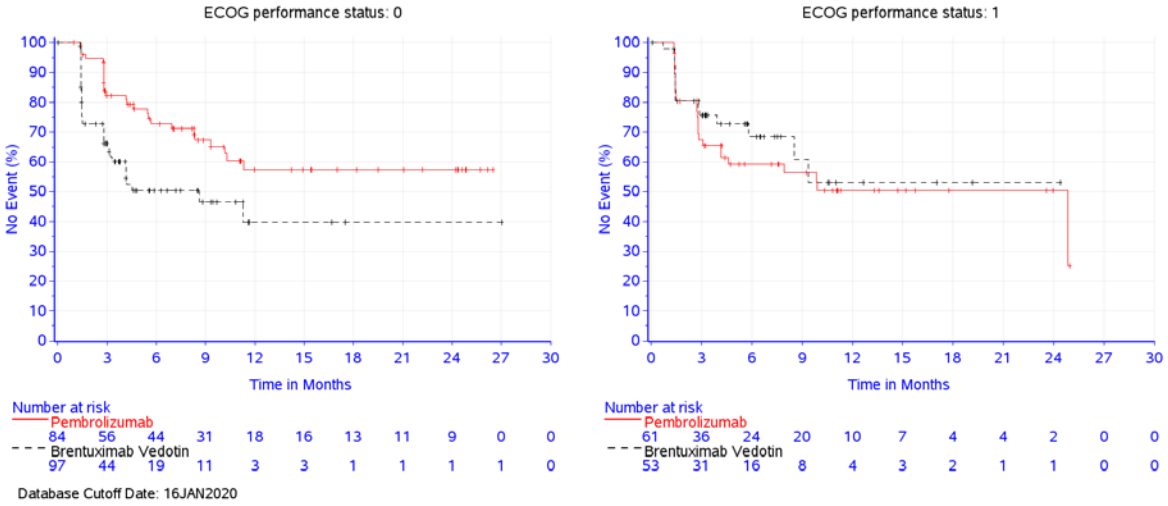


Abbildung 4G-3: Kaplan-Meier-Kurven für die Subgruppenanalyse nach ECOG-Leistungsstatus für die Symptomskala Übelkeit und Erbrechen des EORTC QLQ-C30 der Studie KEYNOTE 204

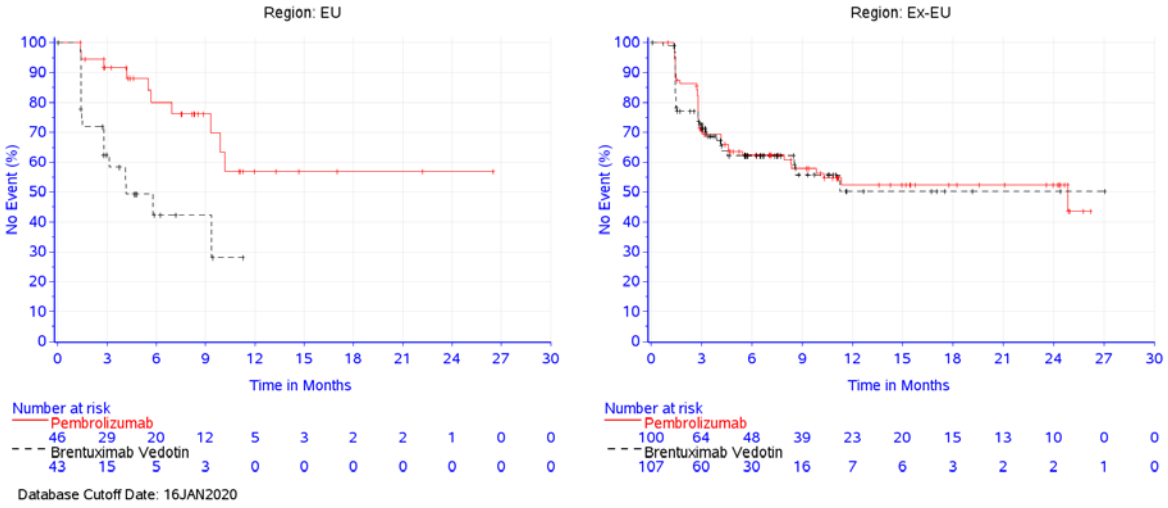


Abbildung 4G-4: Kaplan-Meier-Kurven für die Subgruppenanalyse nach Region für die Symptomskala Übelkeit und Erbrechen des EORTC QLQ-C30 der Studie KEYNOTE 204

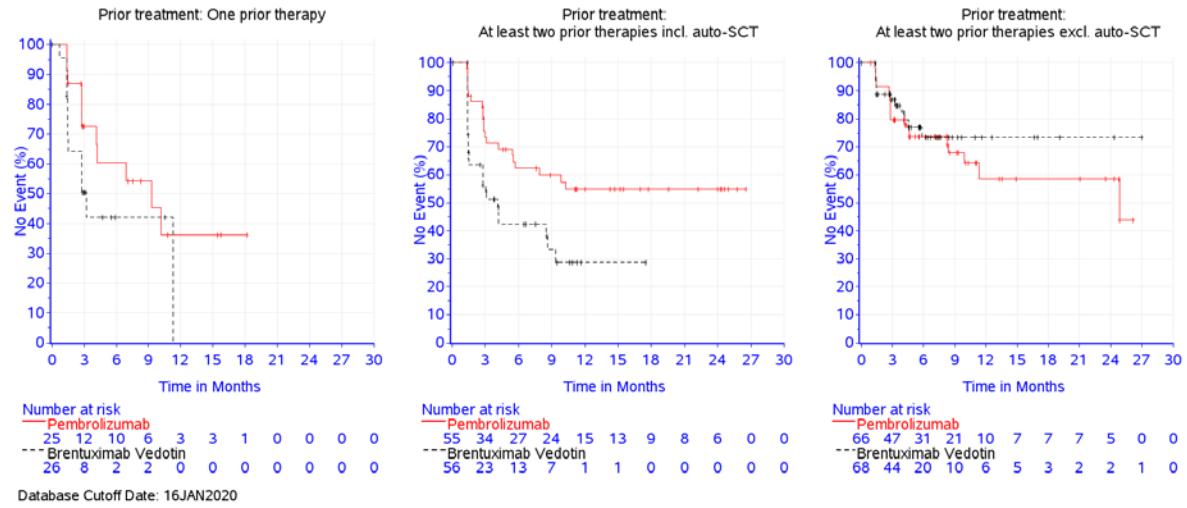


Abbildung 4G-5: Kaplan-Meier-Kurven für die Subgruppenanalyse nach Vorangegangene Therapie (Eine vorangegangene Therapie vs. Mindestens zwei vorangegangene Therapien inkl. auto-SZT vs. mindestens zwei vorangegangene Therapien exkl. auto-SZT) für die Symptomskala Übelkeit und Erbrechen des EORTC QLQ-C30 der Studie KEYNOTE 204

EORTC QLQ-C30: Symptomskala Schlaflosigkeit

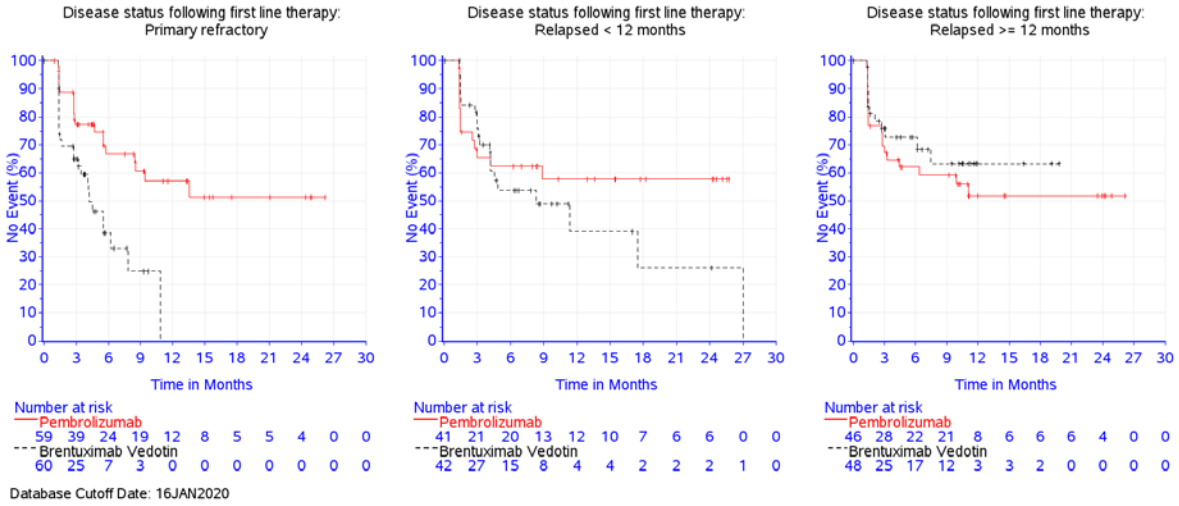


Abbildung 4G-6: Kaplan-Meier-Kurven für die Subgruppenanalyse nach Erkrankungsstatus nach Erstlinientherapie für die Symptomskala Schlaflosigkeit des EORTC QLQ-C30 der Studie KEYNOTE 204

EORTC QLQ-C30: Symptomskala Verstopfung

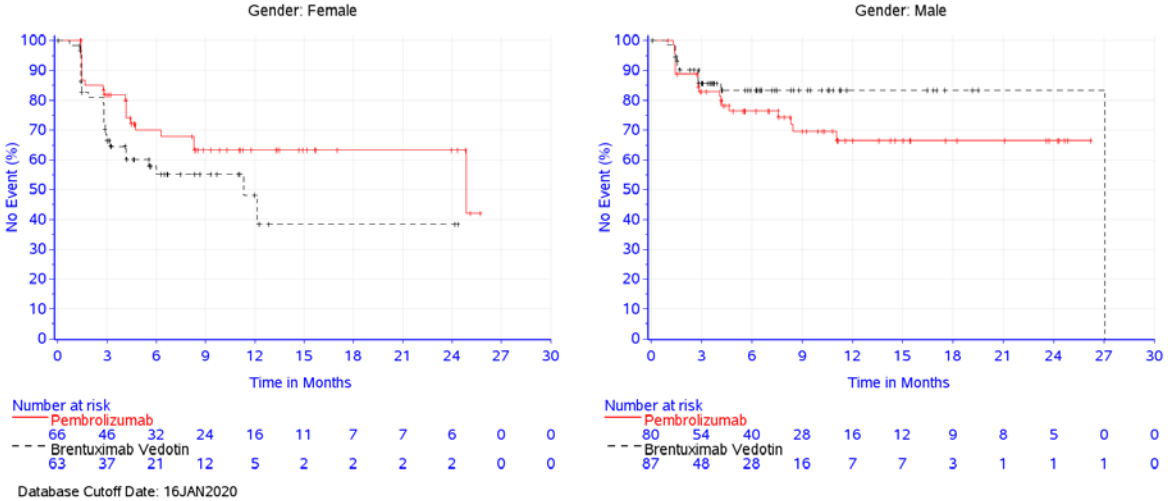


Abbildung 4G-7: Kaplan-Meier-Kurven für die Subgruppenanalyse nach Geschlecht für die Symptomskala Verstopfung des EORTC QLQ-C30 der Studie KEYNOTE 204

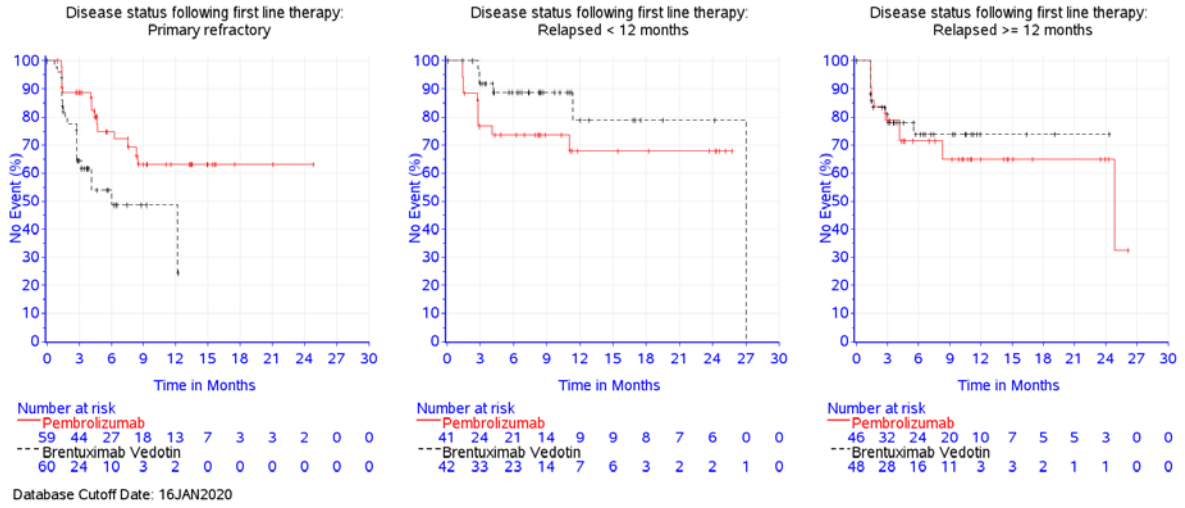


Abbildung 4G-8: Kaplan-Meier-Kurven für die Subgruppenanalyse nach Erkrankungsstatus nach Erstlinientherapie für die Symptomskala Verstopfung des EORTC QLQ-C30 der Studie KEYNOTE 204

B-Symptomatik

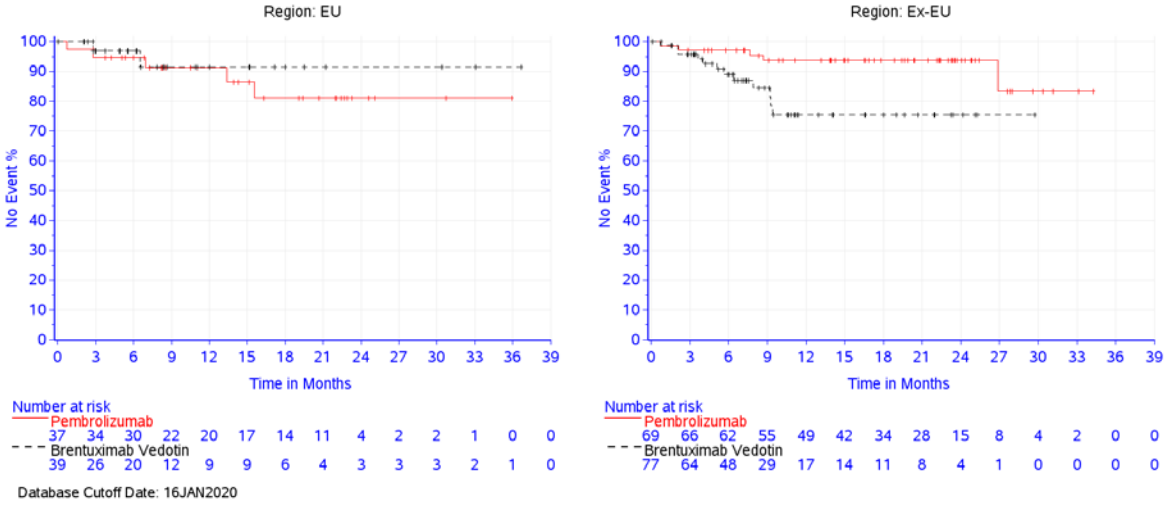


Abbildung 4G-9: Kaplan-Meier-Kurven für die Subgruppenanalyse nach Region für den Endpunkt Zeit bis zum erstmaligen Auftreten von B-Symptomen der Studie KEYNOTE 204

Zeit bis zur ersten Folgetherapie (oder Tod)

Zeit bis zur ersten Folgetherapie oder Tod

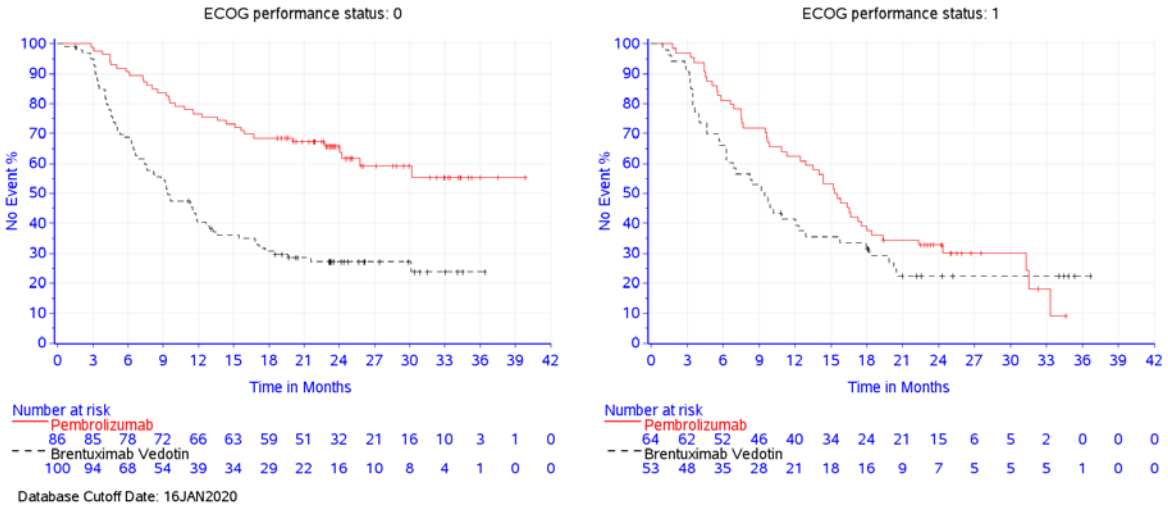


Abbildung 4G-10: Kaplan-Meier-Kurven für die Subgruppenanalyse nach ECOG-Leistungsstatus für den Endpunkt Zeit bis zur ersten Folgetherapie oder Tod der Studie KEYNOTE 204

Zeit bis zur ersten Folgetherapie

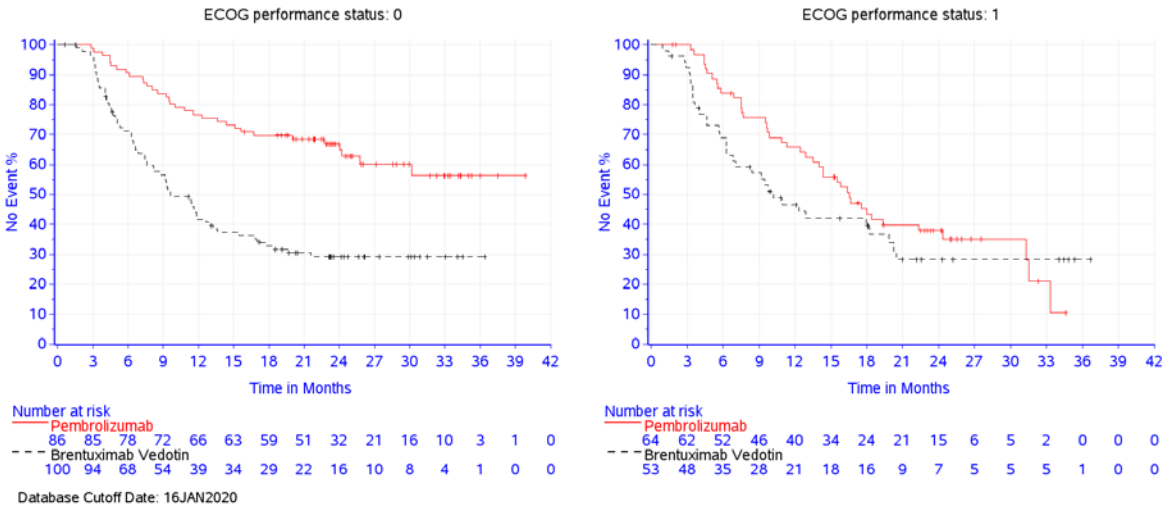


Abbildung 4G-11: Kaplan-Meier-Kurven für die Subgruppenanalyse nach ECOG-Leistungsstatus für den Endpunkt Zeit bis zur ersten Folgetherapie der Studie KEYNOTE 204

Anhang 4-G3.2: Gesundheitsbezogene Lebensqualität

Gesundheitsbezogene Lebensqualität

Im Folgenden werden die Ergebnisse der Subgruppenanalysen für die Hauptanalyse des Endpunkts Gesundheitsbezogene Lebensqualität (Zeit bis zur ersten Verschlechterung) dargestellt, für die ein signifikanter Interaktionstest ($p < 0,05$) vorliegt.

EORTC QLQ-C30: Funktionsskala Körperliche Funktion

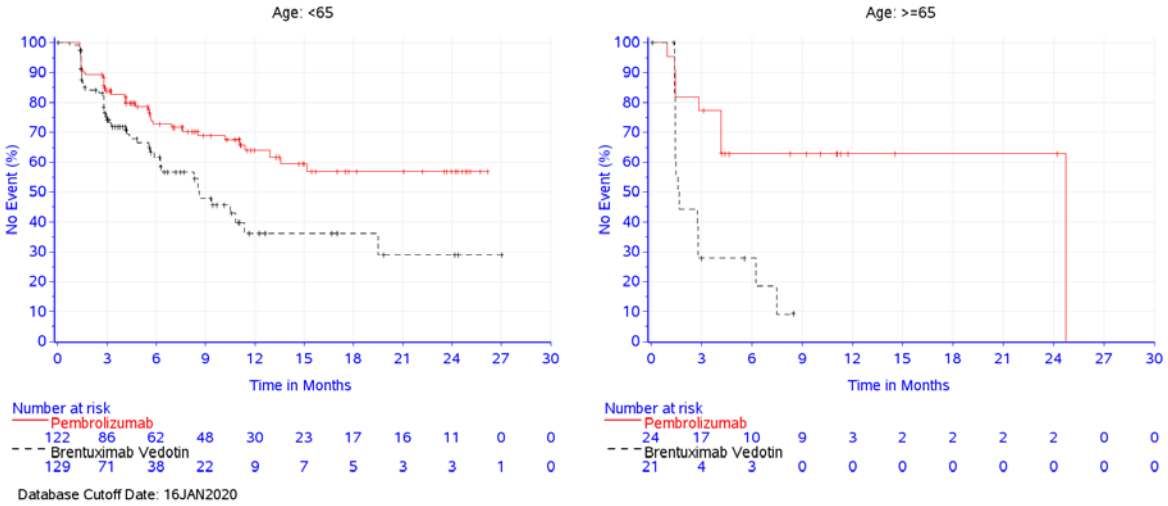


Abbildung 4G-12: Kaplan-Meier-Kurve für die Subgruppenanalyse nach Alter für die Funktionsskala Körperliche Funktion des EORTC QLQ-C30 der Studie KEYNOTE 204

EORTC QLQ-C30: Funktionsskala Emotionale Funktion

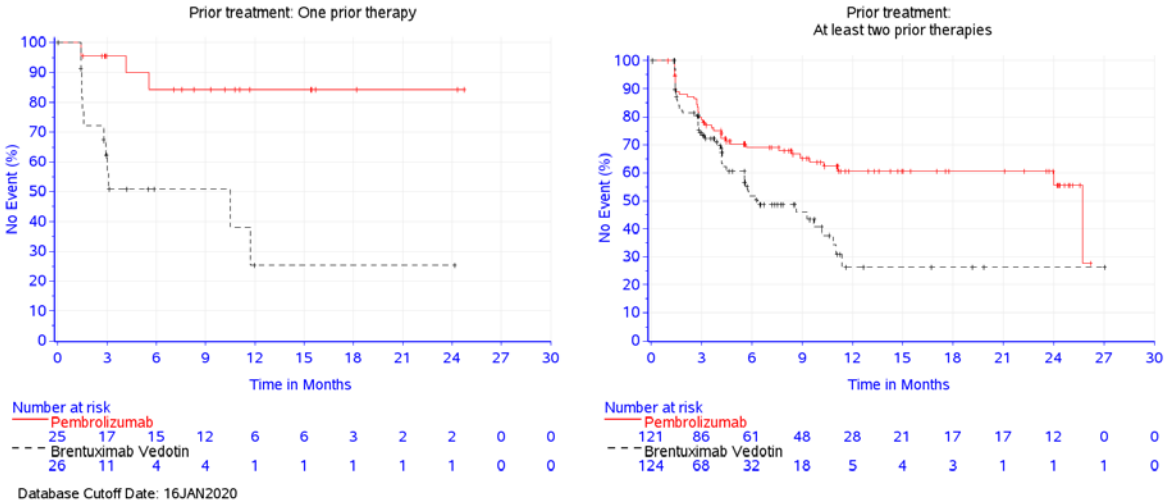


Abbildung 4G-13: Kaplan-Meier-Kurven für die Subgruppenanalyse nach Vorangegangene Therapie (Eine vorangegangene Therapie vs. Mindestens zwei vorangegangene Therapien) für die Funktionsskala Emotionale Funktion des EORTC QLQ-C30 der Studie KEYNOTE 204

Anhang 4-G3.3: Nebenwirkungen

Unerwünschte Ereignisse Gesamtraten

Unerwünschte Ereignisse gesamt

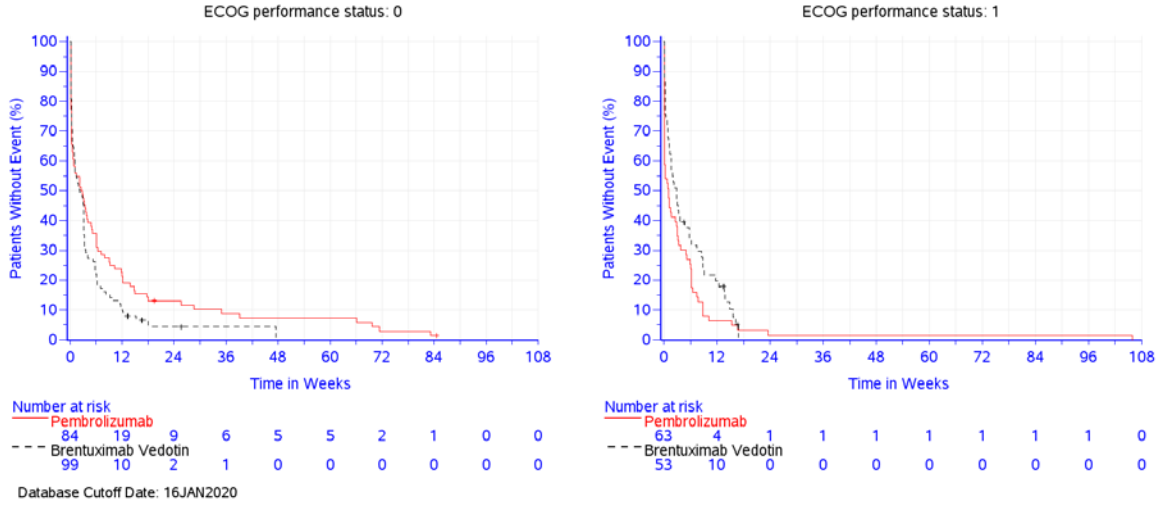


Abbildung 4G-14: Kaplan-Meier-Kurven für die Subgruppenanalyse nach ECOG Leistungsstatus für den Endpunkt Unerwünschte Ereignisse gesamt der Studie KEYNOTE 204

Nicht-schwere unerwünschte Ereignisse (CTCAE-Grad 1-2)

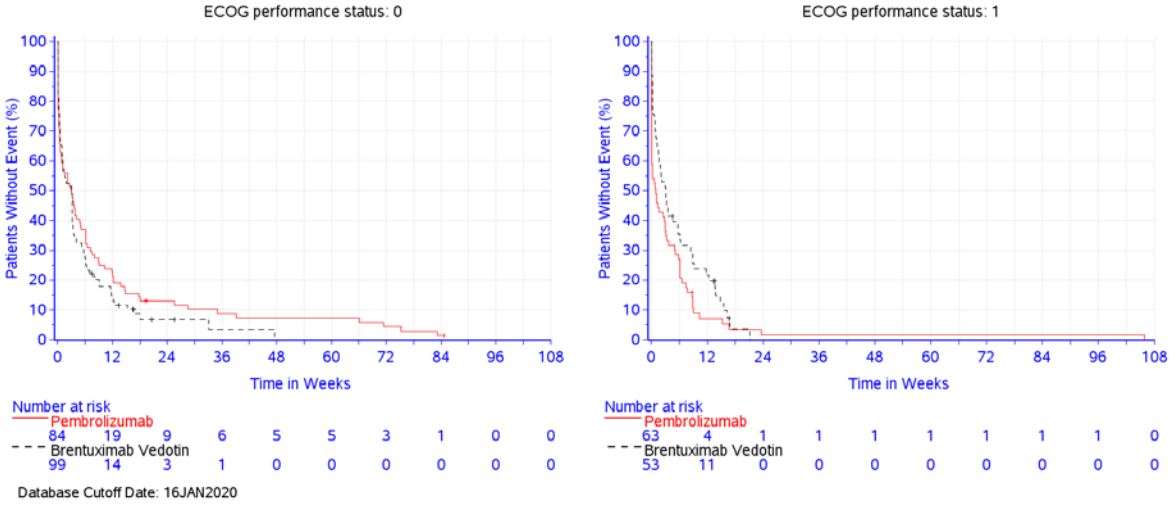


Abbildung 4G-15: Kaplan-Meier-Kurven für die Subgruppenanalyse nach ECOG Leistungsstatus für den Endpunkt Nicht-schwere unerwünschte Ereignisse (CTCAE-Grad 1-2) der Studie KEYNOTE 204

Therapieabbruch wegen unerwünschter Ereignisse

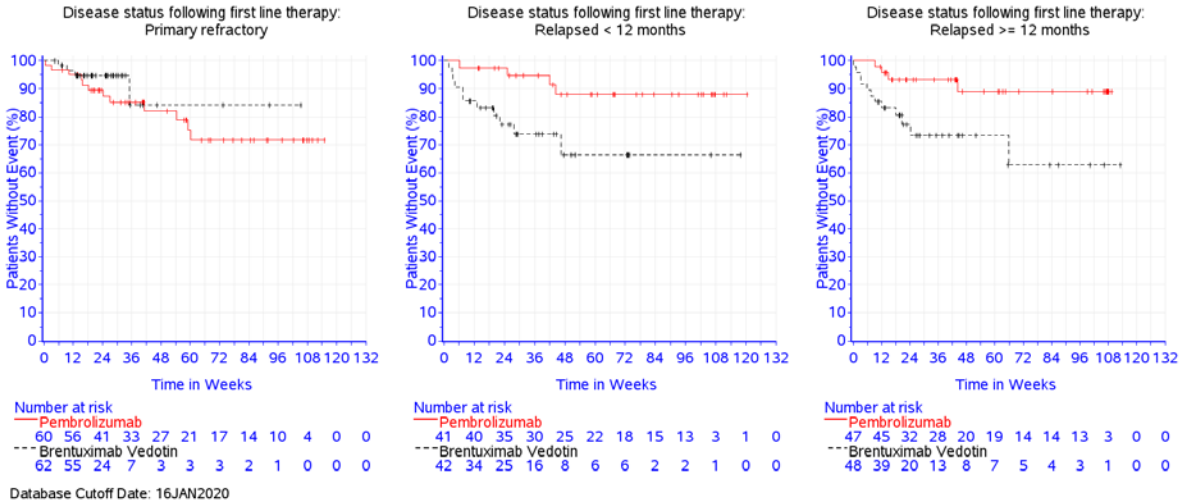


Abbildung 4G-16: Kaplan-Meier-Kurven für die Subgruppenanalyse nach Erkrankungsstatus nach Erstlinientherapie für den Endpunkt Therapieabbruch wegen unerwünschter Ereignisse der Studie KEYNOTE 204

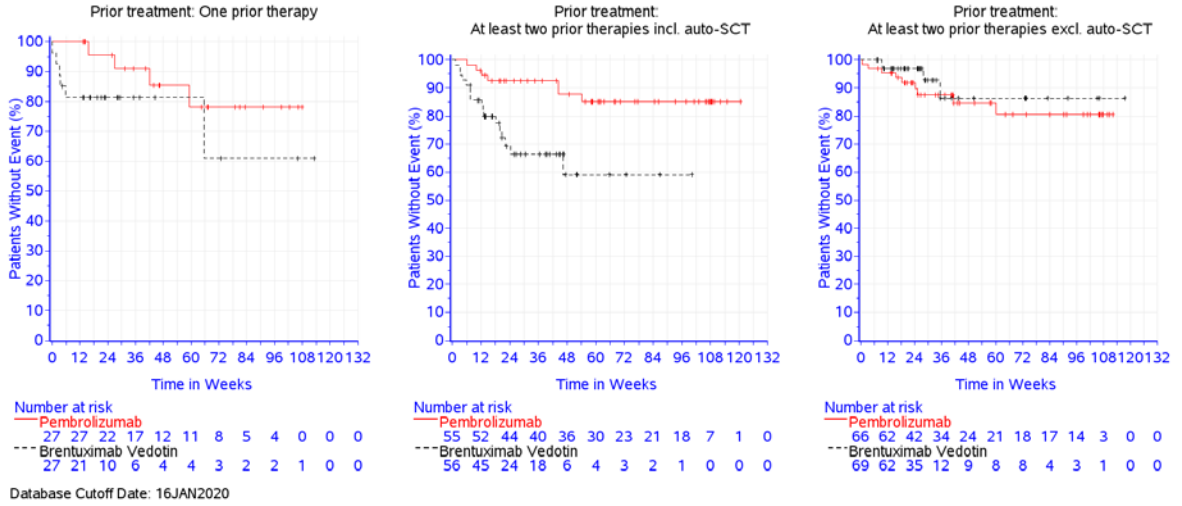


Abbildung 4G-17: Kaplan-Meier-Kurven für die Subgruppenanalyse nach Vorangegangene Therapie (Eine vorangegangene Therapie vs. Mindestens zwei vorangegangene Therapien inkl. auto-SZT vs. Mindestens zwei vorangegangene Therapien exkl. auto-SZT) für den Endpunkt Therapieabbruch wegen unerwünschter Ereignisse der Studie KEYNOTE 204

Unerwünschte Ereignisse (gegliedert nach SOC und PT)

Unerwünschte Ereignisse gesamt (SOC und PT)

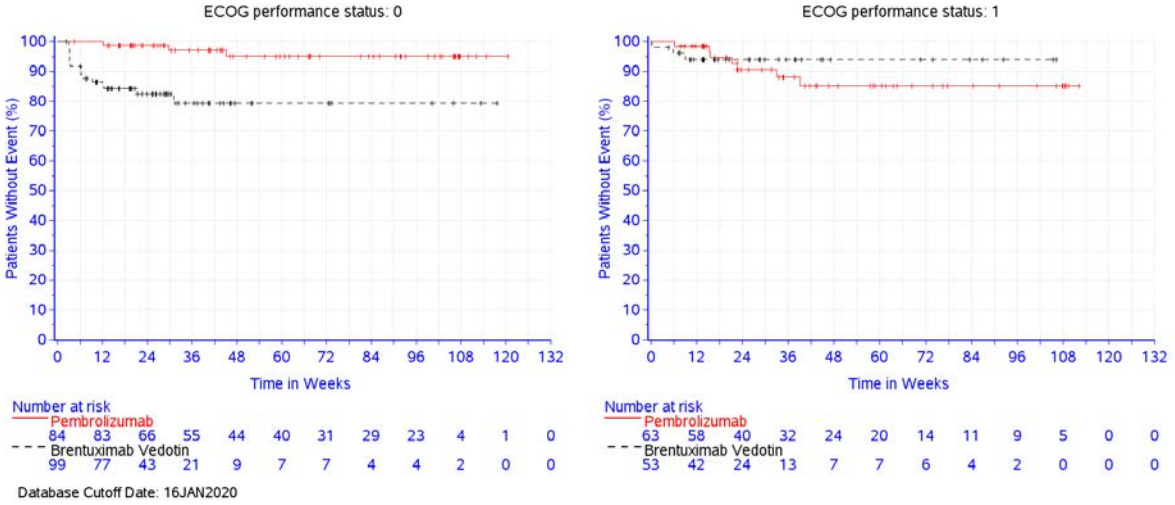


Abbildung 4G-18: Kaplan-Meier-Kurven für die Subgruppenanalyse nach ECOG-Leistungsstatus für den Endpunkt Unerwünschte Ereignisse gesamt (SOC und PT) für den PT „Neutropenie“ (SOC „Erkrankungen des Blutes und des Lymphsystems“) der Studie KEYNOTE 204

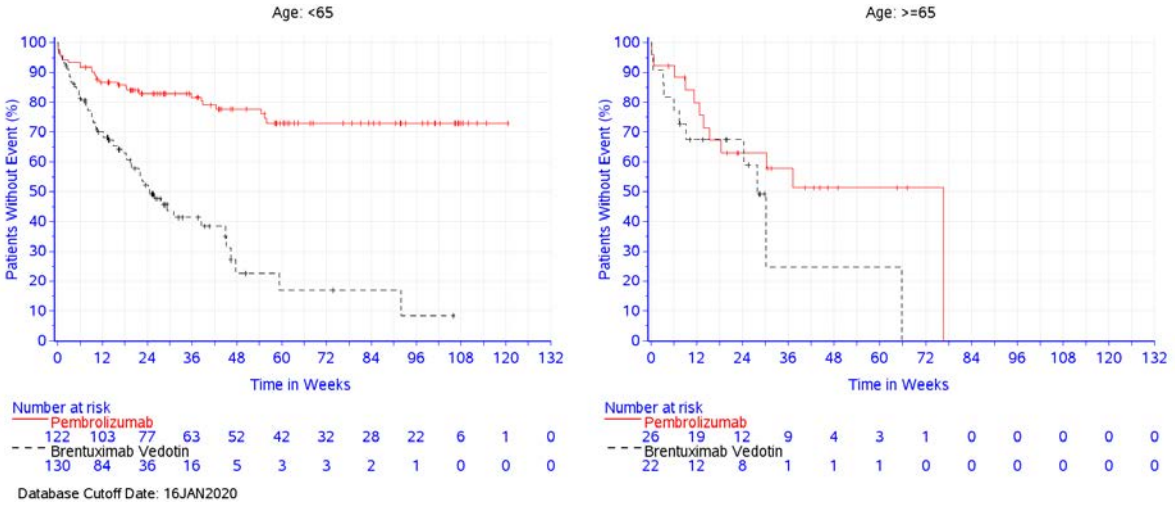


Abbildung 4G-19: Kaplan-Meier-Kurven für die Subgruppenanalyse nach Alter für den Endpunkt Unerwünschte Ereignisse gesamt (SOC und PT) für die SOC „Erkrankungen des Nervensystems“ der Studie KEYNOTE 204

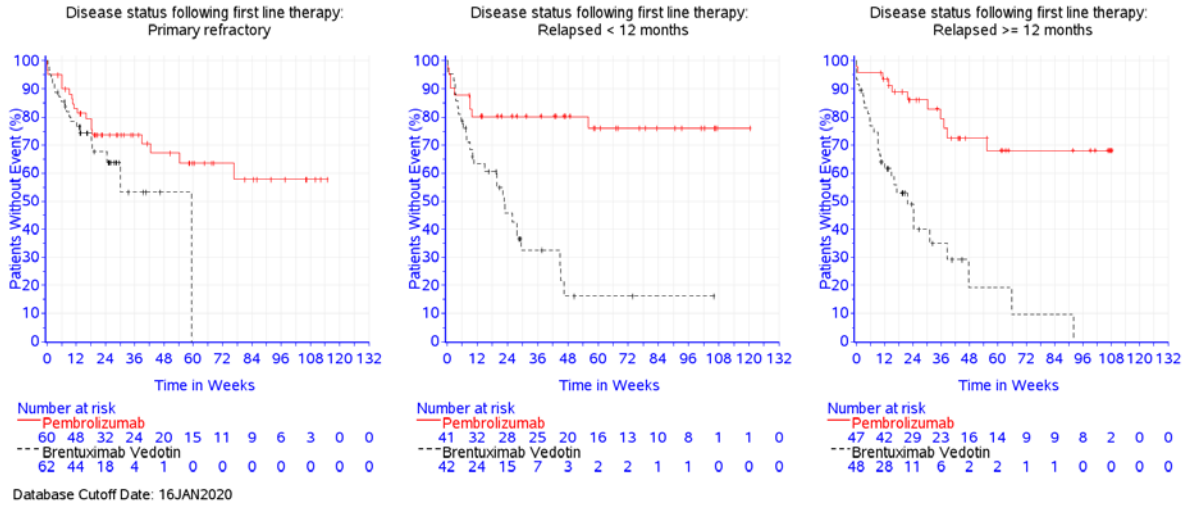


Abbildung 4G-20: Kaplan-Meier-Kurven für die Subgruppenanalyse nach Erkrankungsstatus nach Erstlinientherapie für den Endpunkt Unerwünschte Ereignisse gesamt (SOC und PT) für die SOC „Erkrankungen des Nervensystems“ der Studie KEYNOTE 204

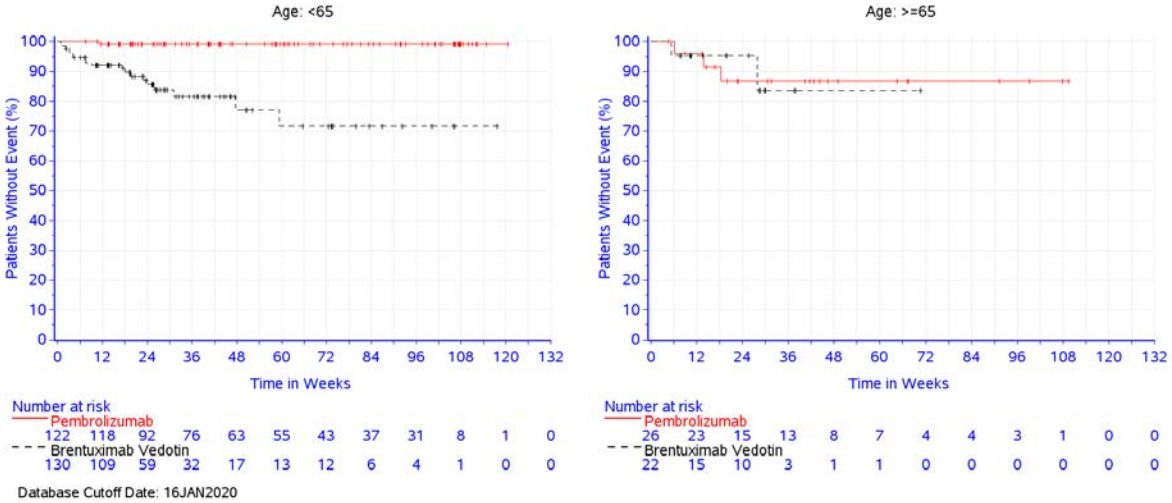


Abbildung 4G-21: Kaplan-Meier-Kurven für die Subgruppenanalyse nach Alter für den Endpunkt Unerwünschte Ereignisse gesamt (SOC und PT) für den PT „Periphere sensorische Neuropathie“ (SOC „Erkrankungen des Nervensystems“) der Studie KEYNOTE 204

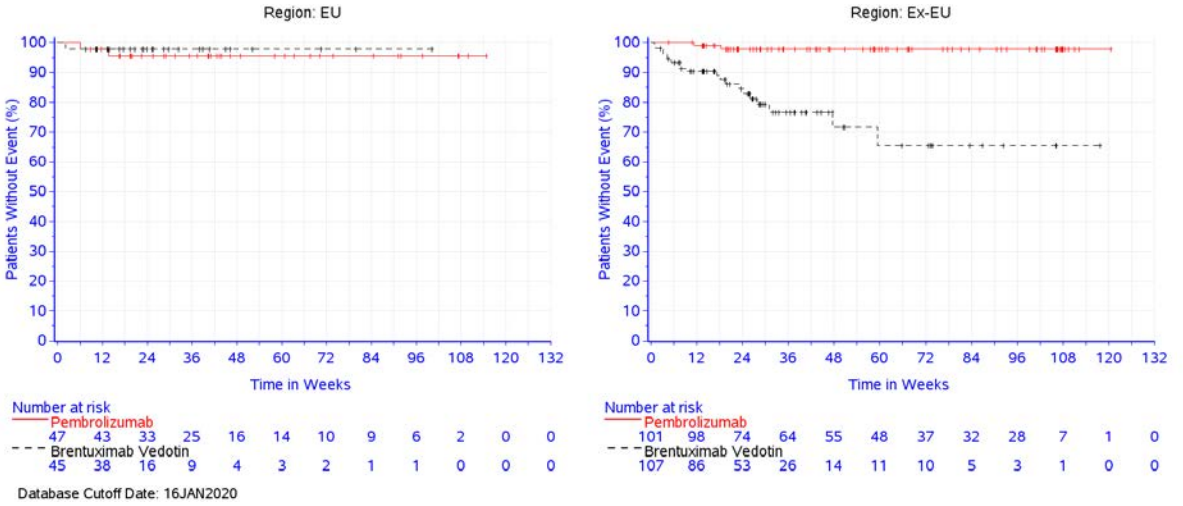


Abbildung 4G-22: Kaplan-Meier-Kurven für die Subgruppenanalyse nach Region für den Endpunkt Unerwünschte Ereignisse gesamt (SOC und PT) für den PT „Periphere sensorische Neuropathie“ (SOC „Erkrankungen des Nervensystems“) der Studie KEYNOTE 204

Nicht-schwere unerwünschte Ereignisse (CTCAE-Grad 1-2) (SOC und PT)

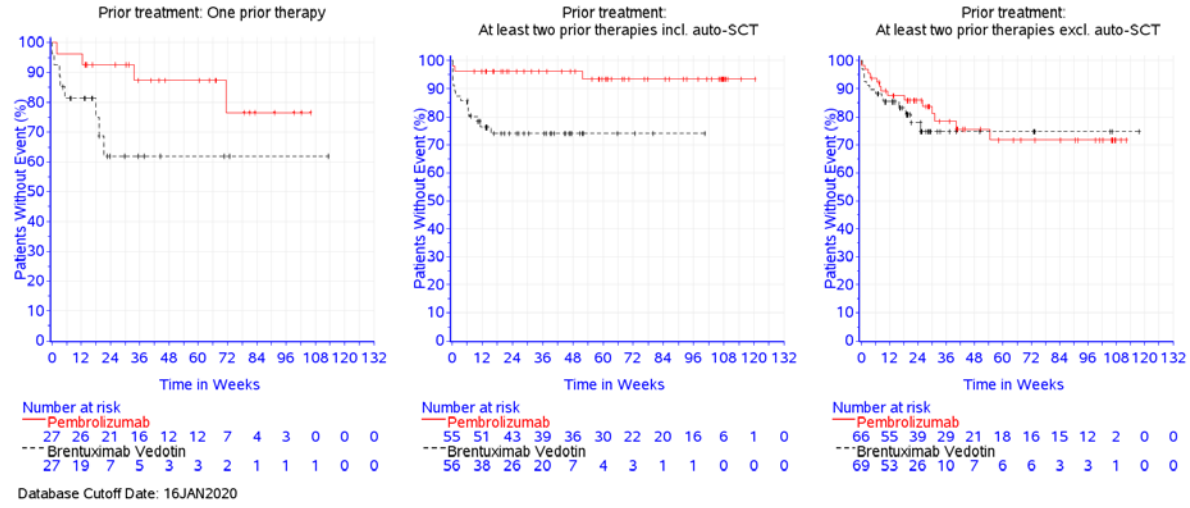


Abbildung 4G-23: Kaplan-Meier-Kurven für die Subgruppenanalyse nach der Subgruppe Vorangegangene Therapie (Eine vorangegangene Therapie vs. Mindestens zwei vorangegangene Therapien inkl. auto-SZT vs. Mindestens zwei vorangegangene Therapien exkl. auto-SZT) für den Endpunkt Nicht-schwere unerwünschte Ereignisse (CTCAE-Grad 1-2) (SOC und PT) für den PT „Übelkeit“ (SOC „Erkrankungen des Gastrointestinaltrakts“) der Studie KEYNOTE 204

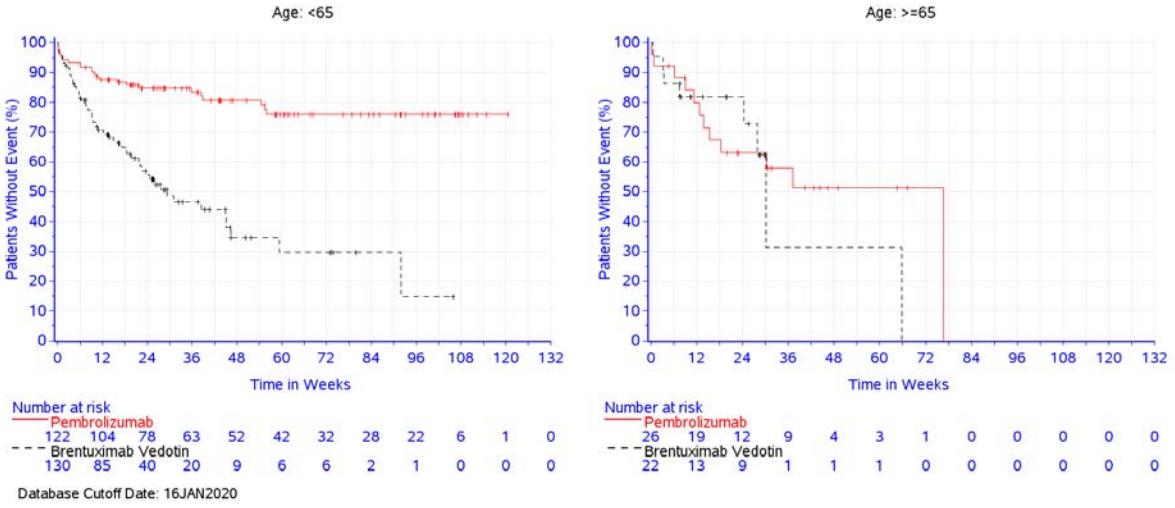


Abbildung 4G-24: Kaplan-Meier-Kurven für die Subgruppenanalyse nach Alter für den Endpunkt Nicht-schwere unerwünschte Ereignisse (CTCAE-Grad 1-2) (SOC und PT) für die SOC „Erkrankungen des Nervensystems“ der Studie KEYNOTE 204

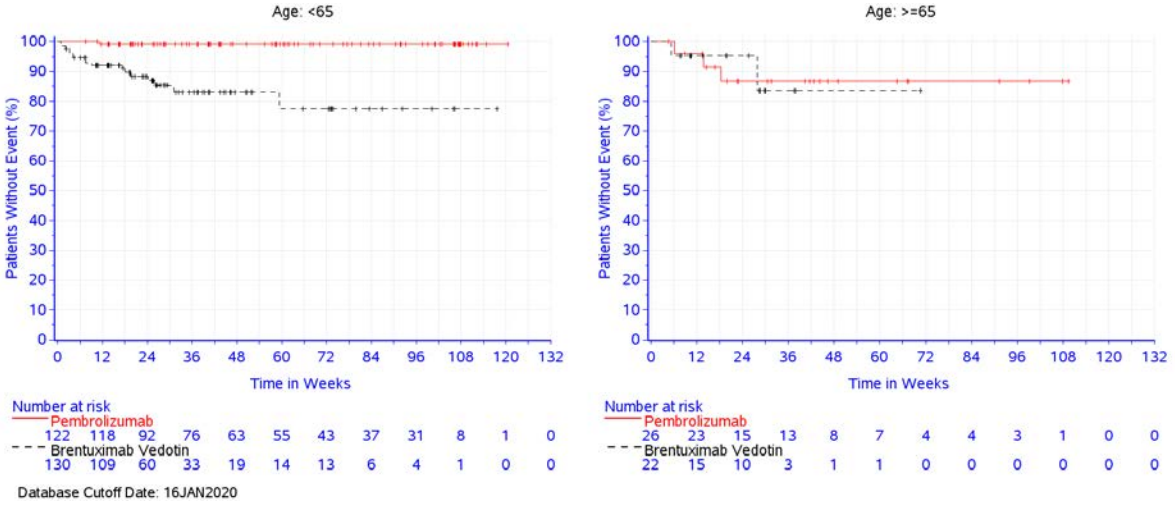


Abbildung 4G-25: Kaplan-Meier-Kurven für die Subgruppenanalyse nach Alter für den Endpunkt Nicht-schwere unerwünschte Ereignisse (CTCAE-Grad 1-2) (SOC und PT) für den PT „Periphere sensorische Neuropathie“ (SOC „Erkrankungen des Nervensystems“) der Studie KEYNOTE 204

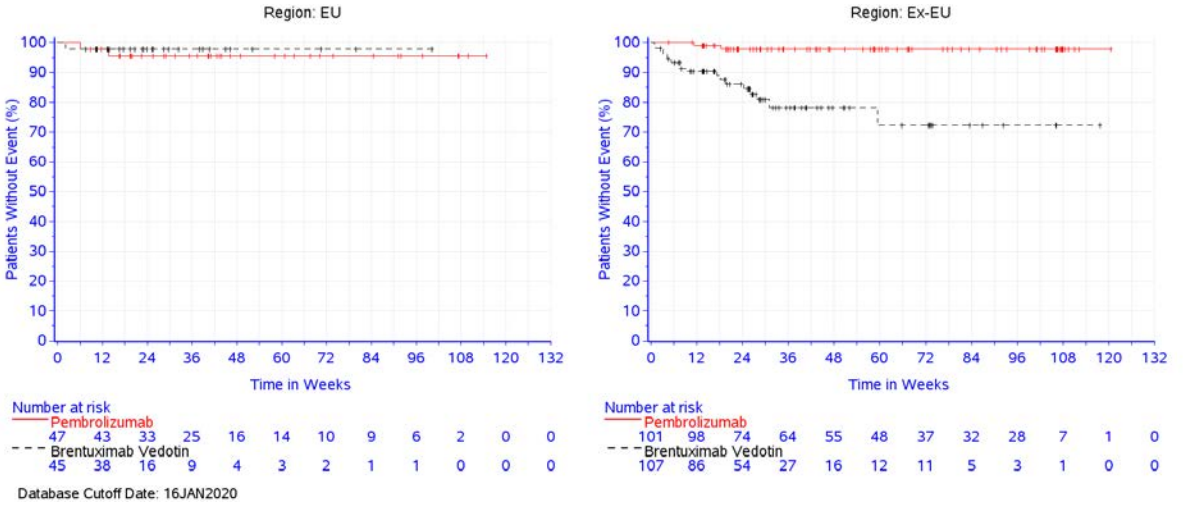


Abbildung 4G-26: Kaplan-Meier-Kurven für die Subgruppenanalyse nach Region für den Endpunkt Nicht-schwere unerwünschte Ereignisse (CTCAE-Grad 1-2) (SOC und PT) für den PT „Periphere sensorische Neuropathie“ (SOC „Erkrankungen des Nervensystems“) der Studie KEYNOTE 204

Schwere unerwünschte Ereignisse (CTCAE-Grad 3-5) (SOC und PT)

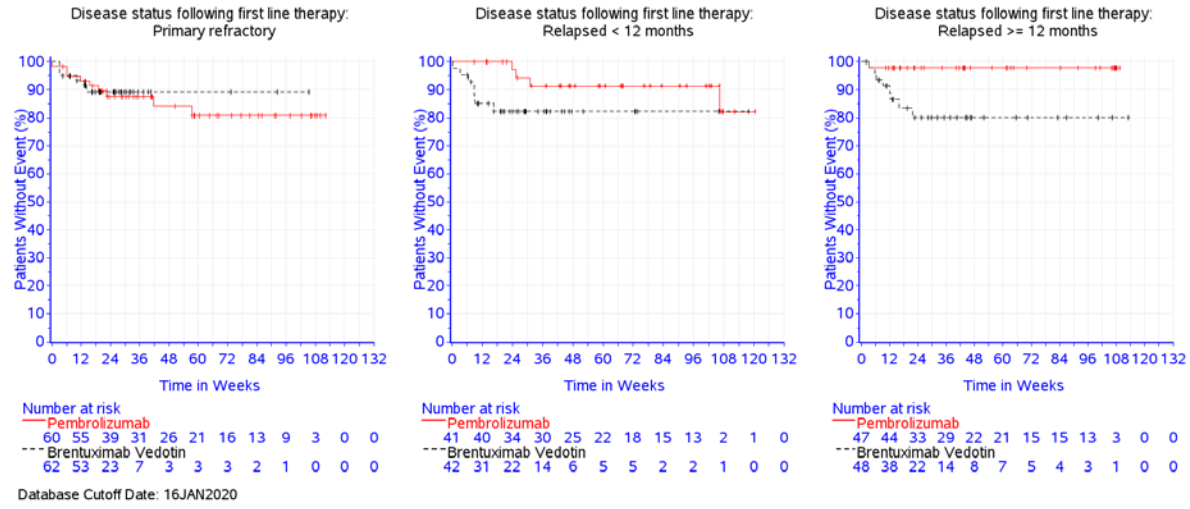


Abbildung 4G-27: Kaplan-Meier-Kurven für die Subgruppenanalyse nach Erkrankungsstatus nach Erstlinientherapie für den Endpunkt Schwere unerwünschte Ereignisse (CTCAE-Grad 3-5) (SOC und PT) für die SOC „Erkrankungen des Blutes und des Lymphsystems“ der Studie KEYNOTE 204

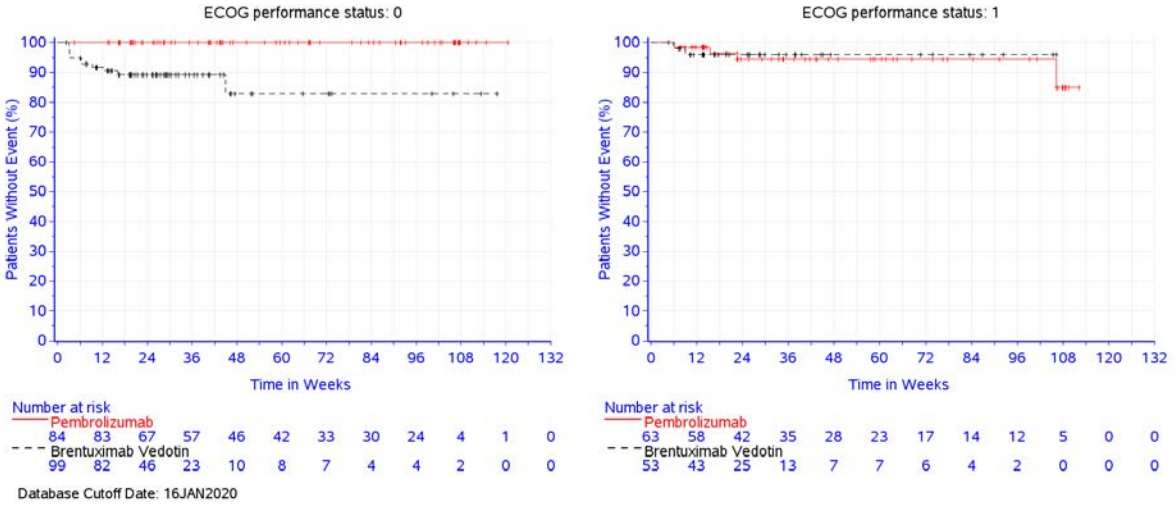


Abbildung 4G-28: Kaplan-Meier-Kurve für die Subgruppenanalyse nach ECOG-Leistungsstatus für den Endpunkt Schwere unerwünschte Ereignisse (CTCAE-Grad 3-5) (SOC und PT) für den PT „Neutropenie“ (SOC „Erkrankungen des Blutes und des Lymphsystems“) der Studie KEYNOTE 204

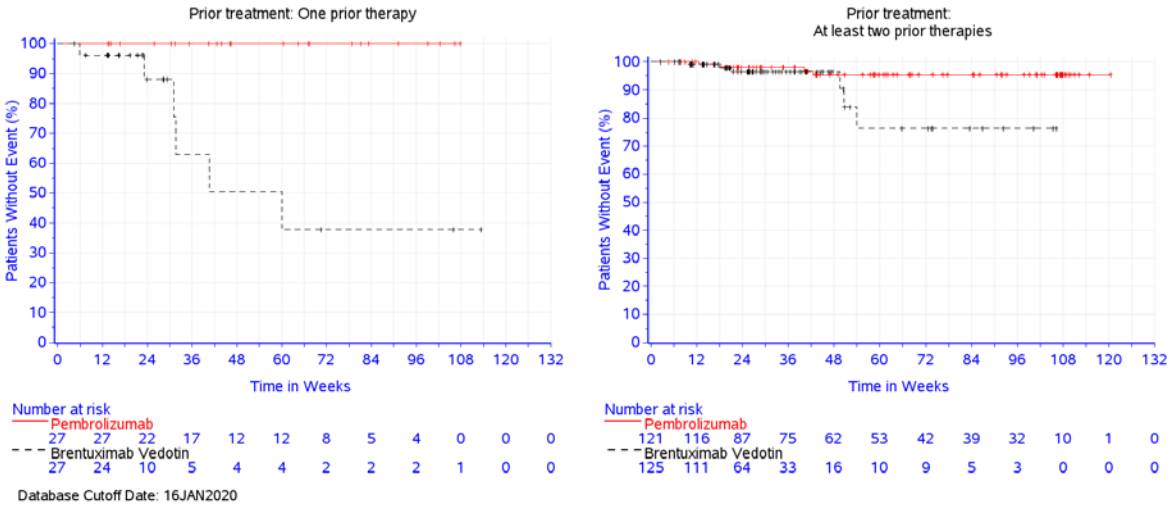


Abbildung 4G-29: Kaplan-Meier-Kurven für die Subgruppenanalyse nach Vorangegangene Therapie (Eine vorangegangene Therapie vs. Mindestens zwei vorangegangene Therapien) für den Endpunkt Schwere unerwünschte Ereignisse (CTCAE-Grad 3-5) (SOC und PT) für die SOC „Erkrankungen des Nervensystems“ der Studie KEYNOTE 204

Anhang 4-G4: Ergebnisse der Subgruppen mit nicht signifikantem Interaktionstest (p ≥ 0,05) der Studie KEYNOTE 204

Im Folgenden werden ergänzend zu Abschnitt 4.3.1.3.2.2 die Ergebnisse der Subgruppenanalysen, für die ein nicht signifikanter Interaktionstest (p ≥ 0,05) vorliegt, dargestellt.

Alle Ergebnisse beziehen sich auf den Datenschnitt vom 16. Januar 2020 der Studie KEYNOTE 204.

Anhang 4-G4.1: Morbidität

Hauptanalyse der Endpunkte Krankheitssymptomatik und Gesundheitszustand

Im Folgenden werden die Ergebnisse der Subgruppenanalysen für die Hauptanalyse der Endpunkte Krankheitssymptomatik und Gesundheitszustand (Zeit bis zur ersten Verschlechterung) dargestellt, für die ein nicht signifikanter Interaktionstest (p ≥ 0,05) vorliegt.

EORTC QLQ-C30: Symptomskala Erschöpfung

Tabelle 4G-20: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für die Symptomskala Erschöpfung des EORTC QLQ-C30 aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE 204[a]	Pembrolizumab			Brentuximab Vedotin			Pembrolizumab vs. Brentuximab Vedotin		
EORTC QLQ-C30 Fatigue[b]	N[c]	Patients with Event n (%)	Median Time[d] in Months [95 %-CI]	N[c]	Patients with Event n (%)	Median Time[d] in Months [95 %-CI]	Hazard Ratio [95 %-CI][e]	p-Value[e,f]	p-Value for Interaction Test[g]
Gender									
Female	66	28 (42.4)	10.3 [5.8; -]	63	37 (58.7)	3.2 [1.5; 8.3]	0.52 [0.31; 0.87]	0.012	0.694
Male	80	32 (40.0)	Not reached [4.6; -]	87	41 (47.1)	4.2 [2.8; 6.0]	0.60 [0.38; 0.97]	0.038	
Age									
<65	122	48 (39.3)	Not reached [8.3; -]	129	65 (50.4)	3.8 [2.8; 6.0]	0.57 [0.39; 0.83]	0.004	0.827
≥65	24	12 (50.0)	5.6 [1.4; -]	21	13 (61.9)	2.2 [1.4; 5.8]	0.48 [0.21; 1.13]	0.093	
ECOG performance status									
0	84	39 (46.4)	9.4 [2.8; -]	97	52 (53.6)	3.2 [1.7; 5.8]	0.66 [0.43; 1.02]	0.062	0.413
1	61	21 (34.4)	Not reached [8.3; -]	53	26 (49.1)	3.4 [2.8; -]	0.46 [0.25; 0.84]	0.011	
Region									
EU	46	17 (37.0)	Not reached [2.8; -]	43	21 (48.8)	2.8 [1.4; 8.3]	0.57 [0.29; 1.12]	0.103	0.766
Ex-EU	100	43 (43.0)	10.3 [7.6; -]	107	57 (53.3)	3.4 [2.8; 5.8]	0.54 [0.36; 0.81]	0.003	
Disease status following first line therapy									
Primary refractory	59	23 (39.0)	9.4 [5.8; -]	60	28 (46.7)	3.4 [2.8; 6.0]	0.49 [0.28; 0.87]	0.015	0.873
Relapsed < 12 months	41	17 (41.5)	10.1 [2.8; -]	42	24 (57.1)	4.2 [2.3; 8.3]	0.68 [0.36; 1.28]	0.233	

Study: KEYNOTE 204[a]	Pembrolizumab			Brentuximab Vedotin			Pembrolizumab vs. Brentuximab Vedotin		
EORTC QLQ-C30 Fatigue[b]	N[c]	Patients with Event n (%)	Median Time[d] in Months [95 %-CI]	N[c]	Patients with Event n (%)	Median Time[d] in Months [95 %-CI]	Hazard Ratio [95 %-CI][e]	p-Value[e,f]	p-Value for Interaction Test[g]
Relapsed ≥ 12 months	46	20 (43.5)	Not reached [2.8; -]	48	26 (54.2)	2.8 [1.4; -]	0.59 [0.33; 1.05]	0.075	
Prior treatment									
One prior therapy[h]	25	11 (44.0)	10.1 [2.8; -]	26	14 (53.8)	2.8 [1.5; 5.9]	0.60 [0.26; 1.38]	0.228	0.909
At least two prior therapies incl. auto-SCT[i]	55	25 (45.5)	10.3 [2.8; -]	56	29 (51.8)	3.2 [1.4; 8.5]	0.66 [0.38; 1.14]	0.135	
At least two prior therapies excl. auto-SCT[h]	66	24 (36.4)	Not reached [5.8; -]	68	35 (51.5)	4.2 [2.3; 7.4]	0.50 [0.29; 0.85]	0.010	
Prior treatment									
One prior therapy	25	11 (44.0)	10.1 [2.8; -]	26	14 (53.8)	2.8 [1.5; 5.9]	0.60 [0.26; 1.38]	0.228	0.837
At least two prior therapies	121	49 (40.5)	Not reached [8.3; -]	124	64 (51.6)	4.1 [2.8; 6.0]	0.57 [0.39; 0.83]	0.004	

a: Database Cutoff Date: 16JAN2020

b: First deterioration is defined as the time to first onset of 10 points or more increase from baseline without confirmation for the EORTC QLQ-C30 symptom scores

c: Number of patients: full-analysis-set population

d: From product-limit (Kaplan-Meier) method

e: Based on stratified Cox regression model with treatment as a covariate stratified by prior auto-SCT status (yes versus no) and HL status after frontline therapy (primary refractory versus relapsed less than 12 months after completion of frontline therapy versus relapse 12 months or more after completion of frontline therapy) using Wald confidence interval

f: Two-sided p-value using Wald test (Score test in case of zero event in one treatment group)

g: Based on stratified Cox regression model with treatment, subgroup, prior auto-SCT (yes versus no) and HL status after frontline therapy (primary refractory versus relapsed less than 12 months after completion of frontline therapy versus relapse 12 months or more after completion of frontline therapy) as covariates, and a treatment-by-subgroup interaction (p-value of likelihood ratio test for interaction term)

h: Auto-SCT was not a treatment option

i: Auto-SCT failure

Auto-SCT: autologous Stem Cell Transplantation; CI: Confidence Interval; ECOG: Eastern Cooperative Oncology Group; EORTC QLQ-C30: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 items; HL: Hodgkin Lymphoma

EORTC QLQ-C30: Symptomskala Übelkeit und Erbrechen

Tabelle 4G-21: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für die Symptomskala Übelkeit und Erbrechen des EORTC QLQ-C30 aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE 204[a]	Pembrolizumab			Brentuximab Vedotin			Pembrolizumab vs. Brentuximab Vedotin		
EORTC QLQ-C30 Nausea and Vomiting[b]	N[c]	Patients with Event n (%)	Median Time[d] in Months [95 %-CI]	N[c]	Patients with Event n (%)	Median Time[d] in Months [95 %-CI]	Hazard Ratio [95 %-CI][e]	p-Value[e,f]	p-Value for Interaction Test[g]
Gender									
Female	66	30 (45.5)	9.9 [3.0; -]	63	30 (47.6)	8.5 [2.8; -]	0.78 [0.46; 1.33]	0.356	0.993
Male	80	22 (27.5)	24.8 [10.2; -]	87	24 (27.6)	Not reached [5.8; -]	0.63 [0.34; 1.14]	0.125	
Age									
<65	122	44	24.8	129	46	11.3	0.75	0.176	0.630

Study: KEYNOTE 204[a]	Pembrolizumab			Brentuximab Vedotin			Pembrolizumab vs. Brentuximab Vedotin		
EORTC QLQ-C30 Nausea and Vomiting[b]	N[c]	Patients with Event n (%)	Median Time[d] in Months [95 %-CI]	N[c]	Patients with Event n (%)	Median Time[d] in Months [95 %-CI]	Hazard Ratio [95 %-CI][e]	p-Value[e,f]	p-Value for Interaction Test[g]
		(36.1)	[9.9; -]		(35.7)	[4.2; -]	[0.49; 1.14]		
≥65	24	8 (33.3)	Not reached [4.2; -]	21	8 (38.1)	5.8 [1.4; -]	0.51 [0.17; 1.53]	0.229	
Disease status following first line therapy									
Primary refractory	59	22 (37.3)	24.8 [5.7; -]	60	15 (25.0)	Not reached [5.8; -]	0.94 [0.48; 1.84]	0.852	0.122
Relapsed < 12 months	41	18 (43.9)	8.3 [2.8; -]	42	18 (42.9)	Not reached [2.9; -]	0.96 [0.50; 1.87]	0.909	
Relapsed ≥ 12 months	46	12 (26.1)	Not reached [10.2; -]	48	21 (43.8)	8.6 [2.8; -]	0.38 [0.19; 0.79]	0.009	
Prior treatment									
One prior therapy	25	11 (44.0)	9.3 [2.8; -]	26	13 (50.0)	3.2 [1.5; 11.3]	0.68 [0.28; 1.65]	0.397	0.773
At least two prior therapies	121	41 (33.9)	24.8 [10.3; -]	124	41 (33.1)	Not reached [5.8; -]	0.72 [0.46; 1.13]	0.155	

a: Database Cutoff Date: 16JAN2020

b: First deterioration is defined as the time to first onset of 10 points or more increase from baseline without confirmation for the EORTC QLQ-C30 symptom scores

c: Number of patients: full-analysis-set population

d: From product-limit (Kaplan-Meier) method

e: Based on stratified Cox regression model with treatment as a covariate stratified by prior auto-SCT status (yes versus no) and HL status after frontline therapy (primary refractory versus relapsed less than 12 months after completion of frontline therapy versus relapse 12 months or more after completion of frontline therapy) using Wald confidence interval

f: Two-sided p-value using Wald test (Score test in case of zero event in one treatment group)

g: Based on stratified Cox regression model with treatment, subgroup, prior auto-SCT (yes versus no) and HL status after frontline therapy (primary refractory versus relapsed less than 12 months after completion of frontline therapy versus relapse 12 months or more after completion of frontline therapy) as covariates, and a treatment-by-subgroup interaction (p-value of likelihood ratio test for interaction term)

Auto-SCT: autologous Stem Cell Transplantation; CI: Confidence Interval; EORTC QLQ-C30: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 items; HL: Hodgkin Lymphoma

EORTC QLQ-C30: Symptomskala Schmerzen

Tabelle 4G-22: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für die Symptomskala Schmerzen des EORTC QLQ-C30 aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE 204[a]	Pembrolizumab			Brentuximab Vedotin			Pembrolizumab vs. Brentuximab Vedotin		
EORTC QLQ-C30 Pain[b]	N[c]	Patients with Event n (%)	Median Time[d] in Months [95 %-CI]	N[c]	Patients with Event n (%)	Median Time[d] in Months [95 %-CI]	Hazard Ratio [95 %-CI][e]	p-Value[e,f]	p-Value for Interaction Test[g]
Gender									
Female	66	29 (43.9)	13.6 [4.2; -]	63	30 (47.6)	6.9 [2.9; 11.0]	0.73 [0.43; 1.26]	0.259	0.128
Male	80	24 (30.0)	24.6 [11.8; -]	87	41 (47.1)	4.2 [3.0; 6.0]	0.35 [0.20; 0.60]	< 0.001	
Age									
<65	122	41 (33.6)	24.6 [13.6; -]	129	60 (46.5)	5.5 [4.1; 8.5]	0.45 [0.30; 0.69]	< 0.001	0.578
≥65	24	12	4.2	21	11	2.8	0.57	0.204	

Study: KEYNOTE 204[a]	Pembrolizumab			Brentuximab Vedotin			Pembrolizumab vs. Brentuximab Vedotin		
EORTC QLQ-C30 Pain[b]	N[c]	Patients with Event n (%)	Median Time[d] in Months [95 %-CI]	N[c]	Patients with Event n (%)	Median Time[d] in Months [95 %-CI]	Hazard Ratio [95 %-CI][e]	p-Value[e,f]	p-Value for Interaction Test[g]
		(50.0)	[2.8; -]		(52.4)	[1.4; -]	[0.23; 1.36]		
ECOG performance status									
0	84	29 (34.5)	24.6 [10.2; -]	97	49 (50.5)	4.6 [3.3; 7.9]	0.41 [0.25; 0.67]	< 0.001	0.399
1	61	24 (39.3)	15.1 [4.4; -]	53	22 (41.5)	5.5 [3.0; -]	0.63 [0.34; 1.17]	0.145	
Region									
EU	46	18 (39.1)	10.2 [4.2; -]	43	20 (46.5)	3.3 [2.8; -]	0.61 [0.31; 1.19]	0.147	0.518
Ex-EU	100	35 (35.0)	24.6 [13.6; -]	107	51 (47.7)	5.5 [4.1; 8.5]	0.47 [0.29; 0.74]	0.001	
Disease status following first line therapy									
Primary refractory	59	17 (28.8)	Not reached [11.4; -]	60	23 (38.3)	5.5 [2.9; -]	0.44 [0.23; 0.84]	0.013	0.754
Relapsed < 12 months	41	17 (41.5)	13.6 [4.2; -]	42	26 (61.9)	4.2 [3.0; 6.9]	0.54 [0.29; 1.03]	0.063	
Relapsed ≥ 12 months	46	19 (41.3)	15.1 [4.2; -]	48	22 (45.8)	6.2 [2.8; 8.7]	0.57 [0.30; 1.07]	0.078	
Prior treatment									
One prior therapy[h]	25	11 (44.0)	6.0 [2.7; -]	26	15 (57.7)	3.0 [1.5; 8.5]	0.61 [0.26; 1.43]	0.258	0.944
At least two prior therapies incl. auto-SCT[i]	55	21 (38.2)	24.6 [11.1; -]	56	25 (44.6)	6.2 [3.0; 11.0]	0.47 [0.26; 0.86]	0.015	
At least two prior therapies excl. auto-SCT[h]	66	21 (31.8)	Not reached [11.4; -]	68	31 (45.6)	5.5 [3.3; 9.7]	0.55 [0.31; 0.99]	0.046	
Prior treatment									
One prior therapy	25	11 (44.0)	6.0 [2.7; -]	26	15 (57.7)	3.0 [1.5; 8.5]	0.61 [0.26; 1.43]	0.258	0.785
At least two prior therapies	121	42 (34.7)	24.6 [11.8; -]	124	56 (45.2)	5.5 [4.1; 8.7]	0.51 [0.33; 0.78]	0.002	

a: Database Cutoff Date: 16JAN2020

b: First deterioration is defined as the time to first onset of 10 points or more increase from baseline without confirmation for the EORTC QLQ-C30 symptom scores

c: Number of patients: full-analysis-set population

d: From product-limit (Kaplan-Meier) method

e: Based on stratified Cox regression model with treatment as a covariate stratified by prior auto-SCT status (yes versus no) and HL status after frontline therapy (primary refractory versus relapsed less than 12 months after completion of frontline therapy versus relapse 12 months or more after completion of frontline therapy) using Wald confidence interval

f: Two-sided p-value using Wald test (Score test in case of zero event in one treatment group)

g: Based on stratified Cox regression model with treatment, subgroup, prior auto-SCT (yes versus no) and HL status after frontline therapy (primary refractory versus relapsed less than 12 months after completion of frontline therapy versus relapse 12 months or more after completion of frontline therapy) as covariates, and a treatment-by-subgroup interaction (p-value of likelihood ratio test for interaction term)

h: Auto-SCT was not a treatment option

i: Auto-SCT failure

Auto-SCT: autologous Stem Cell Transplantation; CI: Confidence Interval; ECOG: Eastern Cooperative Oncology Group; EORTC QLQ-C30: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 items; HL: Hodgkin Lymphoma

EORTC QLQ-C30: Symptomskala Atemnot (Dyspnoe)

Tabelle 4G-23: Subgruppenanalysen mit nicht signifikantem Interaktionstest ($p \geq 0,05$) für die Symptomskala Atemnot (Dyspnoe) des EORTC QLQ-C30 aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE 204[a]	**Pembrolizumab**			**Brentuximab Vedotin**			**Pembrolizumab vs. Brentuximab Vedotin**		
EORTC QLQ-C30 Dyspnea[b]	**N[c]**	**Patients with Event n (%)**	**Median Time[d] in Months [95 %-CI]**	**N[c]**	**Patients with Event n (%)**	**Median Time[d] in Months [95 %-CI]**	**Hazard Ratio [95 %-CI][e]**	**p-Value[e,f]**	**p-Value for Interaction Test[g]**
Gender									
Female	66	17 (25.8)	Not reached [15.1; -]	63	17 (27.0)	12.3 [11.1; -]	0.63 [0.31; 1.25]	0.187	0.746
Male	80	28 (35.0)	Not reached [6.2; -]	87	29 (33.3)	10.8 [5.6; -]	0.78 [0.46; 1.34]	0.369	
Age									
<65	122	37 (30.3)	Not reached [15.1; -]	129	38 (29.5)	12.3 [10.8; -]	0.76 [0.47; 1.21]	0.246	0.571
≥65	24	8 (33.3)	Not reached [3.1; -]	21	8 (38.1)	Not reached [1.4; -]	0.53 [0.18; 1.56]	0.249	
ECOG performance status									
0	84	26 (31.0)	Not reached [11.1; -]	97	33 (34.0)	11.3 [5.7; -]	0.61 [0.36; 1.06]	0.080	0.338
1	61	18 (29.5)	Not reached [8.3; -]	53	13 (24.5)	Not reached [7.4; -]	0.97 [0.46; 2.01]	0.925	
Region									
EU	46	14 (30.4)	Not reached [5.7; -]	43	17 (39.5)	11.1 [2.8; -]	0.60 [0.28; 1.30]	0.198	0.627
Ex-EU	100	31 (31.0)	Not reached [15.1; -]	107	29 (27.1)	Not reached [10.8; -]	0.80 [0.47; 1.35]	0.398	
Disease status following first line therapy									
Primary refractory	59	17 (28.8)	Not reached [8.4; -]	60	18 (30.0)	12.3 [4.7; -]	0.57 [0.29; 1.12]	0.105	0.327
Relapsed < 12 months	41	12 (29.3)	Not reached [10.3; -]	42	11 (26.2)	Not reached [10.8; -]	1.23 [0.54; 2.81]	0.616	
Relapsed ≥ 12 months	46	16 (34.8)	Not reached [11.1; -]	48	17 (35.4)	11.1 [2.9; -]	0.67 [0.33; 1.34]	0.252	
Prior treatment									
One prior therapy[h]	25	8 (32.0)	Not reached [6.2; -]	26	9 (34.6)	10.5 [1.4; -]	0.62 [0.21; 1.79]	0.373	0.133
At least two prior therapies incl. auto-SCT[i]	55	15 (27.3)	Not reached [-; -]	56	20 (35.7)	11.1 [2.9; -]	0.50 [0.25; 1.00]	0.049	
At least two prior therapies excl. auto-SCT[h]	66	22 (33.3)	Not reached [5.7; -]	68	17 (25.0)	Not reached [7.4; -]	1.09 [0.57; 2.08]	0.798	
Prior treatment									
One prior therapy	25	8 (32.0)	Not reached [6.2; -]	26	9 (34.6)	10.5 [1.4; -]	0.62 [0.21; 1.79]	0.373	0.769
At least two prior therapies	121	37 (30.6)	Not reached [15.1; -]	124	37 (29.8)	12.3 [10.8; -]	0.75 [0.47; 1.20]	0.239	

a: Database Cutoff Date: 16JAN2020

b: First deterioration is defined as the time to first onset of 10 points or more increase from baseline without confirmation for the EORTC QLQ-C30 symptom scores

c: Number of patients: full-analysis-set population

d: From product-limit (Kaplan-Meier) method

e: Based on stratified Cox regression model with treatment as a covariate stratified by prior auto-SCT status (yes versus no) and HL status

Study: KEYNOTE 204[a]	Pembrolizumab			Brentuximab Vedotin			Pembrolizumab vs. Brentuximab Vedotin		
EORTC QLQ-C30 Dyspnea[b]	N[c]	Patients with Event n (%)	Median Time[d] in Months [95 %-CI]	N[c]	Patients with Event n (%)	Median Time[d] in Months [95 %-CI]	Hazard Ratio [95 %-CI][e]	p-Value[e,f]	p-Value for Interaction Test[g]
after frontline therapy (primary refractory versus relapsed less than 12 months after completion of frontline therapy versus relapse 12 months or more after completion of frontline therapy) using Wald confidence interval									
f: Two-sided p-value using Wald test (Score test in case of zero event in one treatment group)									
g: Based on stratified Cox regression model with treatment, subgroup, prior auto-SCT (yes versus no) and HL status after frontline therapy (primary refractory versus relapsed less than 12 months after completion of frontline therapy versus relapse 12 months or more after completion of frontline therapy) as covariates, and a treatment-by-subgroup interaction (p-value of likelihood ratio test for interaction term)									
h: Auto-SCT was not a treatment option									
i: Auto-SCT failure									
Auto-SCT: autologous Stem Cell Transplantation; CI: Confidence Interval; ECOG: Eastern Cooperative Oncology Group; EORTC QLQ-C30: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 items; HL: Hodgkin Lymphoma									

EORTC QLQ-C30: Symptomskala Schlaflosigkeit

Tabelle 4G-24: Subgruppenanalysen mit nicht signifikantem Interaktionstest ($p \geq 0,05$) für die Symptomskala Schlaflosigkeit des EORTC QLQ-C30 aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE 204[a]	Pembrolizumab			Brentuximab Vedotin			Pembrolizumab vs. Brentuximab Vedotin		
EORTC QLQ-C30 Insomnia[b]	N[c]	Patients with Event n (%)	Median Time[d] in Months [95 %-CI]	N[c]	Patients with Event n (%)	Median Time[d] in Months [95 %-CI]	Hazard Ratio [95 %-CI][e]	p-Value[e,f]	p-Value for Interaction Test[g]
Gender									
Female	66	23 (34.8)	Not reached [8.5; -]	63	26 (41.3)	10.8 [4.2; -]	0.65 [0.36; 1.16]	0.146	0.638
Male	80	30 (37.5)	Not reached [6.3; -]	87	35 (40.2)	5.6 [4.2; 27.0]	0.75 [0.45; 1.26]	0.280	
Age									
<65	122	45 (36.9)	Not reached [8.9; -]	129	51 (39.5)	10.8 [4.2; 27.0]	0.71 [0.46; 1.08]	0.109	0.574
≥65	24	8 (33.3)	Not reached [1.4; -]	21	10 (47.6)	5.5 [1.6; 7.5]	0.73 [0.25; 2.12]	0.565	
ECOG performance status									
0	84	29 (34.5)	Not reached [8.5; -]	97	38 (39.2)	8.3 [4.2; 17.5]	0.65 [0.39; 1.08]	0.095	0.931
1	61	23 (37.7)	Not reached [5.8; -]	53	23 (43.4)	6.1 [3.2; -]	0.73 [0.40; 1.33]	0.301	
Region									
EU	46	17 (37.0)	8.9 [4.2; -]	43	14 (32.6)	8.3 [3.1; -]	0.89 [0.42; 1.90]	0.759	0.205
Ex-EU	100	36 (36.0)	Not reached [11.1; -]	107	47 (43.9)	7.5 [4.2; 17.5]	0.62 [0.39; 0.97]	0.037	
Prior treatment									
One prior therapy[h]	25	7 (28.0)	Not reached [3.0; -]	26	12 (46.2)	3.1 [2.8; -]	0.56 [0.20; 1.56]	0.268	0.285
At least two prior therapies incl. auto-SCT[i]	55	22 (40.0)	Not reached [6.3; -]	56	17 (30.4)	11.4 [8.3; -]	0.92 [0.48; 1.76]	0.797	
At least two prior	66	24	Not reached	68	32	5.6	0.65	0.133	

Study: KEYNOTE 204[a]	Pembrolizumab			Brentuximab Vedotin			Pembrolizumab vs. Brentuximab Vedotin		
EORTC QLQ-C30 Insomnia[b]	N[c]	Patients with Event n (%)	Median Time[d] in Months [95 %-CI]	N[c]	Patients with Event n (%)	Median Time[d] in Months [95 %-CI]	Hazard Ratio [95 %-CI][e]	p-Value[e,f]	p-Value for Interaction Test[g]
therapies excl. auto-SCT[h]		(36.4)	[5.8; -]		(47.1)	[4.2; 27.0]	[0.37; 1.14]		
Prior treatment									
One prior therapy	25	7 (28.0)	Not reached [3.0; -]	26	12 (46.2)	3.1 [2.8; -]	0.56 [0.20; 1.56]	0.268	0.223
At least two prior therapies	121	46 (38.0)	Not reached [8.5; -]	124	49 (39.5)	8.3 [4.9; 17.5]	0.75 [0.49; 1.15]	0.190	

a: Database Cutoff Date: 16JAN2020
b: First deterioration is defined as the time to first onset of 10 points or more increase from baseline without confirmation for the EORTC QLQ-C30 symptom scores
c: Number of patients: full-analysis-set population
d: From product-limit (Kaplan-Meier) method
e: Based on stratified Cox regression model with treatment as a covariate stratified by prior auto-SCT status (yes versus no) and HL status after frontline therapy (primary refractory versus relapsed less than 12 months after completion of frontline therapy versus relapse 12 months or more after completion of frontline therapy) using Wald confidence interval
f: Two-sided p-value using Wald test (Score test in case of zero event in one treatment group)
g: Based on stratified Cox regression model with treatment, subgroup, prior auto-SCT (yes versus no) and HL status after frontline therapy (primary refractory versus relapsed less than 12 months after completion of frontline therapy versus relapse 12 months or more after completion of frontline therapy) as covariates, and a treatment-by-subgroup interaction (p-value of likelihood ratio test for interaction term)
h: Auto-SCT was not a treatment option
i: Auto-SCT failure
Auto-SCT: autologous Stem Cell Transplantation; CI: Confidence Interval; ECOG: Eastern Cooperative Oncology Group; EORTC QLQ-C30: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 items; HL: Hodgkin Lymphoma

EORTC QLQ-C30: Symptomskala Appetitverlust

Tabelle 4G-25: Subgruppenanalysen mit nicht signifikantem Interaktionstest ($p \geq 0,05$) für die Symptomskala Appetitverlust des EORTC QLQ-C30 aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE 204[a]	Pembrolizumab			Brentuximab Vedotin			Pembrolizumab vs. Brentuximab Vedotin		
EORTC QLQ-C30 Appetite Loss[b]	N[c]	Patients with Event n (%)	Median Time[d] in Months [95 %-CI]	N[c]	Patients with Event n (%)	Median Time[d] in Months [95 %-CI]	Hazard Ratio [95 %-CI][e]	p-Value[e,f]	p-Value for Interaction Test[g]
Gender									
Female	66	17 (25.8)	25.7 [-; -]	63	30 (47.6)	7.8 [3.8; -]	0.38 [0.20; 0.71]	0.003	0.690
Male	80	13 (16.3)	Not reached [-; -]	87	28 (32.2)	11.0 [4.5; -]	0.26 [0.13; 0.53]	< 0.001	
Age									
<65	122	24 (19.7)	25.7 [25.7; -]	129	48 (37.2)	8.7 [4.5; -]	0.31 [0.19; 0.52]	< 0.001	0.854
≥65	24	6 (25.0)	Not reached [4.2; -]	21	10 (47.6)	3.5 [1.4; -]	0.38 [0.14; 1.07]	0.067	
ECOG performance status									
0	84	19 (22.6)	25.7 [25.7; -]	97	39 (40.2)	8.3 [4.2; 11.3]	0.32 [0.18; 0.57]	< 0.001	0.797
1	61	11 (18.0)	Not reached [-; -]	53	19 (35.8)	Not reached [3.2; -]	0.38 [0.18; 0.83]	0.016	

Study: KEYNOTE 204[a]	Pembrolizumab			Brentuximab Vedotin			Pembrolizumab vs. Brentuximab Vedotin		
EORTC QLQ-C30 Appetite Loss[b]	N[c]	Patients with Event n (%)	Median Time[d] in Months [95 %-CI]	N[c]	Patients with Event n (%)	Median Time[d] in Months [95 %-CI]	Hazard Ratio [95 %-CI][e]	p-Value[e,f]	p-Value for Interaction Test[g]
Region									
EU	46	10 (21.7)	Not reached [8.9; -]	43	17 (39.5)	8.3 [2.8; -]	0.31 [0.13; 0.76]	0.011	0.826
Ex-EU	100	20 (20.0)	25.7 [25.7; -]	107	41 (38.3)	8.7 [4.4; -]	0.33 [0.19; 0.57]	< 0.001	
Disease status following first line therapy									
Primary refractory	59	12 (20.3)	Not reached [-; -]	60	24 (40.0)	4.2 [3.0; -]	0.29 [0.14; 0.59]	< 0.001	0.462
Relapsed < 12 months	41	7 (17.1)	25.7 [-; -]	42	18 (42.9)	8.5 [5.6; -]	0.25 [0.10; 0.64]	0.004	
Relapsed ≥ 12 months	46	11 (23.9)	Not reached [11.1; -]	48	16 (33.3)	11.0 [4.2; -]	0.48 [0.22; 1.06]	0.070	
Prior treatment									
One prior therapy[h]	25	4 (16.0)	Not reached [-; -]	26	13 (50.0)	4.4 [1.5; -]	0.24 [0.07; 0.78]	0.018	0.245
At least two prior therapies incl. auto-SCT[i]	55	11 (20.0)	25.7 [-; -]	56	22 (39.3)	8.7 [3.8; 17.5]	0.26 [0.12; 0.56]	< 0.001	
At least two prior therapies excl. auto-SCT[h]	66	15 (22.7)	Not reached [-; -]	68	23 (33.8)	11.3 [4.2; -]	0.49 [0.25; 0.96]	0.038	
Prior treatment									
One prior therapy	25	4 (16.0)	Not reached [-; -]	26	13 (50.0)	4.4 [1.5; -]	0.24 [0.07; 0.78]	0.018	0.173
At least two prior therapies	121	26 (21.5)	25.7 [25.7; -]	124	45 (36.3)	11.0 [4.5; -]	0.37 [0.22; 0.61]	< 0.001	

a: Database Cutoff Date: 16JAN2020

b: First deterioration is defined as the time to first onset of 10 points or more increase from baseline without confirmation for the EORTC QLQ-C30 symptom scores

c: Number of patients: full-analysis-set population

d: From product-limit (Kaplan-Meier) method

e: Based on stratified Cox regression model with treatment as a covariate stratified by prior auto-SCT status (yes versus no) and HL status after frontline therapy (primary refractory versus relapsed less than 12 months after completion of frontline therapy versus relapse 12 months or more after completion of frontline therapy) using Wald confidence interval

f: Two-sided p-value using Wald test (Score test in case of zero event in one treatment group)

g: Based on stratified Cox regression model with treatment, subgroup, prior auto-SCT (yes versus no) and HL status after frontline therapy (primary refractory versus relapsed less than 12 months after completion of frontline therapy versus relapse 12 months or more after completion of frontline therapy) as covariates, and a treatment-by-subgroup interaction (p-value of likelihood ratio test for interaction term)

h: Auto-SCT was not a treatment option

i: Auto-SCT failure

Auto-SCT: autologous Stem Cell Transplantation; CI: Confidence Interval; ECOG: Eastern Cooperative Oncology Group; EORTC QLQ-C30: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 items; HL: Hodgkin Lymphoma

EORTC QLQ-C30: Symptomskala Verstopfung

Tabelle 4G-26: Subgruppenanalysen mit nicht signifikantem Interaktionstest ($p \geq 0,05$) für die Symptomskala Verstopfung des EORTC QLQ-C30 aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE 204[a]	**Pembrolizumab**			**Brentuximab Vedotin**			**Pembrolizumab vs. Brentuximab Vedotin**		
EORTC QLQ-C30 Constipation[b]	**N[c]**	**Patients with Event n (%)**	**Median Time[d] in Months [95 %-CI]**	**N[c]**	**Patients with Event n (%)**	**Median Time[d] in Months [95 %-CI]**	**Hazard Ratio [95 %-CI][e]**	**p-Value[e,f]**	**p-Value for Interaction Test[g]**
Age									
<65	122	31 (25.4)	Not reached [24.9; -]	129	33 (25.6)	27.0 [12.2; 27.0]	0.67 [0.40; 1.12]	0.129	0.194
≥65	24	10 (41.7)	8.3 [4.1; -]	21	5 (23.8)	Not reached [1.9; -]	1.52 [0.50; 4.59]	0.456	
ECOG performance status									
0	84	23 (27.4)	24.9 [24.9; -]	97	22 (22.7)	27.0 [-; -]	0.82 [0.43; 1.54]	0.534	0.684
1	61	18 (29.5)	Not reached [11.0; -]	53	16 (30.2)	12.2 [6.0; -]	0.69 [0.34; 1.39]	0.297	
Region									
EU	46	11 (23.9)	Not reached [7.6; -]	43	11 (25.6)	Not reached [4.2; -]	0.66 [0.26; 1.66]	0.373	0.806
Ex-EU	100	30 (30.0)	24.9 [24.9; -]	107	27 (25.2)	27.0 [12.2; 27.0]	0.86 [0.50; 1.48]	0.576	
Prior treatment									
One prior therapy[h]	25	8 (32.0)	Not reached [4.2; -]	26	7 (26.9)	Not reached [2.9; -]	0.72 [0.22; 2.35]	0.581	0.982
At least two prior therapies incl. auto-SCT[i]	55	16 (29.1)	Not reached [11.0; -]	56	14 (25.0)	Not reached [6.0; -]	0.81 [0.39; 1.69]	0.576	
At least two prior therapies excl. auto-SCT[h]	66	17 (25.8)	24.9 [24.9; -]	68	17 (25.0)	12.2 [11.3; 27.0]	0.81 [0.39; 1.67]	0.568	
Prior treatment									
One prior therapy	25	8 (32.0)	Not reached [4.2; -]	26	7 (26.9)	Not reached [2.9; -]	0.72 [0.22; 2.35]	0.581	0.985
At least two prior therapies	121	33 (27.3)	24.9 [24.9; -]	124	31 (25.0)	27.0 [12.2; 27.0]	0.81 [0.48; 1.36]	0.424	

a: Database Cutoff Date: 16JAN2020

b: First deterioration is defined as the time to first onset of 10 points or more increase from baseline without confirmation for the EORTC QLQ-C30 symptom scores

c: Number of patients: full-analysis-set population

d: From product-limit (Kaplan-Meier) method

e: Based on stratified Cox regression model with treatment as a covariate stratified by prior auto-SCT status (yes versus no) and HL status after frontline therapy (primary refractory versus relapsed less than 12 months after completion of frontline therapy versus relapse 12 months or more after completion of frontline therapy) using Wald confidence interval

f: Two-sided p-value using Wald test (Score test in case of zero event in one treatment group)

g: Based on stratified Cox regression model with treatment, subgroup, prior auto-SCT (yes versus no) and HL status after frontline therapy (primary refractory versus relapsed less than 12 months after completion of frontline therapy versus relapse 12 months or more after completion of frontline therapy) as covariates, and a treatment-by-subgroup interaction (p-value of likelihood ratio test for interaction term)

h: Auto-SCT was not a treatment option

i: Auto-SCT failure

Auto-SCT: autologous Stem Cell Transplantation; CI: Confidence Interval; ECOG: Eastern Cooperative Oncology Group; EORTC QLQ-C30: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 items; HL: Hodgkin Lymphoma

EORTC QLQ-C30: Symptomskala Diarrhoe

Tabelle 4G-27: Subgruppenanalysen mit nicht signifikantem Interaktionstest ($p \geq 0,05$) für die Symptomskala Diarrhoe des EORTC QLQ-C30 aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE 204[a]	**Pembrolizumab**			**Brentuximab Vedotin**			**Pembrolizumab vs. Brentuximab Vedotin**		
EORTC QLQ-C30 Diarrhea[b]	**N[c]**	**Patients with Event n (%)**	**Median Time[d] in Months [95 %-CI]**	**N[c]**	**Patients with Event n (%)**	**Median Time[d] in Months [95 %-CI]**	**Hazard Ratio [95 %-CI][e]**	**p-Value[e,f]**	**p-Value for Interaction Test[g]**
Gender									
Female	66	23 (34.8)	Not reached [8.3; -]	63	26 (41.3)	7.5 [3.2; -]	0.71 [0.40; 1.26]	0.236	0.180
Male	80	24 (30.0)	24.6 [15.0; -]	87	17 (19.5)	Not reached [-; -]	1.23 [0.65; 2.33]	0.529	
Age									
<65	122	37 (30.3)	24.6 [15.0; -]	129	37 (28.7)	Not reached [6.9; -]	0.84 [0.53; 1.35]	0.477	0.485
≥65	24	10 (41.7)	8.6 [2.8; -]	21	6 (28.6)	7.5 [3.5; -]	1.27 [0.44; 3.63]	0.656	
ECOG performance status									
0	84	22 (26.2)	Not reached [15.0; -]	97	27 (27.8)	Not reached [6.9; -]	0.71 [0.39; 1.28]	0.254	0.399
1	61	24 (39.3)	11.1 [7.9; -]	53	16 (30.2)	Not reached [5.8; -]	0.98 [0.51; 1.89]	0.944	
Region									
EU	46	13 (28.3)	Not reached [6.9; -]	43	14 (32.6)	Not reached [3.1; -]	0.77 [0.35; 1.73]	0.533	0.605
Ex-EU	100	34 (34.0)	24.6 [15.0; -]	107	29 (27.1)	Not reached [-; -]	0.96 [0.58; 1.60]	0.883	
Disease status following first line therapy									
Primary refractory	59	15 (25.4)	Not reached [15.0; -]	60	16 (26.7)	Not reached [3.5; -]	0.64 [0.31; 1.31]	0.222	0.394
Relapsed < 12 months	41	16 (39.0)	24.6 [6.9; 24.6]	42	14 (33.3)	Not reached [4.9; -]	1.13 [0.54; 2.34]	0.752	
Relapsed ≥ 12 months	46	16 (34.8)	Not reached [9.0; -]	48	13 (27.1)	Not reached [7.5; -]	1.03 [0.49; 2.16]	0.937	
Prior treatment									
One prior therapy[h]	25	8 (32.0)	Not reached [5.6; -]	26	9 (34.6)	Not reached [2.8; -]	0.59 [0.22; 1.59]	0.302	0.793
At least two prior therapies incl. auto-SCT[i]	55	21 (38.2)	24.6 [8.6; -]	56	18 (32.1)	Not reached [4.2; -]	0.93 [0.48; 1.77]	0.816	
At least two prior therapies excl. auto-SCT[h]	66	18 (27.3)	Not reached [9.0; -]	68	16 (23.5)	Not reached [-; -]	0.89 [0.45; 1.77]	0.738	
Prior treatment									
One prior therapy	25	8 (32.0)	Not reached [5.6; -]	26	9 (34.6)	Not reached [2.8; -]	0.59 [0.22; 1.59]	0.302	0.498
At least two prior therapies	121	39 (32.2)	24.6 [11.1; -]	124	34 (27.4)	Not reached [7.5; -]	0.91 [0.57; 1.45]	0.689	

a: Database Cutoff Date: 16JAN2020

b: First deterioration is defined as the time to first onset of 10 points or more increase from baseline without confirmation for the EORTC QLQ-C30 symptom scores

c: Number of patients: full-analysis-set population

d: From product-limit (Kaplan-Meier) method

e: Based on stratified Cox regression model with treatment as a covariate stratified by prior auto-SCT status (yes versus no) and HL status

Study: KEYNOTE 204[a]	Pembrolizumab			Brentuximab Vedotin			Pembrolizumab vs. Brentuximab Vedotin		
EORTC QLQ-C30 Diarrhea[b]	N[c]	Patients with Event n (%)	Median Time[d] in Months [95 %-CI]	N[c]	Patients with Event n (%)	Median Time[d] in Months [95 %-CI]	Hazard Ratio [95 %-CI][e]	p-Value[e,f]	p-Value for Interaction Test[g]
after frontline therapy (primary refractory versus relapsed less than 12 months after completion of frontline therapy versus relapse 12 months or more after completion of frontline therapy) using Wald confidence interval									
f: Two-sided p-value using Wald test (Score test in case of zero event in one treatment group)									
g: Based on stratified Cox regression model with treatment, subgroup, prior auto-SCT (yes versus no) and HL status after frontline therapy (primary refractory versus relapsed less than 12 months after completion of frontline therapy versus relapse 12 months or more after completion of frontline therapy) as covariates, and a treatment-by-subgroup interaction (p-value of likelihood ratio test for interaction term)									
h: Auto-SCT was not a treatment option									
i: Auto-SCT failure									
Auto-SCT: autologous Stem Cell Transplantation; CI: Confidence Interval; ECOG: Eastern Cooperative Oncology Group; EORTC QLQ-C30: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 items; HL: Hodgkin Lymphoma									

EQ-5D VAS (7 Punkte)

Tabelle 4G-28: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für die EQ-5D VAS (7 Punkte) aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE 204[a]	Pembrolizumab			Brentuximab Vedotin			Pembrolizumab vs. Brentuximab Vedotin		
EQ-5D VAS (7 points)[b]	N[c]	Patients with Event n (%)	Median Time[d] in Months [95 %-CI]	N[c]	Patients with Event n (%)	Median Time[d] in Months [95 %-CI]	Hazard Ratio [95 %-CI][e]	p-Value[e,f]	p-Value for Interaction Test[g]
Gender									
Female	66	22 (33.3)	Not reached [8.9; -]	63	31 (49.2)	8.3 [2.8; -]	0.50 [0.29; 0.89]	0.018	0.354
Male	80	27 (33.8)	Not reached [9.9; -]	87	30 (34.5)	7.5 [5.6; -]	0.78 [0.46; 1.32]	0.352	
Age									
<65	122	38 (31.1)	Not reached [15.1; -]	129	48 (37.2)	8.6 [5.6; -]	0.66 [0.43; 1.02]	0.061	0.409
≥65	24	11 (45.8)	9.9 [1.4; -]	21	13 (61.9)	1.6 [1.4; 7.3]	0.28 [0.10; 0.76]	0.012	
ECOG performance status									
0	84	27 (32.1)	Not reached [10.1; -]	97	42 (43.3)	7.3 [3.2; 11.3]	0.57 [0.34; 0.93]	0.026	0.550
1	61	22 (36.1)	Not reached [5.6; -]	53	19 (35.8)	Not reached [2.8; -]	0.78 [0.42; 1.46]	0.436	
Region									
EU	46	20 (43.5)	8.9 [3.7; -]	43	17 (39.5)	8.3 [2.8; -]	0.80 [0.40; 1.63]	0.546	0.193
Ex-EU	100	29 (29.0)	Not reached [-; -]	107	44 (41.1)	8.3 [5.5; -]	0.56 [0.35; 0.90]	0.017	
Disease status following first line therapy									
Primary refractory	59	15 (25.4)	Not reached [-; -]	60	17 (28.3)	Not reached [5.5; -]	0.72 [0.36; 1.45]	0.362	0.905
Relapsed < 12 months	41	13 (31.7)	Not reached [8.9; -]	42	21 (50.0)	7.3 [3.2; 11.3]	0.50 [0.24; 1.04]	0.062	
Relapsed ≥ 12 months	46	21 (45.7)	10.2 [4.2; -]	48	23 (47.9)	2.8 [1.6; -]	0.68 [0.38; 1.24]	0.212	

Study: KEYNOTE 204[a]	Pembrolizumab			Brentuximab Vedotin			Pembrolizumab vs. Brentuximab Vedotin		
EQ-5D VAS (7 points)[b]	N[c]	Patients with Event n (%)	Median Time[d] in Months [95 %-CI]	N[c]	Patients with Event n (%)	Median Time[d] in Months [95 %-CI]	Hazard Ratio [95 %-CI][e]	p-Value[e,f]	p-Value for Interaction Test[g]
Prior treatment									
One prior therapy[h]	25	11 (44.0)	10.2 [4.2; -]	26	16 (61.5)	2.8 [1.5; 5.7]	0.56 [0.25; 1.26]	0.164	0.556
At least two prior therapies incl. auto-SCT[i]	55	20 (36.4)	Not reached [5.6; -]	56	19 (33.9)	8.6 [3.2; -]	0.82 [0.43; 1.57]	0.550	
At least two prior therapies excl. auto-SCT[h]	66	18 (27.3)	Not reached [9.9; -]	68	26 (38.2)	8.3 [5.5; -]	0.59 [0.32; 1.10]	0.098	
Prior treatment									
One prior therapy	25	11 (44.0)	10.2 [4.2; -]	26	16 (61.5)	2.8 [1.5; 5.7]	0.56 [0.25; 1.26]	0.164	0.545
At least two prior therapies	121	38 (31.4)	Not reached [15.1; -]	124	45 (36.3)	8.6 [5.6; -]	0.69 [0.44; 1.08]	0.105	

a: Database Cutoff Date: 16JAN2020

b: First deterioration is defined as the first onset of 10 (7) points or more decrease from baseline without confirmation for the EQ-5D VAS score

c: Number of patients: full-analysis-set population

d: From product-limit (Kaplan-Meier) method

e: Based on stratified Cox regression model with treatment as a covariate stratified by prior auto-SCT status (yes versus no) and HL status after frontline therapy (primary refractory versus relapsed less than 12 months after completion of frontline therapy versus relapse 12 months or more after completion of frontline therapy) using Wald confidence interval

f: Two-sided p-value using Wald test (Score test in case of zero event in one treatment group)

g: Based on stratified Cox regression model with treatment, subgroup, prior auto-SCT (yes versus no) and HL status after frontline therapy (primary refractory versus relapsed less than 12 months after completion of frontline therapy versus relapse 12 months or more after completion of frontline therapy) as covariates, and a treatment-by-subgroup interaction (p-value of likelihood ratio test for interaction term)

h: Auto-SCT was not a treatment option

i: Auto-SCT failure

Auto-SCT: autologous Stem Cell Transplantation; CI: Confidence Interval; ECOG: Eastern Cooperative Oncology Group; EQ-5D VAS: European Quality of Life 5 Dimensions Visual Analog Scale; HL: Hodgkin Lymphoma

EQ-5D VAS (10 Punkte)

Tabelle 4G-29: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für die EQ-5D VAS (10 Punkte) aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE 204[a]	**Pembrolizumab**			**Brentuximab Vedotin**			**Pembrolizumab vs. Brentuximab Vedotin**		
EQ-5D VAS (10 points)[b]	**N[c]**	**Patients with Event n (%)**	**Median Time[d] in Months [95 %-CI]**	**N[c]**	**Patients with Event n (%)**	**Median Time[d] in Months [95 %-CI]**	**Hazard Ratio [95 %-CI][e]**	**p-Value[e,f]**	**p-Value for Interaction Test[g]**
Gender									
Female	66	19 (28.8)	Not reached [15.1; -]	63	30 (47.6)	8.6 [2.8; 11.4]	0.42 [0.23; 0.76]	0.004	0.165
Male	80	25 (31.3)	Not reached [10.2; -]	87	28 (32.2)	10.5 [5.7; -]	0.79 [0.46; 1.37]	0.400	
Age									
<65	122	34 (27.9)	Not reached [-; -]	129	46 (35.7)	11.0 [7.5; -]	0.61 [0.39; 0.96]	0.032	0.617
≥65	24	10 (41.7)	Not reached [1.4; -]	21	12 (57.1)	2.8 [1.4; 7.3]	0.35 [0.13; 0.94]	0.038	
ECOG performance status									
0	84	26 (31.0)	Not reached [10.2; -]	97	39 (40.2)	8.6 [5.7; 11.4]	0.60 [0.36; 1.00]	0.050	0.863
1	61	18 (29.5)	Not reached [15.1; -]	53	19 (35.8)	Not reached [2.8; -]	0.61 [0.32; 1.18]	0.144	
Region									
EU	46	17 (37.0)	8.9 [4.2; -]	43	17 (39.5)	8.3 [3.0; 11.0]	0.76 [0.37; 1.56]	0.458	0.373
Ex-EU	100	27 (27.0)	Not reached [-; -]	107	41 (38.3)	11.3 [5.7; -]	0.54 [0.33; 0.89]	0.015	
Disease status following first line therapy									
Primary refractory	59	13 (22.0)	Not reached [-; -]	60	17 (28.3)	Not reached [5.5; -]	0.58 [0.28; 1.21]	0.144	0.901
Relapsed < 12 months	41	12 (29.3)	Not reached [8.9; -]	42	19 (45.2)	8.6 [5.7; 11.4]	0.57 [0.27; 1.19]	0.135	
Relapsed ≥ 12 months	46	19 (41.3)	15.1 [5.6; -]	48	22 (45.8)	10.5 [2.8; -]	0.65 [0.35; 1.20]	0.167	
Prior treatment									
One prior therapy[h]	25	10 (40.0)	10.2 [4.2; -]	26	15 (57.7)	3.0 [1.5; 5.9]	0.59 [0.26; 1.37]	0.220	0.314
At least two prior therapies incl. auto-SCT[i]	55	19 (34.5)	Not reached [8.7; -]	56	17 (30.4)	11.4 [8.3; -]	0.89 [0.46; 1.73]	0.730	
At least two prior therapies excl. auto-SCT[h]	66	15 (22.7)	Not reached [-; -]	68	26 (38.2)	9.7 [5.5; -]	0.48 [0.25; 0.93]	0.028	
Prior treatment									
One prior therapy	25	10 (40.0)	10.2 [4.2; -]	26	15 (57.7)	3.0 [1.5; 5.9]	0.59 [0.26; 1.37]	0.220	0.792
At least two prior therapies	121	34 (28.1)	Not reached [-; -]	124	43 (34.7)	11.0 [7.5; -]	0.65 [0.41; 1.03]	0.065	

a: Database Cutoff Date: 16JAN2020

b: First deterioration is defined as the first onset of 10 (7) points or more decrease from baseline without confirmation for the EQ-5D VAS score

c: Number of patients: full-analysis-set population

d: From product-limit (Kaplan-Meier) method

e: Based on stratified Cox regression model with treatment as a covariate stratified by prior auto-SCT status (yes versus no) and HL status after frontline therapy (primary refractory versus relapsed less than 12 months after completion of frontline therapy versus relapse 12 months or more after completion of frontline therapy) using Wald confidence interval

Study: KEYNOTE 204[a]	Pembrolizumab			Brentuximab Vedotin			Pembrolizumab vs. Brentuximab Vedotin		
EQ-5D VAS (10 points)[b]	N[c]	Patients with Event n (%)	Median Time[d] in Months [95 %-CI]	N[c]	Patients with Event n (%)	Median Time[d] in Months [95 %-CI]	Hazard Ratio [95 %-CI][e]	p-Value[e,f]	p-Value for Interaction Test[g]

f: Two-sided p-value using Wald test (Score test in case of zero event in one treatment group)

g: Based on stratified Cox regression model with treatment, subgroup, prior auto-SCT (yes versus no) and HL status after frontline therapy (primary refractory versus relapsed less than 12 months after completion of frontline therapy versus relapse 12 months or more after completion of frontline therapy) as covariates, and a treatment-by-subgroup interaction (p-value of likelihood ratio test for interaction term)

h: Auto-SCT was not a treatment option

i: Auto-SCT failure

Auto-SCT: autologous Stem Cell Transplantation; CI: Confidence Interval; ECOG: Eastern Cooperative Oncology Group; EQ-5D VAS: European Quality of Life 5 Dimensions Visual Analog Scale; HL: Hodgkin Lymphoma

B-Symptomatik

Tabelle 4G-30: Subgruppenanalysen mit nicht signifikantem Interaktionstest ($p \geq 0,05$) für den Endpunkt Rückgangsrate der B-Symptomatik des EORTC QLQ-C30 aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE 204[a]	**Pembrolizumab**		**Brentuximab Vedotin**		**Pembrolizumab vs. Brentuximab Vedotin**			
B-Symptom Resolution	**N[b]**	**Patients with Event n (%)**	**N[b]**	**Patients with Event n (%)**	**Risk Ratio/ Peto-Odds Ratio[c] [95 %-CI]**	**p-Value[d]**	**Adjusted Difference[e] [95 %-CI]**	**p-Value for Interaction[f] Test**
Gender								
Female	22	21 (95.5)	20	17 (85.0)	1.15 [0.92; 1.43]	0.217	12.48 [-9.30; 36.94]	0.153
Male	20	19 (95.0)	16	10 (62.5)	1.60 [1.01; 2.54]	0.044	36.37 [7.19; 63.69]	
Age								
<65	32	32 (100.0)	31	24 (77.4)	7.09 [1.47; 34.23]	0.015	20.42 [4.67; 38.86]	n.a.
≥65	10	8 (80.0)	5	3 (60.0)	1.00 [0.08; 12.27]	> 0.999	0.00 [-45.83; 56.00]	
ECOG performance status								
0	11	11 (100.0)	18	15 (83.3)	6.18 [0.52; 74.15]	0.151	18.10 [-13.88; 46.35]	n.a.
1	31	29 (93.5)	18	12 (66.7)	5.37 [1.12; 25.67]	0.035	26.78 [1.88; 52.71]	
Region								
EU	10	9 (90.0)	6	4 (66.7)	0.90 [0.72; 1.11]	0.318	-10.34 [-55.42; 49.01]	0.834
Ex-EU	32	31 (96.9)	30	23 (76.7)	1.24 [1.02; 1.50]	0.028	18.84 [1.35; 38.10]	
Disease status following first line therapy								
Primary refractory	17	17 (100.0)	18	13 (72.2)	8.41 [1.32; 53.47]	0.024	27.39 [5.44; 51.19]	n.a.
Relapsed < 12 months	9	8 (88.9)	6	5 (83.3)	1.51 [0.08; 29.77]	0.786	5.56 [-36.16; 51.10]	
Relapsed ≥ 12 months	16	15 (93.8)	12	9 (75.0)	3.96 [0.49; 32.20]	0.198	18.20 [-10.53; 48.94]	
Prior treatment								
One prior therapy[g]	5	4 (80.0)	4	3 (75.0)	n.c.	n.c.	n.c.	n.c.
At least two prior therapies incl. auto-SCT[h]	15	14 (93.3)	13	9 (69.2)	n.c.	n.c.	n.c.	
At least two prior therapies excl. auto-SCT[g]	22	22 (100.0)	19	15 (78.9)	n.c.	n.c.	n.c.	
Prior treatment								
One prior therapy	5	4 (80.0)	4	3 (75.0)	n.c.	n.c.	n.c.	n.c.
At least two prior therapies	37	36 (97.3)	32	24 (75.0)	n.c.	n.c.	n.c.	

a: Database Cutoff Date: 16JAN2020

b: Number of patients: all-subjects-as-treated population with B-Symptoms at baseline

c: Peto-Odds Ratio instead of Mantel-Haenszel Relative Risk if incidence is <= 1 % or >= 99 % in at least one cell, stratified by prior auto-SCT (yes versus no) and HL status after frontline therapy (primary refractory versus relapsed less than 12 months after completion of

Study: KEYNOTE 204[a]	Pembrolizumab		Brentuximab Vedotin		Pembrolizumab vs. Brentuximab Vedotin			
B-Symptom Resolution	N[b]	Patients with Event n (%)	N[b]	Patients with Event n (%)	Risk Ratio/ Peto-Odds Ratio[c] [95 %-CI]	p-Value[d]	Adjusted Difference[e] [95 %-CI]	p-Value for Interaction[f] Test
frontline therapy versus relapse 12 months or more after completion of frontline therapy)								
d: Two-sided p-value based on Wald test								
e: Miettinen and Nurminen method stratified by prior auto-SCT (yes versus no) and HL status after frontline therapy (primary refractory versus relapsed less than 12 months after completion of frontline therapy versus relapse 12 months or more after completion of frontline therapy)								
f: Based on a generalized linear model with subgroup and treatment as covariates as well as treatment by subgroup interaction, considering a binomial distribution with log link function. (p-value of likelihood ratio test for interaction term)								
g: Auto-SCT was not a treatment option								
h: Auto-SCT failure								
auto-SCT: autologous Stem Cell Transplantation; CI: Confidence Interval; ECOG: Eastern Cooperative Oncology Group; HL: Hodgkin Lymphoma; n.a.: not applicable (when estimation not possible); n.c.: not calculated (at least 10 subjects per subgroup and at least 10 events in one of the subgroups necessary)								

Tabelle 4G-31: Subgruppenanalysen mit nicht signifikantem Interaktionstest ($p \geq 0,05$) für den Endpunkt Zeit bis zum erstmaligen Auftreten von B-Symptomen des EORTC QLQ-C30 aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE 204[a]	Pembrolizumab			Brentuximab Vedotin			Pembrolizumab vs. Brentuximab Vedotin		
Time to First B-Symptom	N[b]	Patients with Event n (%)	Median Time[c] in Months [95 %-CI]	N[b]	Patients with Event n (%)	Median Time[c] in Months [95 %-CI]	Hazard Ratio [95 %-CI][d]	p-Value[d,e]	p-Value for Interaction Test[f]
Gender									
Female	45	6 (13.3)	Not reached [26.9; -]	43	6 (14.0)	Not reached [-; -]	0.65 [0.19; 2.17]	0.481	0.597
Male	61	4 (6.6)	Not reached [-; -]	73	8 (11.0)	Not reached [-; -]	0.33 [0.10; 1.13]	0.079	
Age									
<65	90	7 (7.8)	Not reached [-; -]	99	12 (12.1)	Not reached [-; -]	0.37 [0.13; 1.02]	0.055	0.390
≥65	16	3 (18.8)	Not reached [8.7; -]	17	2 (11.8)	Not reached [6.4; -]	0.50 [0.07; 3.62]	0.493	
ECOG performance status									
0	73	6 (8.2)	Not reached [-; -]	81	9 (11.1)	Not reached [-; -]	0.34 [0.10; 1.12]	0.077	0.661
1	32	4 (12.5)	Not reached [-; -]	35	5 (14.3)	Not reached [-; -]	0.74 [0.20; 2.78]	0.657	
Disease status following first line therapy									
Primary refractory	43	2 (4.7)	n.c.	44	7 (15.9)	n.c.	n.c.	n.c.	n.c.
Relapsed < 12 months	32	4 (12.5)	n.c.	36	5 (13.9)	n.c.	n.c.	n.c.	
Relapsed ≥ 12 months	31	4 (12.9)	n.c.	36	2 (5.6)	n.c.	n.c.	n.c.	
Prior treatment									
One prior therapy[g]	22	2 (9.1)	Not reached [-; -]	23	2 (8.7)	Not reached [-; -]	0.66 [0.08; 5.33]	0.699	0.710
At least two prior	40	3	Not reached	43	6	Not reached	0.16	0.033	

Study: KEYNOTE 204[a]	Pembrolizumab			Brentuximab Vedotin			Pembrolizumab vs. Brentuximab Vedotin		
Time to First B-Symptom	N[b]	Patients with Event n (%)	Median Time[c] in Months [95 %-CI]	N[b]	Patients with Event n (%)	Median Time[c] in Months [95 %-CI]	Hazard Ratio [95 %-CI][d]	p-Value[d,e]	p-Value for Interaction Test[f]
therapies incl. auto-SCT[h]		(7.5)	[26.9; -]		(14.0)	[-; -]	[0.03; 0.86]		
At least two prior therapies excl. auto-SCT[g]	44	5 (11.4)	Not reached [-; -]	50	6 (12.0)	Not reached [-; -]	0.73 [0.22; 2.42]	0.601	
Prior treatment									
One prior therapy	22	2 (9.1)	Not reached [-; -]	23	2 (8.7)	Not reached [-; -]	0.66 [0.08; 5.33]	0.699	0.744
At least two prior therapies	84	8 (9.5)	Not reached [-; -]	93	12 (12.9)	Not reached [-; -]	0.40 [0.15; 1.06]	0.067	

a: Database Cutoff Date: 16JAN2020
b: Number of patients: all-subjects-as-treated population without B-Symptoms at baseline
c: From product-limit (Kaplan-Meier) method
d: Based on stratified Cox regression model with treatment as a covariate stratified by Prior auto-SCT status (yes versus no) and HL status after frontline therapy (primary refractory versus relapsed less than 12 months after completion of frontline therapy versus relapse 12 months or more after completion of frontline therapy) using Wald confidence interval
e: Two-sided p-value using Wald test (Score test in case of zero event in one treatment group)
f: Based on stratified Cox regression model with treatment, subgroup, prior auto-SCT (yes versus no) and HL status after frontline therapy (primary refractory versus relapsed less than 12 months after completion of frontline therapy versus relapse 12 months or more after completion of frontline therapy) as covariates, and a treatment-by-subgroup interaction (p-value of likelihood ratio test for interaction term)
g: Auto-SCT was not a treatment option
h: Auto-SCT failure
auto-SCT: autologous Stem Cell Transplantation; CI: Confidence Interval; ECOG: Eastern Cooperative Oncology Group; HL: Hodgkin Lymphoma; n.c.: not calculated (at least 10 subjects per subgroup and at least 10 events in one of the subgroups necessary)

Zeit bis zur ersten Folgetherapie (oder Tod)

Zeit bis zur ersten Folgetherapie oder Tod

Tabelle 4G-32: Subgruppenanalysen mit nicht signifikantem Interaktionstest ($p \geq 0,05$) für den Endpunkt Zeit bis zur ersten Folgetherapie oder Tod aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE 204[a]	Pembrolizumab			Brentuximab Vedotin			Pembrolizumab vs. Brentuximab Vedotin		
Time to First Subsequent Therapy or Death	N[b]	Patients with Event n (%)	Median Time[c] in Months [95 %-CI]	N[b]	Patients with Event n (%)	Median Time[c] in Months [95 %-CI]	Hazard Ratio [95 %-CI][d]	p-Value[d,e]	p-Value for Interaction Test[f]
Gender									
Female	67	38 (56.7)	24.0 [15.2; 33.3]	63	48 (76.2)	9.6 [6.9; 12.6]	0.40 [0.25; 0.64]	< 0.001	0.730
Male	84	43 (51.2)	25.8 [15.8; -]	90	64 (71.1)	9.3 [6.3; 12.3]	0.50 [0.34; 0.74]	< 0.001	
Age									
<65	124	66 (53.2)	24.2 [16.6; 33.3]	131	94 (71.8)	9.6 [7.6; 12.9]	0.50 [0.36; 0.69]	< 0.001	0.528
≥65	27	15 (55.6)	17.5 [7.7; -]	22	18 (81.8)	9.2 [4.0; 10.9]	0.43 [0.20; 0.90]	0.025	
Region									

Study: KEYNOTE 204[a]	Pembrolizumab			Brentuximab Vedotin			Pembrolizumab vs. Brentuximab Vedotin		
Time to First Subsequent Therapy or Death	N[b]	Patients with Event n (%)	Median Time[c] in Months [95 %-CI]	N[b]	Patients with Event n (%)	Median Time[c] in Months [95 %-CI]	Hazard Ratio [95 %-CI][d]	p-Value[d,e]	p-Value for Interaction Test[f]
EU	49	25 (51.0)	24.0 [13.5; -]	46	32 (69.6)	7.5 [4.9; 12.1]	0.49 [0.29; 0.85]	0.011	0.860
Ex-EU	102	56 (54.9)	24.2 [16.4; 33.3]	107	80 (74.8)	9.6 [8.2; 12.9]	0.46 [0.32; 0.65]	< 0.001	
Disease status following first line therapy									
Primary refractory	61	33 (54.1)	22.7 [14.3; -]	62	48 (77.4)	6.9 [4.6; 9.4]	0.43 [0.27; 0.67]	< 0.001	0.558
Relapsed < 12 months	42	19 (45.2)	25.8 [17.5; -]	42	28 (66.7)	12.1 [8.4; 18.2]	0.48 [0.27; 0.87]	0.016	
Relapsed ≥ 12 months	48	29 (60.4)	16.2 [12.3; 33.3]	49	36 (73.5)	9.7 [6.8; 17.2]	0.59 [0.36; 0.98]	0.040	
Prior treatment									
One prior therapy[g]	27	8 (29.6)	Not reached [18.4; -]	28	15 (53.6)	12.2 [7.4; -]	0.48 [0.20; 1.17]	0.106	0.847
At least two prior therapies incl. auto-SCT[h]	56	33 (58.9)	22.7 [16.6; 31.5]	56	42 (75.0)	11.3 [8.2; 15.4]	0.49 [0.31; 0.77]	0.002	
At least two prior therapies excl. auto-SCT[g]	68	40 (58.8)	16.1 [10.9; -]	69	55 (79.7)	7.1 [5.7; 9.9]	0.52 [0.35; 0.79]	0.002	
Prior treatment									
One prior therapy	27	8 (29.6)	Not reached [18.4; -]	28	15 (53.6)	12.2 [7.4; -]	0.48 [0.20; 1.17]	0.106	0.569
At least two prior therapies	124	73 (58.9)	19.3 [15.3; 30.2]	125	97 (77.6)	9.2 [6.8; 11.6]	0.50 [0.37; 0.69]	< 0.001	

a: Database Cutoff Date: 16JAN2020

b: Number of patients: intention-to-treat population

c: From product-limit (Kaplan-Meier) method

d: Based on stratified Cox regression model with treatment as a covariate stratified by prior auto-SCT status (yes versus no) and HL status after frontline therapy (primary refractory versus relapsed less than 12 months after completion of frontline therapy versus relapse 12 months or more after completion of frontline therapy) using Wald confidence interval

e: Two-sided p-value using Wald test (Score test in case of zero event in one treatment group)

f: Based on stratified Cox regression model with treatment, subgroup, prior auto-SCT (yes versus no) and HL status after frontline therapy (primary refractory versus relapsed less than 12 months after completion of frontline therapy versus relapse 12 months or more after completion of frontline therapy) as covariates, and a treatment-by-subgroup interaction (p-value of likelihood ratio test for interaction term)

g: Auto-SCT was not a treatment option

h: Auto-SCT failure

auto-SCT: autologous Stem Cell Transplantation; CI: Confidence Interval; HL: Hodgkin Lymphoma

Zeit bis zur ersten Folgetherapie

Tabelle 4G-33: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für den Endpunkt Zeit bis zur ersten Folgetherapie aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE 204[a]	Pembrolizumab			Brentuximab Vedotin			Pembrolizumab vs. Brentuximab Vedotin		
Time to First Subsequent Therapy	N[b]	Patients with Event n (%)	Median Time[c] in Months [95 %-CI]	N[b]	Patients with Event n (%)	Median Time[c] in Months [95 %-CI]	Hazard Ratio [95 %-CI][d]	p-Value[d,e]	p-Value for Interaction Test[f]

Gender									
Female	67	33 (49.3)	24.3 [16.6; -]	63	43 (68.3)	10.2 [8.2; 13.3]	0.38 [0.23; 0.62]	< 0.001	0.930
Male	84	41 (48.8)	25.8 [15.8; -]	90	58 (64.4)	9.6 [7.4; 13.6]	0.52 [0.35; 0.79]	0.002	
Age									
<65	124	61 (49.2)	25.8 [18.4; -]	131	86 (65.6)	11.5 [8.2; 13.6]	0.50 [0.36; 0.70]	< 0.001	0.638
≥65	27	13 (48.1)	31.3 [10.8; -]	22	15 (68.2)	9.2 [5.1; 11.4]	0.47 [0.21; 1.03]	0.059	
Region									
EU	49	22 (44.9)	25.8 [14.4; -]	46	30 (65.2)	7.5 [4.9; 20.2]	0.46 [0.26; 0.81]	0.008	0.843
Ex-EU	102	52 (51.0)	30.2 [18.0; -]	107	71 (66.4)	11.5 [9.1; 13.6]	0.48 [0.34; 0.70]	< 0.001	
Disease status following first line therapy									
Primary refractory	61	29 (47.5)	24.2 [14.4; -]	62	43 (69.4)	7.6 [5.1; 11.4]	0.42 [0.26; 0.68]	< 0.001	0.489
Relapsed < 12 months	42	18 (42.9)	30.2 [17.5; -]	42	25 (59.5)	12.6 [9.3; -]	0.51 [0.28; 0.94]	0.031	
Relapsed ≥ 12 months	48	27 (56.3)	18.4 [12.3; 33.3]	49	33 (67.3)	10.2 [7.6; 19.8]	0.61 [0.36; 1.01]	0.056	
Prior treatment									
One prior therapy[g]	27	8 (29.6)	Not reached [18.4; -]	28	15 (53.6)	12.2 [7.4; -]	0.48 [0.20; 1.17]	0.106	0.808
At least two prior therapies incl. auto-SCT[h]	56	30 (53.6)	25.8 [16.7; 33.3]	56	36 (64.3)	11.9 [8.8; 18.5]	0.51 [0.31; 0.83]	0.007	
At least two prior therapies excl. auto-SCT[g]	68	36 (52.9)	20.0 [11.3; -]	69	50 (72.5)	7.6 [6.2; 11.6]	0.51 [0.33; 0.79]	0.002	
Prior treatment									
One prior therapy	27	8 (29.6)	Not reached [18.4; -]	28	15 (53.6)	12.2 [7.4; -]	0.48 [0.20; 1.17]	0.106	0.561
At least two prior therapies	124	66 (53.2)	24.0 [16.6; 31.5]	125	86 (68.8)	9.5 [7.4; 12.3]	0.51 [0.37; 0.71]	< 0.001	

a: Database Cutoff Date: 16JAN2020

b: Number of patients: intention-to-treat population

c: From product-limit (Kaplan-Meier) method

d: Based on stratified Cox regression model with treatment as a covariate stratified by prior auto-SCT status (yes versus no) and HL status after frontline therapy (primary refractory versus relapsed less than 12 months after completion of frontline therapy versus relapse 12 months or more after completion of frontline therapy) using Wald confidence interval

e: Two-sided p-value using Wald test (Score test in case of zero event in one treatment group)

f: Based on stratified Cox regression model with treatment, subgroup, prior auto-SCT (yes versus no) and HL status after frontline therapy (primary refractory versus relapsed less than 12 months after completion of frontline therapy versus relapse 12 months or more after completion of frontline therapy) as covariates, and a treatment-by-subgroup interaction (p-value of likelihood ratio test for interaction term)

g: Auto-SCT was not a treatment option

h: Auto-SCT failure

auto-SCT: autologous Stem Cell Transplantation; CI: Confidence Interval; HL: Hodgkin Lymphoma

Rate an SZT als Folgetherapie

Tabelle 4G-34: Subgruppenanalysen mit nicht signifikantem Interaktionstest ($p \geq 0,05$) für den Endpunkt Rate an SZT als Folgetherapie aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE 204[a]	**Pembrolizumab**		**Brentuximab Vedotin**		**Pembrolizumab vs. Brentuximab Vedotin**			
Subsequent SCT	**N[b]**	**Patients with Event n (%)**	**N[b]**	**Patients with Event n (%)**	**Risk Ratio/ Peto-Odds Ratio[c] [95 %-CI]**	**p-Value[d]**	**Adjusted Difference[e] [95 %-CI]**	**p-Value for Interaction[f] Test**
Gender								
Female	67	19 (28.4)	63	19 (30.2)	0.96 [0.58; 1.59]	0.884	-1.11 [-16.67; 14.03]	0.915
Male	84	24 (28.6)	90	26 (28.9)	1.01 [0.63; 1.63]	0.962	0.32 [-13.11; 13.41]	
Age								
<65	124	42 (33.9)	131	42 (32.1)	1.07 [0.76; 1.49]	0.708	2.11 [-9.03; 13.14]	0.201
≥65	27	1 (3.7)	22	3 (13.6)	0.27 [0.03; 2.69]	0.266	-9.67 [-31.50; 8.69]	
ECOG performance status								
0	86	26 (30.2)	100	35 (35.0)	0.84 [0.56; 1.25]	0.383	-5.83 [-18.61; 7.28]	0.139
1	64	16 (25.0)	53	10 (18.9)	1.48 [0.74; 2.95]	0.269	8.59 [-7.17; 23.79]	
Region								
EU	49	16 (32.7)	46	15 (32.6)	1.04 [0.56; 1.92]	0.908	1.13 [-17.77; 19.09]	0.852
Ex-EU	102	27 (26.5)	107	30 (28.0)	0.95 [0.62; 1.47]	0.835	-1.26 [-13.25; 10.46]	
Disease status following first line therapy								
Primary refractory	61	21 (34.4)	62	26 (41.9)	0.81 [0.52; 1.28]	0.374	-7.77 [-24.20; 9.32]	0.683
Relapsed < 12 months	42	12 (28.6)	42	11 (26.2)	1.11 [0.56; 2.20]	0.764	2.86 [-16.27; 21.55]	
Relapsed ≥ 12 months	48	10 (20.8)	49	8 (16.3)	1.29 [0.56; 2.95]	0.549	4.67 [-11.27; 20.32]	
Prior treatment								
One prior therapy[g]	27	7 (25.9)	28	10 (35.7)	0.65 [0.29; 1.48]	0.303	-13.18 [-36.89; 12.50]	0.583
At least two prior therapies incl. auto-SCT[h]	56	9 (16.1)	56	8 (14.3)	1.13 [0.46; 2.81]	0.785	1.89 [-12.17; 15.49]	
At least two prior therapies excl. auto-SCT[g]	68	27 (39.7)	69	27 (39.1)	1.06 [0.70; 1.60]	0.799	2.12 [-14.30; 18.31]	
Prior treatment								
One prior therapy	27	7 (25.9)	28	10 (35.7)	0.65 [0.29; 1.48]	0.303	-13.18 [-36.89; 12.50]	0.299
At least two prior therapies	124	36 (29.0)	125	35 (28.0)	1.07 [0.73; 1.57]	0.715	2.02 [-8.97; 12.83]	

a: Database Cutoff Date: 16JAN2020

b: Number of patients: intention-to-treat population

c: Peto-Odds Ratio instead of Mantel-Haenszel Relative Risk if incidence is <= 1 % or >= 99 % in at least one cell, stratified by prior auto-SCT (yes versus no) and HL status after frontline therapy (primary refractory versus relapsed less than 12 months after completion of frontline therapy versus relapse 12 months or more after completion of frontline therapy)

d: Two-sided p-value based on Wald test

e: Miettinen and Nurminen method stratified by prior auto-SCT (yes versus no) and HL status after frontline therapy (primary refractory versus relapsed less than 12 months after completion of frontline therapy versus relapse 12 months or more after completion of frontline therapy)

f: Based on a generalized linear model with subgroup, treatment and stratification factors (prior auto-SCT (yes versus no), HL status after

Study: KEYNOTE 204[a]	Pembrolizumab		Brentuximab Vedotin		Pembrolizumab vs. Brentuximab Vedotin			
Subsequent SCT	N[b]	Patients with Event n (%)	N[b]	Patients with Event n (%)	Risk Ratio/ Peto-Odds Ratio[c] [95 %-CI]	p-Value[d]	Adjusted Difference[e] [95 %-CI]	p-Value for Interaction[f] Test
frontline therapy (primary refractory versus relapsed less than 12 months after completion of frontline therapy versus relapse 12 months or more after completion of frontline therapy)) as covariates as well as treatment by subgroup interaction, considering a binomial distribution with log link function. (p-value of likelihood ratio test for interaction term)								
g: Auto-SCT was not a treatment option								
h: Auto-SCT failure								
allo-SCT: allogenic Stem Cell Transplantation; auto-SCT: autologous Stem Cell Transplantation; CI: Confidence Interval; ECOG: Eastern Cooperative Oncology Group; HL: Hodgkin Lymphoma; SCT: Stem Cell Transplantation								

Objektive Ansprechrate und Komplette Remission

Tabelle 4G-35: Subgruppenanalysen mit nicht signifikantem Interaktionstest ($p \geq 0,05$) für den Endpunkt Objektive Ansprechrate aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE 204[a]	Pembrolizumab		Brentuximab Vedotin		Pembrolizumab vs. Brentuximab Vedotin			
Objective Response[b]	N[c]	Patients with Event n (%)	N[c]	Patients with Event n (%)	Risk Ratio/ Peto-Odds Ratio[d] [95 %-CI]	p-Value[e]	Adjusted Difference[f] [95 %-CI]	p-Value for Interaction[g] Test
Gender								
Female	67	48 (71.6)	63	33 (52.4)	1.40 [1.05; 1.87]	0.022	20.46 [3.54; 36.38]	0.248
Male	84	51 (60.7)	90	50 (55.6)	1.12 [0.86; 1.44]	0.405	6.30 [-8.45; 20.77]	
Age								
<65	124	86 (69.4)	131	72 (55.0)	1.26 [1.04; 1.53]	0.019	14.36 [2.42; 25.93]	0.382
≥65	27	13 (48.1)	22	11 (50.0)	0.94 [0.52; 1.68]	0.828	-3.16 [-31.25; 25.26]	
ECOG performance status								
0	86	62 (72.1)	100	56 (56.0)	1.30 [1.05; 1.62]	0.016	16.85 [3.00; 30.02]	0.421
1	64	37 (57.8)	53	27 (50.9)	1.13 [0.81; 1.56]	0.473	6.67 [-11.71; 24.74]	
Region								
EU	49	29 (59.2)	46	28 (60.9)	0.96 [0.70; 1.32]	0.808	-2.35 [-21.69; 17.25]	0.149
Ex-EU	102	70 (68.6)	107	55 (51.4)	1.33 [1.06; 1.67]	0.013	17.15 [3.85; 29.94]	
Disease status following first line therapy								
Primary refractory	61	41 (67.2)	62	27 (43.5)	1.55 [1.11; 2.16]	0.010	23.86 [6.32; 39.98]	0.122
Relapsed < 12 months	42	27 (64.3)	42	27 (64.3)	1.00 [0.73; 1.37]	0.981	-0.25 [-20.47; 20.15]	
Relapsed ≥ 12 months	48	31 (64.6)	49	29 (59.2)	1.09 [0.80; 1.49]	0.589	5.35 [-14.04; 24.31]	
Prior treatment								
One prior therapy[h]	27	18 (66.7)	28	15 (53.6)	1.26 [0.80; 1.98]	0.324	13.63 [-13.55; 38.79]	0.607
At least two prior therapies incl. auto-SCT[i]	56	39 (69.6)	56	36 (64.3)	1.08 [0.83; 1.41]	0.554	5.30 [-12.27; 22.63]	
At least two prior therapies excl. auto-SCT[h]	68	42 (61.8)	69	32 (46.4)	1.32 [0.96; 1.80]	0.083	14.94 [-1.99; 31.08]	

Study: KEYNOTE 204[a]	Pembrolizumab		Brentuximab Vedotin		Pembrolizumab vs. Brentuximab Vedotin			
Objective Response[b]	N[c]	Patients with Event n (%)	N[c]	Patients with Event n (%)	Risk Ratio/ Peto-Odds Ratio[d] [95 %-CI]	p-Value[e]	Adjusted Difference[f] [95 %-CI]	p-Value for Interaction[g] Test
Prior treatment								
One prior therapy	27	18 (66.7)	28	15 (53.6)	1.26 [0.80; 1.98]	0.324	13.63 [-13.55; 38.79]	0.772
At least two prior therapies	124	81 (65.3)	125	68 (54.4)	1.19 [0.97; 1.46]	0.089	10.57 [-1.66; 22.55]	

a: Database Cutoff Date: 16JAN2020

b: Responses are based on BICR assessments per IWG 2007 Criterion and excludes data after auto-SCT or allo-SCT

c: Number of patients: intention-to-treat population

d: Peto-Odds Ratio instead of Mantel-Haenszel Relative Risk if incidence is <= 1 % or >= 99 % in at least one cell, stratified by prior auto-SCT (yes versus no) and HL status after frontline therapy (primary refractory versus relapsed less than 12 months after completion of frontline therapy versus relapse 12 months or more after completion of frontline therapy)

e: Two-sided p-value based on Wald test

f: Miettinen and Nurminen method stratified by prior auto-SCT (yes versus no) and HL status after frontline therapy (primary refractory versus relapsed less than 12 months after completion of frontline therapy versus relapse 12 months or more after completion of frontline therapy)

g: Based on a generalized linear model with subgroup, and treatment and stratification factors (prior auto-SCT status (yes versus no), HL status after frontline therapy (primary refractory versus relapsed less than 12 months after completion of frontline therapy versus relapse 12 months or more after completion of frontline therapy)) as covariates as well as treatment by subgroup interaction, considering a binomial distribution with log link function. (p-value of likelihood ratio test for interaction term)

h: Auto-SCT was not a treatment option

i: Auto-SCT failure

allo-SCT: allogenic Stem Cell Transplantation; auto-SCT: autologous Stem Cell Transplantation; BICR: Blinded Independent Central Review; CI: Confidence Interval; ECOG: Eastern Cooperative Oncology Group; HL: Hodgkin Lymphoma; IWG: International Working Group

Tabelle 4G-36: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für den Endpunkt Komplette Remission aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE 204[a]	Pembrolizumab		Brentuximab Vedotin		Pembrolizumab vs. Brentuximab Vedotin			
Complete Remission[b]	N[c]	Patients with Event n (%)	N[c]	Patients with Event n (%)	Risk Ratio/ Peto-Odds Ratio[d] [95 %-CI]	p-Value[e]	Adjusted Difference[f] [95 %-CI]	p-Value for Interaction[g] Test
Gender								
Female	67	17 (25.4)	63	14 (22.2)	1.13 [0.60; 2.13]	0.699	2.93 [-12.14; 17.68]	0.571
Male	84	20 (23.8)	90	23 (25.6)	0.94 [0.55; 1.59]	0.804	-1.67 [-14.73; 11.41]	
Age								
<65	124	33 (26.6)	131	34 (26.0)	1.02 [0.68; 1.54]	0.917	0.57 [-10.27; 11.37]	0.897
≥65	27	4 (14.8)	22	3 (13.6)	0.86 [0.19; 3.85]	0.848	-1.81 [-24.81; 19.73]	
ECOG performance status								
0	86	22 (25.6)	100	28 (28.0)	0.92 [0.56; 1.50]	0.728	-2.31 [-15.10; 10.74]	0.447
1	64	15 (23.4)	53	9 (17.0)	1.26 [0.63; 2.51]	0.520	4.76 [-10.76; 19.09]	
Region								
EU	49	11 (22.4)	46	11 (23.9)	1.00 [0.51; 1.96]	> 0.999	0.00 [-17.39; 17.63]	0.922
Ex-EU	102	26 (25.5)	107	26 (24.3)	1.05 [0.66; 1.67]	0.848	1.14 [-10.64; 12.60]	
Disease status following first line therapy								

Study: KEYNOTE 204[a]	Pembrolizumab		Brentuximab Vedotin		Pembrolizumab vs. Brentuximab Vedotin			
Complete Remission[b]	**N[c]**	**Patients with Event n (%)**	**N[c]**	**Patients with Event n (%)**	**Risk Ratio/ Peto-Odds Ratio[d] [95 %-CI]**	**p-Value[e]**	**Adjusted Difference[f] [95 %-CI]**	**p-Value for Interaction[g] Test**
Primary refractory	61	16 (26.2)	62	11 (17.7)	1.48 [0.74; 2.93]	0.265	8.49 [-6.37; 23.23]	0.193
Relapsed < 12 months	42	9 (21.4)	42	14 (33.3)	0.64 [0.31; 1.30]	0.216	-12.24 [-31.03; 6.89]	
Relapsed ≥ 12 months	48	12 (25.0)	49	12 (24.5)	1.02 [0.51; 2.05]	0.946	0.59 [-16.82; 17.92]	
Prior treatment								
One prior therapy[h]	27	4 (14.8)	28	10 (35.7)	0.44 [0.17; 1.13]	0.089	-21.84 [-44.66; 2.77]	0.163
At least two prior therapies incl. auto-SCT[i]	56	15 (26.8)	56	14 (25.0)	1.06 [0.56; 2.00]	0.854	1.56 [-14.94; 17.61]	
At least two prior therapies excl. auto-SCT[h]	68	18 (26.5)	69	13 (18.8)	1.34 [0.73; 2.46]	0.348	6.78 [-7.55; 20.92]	
Prior treatment								
One prior therapy	27	4 (14.8)	28	10 (35.7)	0.44 [0.17; 1.13]	0.089	-21.84 [-44.66; 2.77]	0.079
At least two prior therapies	124	33 (26.6)	125	27 (21.6)	1.20 [0.77; 1.86]	0.422	4.42 [-6.37; 15.02]	

a: Database Cutoff Date: 16JAN2020

b: Responses are based on BICR assessments per IWG 2007 Criterion and excludes data after auto-SCT or allo-SCT

c: Number of patients: intention-to-treat population

d: Peto-Odds Ratio instead of Mantel-Haenszel Relative Risk if incidence is <= 1 % or >= 99 % in at least one cell, stratified by prior auto-SCT (yes versus no) and HL status after frontline therapy (primary refractory versus relapsed less than 12 months after completion of frontline therapy versus relapse 12 months or more after completion of frontline therapy)

e: Two-sided p-value based on Wald test

f: Miettinen and Nurminen method stratified by prior auto-SCT (yes versus no) and HL status after frontline therapy (primary refractory versus relapsed less than 12 months after completion of frontline therapy versus relapse 12 months or more after completion of frontline therapy)

g: Based on a generalized linear model with subgroup, and treatment and stratification factors (prior auto-SCT status (yes versus no), HL status after frontline therapy (primary refractory versus relapsed less than 12 months after completion of frontline therapy versus relapse 12 months or more after completion of frontline therapy)) as covariates as well as treatment by subgroup interaction, considering a binomial distribution with log link function. (p-value of likelihood ratio test for interaction term)

h: Auto-SCT was not a treatment option

i: Auto-SCT failure

allo-SCT: allogenic Stem Cell Transplantation; auto-SCT: autologous Stem Cell Transplantation; BICR: Blinded Independent Central Review; CI: Confidence Interval; ECOG: Eastern Cooperative Oncology Group; HL: Hodgkin Lymphoma; IWG: International Working Group

Tabelle 4G-37: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für den Endpunkt Komplette Remission bei Patienten mit B-Symptomen zu Studienbeginn aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE 204[a]	**Pembrolizumab**		**Brentuximab Vedotin**		**Pembrolizumab vs. Brentuximab Vedotin**			
Complete Remission[b]		**Patients with Event**		**Patients with Event**	**Risk Ratio/ Peto-Odds Ratio[d]**		**Adjusted Difference[f]**	**p-Value for Interaction[g]**
	N[c]	**n (%)**	**N[c]**	**n (%)**	**[95 %-CI]**	**p-Value[e]**	**[95 %-CI]**	**Test**
Gender								
Female	22	6 (27.3)	20	4 (20.0)	1.21 [0.39; 3.78]	0.740	4.51 [-24.24; 32.21]	0.697
Male	21	1 (4.8)	16	1 (6.3)	1.50 [0.11; 19.64]	0.757	2.91 [-25.03; 30.07]	
Age								
<65	32	5 (15.6)	31	5 (16.1)	0.63 [0.15; 2.57]	0.515	-6.09 [-26.38; 13.94]	n.a.
≥65	11	2 (18.2)	5	0 (0.0)	4.48 [0.07; 286.49]	0.480	12.50 [-44.26; 50.75]	
ECOG performance status								
0	11	0 (0.0)	18	4 (22.2)	n.c.	n.c.	n.c.	n.c.
1	32	7 (21.9)	18	1 (5.6)	n.c.	n.c.	n.c.	
Region								
EU	11	2 (18.2)	6	1 (16.7)	n.c.	n.c.	n.c.	n.c.
Ex-EU	32	5 (15.6)	30	4 (13.3)	n.c.	n.c.	n.c.	
Disease status following first line therapy								
Primary refractory	17	4 (23.5)	18	2 (11.1)	n.c.	n.c.	n.c.	n.c.
Relapsed < 12 months	10	1 (10.0)	6	1 (16.7)	n.c.	n.c.	n.c.	
Relapsed ≥ 12 months	16	2 (12.5)	12	2 (16.7)	n.c.	n.c.	n.c.	
Prior treatment								
One prior therapy[h]	5	1 (20.0)	4	2 (50.0)	n.c.	n.c.	n.c.	n.c.
At least two prior therapies incl. auto-SCT[i]	15	2 (13.3)	13	2 (15.4)	n.c.	n.c.	n.c.	
At least two prior therapies excl. auto-SCT[h]	23	4 (17.4)	19	1 (5.3)	n.c.	n.c.	n.c.	
Prior treatment								
One prior therapy	5	1 (20.0)	4	2 (50.0)	n.c.	n.c.	n.c.	n.c.
At least two prior therapies	38	6 (15.8)	32	3 (9.4)	n.c.	n.c.	n.c.	

a: Database Cutoff Date: 16JAN2020

b: Responses are based on BICR assessments per IWG 2007 Criterion and excludes data after auto-SCT or allo-SCT

c: Number of patients: intention-to-treat population without B-Symptoms at baseline

d: Peto-Odds Ratio instead of Mantel-Haenszel Relative Risk if incidence is <= 1 % or >= 99 % in at least one cell, stratified by prior auto-SCT (yes versus no) and HL status after frontline therapy (primary refractory versus relapsed less than 12 months after completion of frontline therapy versus relapse 12 months or more after completion of frontline therapy)

e: Two-sided p-value based on Wald test

f: Miettinen and Nurminen method stratified by prior auto-SCT (yes versus no) and HL status after frontline therapy (primary refractory versus relapsed less than 12 months after completion of frontline therapy versus relapse 12 months or more after completion of frontline

Study: KEYNOTE 204[a]	Pembrolizumab		Brentuximab Vedotin		Pembrolizumab vs. Brentuximab Vedotin			
Complete Remission[b]	N[c]	Patients with Event n (%)	N[c]	Patients with Event n (%)	Risk Ratio/ Peto-Odds Ratio[d] [95 %-CI]	p-Value[e]	Adjusted Difference[f] [95 %-CI]	p-Value for Interaction[g] Test

therapy)

g: Based on a generalized linear model with subgroup and treatment as covariates as well as treatment by subgroup interaction, considering a binomial distribution with log link function. (p-value of likelihood ratio test for interaction term)

h: Auto-SCT was not a treatment option

i: Auto-SCT failure

allo-SCT: allogenic Stem Cell Transplantation; auto-SCT: autologous Stem Cell Transplantation; BICR: Blinded Independent Central Review; CI: Confidence Interval; ECOG: Eastern Cooperative Oncology Group; HL: Hodgkin Lymphoma; IWG: International Working Group; n.a.: not applicable (when estimation not possible); n.c.: not calculated (at least 10 subjects per subgroup and at least 10 events in one of the subgroups necessary)

Ergänzende Morbiditätsendpunkte (Progressionsfreies Überleben)

Tabelle 4G-38: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für den Endpunkt Progressionsfreies Überleben aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE 204[a]	Pembrolizumab			Brentuximab Vedotin			Pembrolizumab vs. Brentuximab Vedotin		p-Value for Interaction Test[g]
Progression-Free Survival (BICR, Primary Analysis[b])	N[c]	Patients with Event n (%)	Median Time[d] in Months [95 %-CI]	N[c]	Patients with Event n (%)	Median Time[d] in Months [95 %-CI]	Hazard Ratio [95 %-CI][e]	p-Value[e,f]	
Gender									
Female	67	38 (56.7)	15.2 [11.1; 19.6]	63	43 (68.3)	5.7 [5.6; 8.8]	0.49 [0.31; 0.78]	0.003	0.417
Male	84	43 (51.2)	11.4 [8.2; -]	90	45 (50.0)	8.4 [5.8; 14.0]	0.75 [0.49; 1.14]	0.176	
Age									
<65	124	60 (48.4)	19.3 [11.3; -]	131	72 (55.0)	8.3 [5.7; 11.0]	0.59 [0.42; 0.84]	0.003	0.392
≥65	27	21 (77.8)	8.2 [3.0; 11.4]	22	16 (72.7)	5.5 [3.9; 8.3]	0.64 [0.32; 1.30]	0.222	
ECOG performance status									
0	86	40 (46.5)	19.4 [13.6; -]	100	51 (51.0)	8.4 [5.8; 11.0]	0.54 [0.35; 0.83]	0.005	0.339
1	64	40 (62.5)	8.2 [5.6; 12.5]	53	37 (69.8)	5.6 [4.3; 8.3]	0.76 [0.48; 1.21]	0.249	
Region									
EU	49	24 (49.0)	16.4 [6.4; -]	46	19 (41.3)	8.3 [5.6; -]	0.93 [0.50; 1.74]	0.832	0.242
Ex-EU	102	57 (55.9)	13.2 [9.1; 19.4]	107	69 (64.5)	8.2 [5.6; 9.1]	0.53 [0.37; 0.76]	< 0.001	
Disease status following first line therapy									
Primary refractory	61	34 (55.7)	12.5 [8.2; 23.4]	62	38 (61.3)	5.5 [3.1; 8.2]	0.52 [0.33; 0.83]	0.007	0.330
Relapsed < 12 months	42	22 (52.4)	16.4 [8.3; -]	42	24 (57.1)	11.0 [8.2; 16.6]	0.82 [0.45; 1.48]	0.506	
Relapsed ≥ 12 months	48	25 (52.1)	13.6 [7.0; -]	49	26 (53.1)	8.3 [5.6; 14.0]	0.72 [0.41; 1.25]	0.239	
Prior treatment									
One prior therapy[h]	27	13	16.4	28	13	8.4	0.70	0.392	0.762

Study: KEYNOTE 204[a]	Pembrolizumab			Brentuximab Vedotin			Pembrolizumab vs. Brentuximab Vedotin		
Progression-Free Survival (BICR, Primary Analysis[b])	**N[c]**	**Patients with Event n (%)**	**Median Time[d] in Months [95 %-CI]**	**N[c]**	**Patients with Event n (%)**	**Median Time[d] in Months [95 %-CI]**	**Hazard Ratio [95 %-CI][e]**	**p-Value[e,f]**	**p-Value for Interaction Test[g]**
		(48.1)	[8.3; -]		(46.4)	[5.4; -]	[0.31; 1.59]		
At least two prior therapies incl. auto-SCT[i]	56	30 (53.6)	14.7 [8.3; -]	56	27 (48.2)	10.8 [5.8; 19.6]	0.72 [0.42; 1.23]	0.235	
At least two prior therapies excl. auto-SCT[h]	68	38 (55.9)	11.1 [7.0; 19.2]	69	48 (69.6)	5.7 [5.3; 8.2]	0.62 [0.40; 0.95]	0.029	
Prior treatment									
One prior therapy	27	13 (48.1)	16.4 [8.3; -]	28	13 (46.4)	8.4 [5.4; -]	0.70 [0.31; 1.59]	0.392	0.870
At least two prior therapies	124	68 (54.8)	12.6 [8.7; 19.4]	125	75 (60.0)	8.2 [5.6; 8.8]	0.66 [0.47; 0.92]	0.014	
Prior auto-SCT									
Yes	56	30 (53.6)	14.7 [8.3; -]	56	27 (48.2)	10.8 [5.8; 19.6]	0.72 [0.42; 1.23]	0.235	0.423
No	95	51 (53.7)	12.5 [8.3; 19.4]	97	61 (62.9)	5.7 [5.5; 8.3]	0.61 [0.42; 0.89]	0.011	
Prior use of Brentuximab Vedotin									
Yes	5	1 (20.0)	Not reached [2.9; -]	10	6 (60.0)	5.6 [2.6; 8.4]	0.34 [0.04; 3.10]	0.336	0.097
No	146	80 (54.8)	12.7 [9.1; 19.3]	143	82 (57.3)	8.3 [5.7; 10.8]	0.67 [0.49; 0.92]	0.014	
Age									
<65	124	60 (48.4)	19.3 [11.3; -]	131	72 (55.0)	8.3 [5.7; 11.0]	0.59 [0.42; 0.84]	0.003	0.258
65-74	18	16 (88.9)	8.0 [2.8; 11.4]	16	10 (62.5)	5.7 [3.9; 8.4]	0.79 [0.31; 1.98]	0.609	
≥ 75	9	5 (55.6)	8.3 [2.8; -]	6	6 (100.0)	3.5 [0.9; 14.8]	0.25 [0.05; 1.30]	0.099	

a: Database Cutoff Date: 16JAN2020

b: The primary Progression-Free Survival analysis is based on BICR assessments per IWG Criterion and includes clinical and imaging data following auto-SCT or allo-SCT

c: Number of patients: intention-to-treat population

d: From product-limit (Kaplan-Meier) method

e: Based on stratified Cox regression model with treatment as a covariate stratified by prior auto-SCT status (yes versus no) and HL status after frontline therapy (primary refractory versus relapsed less than 12 months after completion of frontline therapy versus relapse 12 months or more after completion of frontline therapy) using Wald confidence interval

f: Two-sided p-value using Wald test (Score test in case of zero event in one treatment group)

g: Based on stratified Cox regression model with treatment, subgroup, prior auto-SCT (yes versus no) and HL status after frontline therapy (primary refractory versus relapsed less than 12 months after completion of frontline therapy versus relapse 12 months or more after completion of frontline therapy) as covariates, and a treatment-by-subgroup interaction (p-value of likelihood ratio test for interaction term)

h: Auto-SCT was not a treatment option

i: Auto-SCT failure

allo-SCT: allogenic Stem Cell Transplantation; auto-SCT: autologous Stem Cell Transplantation; BICR: Blinded Independent Central Review; CI: Confidence Interval; ECOG: Eastern Cooperative Oncology Group; HL: Hodgkin Lymphoma; IWG: International Working Group

Anhang 4-G4.2: Gesundheitsbezogene Lebensqualität

Hauptanalyse des Endpunkts Gesundheitsbezogene Lebensqualität

Im Folgenden werden die Ergebnisse der Subgruppenanalysen für die Hauptanalyse des Endpunkts Gesundheitsbezogene Lebensqualität (Zeit bis zur ersten Verschlechterung) dargestellt, für die ein nicht signifikanter Interaktionstest ($p \geq 0,05$) vorliegt.

EORTC QLQ-C30: Globaler Gesundheitsstatus

Tabelle 4G-39: Subgruppenanalysen mit nicht signifikantem Interaktionstest ($p \geq 0,05$) für den globalen Gesundheitsstatus des EORTC QLQ-C30 aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE 204[a]	**Pembrolizumab**			**Brentuximab Vedotin**			**Pembrolizumab vs. Brentuximab Vedotin**		
EORTC QLQ-C30 Global Health Status/ QoL[b]	**N[c]**	**Patients with Event n (%)**	**Median Time[d] in Months [95 %-CI]**	**N[c]**	**Patients with Event n (%)**	**Median Time[d] in Months [95 %-CI]**	**Hazard Ratio [95 %-CI][e]**	**p-Value[e,f]**	**p-Value for Interaction Test[g]**
Gender									
Female	66	21 (31.8)	Not reached [11.0; -]	63	32 (50.8)	5.5 [3.2; 24.1]	0.40 [0.22; 0.70]	0.002	0.315
Male	80	31 (38.8)	13.6 [10.1; 26.2]	87	38 (43.7)	4.9 [3.0; 11.6]	0.60 [0.37; 0.99]	0.047	
Age									
<65	122	42 (34.4)	19.5 [11.1; 26.2]	129	57 (44.2)	6.1 [4.1; 11.6]	0.51 [0.33; 0.77]	0.002	0.216
≥65	24	10 (41.7)	9.9 [2.8; -]	21	13 (61.9)	1.6 [1.4; 4.4]	0.37 [0.15; 0.94]	0.036	
ECOG performance status									
0	84	36 (42.9)	11.1 [8.9; 26.2]	97	44 (45.4)	5.6 [3.2; 11.6]	0.66 [0.41; 1.06]	0.084	0.101
1	61	16 (26.2)	Not reached [13.6; -]	53	26 (49.1)	4.9 [2.8; -]	0.35 [0.18; 0.69]	0.002	
Region									
EU	46	13 (28.3)	Not reached [8.9; -]	43	18 (41.9)	4.2 [2.8; -]	0.46 [0.21; 0.99]	0.048	0.829
Ex-EU	100	39 (39.0)	19.5 [11.1; 26.2]	107	52 (48.6)	6.1 [3.2; 11.6]	0.50 [0.32; 0.77]	0.002	
Disease status following first line therapy									
Primary refractory	59	22 (37.3)	19.5 [11.1; -]	60	23 (38.3)	5.5 [3.0; -]	0.63 [0.34; 1.15]	0.129	0.512
Relapsed < 12 months	41	15 (36.6)	17.2 [8.9; -]	42	23 (54.8)	5.5 [3.2; 24.1]	0.51 [0.26; 1.01]	0.054	
Relapsed ≥ 12 months	46	15 (32.6)	26.2 [9.9; 26.2]	48	24 (50.0)	5.6 [2.8; 11.6]	0.36 [0.18; 0.70]	0.003	
Prior treatment									
One prior therapy[h]	25	9 (36.0)	10.2 [4.2; -]	26	18 (69.2)	1.6 [1.4; 3.2]	0.27 [0.11; 0.67]	0.005	0.180
At least two prior therapies incl. auto-SCT[i]	55	22 (40.0)	17.2 [10.3; -]	56	23 (41.1)	8.3 [3.2; -]	0.57 [0.31; 1.05]	0.071	
At least two prior	66	21	26.2	68	29	6.2	0.56	0.057	

Study: KEYNOTE 204[a]	Pembrolizumab			Brentuximab Vedotin			Pembrolizumab vs. Brentuximab Vedotin		
EORTC QLQ-C30 Global Health Status/ QoL[b]	N[c]	Patients with Event n (%)	Median Time[d] in Months [95 %-CI]	N[c]	Patients with Event n (%)	Median Time[d] in Months [95 %-CI]	Hazard Ratio [95 %-CI][e]	p-Value[e,f]	p-Value for Interaction Test[g]
therapies excl. auto-SCT[h]		(31.8)	[9.9; 26.2]		(42.6)	[4.1; -]	[0.31; 1.02]		
Prior treatment									
One prior therapy	25	9 (36.0)	10.2 [4.2; -]	26	18 (69.2)	1.6 [1.4; 3.2]	0.27 [0.11; 0.67]	0.005	0.069
At least two prior therapies	121	43 (35.5)	19.5 [11.1; 26.2]	124	52 (41.9)	6.5 [4.4; 11.6]	0.57 [0.37; 0.87]	0.009	

a: Database Cutoff Date: 16JAN2020
b: First deterioration is defined as the time to first onset of 10 points or more decrease from baseline without confirmation for the EORTC QLQ-C30 functional scores
c: Number of patients: full-analysis-set population
d: From product-limit (Kaplan-Meier) method
e: Based on stratified Cox regression model with treatment as a covariate stratified by prior auto-SCT status (yes versus no) and HL status after frontline therapy (primary refractory versus relapsed less than 12 months after completion of frontline therapy versus relapse 12 months or more after completion of frontline therapy) using Wald confidence interval
f: Two-sided p-value using Wald test (Score test in case of zero event in one treatment group)
g: Based on stratified Cox regression model with treatment, subgroup, prior auto-SCT (yes versus no) and HL status after frontline therapy (primary refractory versus relapsed less than 12 months after completion of frontline therapy versus relapse 12 months or more after completion of frontline therapy) as covariates, and a treatment-by-subgroup interaction (p-value of likelihood ratio test for interaction term)
h: Auto-SCT was not a treatment option
i: Auto-SCT failure
Auto-SCT: autologous Stem Cell Transplantation; CI: Confidence Interval; ECOG: Eastern Cooperative Oncology Group; EORTC QLQ-C30: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 items; HL: Hodgkin Lymphoma; QoL: Quality of Life

EORTC QLQ-C30: Funktionsskala Körperliche Funktion

Tabelle 4G-40: Subgruppenanalysen mit nicht signifikantem Interaktionstest ($p \geq 0,05$) für die Funktionsskala Körperliche Funktion des EORTC QLQ-C30 aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE 204[a]	Pembrolizumab			Brentuximab Vedotin			Pembrolizumab vs. Brentuximab Vedotin		
EORTC QLQ-C30 Physical Functioning[b]	N[c]	Patients with Event n (%)	Median Time[d] in Months [95 %-CI]	N[c]	Patients with Event n (%)	Median Time[d] in Months [95 %-CI]	Hazard Ratio [95 %-CI][e]	p-Value[e,f]	p-Value for Interaction Test[g]
Gender									
Female	66	24 (36.4)	24.7 [8.5; -]	63	28 (44.4)	8.3 [3.3; -]	0.54 [0.30; 0.95]	0.033	0.352
Male	80	22 (27.5)	Not reached [13.6; -]	87	36 (41.4)	6.2 [4.9; 10.5]	0.42 [0.24; 0.72]	0.002	
ECOG performance status									
0	84	26 (31.0)	Not reached [11.4; -]	97	37 (38.1)	8.5 [5.9; 11.4]	0.60 [0.35; 1.00]	0.051	0.333
1	61	20 (32.8)	24.7 [11.1; -]	53	27 (50.9)	6.2 [2.8; 10.5]	0.34 [0.18; 0.63]	< 0.001	
Region									
EU	46	14 (30.4)	12.9 [5.7; -]	43	20 (46.5)	5.9 [2.8; 9.4]	0.45 [0.21; 0.94]	0.033	0.941

Study: KEYNOTE 204[a]	Pembrolizumab			Brentuximab Vedotin			Pembrolizumab vs. Brentuximab Vedotin		
EORTC QLQ-C30 Physical Functioning[b]	N[c]	Patients with Event n (%)	Median Time[d] in Months [95 %-CI]	N[c]	Patients with Event n (%)	Median Time[d] in Months [95 %-CI]	Hazard Ratio [95 %-CI][e]	p-Value[e,f]	p-Value for Interaction Test[g]
Ex-EU	100	32 (32.0)	Not reached [13.6; -]	107	44 (41.1)	8.5 [5.6; 11.4]	0.48 [0.30; 0.77]	0.003	
Disease status following first line therapy									
Primary refractory	59	18 (30.5)	Not reached [8.5; -]	60	21 (35.0)	6.4 [2.8; -]	0.57 [0.30; 1.09]	0.092	0.487
Relapsed < 12 months	41	13 (31.7)	Not reached [5.5; -]	42	18 (42.9)	10.8 [5.9; 19.5]	0.60 [0.29; 1.26]	0.179	
Relapsed ≥ 12 months	46	15 (32.6)	24.7 [11.1; -]	48	25 (52.1)	6.2 [2.8; 8.6]	0.33 [0.17; 0.64]	0.001	
Prior treatment									
One prior therapy[h]	25	8 (32.0)	24.7 [6.9; 24.7]	26	15 (57.7)	4.2 [1.5; 6.2]	0.30 [0.12; 0.76]	0.011	0.468
At least two prior therapies incl. auto-SCT[i]	55	19 (34.5)	Not reached [11.1; -]	56	24 (42.9)	8.5 [5.6; 11.4]	0.50 [0.27; 0.93]	0.028	
At least two prior therapies excl. auto-SCT[h]	66	19 (28.8)	Not reached [11.4; -]	68	25 (36.8)	8.5 [4.9; -]	0.53 [0.29; 0.99]	0.047	
Prior treatment									
One prior therapy	25	8 (32.0)	24.7 [6.9; 24.7]	26	15 (57.7)	4.2 [1.5; 6.2]	0.30 [0.12; 0.76]	0.011	0.220
At least two prior therapies	121	38 (31.4)	Not reached [12.9; -]	124	49 (39.5)	8.5 [6.2; 19.5]	0.52 [0.33; 0.80]	0.003	

a: Database Cutoff Date: 16JAN2020

b: First deterioration is defined as the time to first onset of 10 points or more decrease from baseline without confirmation for the EORTC QLQ-C30 functional scores

c: Number of patients: full-analysis-set population

d: From product-limit (Kaplan-Meier) method

e: Based on stratified Cox regression model with treatment as a covariate stratified by prior auto-SCT status (yes versus no) and HL status after frontline therapy (primary refractory versus relapsed less than 12 months after completion of frontline therapy versus relapse 12 months or more after completion of frontline therapy) using Wald confidence interval

f: Two-sided p-value using Wald test (Score test in case of zero event in one treatment group)

g: Based on stratified Cox regression model with treatment, subgroup, prior auto-SCT (yes versus no) and HL status after frontline therapy (primary refractory versus relapsed less than 12 months after completion of frontline therapy versus relapse 12 months or more after completion of frontline therapy) as covariates, and a treatment-by-subgroup interaction (p-value of likelihood ratio test for interaction term)

h: Auto-SCT was not a treatment option

i: Auto-SCT failure

Auto-SCT: autologous Stem Cell Transplantation; CI: Confidence Interval; ECOG: Eastern Cooperative Oncology Group; EORTC QLQ-C30: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 items; HL: Hodgkin Lymphoma

EORTC QLQ-C30: Funktionsskala Rollenfunktion

Tabelle 4G-41: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für die Funktionsskala Rollenfunktion des EORTC QLQ-C30 aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE 204[a]	**Pembrolizumab**			**Brentuximab Vedotin**			**Pembrolizumab vs. Brentuximab Vedotin**		
EORTC QLQ-C30 Role Functioning[b]	**N[c]**	**Patients with Event n (%)**	**Median Time[d] in Months [95 %-CI]**	**N[c]**	**Patients with Event n (%)**	**Median Time[d] in Months [95 %-CI]**	**Hazard Ratio [95 %-CI][e]**	**p-Value[e,f]**	**p-Value for Interaction Test[g]**
Gender									
Female	66	28 (42.4)	10.3 [4.7; -]	63	40 (63.5)	3.2 [1.6; 4.6]	0.49 [0.30; 0.81]	0.005	0.465
Male	80	30 (37.5)	Not reached [7.1; -]	87	40 (46.0)	5.8 [3.5; 8.9]	0.59 [0.36; 0.97]	0.037	
Age									
<65	122	45 (36.9)	Not reached [8.5; -]	129	65 (50.4)	4.5 [4.1; 8.5]	0.51 [0.35; 0.76]	< 0.001	0.618
≥65	24	13 (54.2)	4.9 [1.4; -]	21	15 (71.4)	1.7 [1.4; 2.8]	0.36 [0.15; 0.85]	0.019	
ECOG performance status									
0	84	32 (38.1)	11.1 [8.4; -]	97	51 (52.6)	4.5 [3.0; 6.9]	0.53 [0.33; 0.84]	0.006	0.949
1	61	26 (42.6)	8.5 [4.2; -]	53	29 (54.7)	3.2 [1.7; 8.5]	0.55 [0.32; 0.96]	0.036	
Region									
EU	46	16 (34.8)	Not reached [3.7; -]	43	20 (46.5)	4.2 [2.8; 11.0]	0.59 [0.30; 1.19]	0.142	0.629
Ex-EU	100	42 (42.0)	11.1 [7.1; -]	107	60 (56.1)	4.4 [2.8; 6.9]	0.49 [0.32; 0.74]	< 0.001	
Disease status following first line therapy									
Primary refractory	59	25 (42.4)	8.5 [5.7; -]	60	25 (41.7)	3.8 [2.8; -]	0.66 [0.37; 1.16]	0.149	0.399
Relapsed < 12 months	41	15 (36.6)	Not reached [2.8; -]	42	25 (59.5)	4.5 [2.9; 17.0]	0.61 [0.32; 1.19]	0.149	
Relapsed ≥ 12 months	46	18 (39.1)	Not reached [4.2; -]	48	30 (62.5)	4.4 [1.9; 5.8]	0.35 [0.19; 0.65]	< 0.001	
Prior treatment									
One prior therapy[h]	25	11 (44.0)	7.1 [2.8; -]	26	17 (65.4)	4.1 [1.5; 4.5]	0.64 [0.28; 1.47]	0.297	0.531
At least two prior therapies incl. auto-SCT[i]	55	25 (45.5)	11.1 [4.1; -]	56	27 (48.2)	5.8 [3.0; 11.0]	0.63 [0.36; 1.10]	0.102	
At least two prior therapies excl. auto-SCT[h]	66	22 (33.3)	Not reached [7.6; -]	68	36 (52.9)	4.5 [1.9; 8.5]	0.42 [0.25; 0.73]	0.002	
Prior treatment									
One prior therapy	25	11 (44.0)	7.1 [2.8; -]	26	17 (65.4)	4.1 [1.5; 4.5]	0.64 [0.28; 1.47]	0.297	0.930
At least two prior therapies	121	47 (38.8)	Not reached [8.4; -]	124	63 (50.8)	4.5 [3.0; 8.5]	0.51 [0.35; 0.76]	< 0.001	

a: Database Cutoff Date: 16JAN2020

b: First deterioration is defined as the time to first onset of 10 points or more decrease from baseline without confirmation for the EORTC QLQ-C30 functional scores

c: Number of patients: full-analysis-set population

d: From product-limit (Kaplan-Meier) method

e: Based on stratified Cox regression model with treatment as a covariate stratified by prior auto-SCT status (yes versus no) and HL status

Study: KEYNOTE 204[a]	Pembrolizumab			Brentuximab Vedotin			Pembrolizumab vs. Brentuximab Vedotin		
EORTC QLQ-C30 Role Functioning[b]	N[c]	Patients with Event n (%)	Median Time[d] in Months [95 %-CI]	N[c]	Patients with Event n (%)	Median Time[d] in Months [95 %-CI]	Hazard Ratio [95 %-CI][e]	p-Value[e,f]	p-Value for Interaction Test[g]
after frontline therapy (primary refractory versus relapsed less than 12 months after completion of frontline therapy versus relapse 12 months or more after completion of frontline therapy) using Wald confidence interval									
f: Two-sided p-value using Wald test (Score test in case of zero event in one treatment group)									
g: Based on stratified Cox regression model with treatment, subgroup, prior auto-SCT (yes versus no) and HL status after frontline therapy (primary refractory versus relapsed less than 12 months after completion of frontline therapy versus relapse 12 months or more after completion of frontline therapy) as covariates, and a treatment-by-subgroup interaction (p-value of likelihood ratio test for interaction term)									
h: Auto-SCT was not a treatment option									
i: Auto-SCT failure									
Auto-SCT: autologous Stem Cell Transplantation; CI: Confidence Interval; ECOG: Eastern Cooperative Oncology Group; EORTC QLQ-C30: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 items; HL: Hodgkin Lymphoma									

EORTC QLQ-C30: Funktionsskala Emotionale Funktion

Tabelle 4G-42: Subgruppenanalysen mit nicht signifikantem Interaktionstest ($p \geq 0,05$) für die Funktionsskala Emotionale Funktion des EORTC QLQ-C30 aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE 204[a]	Pembrolizumab			Brentuximab Vedotin			Pembrolizumab vs. Brentuximab Vedotin		
EORTC QLQ-C30 Emotional Functioning	N[b]	Patients with Event n (%)	Median Time[c] in Months [95 %-CI]	N[b]	Patients with Event n (%)	Median Time[c] in Months [95 %-CI]	Hazard Ratio [95 %-CI][d]	p-Value[d,e]	p-Value for Interaction Test[f]
Gender									
Female	66	25 (37.9)	25.7 [9.4; 25.7]	63	29 (46.0)	9.7 [4.2; 11.0]	0.54 [0.30; 0.94]	0.031	0.233
Male	80	19 (23.8)	Not reached [-; -]	87	36 (41.4)	5.7 [4.2; 10.5]	0.38 [0.22; 0.67]	< 0.001	
Age									
<65	122	38 (31.1)	25.7 [24.0; -]	129	55 (42.6)	8.6 [4.5; 10.8]	0.48 [0.31; 0.75]	0.001	0.342
≥65	24	6 (25.0)	Not reached [4.2; -]	21	10 (47.6)	5.6 [1.6; -]	0.39 [0.14; 1.13]	0.084	
ECOG performance status									
0	84	23 (27.4)	25.7 [24.0; -]	97	43 (44.3)	6.2 [4.2; 10.8]	0.36 [0.21; 0.62]	< 0.001	0.517
1	61	20 (32.8)	Not reached [7.6; -]	53	22 (41.5)	10.2 [3.9; 11.0]	0.60 [0.32; 1.11]	0.103	
Region									
EU	46	15 (32.6)	Not reached [4.7; -]	43	15 (34.9)	8.6 [2.9; -]	0.66 [0.31; 1.39]	0.270	0.292
Ex-EU	100	29 (29.0)	25.7 [24.0; -]	107	50 (46.7)	6.2 [4.2; 10.8]	0.37 [0.23; 0.60]	< 0.001	
Disease status following first line therapy									
Primary refractory	59	16 (27.1)	24.0 [9.4; -]	60	22 (36.7)	5.8 [3.8; 10.8]	0.43 [0.22; 0.84]	0.014	0.871
Relapsed < 12 months	41	13 (31.7)	25.7 [8.9; 25.7]	42	20 (47.6)	9.7 [4.2; 11.7]	0.50 [0.24; 1.04]	0.065	
Relapsed ≥ 12 months	46	15	Not reached	48	23	5.6	0.42	0.011	

Study: KEYNOTE 204[a]	Pembrolizumab			Brentuximab Vedotin			Pembrolizumab vs. Brentuximab Vedotin		
EORTC QLQ-C30 Emotional Functioning	N[b]	Patients with Event n (%)	Median Time[c] in Months [95 %-CI]	N[b]	Patients with Event n (%)	Median Time[c] in Months [95 %-CI]	Hazard Ratio [95 %-CI][d]	p-Value[d,e]	p-Value for Interaction Test[f]
		(32.6)	[11.1; -]		(47.9)	[3.9; 10.5]	[0.22; 0.82]		
Prior treatment									
One prior therapy[g]	25	3 (12.0)	Not reached [-; -]	26	12 (46.2)	10.5 [1.6; -]	0.20 [0.06; 0.72]	0.014	0.126
At least two prior therapies incl. auto-SCT[h]	55	18 (32.7)	25.7 [11.1; 25.7]	56	21 (37.5)	10.2 [4.5; 11.4]	0.50 [0.25; 0.96]	0.038	
At least two prior therapies excl. auto-SCT[g]	66	23 (34.8)	24.0 [7.6; -]	68	32 (47.1)	5.8 [4.2; 9.7]	0.56 [0.32; 0.99]	0.045	

a: Database Cutoff Date: 16JAN2020

b: Number of patients: full-analysis-set population

c: From product-limit (Kaplan-Meier) method

d: Based on stratified Cox regression model with treatment as a covariate stratified by prior auto-SCT status (yes versus no) and HL status after frontline therapy (primary refractory vs. versus relapsed less than 12 months after completion of frontline therapy versus relapse 12 months or more after completion of frontline therapy) using Wald confidence interval

e: Two-sided p-value using Wald test (Score test in case of zero event in one treatment group)

f: Based on stratified Cox regression model with treatment, subgroup, prior auto-SCT (yes versus no) and HL status after frontline therapy (primary refractory vs. versus relapsed less than 12 months after completion of frontline therapy versus relapse 12 months or more after completion of frontline therapy) as covariates, and a treatment-by-subgroup interaction (p-value of likelihood ratio test for interaction term)

g: Auto-SCT was not a treatment option

h: Auto-SCT failure

First deterioration is defined as the time to first onset of 10 points or more decrease from baseline without confirmation for the EORTC QLQ-C30 functional scores

Auto-SCT: autologous Stem Cell Transplantation; CI: Confidence Interval; ECOG: Eastern Cooperative Oncology Group; EORTC QLQ-C30: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 items; HL: Hodgkin Lymphoma

EORTC QLQ-C30: Funktionsskala Kognitive Funktion

Tabelle 4G-43: Subgruppenanalysen mit nicht signifikantem Interaktionstest ($p \geq 0,05$) für die Funktionsskala Kognitive Funktion des EORTC QLQ-C30 aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE 204[a]	Pembrolizumab			Brentuximab Vedotin			Pembrolizumab vs. Brentuximab Vedotin		
EORTC QLQ-C30 Cognitive Functioning[b]	N[c]	Patients with Event n (%)	Median Time[d] in Months [95 %-CI]	N[c]	Patients with Event n (%)	Median Time[d] in Months [95 %-CI]	Hazard Ratio [95 %-CI][e]	p-Value[e,f]	p-Value for Interaction Test[g]
Gender									
Female	66	38 (57.6)	5.7 [4.2; 11.1]	63	32 (50.8)	4.2 [2.8; -]	0.82 [0.50; 1.34]	0.430	0.278
Male	80	24 (30.0)	Not reached [23.4; -]	87	33 (37.9)	5.8 [4.2; 17.5]	0.62 [0.36; 1.08]	0.091	
Age									
<65	122	48 (39.3)	15.1 [8.9; -]	129	54 (41.9)	5.8 [4.2; 17.5]	0.70 [0.47; 1.04]	0.076	0.726
≥65	24	14 (58.3)	4.2 [1.4; -]	21	11 (52.4)	4.2 [1.4; -]	0.95 [0.42; 2.15]	0.899	
ECOG performance status									
0	84	30 (35.7)	Not reached [8.4; -]	97	40 (41.2)	5.8 [4.2; 17.5]	0.64 [0.39; 1.04]	0.070	0.351

Study: KEYNOTE 204[a]	Pembrolizumab			Brentuximab Vedotin			Pembrolizumab vs. Brentuximab Vedotin		
EORTC QLQ-C30 Cognitive Functioning[b]	N[c]	Patients with Event n (%)	Median Time[d] in Months [95 %-CI]	N[c]	Patients with Event n (%)	Median Time[d] in Months [95 %-CI]	Hazard Ratio [95 %-CI][e]	p-Value[e,f]	p-Value for Interaction Test[g]
1	61	32 (52.5)	5.8 [4.2; 15.1]	53	25 (47.2)	4.9 [2.8; -]	0.83 [0.48; 1.44]	0.513	
Region									
EU	46	18 (39.1)	8.4 [2.8; -]	43	16 (37.2)	4.2 [3.1; -]	0.98 [0.48; 1.98]	0.949	0.421
Ex-EU	100	44 (44.0)	15.1 [5.7; -]	107	49 (45.8)	5.8 [4.2; 17.5]	0.67 [0.44; 1.02]	0.061	
Disease status following first line therapy									
Primary refractory	59	20 (33.9)	23.4 [5.7; -]	60	21 (35.0)	6.4 [3.2; -]	0.66 [0.35; 1.24]	0.195	0.773
Relapsed < 12 months	41	20 (48.8)	8.9 [4.2; 24.3]	42	20 (47.6)	5.8 [2.8; -]	0.87 [0.46; 1.63]	0.667	
Relapsed ≥ 12 months	46	22 (47.8)	11.1 [3.0; -]	48	24 (50.0)	4.9 [2.8; 6.2]	0.73 [0.40; 1.32]	0.292	
Prior treatment									
One prior therapy[h]	25	10 (40.0)	24.3 [4.2; 24.3]	26	15 (57.7)	4.2 [1.4; 11.7]	0.46 [0.19; 1.09]	0.078	0.423
At least two prior therapies incl. auto-SCT[i]	55	26 (47.3)	11.1 [5.6; -]	56	23 (41.1)	5.8 [3.5; 17.5]	0.81 [0.46; 1.45]	0.481	
At least two prior therapies excl. auto-SCT[h]	66	26 (39.4)	23.4 [4.4; -]	68	27 (39.7)	6.1 [4.2; -]	0.85 [0.49; 1.49]	0.578	
Prior treatment									
One prior therapy	25	10 (40.0)	24.3 [4.2; 24.3]	26	15 (57.7)	4.2 [1.4; 11.7]	0.46 [0.19; 1.09]	0.078	0.192
At least two prior therapies	121	52 (43.0)	13.1 [5.7; -]	124	50 (40.3)	6.1 [4.2; -]	0.83 [0.56; 1.24]	0.375	

a: Database Cutoff Date: 16JAN2020

b: First deterioration is defined as the time to first onset of 10 points or more decrease from baseline without confirmation for the EORTC QLQ-C30 functional scores

c: Number of patients: full-analysis-set population

d: From product-limit (Kaplan-Meier) method

e: Based on stratified Cox regression model with treatment as a covariate stratified by prior auto-SCT status (yes versus no) and HL status after frontline therapy (primary refractory versus relapsed less than 12 months after completion of frontline therapy versus relapse 12 months or more after completion of frontline therapy) using Wald confidence interval

f: Two-sided p-value using Wald test (Score test in case of zero event in one treatment group)

g: Based on stratified Cox regression model with treatment, subgroup, prior auto-SCT (yes versus no) and HL status after frontline therapy (primary refractory versus relapsed less than 12 months after completion of frontline therapy versus relapse 12 months or more after completion of frontline therapy) as covariates, and a treatment-by-subgroup interaction (p-value of likelihood ratio test for interaction term)

h: Auto-SCT was not a treatment option

i: Auto-SCT failure

Auto-SCT: autologous Stem Cell Transplantation; CI: Confidence Interval; ECOG: Eastern Cooperative Oncology Group; EORTC QLQ-C30: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 items; HL: Hodgkin Lymphoma

EORTC QLQ-C30: Funktionsskala Soziale Funktion

Tabelle 4G-44: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für die Funktionsskala Soziale Funktion des EORTC QLQ-C30 aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE 204[a]	**Pembrolizumab**			**Brentuximab Vedotin**			**Pembrolizumab vs. Brentuximab Vedotin**		
EORTC QLQ-C30 Social Functioning[b]	**N[c]**	**Patients with Event n (%)**	**Median Time[d] in Months [95 %-CI]**	**N[c]**	**Patients with Event n (%)**	**Median Time[d] in Months [95 %-CI]**	**Hazard Ratio [95 %-CI][e]**	**p-Value[e,f]**	**p-Value for Interaction Test[g]**
Gender									
Female	66	22 (33.3)	17.0 [13.3; -]	63	30 (47.6)	4.4 [3.0; -]	0.37 [0.20; 0.69]	0.002	0.206
Male	80	32 (40.0)	17.7 [5.7; -]	87	33 (37.9)	5.9 [4.2; 11.1]	0.64 [0.38; 1.08]	0.092	
Age									
<65	122	45 (36.9)	17.0 [13.3; -]	129	49 (38.0)	7.9 [4.4; 11.4]	0.56 [0.36; 0.87]	0.010	0.155
≥65	24	9 (37.5)	Not reached [2.9; -]	21	14 (66.7)	3.0 [1.4; 4.2]	0.42 [0.17; 1.09]	0.074	
ECOG performance status									
0	84	29 (34.5)	Not reached [9.8; -]	97	38 (39.2)	7.9 [4.2; 11.4]	0.62 [0.37; 1.04]	0.069	0.807
1	61	25 (41.0)	13.6 [11.1; 24.8]	53	25 (47.2)	4.2 [3.0; -]	0.43 [0.23; 0.81]	0.009	
Region									
EU	46	18 (39.1)	9.8 [4.7; -]	43	15 (34.9)	4.7 [3.7; -]	0.70 [0.32; 1.49]	0.351	0.163
Ex-EU	100	36 (36.0)	24.8 [13.6; -]	107	48 (44.9)	6.1 [4.2; 11.1]	0.44 [0.28; 0.71]	< 0.001	
Disease status following first line therapy									
Primary refractory	59	24 (40.7)	13.6 [5.7; -]	60	24 (40.0)	4.5 [3.4; 7.9]	0.53 [0.29; 0.98]	0.042	0.822
Relapsed < 12 months	41	12 (29.3)	Not reached [10.3; -]	42	16 (38.1)	11.1 [8.3; -]	0.55 [0.24; 1.24]	0.150	
Relapsed ≥ 12 months	46	18 (39.1)	17.0 [9.8; -]	48	23 (47.9)	4.2 [2.9; -]	0.48 [0.25; 0.92]	0.027	
Prior treatment									
One prior therapy[h]	25	8 (32.0)	Not reached [3.3; -]	26	13 (50.0)	3.4 [2.8; 5.9]	0.36 [0.14; 0.94]	0.037	0.568
At least two prior therapies incl. auto-SCT[i]	55	24 (43.6)	15.1 [8.9; -]	56	22 (39.3)	8.3 [4.1; 11.4]	0.60 [0.32; 1.12]	0.106	
At least two prior therapies excl. auto-SCT[h]	66	22 (33.3)	24.8 [13.3; -]	68	28 (41.2)	6.1 [4.2; -]	0.48 [0.26; 0.89]	0.019	
Prior treatment									
One prior therapy	25	8 (32.0)	Not reached [3.3; -]	26	13 (50.0)	3.4 [2.8; 5.9]	0.36 [0.14; 0.94]	0.037	0.389
At least two prior therapies	121	46 (38.0)	17.0 [11.1; -]	124	50 (40.3)	7.9 [4.2; 11.4]	0.54 [0.35; 0.83]	0.005	

a: Database Cutoff Date: 16JAN2020

b: First deterioration is defined as the time to first onset of 10 points or more decrease from baseline without confirmation for the EORTC QLQ-C30 functional scores

c: Number of patients: full-analysis-set population

d: From product-limit (Kaplan-Meier) method

e: Based on stratified Cox regression model with treatment as a covariate stratified by prior auto-SCT status (yes versus no) and HL status

Study: KEYNOTE 204[a]	Pembrolizumab			Brentuximab Vedotin			Pembrolizumab vs. Brentuximab Vedotin		
EORTC QLQ-C30 Social Functioning[b]	N[c]	Patients with Event n (%)	Median Time[d] in Months [95 %-CI]	N[c]	Patients with Event n (%)	Median Time[d] in Months [95 %-CI]	Hazard Ratio [95 %-CI][e]	p-Value[e,f]	p-Value for Interaction Test[g]
after frontline therapy (primary refractory versus relapsed less than 12 months after completion of frontline therapy versus relapse 12 months or more after completion of frontline therapy) using Wald confidence interval									
f: Two-sided p-value using Wald test (Score test in case of zero event in one treatment group)									
g: Based on stratified Cox regression model with treatment, subgroup, prior auto-SCT (yes versus no) and HL status after frontline therapy (primary refractory versus relapsed less than 12 months after completion of frontline therapy versus relapse 12 months or more after completion of frontline therapy) as covariates, and a treatment-by-subgroup interaction (p-value of likelihood ratio test for interaction term)									
h: Auto-SCT was not a treatment option									
i: Auto-SCT failure									
Auto-SCT: autologous Stem Cell Transplantation; CI: Confidence Interval; ECOG: Eastern Cooperative Oncology Group; EORTC QLQ-C30: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 items; HL: Hodgkin Lymphoma									

Anhang 4-G4.3: Nebenwirkungen

Unerwünschte Ereignisse Gesamtraten

Unerwünschte Ereignisse gesamt

Tabelle 4G-45: Subgruppenanalysen mit nicht signifikantem Interaktionstest ($p \geq 0,05$) für den Endpunkt Unerwünschte Ereignisse gesamt aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE 204[a]	Pembrolizumab			Brentuximab Vedotin			Pembrolizumab vs. Brentuximab Vedotin		
Adverse Events	N[b]	Patients with Event n (%)	Median Time[c] in weeks [95 %-CI]	N[b]	Patients with Event n (%)	Median Time[c] in weeks [95 %-CI]	Hazard Ratio [95 %-CI][d]	p-Value[d,e]	p-Value for Interaction Test[f]
Gender									
Female	67	66 (98.5)	1.1 [0.4; 3.0]	63	57 (90.5)	3.0 [1.1; 3.3]	1.26 [0.88; 1.80]	0.204	0.130
Male	81	79 (97.5)	2.6 [0.4; 3.6]	89	86 (96.6)	2.0 [1.0; 3.1]	0.82 [0.60; 1.12]	0.216	
Age									
<65	122	119 (97.5)	2.1 [0.7; 3.4]	130	121 (93.1)	2.3 [1.1; 3.1]	0.95 [0.74; 1.24]	0.720	0.711
≥65	26	26 (100.0)	0.6 [0.1; 2.9]	22	22 (100.0)	2.9 [0.7; 3.3]	1.04 [0.58; 1.87]	0.895	
Region									
EU	47	44 (93.6)	2.6 [0.6; 5.9]	45	42 (93.3)	3.1 [1.9; 5.7]	0.97 [0.63; 1.50]	0.889	0.879
Ex-EU	101	101 (100.0)	1.0 [0.4; 3.0]	107	101 (94.4)	1.6 [0.9; 3.0]	0.98 [0.74; 1.29]	0.861	
Disease status following first line therapy									
Primary refractory	60	59 (98.3)	0.6 [0.1; 2.1]	62	55 (88.7)	2.6 [1.0; 3.6]	1.35 [0.93; 1.96]	0.119	0.125
Relapsed < 12 months	41	41 (100.0)	3.0 [0.4; 6.1]	42	41 (97.6)	2.9 [0.9; 3.3]	0.73 [0.46; 1.15]	0.172	
Relapsed ≥ 12 months	47	45 (95.7)	2.6 [0.7; 6.1]	48	47 (97.9)	1.8 [0.4; 3.1]	0.83 [0.54; 1.25]	0.365	
Prior treatment									
One prior therapy[g]	27	27 (100.0)	1.4 [0.1; 6.4]	27	24 (88.9)	3.1 [1.0; 6.1]	1.03 [0.58; 1.83]	0.918	0.801
At least two prior therapies incl. auto-SCT[h]	55	53 (96.4)	2.6 [0.7; 3.9]	56	54 (96.4)	1.9 [1.1; 3.1]	0.89 [0.60; 1.30]	0.542	
At least two prior therapies excl. auto-SCT[g]	66	65 (98.5)	1.0 [0.3; 3.4]	69	65 (94.2)	2.3 [0.9; 3.1]	1.03 [0.73; 1.47]	0.860	
Prior treatment									
One prior therapy	27	27 (100.0)	1.4 [0.1; 6.4]	27	24 (88.9)	3.1 [1.0; 6.1]	1.03 [0.58; 1.83]	0.918	0.737
At least two prior therapies	121	118 (97.5)	2.1 [0.6; 3.1]	125	119 (95.2)	2.1 [1.1; 3.1]	0.97 [0.75; 1.25]	0.801	

a: Database Cutoff Date: 16JAN2020
b: Number of patients: all-subjects-as-treated population
c: From product-limit (Kaplan-Meier) method
d: Based on Cox regression model with treatment as a covariate using Wald confidence interval
e: Two-sided p-value using Wald test (Score test in case of zero event in one treatment group)
f: Based on Cox regression model with treatment and subgroup as covariates, and treatment-by-subgroup interaction (p-value of likelihood ratio test for interaction term)
g: auto-SCT was not a treatment option

Study: KEYNOTE 204[a]	Pembrolizumab			Brentuximab Vedotin			Pembrolizumab vs. Brentuximab Vedotin		
Adverse Events	N[b]	Patients with Event n (%)	Median Time[c] in weeks [95 %-CI]	N[b]	Patients with Event n (%)	Median Time[c] in weeks [95 %-CI]	Hazard Ratio [95 %-CI][d]	p-Value[d,e]	p-Value for Interaction Test[f]
h: auto-SCT failure									
auto-SCT: autologous Stem Cell Transplantation; CI: Confidence Interval									

Schwerwiegende unerwünschte Ereignisse

Tabelle 4G-46: Subgruppenanalysen mit nicht signifikantem Interaktionstest ($p \geq 0,05$) für den Endpunkt Schwerwiegende unerwünschte Ereignisse aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE 204[a]	Pembrolizumab			Brentuximab Vedotin			Pembrolizumab vs. Brentuximab Vedotin		
Serious Adverse Events	N[b]	Patients with Event n (%)	Median Time[c] in weeks [95 %-CI]	N[b]	Patients with Event n (%)	Median Time[c] in weeks [95 %-CI]	Hazard Ratio [95 %-CI][d]	p-Value[d,e]	p-Value for Interaction Test[f]
Gender									
Female	67	23 (34.3)	Not reached [69.6; -]	63	14 (22.2)	Not reached [-; -]	1.18 [0.60; 2.32]	0.627	0.703
Male	81	21 (25.9)	Not reached [-; -]	89	18 (20.2)	66.6 [52.0; -]	0.88 [0.46; 1.71]	0.713	
Age									
<65	122	30 (24.6)	Not reached [-; -]	130	25 (19.2)	Not reached [66.6; -]	0.94 [0.54; 1.61]	0.817	0.581
≥65	26	14 (53.8)	69.7 [21.4; -]	22	7 (31.8)	Not reached [27.3; -]	1.29 [0.51; 3.30]	0.588	
ECOG performance status									
0	84	25 (29.8)	Not reached [69.7; -]	99	18 (18.2)	Not reached [59.4; -]	1.11 [0.59; 2.07]	0.750	0.510
1	63	19 (30.2)	112.6 [82.0; -]	53	14 (26.4)	Not reached [-; -]	0.93 [0.46; 1.87]	0.829	
Region									
EU	47	15 (31.9)	Not reached [38.6; -]	45	7 (15.6)	Not reached [66.6; -]	1.80 [0.73; 4.45]	0.205	0.158
Ex-EU	101	29 (28.7)	Not reached [112.6; -]	107	25 (23.4)	Not reached [59.4; -]	0.84 [0.48; 1.46]	0.532	
Disease status following first line therapy									
Primary refractory	60	15 (25.0)	Not reached [-; -]	62	14 (22.6)	52.0 [52.0; -]	0.74 [0.35; 1.57]	0.429	0.244
Relapsed < 12 months	41	13 (31.7)	Not reached [69.6; -]	42	11 (26.2)	Not reached [66.6; -]	0.95 [0.42; 2.15]	0.903	
Relapsed ≥ 12 months	47	16 (34.0)	112.6 [56.9; -]	48	7 (14.6)	Not reached [59.4; -]	1.82 [0.74; 4.51]	0.193	
Prior treatment									
One prior therapy[g]	27	8 (29.6)	Not reached [69.6; -]	27	2 (7.4)	Not reached [40.7; -]	3.12 [0.66; 14.85]	0.153	0.209
At least two prior therapies incl. auto-SCT[h]	55	21 (38.2)	Not reached [44.4; -]	56	15 (26.8)	66.6 [59.4; -]	1.03 [0.52; 2.05]	0.922	
At least two prior therapies excl. auto-SCT[g]	66	15 (22.7)	Not reached [-; -]	69	15 (21.7)	Not reached [52.0; -]	0.80 [0.39; 1.67]	0.554	
Prior treatment									

Study: KEYNOTE 204[a]	Pembrolizumab			Brentuximab Vedotin			Pembrolizumab vs. Brentuximab Vedotin		
Serious Adverse Events	N[b]	Patients with Event n (%)	Median Time[c] in weeks [95 %-CI]	N[b]	Patients with Event n (%)	Median Time[c] in weeks [95 %-CI]	Hazard Ratio [95 %-CI][d]	p-Value[d,e]	p-Value for Interaction Test[f]
One prior therapy	27	8 (29.6)	Not reached [69.6; -]	27	2 (7.4)	Not reached [40.7; -]	3.12 [0.66; 14.85]	0.153	0.096
At least two prior therapies	121	36 (29.8)	Not reached [112.6; -]	125	30 (24.0)	Not reached [59.4; -]	0.92 [0.56; 1.51]	0.736	

a: Database Cutoff Date: 16JAN2020
b: Number of patients: all-subjects-as-treated population
c: From product-limit (Kaplan-Meier) method
d: Based on Cox regression model with treatment as a covariate using Wald confidence interval
e: Two-sided p-value using Wald test (Score test in case of zero event in one treatment group)
f: Based on Cox regression model with treatment and subgroup as covariates, and treatment-by-subgroup interaction (p-value of likelihood ratio test for interaction term)
g: auto-SCT was not a treatment option
h: auto-SCT failure
auto-SCT: autologous Stem Cell Transplantation; CI: Confidence Interval; ECOG: Eastern Cooperative Oncology Group

Nicht-schwere unerwünschte Ereignisse (CTCAE-Grad 1-2)

Tabelle 4G-47: Subgruppenanalysen mit nicht signifikantem Interaktionstest ($p \geq 0,05$) für den Endpunkt Nicht-schwere unerwünschte Ereignisse (CTCAE-Grad 1-2) aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE 204[a]	Pembrolizumab			Brentuximab Vedotin			Pembrolizumab vs. Brentuximab Vedotin		
Non-Severe Adverse Events (CTCAE-Grade 1-2)	N[b]	Patients with Event n (%)	Median Time[c] in weeks [95 %-CI]	N[b]	Patients with Event n (%)	Median Time[c] in weeks [95 %-CI]	Hazard Ratio [95 %-CI][d]	p-Value[d,e]	p-Value for Interaction Test[f]
Gender									
Female	67	65 (97.0)	1.4 [0.4; 3.7]	63	57 (90.5)	3.1 [1.6; 5.7]	1.29 [0.90; 1.85]	0.163	0.217
Male	81	79 (97.5)	2.6 [0.4; 3.6]	89	84 (94.4)	2.3 [1.1; 3.3]	0.90 [0.66; 1.23]	0.514	
Age									
<65	122	119 (97.5)	2.6 [0.7; 3.7]	130	120 (92.3)	2.6 [1.3; 3.1]	1.01 [0.78; 1.30]	0.960	0.640
≥65	26	25 (96.2)	0.6 [0.1; 2.9]	22	21 (95.5)	3.1 [1.0; 5.7]	1.17 [0.64; 2.14]	0.601	
Region									
EU	47	43 (91.5)	3.0 [0.6; 6.1]	45	41 (91.1)	3.3 [2.1; 5.7]	0.95 [0.61; 1.48]	0.818	0.773
Ex-EU	101	101 (100.0)	1.1 [0.4; 3.0]	107	100 (93.5)	1.7 [1.0; 3.1]	1.07 [0.80; 1.41]	0.653	
Disease status following first line therapy									
Primary refractory	60	59 (98.3)	0.6 [0.1; 2.1]	62	55 (88.7)	2.6 [1.0; 4.1]	1.37 [0.94; 2.00]	0.097	0.220
Relapsed < 12 months	41	40 (97.6)	3.0 [0.4; 6.1]	42	40 (95.2)	3.2 [1.1; 4.1]	0.85 [0.54; 1.34]	0.479	
Relapsed ≥ 12 months	47	45 (95.7)	3.1 [0.7; 6.1]	48	46 (95.8)	2.0 [0.6; 3.1]	0.87 [0.57; 1.31]	0.495	
Prior treatment									
One prior therapy[g]	27	27 (100.0)	1.4 [0.1; 6.4]	27	23 (85.2)	3.4 [1.0; 6.3]	1.13 [0.63; 2.02]	0.678	0.601
At least two prior	55	52	2.9	56	54	1.9	0.89	0.571	

Study: KEYNOTE 204[a]	Pembrolizumab			Brentuximab Vedotin			Pembrolizumab vs. Brentuximab Vedotin		
Non-Severe Adverse Events (CTCAE-Grade 1-2)	N[b]	Patients with Event n (%)	Median Time[c] in weeks [95 %-CI]	N[b]	Patients with Event n (%)	Median Time[c] in weeks [95 %-CI]	Hazard Ratio [95 %-CI][d]	p-Value[d,e]	p-Value for Interaction Test[f]
therapies incl. auto-SCT[h]		(94.5)	[0.7; 4.9]		(96.4)	[1.1; 3.1]	[0.61; 1.31]		
At least two prior therapies excl. auto-SCT[g]	66	65 (98.5)	1.1 [0.3; 3.6]	69	64 (92.8)	3.0 [1.0; 4.7]	1.12 [0.79; 1.60]	0.517	
Prior treatment									
One prior therapy	27	27 (100.0)	1.4 [0.1; 6.4]	27	23 (85.2)	3.4 [1.0; 6.3]	1.13 [0.63; 2.02]	0.678	0.605
At least two prior therapies	121	117 (96.7)	2.1 [0.6; 3.3]	125	118 (94.4)	2.3 [1.1; 3.1]	1.02 [0.78; 1.32]	0.906	

a: Database Cutoff Date: 16JAN2020
b: Number of patients: all-subjects-as-treated population
c: From product-limit (Kaplan-Meier) method
d: Based on Cox regression model with treatment as a covariate using Wald confidence interval
e: Two-sided p-value using Wald test (Score test in case of zero event in one treatment group)
f: Based on Cox regression model with treatment and subgroup as covariates, and treatment-by-subgroup interaction (p-value of likelihood ratio test for interaction term)
g: auto-SCT was not a treatment option
h: auto-SCT failure
auto-SCT: autologous Stem Cell Transplantation; CI: Confidence Interval; CTCAE: Common Terminology Criteria for Adverse Events

Schwere unerwünschte Ereignisse (CTCAE-Grad 3-5)

Tabelle 4G-48: Subgruppenanalysen mit nicht signifikantem Interaktionstest ($p \geq 0,05$) für den Endpunkt Schwere unerwünschte Ereignisse (CTCAE-Grad 3-5) aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE 204[a]	Pembrolizumab			Brentuximab Vedotin			Pembrolizumab vs. Brentuximab Vedotin		
Severe Adverse Events (CTCAE-Grade 3-5)	N[b]	Patients with Event n (%)	Median Time[c] in weeks [95 %-CI]	N[b]	Patients with Event n (%)	Median Time[c] in weeks [95 %-CI]	Hazard Ratio [95 %-CI][d]	p-Value[d,e]	p-Value for Interaction Test[f]
Gender									
Female	67	31 (46.3)	59.9 [28.7; -]	63	27 (42.9)	Not reached [15.4; -]	0.77 [0.46; 1.30]	0.328	0.556
Male	81	34 (42.0)	69.7 [46.1; -]	89	39 (43.8)	35.1 [26.1; 54.0]	0.52 [0.32; 0.84]	0.008	
Age									
<65	122	50 (41.0)	81.3 [44.4; -]	130	51 (39.2)	50.6 [29.1; -]	0.68 [0.46; 1.02]	0.063	0.338
≥65	26	15 (57.7)	46.1 [23.3; -]	22	15 (68.2)	17.7 [3.6; 31.7]	0.47 [0.22; 0.99]	0.046	
ECOG performance status									
0	84	33 (39.3)	96.7 [48.3; -]	99	43 (43.4)	45.6 [23.1; 61.7]	0.52 [0.33; 0.84]	0.007	0.436
1	63	31 (49.2)	46.1 [28.7; -]	53	23 (43.4)	31.0 [15.4; -]	0.77 [0.45; 1.34]	0.358	
Region									
EU	47	17 (36.2)	96.7 [28.7; -]	45	17 (37.8)	31.0 [18.0; -]	0.63 [0.32; 1.24]	0.181	0.909
Ex-EU	101	48 (47.5)	63.1 [44.4; -]	107	49 (45.8)	45.6 [24.3; 61.7]	0.64 [0.43; 0.97]	0.034	

Study: KEYNOTE 204[a]	Pembrolizumab			Brentuximab Vedotin			Pembrolizumab vs. Brentuximab Vedotin		
Severe Adverse Events (CTCAE-Grade 3-5)	N[b]	Patients with Event n (%)	Median Time[c] in weeks [95 %-CI]	N[b]	Patients with Event n (%)	Median Time[c] in weeks [95 %-CI]	Hazard Ratio [95 %-CI][d]	p-Value[d,e]	p-Value for Interaction Test[f]
Disease status following first line therapy									
Primary refractory	60	27 (45.0)	63.1 [28.7; -]	62	22 (35.5)	35.1 [24.1; -]	0.70 [0.39; 1.26]	0.236	0.795
Relapsed < 12 months	41	20 (48.8)	69.6 [26.7; -]	42	22 (52.4)	35.6 [8.7; -]	0.61 [0.33; 1.13]	0.117	
Relapsed ≥ 12 months	47	18 (38.3)	81.3 [44.3; -]	48	22 (45.8)	50.6 [18.1; -]	0.60 [0.32; 1.13]	0.113	
Prior treatment									
One prior therapy[g]	27	10 (37.0)	Not reached [28.7; -]	27	11 (40.7)	31.0 [21.0; -]	0.49 [0.20; 1.18]	0.110	0.730
At least two prior therapies incl. auto-SCT[h]	55	26 (47.3)	63.1 [38.6; -]	56	22 (39.3)	50.6 [18.1; -]	0.78 [0.44; 1.41]	0.418	
At least two prior therapies excl. auto-SCT[g]	66	29 (43.9)	56.0 [33.3; -]	69	33 (47.8)	35.1 [14.0; -]	0.59 [0.36; 0.99]	0.045	
Prior treatment									
One prior therapy	27	10 (37.0)	Not reached [28.7; -]	27	11 (40.7)	31.0 [21.0; -]	0.49 [0.20; 1.18]	0.110	0.652
At least two prior therapies	121	55 (45.5)	58.4 [40.1; -]	125	55 (44.0)	45.6 [24.3; -]	0.67 [0.46; 0.99]	0.043	

a: Database Cutoff Date: 16JAN2020
b: Number of patients: all-subjects-as-treated population
c: From product-limit (Kaplan-Meier) method
d: Based on Cox regression model with treatment as a covariate using Wald confidence interval
e: Two-sided p-value using Wald test (Score test in case of zero event in one treatment group)
f: Based on Cox regression model with treatment and subgroup as covariates, and treatment-by-subgroup interaction (p-value of likelihood ratio test for interaction term)
g: auto-SCT was not a treatment option
h: auto-SCT failure
auto-SCT: autologous Stem Cell Transplantation; CI: Confidence Interval; CTCAE: Common Terminology Criteria for Adverse Events; ECOG: Eastern Cooperative Oncology Group

Therapieabbruch wegen unerwünschter Ereignisse

Tabelle 4G-49: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für den Endpunkt Therapieabbruch wegen unerwünschter Ereignisse aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE 204[a]	Pembrolizumab			Brentuximab Vedotin			Pembrolizumab vs. Brentuximab Vedotin		
Adverse Events Leading to Treatment Discontinuation	N[b]	Patients with Event n (%)	Median Time[c] in weeks [95 %-CI]	N[b]	Patients with Event n (%)	Median Time[c] in weeks [95 %-CI]	Hazard Ratio [95 %-CI][d]	p-Value[d,e]	p-Value for Interaction Test[f]
Gender									
Female	67	12 (17.9)	Not reached [-; -]	63	10 (15.9)	Not reached [65.7; -]	0.72 [0.31; 1.71]	0.463	0.162
Male	81	8 (9.9)	Not reached [-; -]	89	17 (19.1)	Not reached [-; -]	0.37 [0.16; 0.87]	0.023	
Age									
<65	122	14 (11.5)	Not reached [-; -]	130	17 (13.1)	Not reached [-; -]	0.58 [0.28; 1.19]	0.138	0.246
≥65	26	6	Not reached	22	10	35.1	0.29	0.025	

Study: KEYNOTE 204[a]	Pembrolizumab			Brentuximab Vedotin			Pembrolizumab vs. Brentuximab Vedotin		
Adverse Events Leading to Treatment Discontinuation	N[b]	Patients with Event n (%)	Median Time[c] in weeks [95 %-CI]	N[b]	Patients with Event n (%)	Median Time[c] in weeks [95 %-CI]	Hazard Ratio [95 %-CI][d]	p-Value[d,e]	p-Value for Interaction Test[f]
		(23.1)	[42.0; -]		(45.5)	[7.4; 65.7]	[0.10; 0.86]		
ECOG performance status									
0	84	12 (14.3)	Not reached [-; -]	99	20 (20.2)	Not reached [-; -]	0.43 [0.20; 0.90]	0.025	0.470
1	63	8 (12.7)	Not reached [-; -]	53	7 (13.2)	Not reached [65.7; -]	0.75 [0.27; 2.08]	0.574	
Region									
EU	47	6 (12.8)	Not reached [-; -]	45	9 (20.0)	65.7 [65.7; -]	0.45 [0.15; 1.30]	0.140	0.666
Ex-EU	101	14 (13.9)	Not reached [-; -]	107	18 (16.8)	Not reached [-; -]	0.53 [0.26; 1.08]	0.082	
Prior treatment									
One prior therapy	27	4 (14.8)	Not reached [-; -]	27	6 (22.2)	Not reached [65.7; -]	0.41 [0.11; 1.49]	0.176	0.712
At least two prior therapies	121	16 (13.2)	Not reached [-; -]	125	21 (16.8)	Not reached [-; -]	0.54 [0.28; 1.06]	0.072	

a: Database Cutoff Date: 16JAN2020
b: Number of patients: all-subjects-as-treated population
c: From product-limit (Kaplan-Meier) method
d: Based on Cox regression model with treatment as a covariate using Wald confidence interval
e: Two-sided p-value using Wald test (Score test in case of zero event in one treatment group)
f: Based on Cox regression model with treatment and subgroup as covariates, and treatment-by-subgroup interaction (p-value of likelihood ratio test for interaction term)
CI: Confidence Interval; ECOG: Eastern Cooperative Oncology Group

Unerwünschte Ereignisse (gegliedert nach SOC und PT)

Unerwünschte Ereignisse gesamt (SOC und PT)

Tabelle 4G-50: Subgruppenanalysen mit nicht signifikantem Interaktionstest ($p \geq 0,05$) für den Endpunkt Unerwünschte Ereignisse gesamt (SOC und PT) für die SOC „Erkrankungen des Blutes und des Lymphsystems“ aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE 204[a]	**Pembrolizumab**			**Brentuximab Vedotin**			**Pembrolizumab vs. Brentuximab Vedotin**		
Adverse Events: SOC[g]	**N[b]**	**Patients with Event n (%)**	**Median Time[c] in weeks [95 %-CI]**	**N[b]**	**Patients with Event n (%)**	**Median Time[c] in weeks [95 %-CI]**	**Hazard Ratio [95 %-CI][d]**	**p-Value[d,e]**	**p-Value for Interaction Test[f]**
Gender									
Female	67	15 (22.4)	Not reached [-; -]	63	18 (28.6)	Not reached [-; -]	0.54 [0.27; 1.08]	0.083	0.700
Male	81	12 (14.8)	Not reached [-; -]	89	21 (23.6)	Not reached [42.1; -]	0.38 [0.18; 0.80]	0.011	
Age									
<65	122	25 (20.5)	Not reached [-; -]	130	36 (27.7)	Not reached [47.6; -]	0.50 [0.30; 0.84]	0.009	0.730
≥65	26	2 (7.7)	Not reached [75.1; -]	22	3 (13.6)	Not reached [-; -]	0.25 [0.03; 2.38]	0.226	
ECOG performance status									
0	84	13 (15.5)	Not reached [-; -]	99	29 (29.3)	Not reached [42.1; -]	0.32 [0.16; 0.64]	0.001	0.074
1	63	14 (22.2)	Not reached [-; -]	53	10 (18.9)	Not reached [-; -]	0.84 [0.37; 1.92]	0.679	
Region									
EU	47	7 (14.9)	Not reached [-; -]	45	11 (24.4)	Not reached [-; -]	0.37 [0.14; 1.00]	0.050	0.618
Ex-EU	101	20 (19.8)	Not reached [-; -]	107	28 (26.2)	Not reached [47.6; -]	0.51 [0.28; 0.92]	0.026	
Disease status following first line therapy									
Primary refractory	60	13 (21.7)	Not reached [86.9; -]	62	11 (17.7)	Not reached [-; -]	0.80 [0.35; 1.84]	0.598	0.200
Relapsed < 12 months	41	8 (19.5)	Not reached [-; -]	42	12 (28.6)	Not reached [42.1; -]	0.45 [0.18; 1.13]	0.088	
Relapsed ≥ 12 months	47	6 (12.8)	Not reached [-; -]	48	16 (33.3)	47.6 [19.6; -]	0.26 [0.10; 0.66]	0.005	
Prior treatment									
One prior therapy[h]	27	2 (7.4)	Not reached [75.1; -]	27	5 (18.5)	Not reached [-; -]	0.27 [0.05; 1.43]	0.123	0.706
At least two prior therapies incl. auto-SCT[i]	55	11 (20.0)	Not reached [-; -]	56	15 (26.8)	Not reached [42.1; -]	0.41 [0.18; 0.94]	0.034	
At least two prior therapies excl. auto-SCT[h]	66	14 (21.2)	Not reached [-; -]	69	19 (27.5)	Not reached [-; -]	0.58 [0.29; 1.17]	0.126	
Prior treatment									
One prior therapy	27	2 (7.4)	Not reached [75.1; -]	27	5 (18.5)	Not reached [-; -]	0.27 [0.05; 1.43]	0.123	0.442
At least two prior therapies	121	25 (20.7)	Not reached [-; -]	125	34 (27.2)	Not reached [47.6; -]	0.51 [0.30; 0.86]	0.012	

a: Database Cutoff Date: 16JAN2020
b: Number of patients: all-subjects-as-treated population
c: From product-limit (Kaplan-Meier) method
d: Based on Cox regression model with treatment as a covariate using Wald confidence interval
e: Two-sided p-value using Wald test (Score test in case of zero event in one treatment group)

Study: KEYNOTE 204[a]	Pembrolizumab			Brentuximab Vedotin			Pembrolizumab vs. Brentuximab Vedotin		
Adverse Events: SOC[g]	N[b]	Patients with Event n (%)	Median Time[c] in weeks [95 %-CI]	N[b]	Patients with Event n (%)	Median Time[c] in weeks [95 %-CI]	Hazard Ratio [95 %-CI][d]	p-Value[d,e]	p-Value for Interaction Test[f]
f: Based on Cox regression model with treatment and subgroup as covariates, and treatment-by-subgroup interaction (p-value of likelihood ratio test for interaction term)									
g: SOC: Blood and lymphatic system disorders									
h: auto-SCT was not a treatment option									
i: auto-SCT failure									
auto-SCT: autologous Stem Cell Transplantation; CI: Confidence Interval; ECOG: Eastern Cooperative Oncology Group; SOC: System Organ Class									

Tabelle 4G-51: Subgruppenanalysen mit nicht signifikantem Interaktionstest ($p \geq 0,05$) für den Endpunkt Unerwünschte Ereignisse gesamt (SOC und PT) für den PT „Neutropenie“ (SOC „Erkrankungen des Blutes und des Lymphsystems“) aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE 204[a]	Pembrolizumab			Brentuximab Vedotin			Pembrolizumab vs. Brentuximab Vedotin		
Adverse Events: PT[g]	N[b]	Patients with Event n (%)	Median Time[c] in weeks [95 %-CI]	N[b]	Patients with Event n (%)	Median Time[c] in weeks [95 %-CI]	Hazard Ratio [95 %-CI][d]	p-Value[d,e]	p-Value for Interaction Test[f]
Gender									
Female	67	6 (9.0)	Not reached [-; -]	63	10 (15.9)	Not reached [-; -]	0.40 [0.14; 1.12]	0.081	0.816
Male	81	4 (4.9)	Not reached [-; -]	89	10 (11.2)	Not reached [-; -]	0.32 [0.10; 1.04]	0.059	
Age									
<65	122	10 (8.2)	Not reached [-; -]	130	19 (14.6)	Not reached [-; -]	0.41 [0.19; 0.89]	0.023	0.320
≥65	26	0 (0.0)	Not reached [-; -]	22	1 (4.5)	Not reached [-; -]	n.a. [n.a.; n.a.]	0.261	
Region									
EU	47	3 (6.4)	Not reached [-; -]	45	6 (13.3)	Not reached [-; -]	0.27 [0.06; 1.15]	0.076	0.871
Ex-EU	101	7 (6.9)	Not reached [-; -]	107	14 (13.1)	Not reached [-; -]	0.42 [0.17; 1.05]	0.063	
Disease status following first line therapy									
Primary refractory	60	4 (6.7)	Not reached [-; -]	62	5 (8.1)	Not reached [-; -]	0.56 [0.14; 2.21]	0.406	0.421
Relapsed < 12 months	41	4 (9.8)	Not reached [-; -]	42	6 (14.3)	Not reached [-; -]	0.49 [0.14; 1.77]	0.276	
Relapsed ≥ 12 months	47	2 (4.3)	Not reached [-; -]	48	9 (18.8)	Not reached [-; -]	0.18 [0.04; 0.84]	0.029	
Prior treatment									
One prior therapy[h]	27	1 (3.7)	Not reached [-; -]	27	3 (11.1)	Not reached [-; -]	0.30 [0.03; 2.87]	0.294	0.493
At least two prior therapies incl. auto-SCT[i]	55	2 (3.6)	Not reached [-; -]	56	7 (12.5)	Not reached [-; -]	0.17 [0.03; 0.87]	0.033	
At least two prior therapies excl. auto-SCT[h]	66	7 (10.6)	Not reached [-; -]	69	10 (14.5)	Not reached [-; -]	0.56 [0.21; 1.48]	0.238	
Prior treatment									
One prior therapy	27	1 (3.7)	Not reached [-; -]	27	3 (11.1)	Not reached [-; -]	0.30 [0.03; 2.87]	0.294	0.664

Study: KEYNOTE 204[a]	Pembrolizumab			Brentuximab Vedotin			Pembrolizumab vs. Brentuximab Vedotin		
Adverse Events: PT[g]	N[b]	Patients with Event n (%)	Median Time[c] in weeks [95 %-CI]	N[b]	Patients with Event n (%)	Median Time[c] in weeks [95 %-CI]	Hazard Ratio [95 %-CI][d]	p-Value[d,e]	p-Value for Interaction Test[f]
At least two prior therapies	121	9 (7.4)	Not reached [-; -]	125	17 (13.6)	Not reached [-; -]	0.39 [0.17; 0.88]	0.024	

a: Database Cutoff Date: 16JAN2020
b: Number of patients: all-subjects-as-treated population
c: From product-limit (Kaplan-Meier) method
d: Based on Cox regression model with treatment as a covariate using Wald confidence interval
e: Two-sided p-value using Wald test (Score test in case of zero event in one treatment group)
f: Based on Cox regression model with treatment and subgroup as covariates, and treatment-by-subgroup interaction (p-value of likelihood ratio test for interaction term)
g: PT: Neutropenia
h: auto-SCT was not a treatment option
i: auto-SCT failure
auto-SCT: autologous Stem Cell Transplantation; CI: Confidence Interval; n.a.: not applicable (when estimation not possible); PT: Preferred Term

Tabelle 4G-52: Subgruppenanalysen mit nicht signifikantem Interaktionstest ($p \geq 0,05$) für den Endpunkt Unerwünschte Ereignisse gesamt (SOC und PT) für die SOC „Endokrine Erkrankungen“ aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE 204[a]	Pembrolizumab			Brentuximab Vedotin			Pembrolizumab vs. Brentuximab Vedotin		
Adverse Events: SOC[g]	N[b]	Patients with Event n (%)	Median Time[c] in weeks [95 %-CI]	N[b]	Patients with Event n (%)	Median Time[c] in weeks [95 %-CI]	Hazard Ratio [95 %-CI][d]	p-Value[d,e]	p-Value for Interaction Test[f]
Gender									
Female	67	15 (22.4)	Not reached [105.9; -]	63	2 (3.2)	Not reached [56.9; -]	5.14 [1.16; 22.80]	0.031	0.548
Male	81	15 (18.5)	Not reached [-; -]	89	4 (4.5)	Not reached [-; -]	3.93 [1.30; 11.87]	0.015	
Age									
<65	122	21 (17.2)	Not reached [-; -]	130	6 (4.6)	Not reached [92.0; -]	2.91 [1.16; 7.29]	0.023	0.052
≥65	26	9 (34.6)	Not reached [13.4; -]	22	0 (0.0)	Not reached [-; -]	n.a. [n.a.; n.a.]	0.007	
ECOG performance status									
0	84	16 (19.0)	Not reached [-; -]	99	5 (5.1)	Not reached [92.0; -]	3.48 [1.27; 9.57]	0.016	0.255
1	63	14 (22.2)	Not reached [105.9; -]	53	1 (1.9)	Not reached [56.9; -]	8.76 [1.14; 67.11]	0.037	
Region									
EU	47	9 (19.1)	Not reached [-; -]	45	0 (0.0)	Not reached [-; -]	n.a. [n.a.; n.a.]	0.007	0.056
Ex-EU	101	21 (20.8)	Not reached [-; -]	107	6 (5.6)	Not reached [92.0; -]	3.04 [1.21; 7.61]	0.018	
Disease status following first line therapy									
Primary refractory	60	13 (21.7)	Not reached [-; -]	62	2 (3.2)	Not reached [-; -]	6.12 [1.37; 27.30]	0.017	0.774
Relapsed < 12 months	41	7 (17.1)	Not reached [105.9; -]	42	1 (2.4)	Not reached [56.9; -]	5.18 [0.62; 43.07]	0.128	
Relapsed ≥ 12 months	47	10 (21.3)	Not reached [-; -]	48	3 (6.3)	Not reached [92.0; -]	2.82 [0.77; 10.39]	0.119	

Study: KEYNOTE 204[a]	Pembrolizumab			Brentuximab Vedotin			Pembrolizumab vs. Brentuximab Vedotin		
Adverse Events: SOC[g]	N[b]	Patients with Event n (%)	Median Time[c] in weeks [95 %-CI]	N[b]	Patients with Event n (%)	Median Time[c] in weeks [95 %-CI]	Hazard Ratio [95 %-CI][d]	p-Value[d,e]	p-Value for Interaction Test[f]
Prior treatment									
One prior therapy[h]	27	7 (25.9)	Not reached [-; -]	27	1 (3.7)	Not reached [92.0; -]	7.53 [0.93; 61.21]	0.059	0.877
At least two prior therapies incl. auto-SCT[i]	55	10 (18.2)	Not reached [-; -]	56	2 (3.6)	Not reached [-; -]	4.10 [0.89; 18.81]	0.070	
At least two prior therapies excl. auto-SCT[h]	66	13 (19.7)	Not reached [105.9; -]	69	3 (4.3)	Not reached [56.9; -]	3.65 [1.02; 12.98]	0.046	
Prior treatment									
One prior therapy	27	7 (25.9)	Not reached [-; -]	27	1 (3.7)	Not reached [92.0; -]	7.53 [0.93; 61.21]	0.059	0.603
At least two prior therapies	121	23 (19.0)	Not reached [-; -]	125	5 (4.0)	Not reached [-; -]	3.70 [1.39; 9.84]	0.009	

a: Database Cutoff Date: 16JAN2020
b: Number of patients: all-subjects-as-treated population
c: From product-limit (Kaplan-Meier) method
d: Based on Cox regression model with treatment as a covariate using Wald confidence interval
e: Two-sided p-value using Wald test (Score test in case of zero event in one treatment group)
f: Based on Cox regression model with treatment and subgroup as covariates, and treatment-by-subgroup interaction (p-value of likelihood ratio test for interaction term)
g: SOC: Endocrine disorders
h: auto-SCT was not a treatment option
i: auto-SCT failure
auto-SCT: autologous Stem Cell Transplantation; CI: Confidence Interval; ECOG: Eastern Cooperative Oncology Group; n.a.: not applicable (when estimation not possible); SOC: System Organ Class

Tabelle 4G-53: Subgruppenanalysen mit nicht signifikantem Interaktionstest ($p \geq 0,05$) für den Endpunkt Unerwünschte Ereignisse gesamt (SOC und PT) für den PT „Hypothyreose“ (SOC „Endokrine Erkrankungen“) aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE 204[a]	Pembrolizumab			Brentuximab Vedotin			Pembrolizumab vs. Brentuximab Vedotin		
Adverse Events: PT[g]	N[b]	Patients with Event n (%)	Median Time[c] in weeks [95 %-CI]	N[b]	Patients with Event n (%)	Median Time[c] in weeks [95 %-CI]	Hazard Ratio [95 %-CI][d]	p-Value[d,e]	p-Value for Interaction Test[f]
Gender									
Female	67	13 (19.4)	Not reached [-; -]	63	2 (3.2)	Not reached [56.9; -]	3.98 [0.88; 17.97]	0.072	0.762
Male	81	15 (18.5)	Not reached [-; -]	89	2 (2.2)	Not reached [-; -]	7.70 [1.76; 33.70]	0.007	
Age									
<65	122	20 (16.4)	Not reached [-; -]	130	4 (3.1)	Not reached [92.0; -]	4.00 [1.35; 11.83]	0.012	0.133
≥65	26	8 (30.8)	Not reached [21.1; -]	22	0 (0.0)	Not reached [-; -]	n.a. [n.a.; n.a.]	0.016	
ECOG performance status									
0	84	16 (19.0)	Not reached [-; -]	99	3 (3.0)	Not reached [92.0; -]	5.63 [1.63; 19.44]	0.006	0.672
1	63	12 (19.0)	Not reached [105.9; -]	53	1 (1.9)	Not reached [56.9; -]	6.71 [0.86; 52.19]	0.069	
Region									

Study: KEYNOTE 204[a]	Pembrolizumab			Brentuximab Vedotin			Pembrolizumab vs. Brentuximab Vedotin		
Adverse Events: PT[g]	N[b]	Patients with Event n (%)	Median Time[c] in weeks [95 %-CI]	N[b]	Patients with Event n (%)	Median Time[c] in weeks [95 %-CI]	Hazard Ratio [95 %-CI][d]	p-Value[d,e]	p-Value for Interaction Test[f]
EU	47	8 (17.0)	Not reached [-; -]	45	0 (0.0)	Not reached [-; -]	n.a. [n.a.; n.a.]	0.014	0.130
Ex-EU	101	20 (19.8)	Not reached [-; -]	107	4 (3.7)	Not reached [92.0; -]	4.15 [1.40; 12.27]	0.010	
Disease status following first line therapy									
Primary refractory	60	11 (18.3)	Not reached [-; -]	62	0 (0.0)	Not reached [-; -]	n.a. [n.a.; n.a.]	0.002	0.154
Relapsed < 12 months	41	7 (17.1)	Not reached [105.9; -]	42	1 (2.4)	Not reached [56.9; -]	5.07 [0.61; 42.15]	0.133	
Relapsed ≥ 12 months	47	10 (21.3)	Not reached [-; -]	48	3 (6.3)	Not reached [92.0; -]	2.79 [0.76; 10.29]	0.123	
Prior treatment									
One prior therapy[h]	27	5 (18.5)	Not reached [-; -]	27	1 (3.7)	Not reached [92.0; -]	4.86 [0.57; 41.59]	0.149	0.620
At least two prior therapies incl. auto-SCT[i]	55	10 (18.2)	Not reached [-; -]	56	2 (3.6)	Not reached [-; -]	4.03 [0.88; 18.50]	0.073	
At least two prior therapies excl. auto-SCT[h]	66	13 (19.7)	Not reached [105.9; -]	69	1 (1.4)	Not reached [56.9; -]	10.97 [1.42; 84.60]	0.022	
Prior treatment									
One prior therapy	27	5 (18.5)	Not reached [-; -]	27	1 (3.7)	Not reached [92.0; -]	4.86 [0.57; 41.59]	0.149	0.754
At least two prior therapies	121	23 (19.0)	Not reached [-; -]	125	3 (2.4)	Not reached [-; -]	6.12 [1.82; 20.56]	0.003	

a: Database Cutoff Date: 16JAN2020
b: Number of patients: all-subjects-as-treated population
c: From product-limit (Kaplan-Meier) method
d: Based on Cox regression model with treatment as a covariate using Wald confidence interval
e: Two-sided p-value using Wald test (Score test in case of zero event in one treatment group)
f: Based on Cox regression model with treatment and subgroup as covariates, and treatment-by-subgroup interaction (p-value of likelihood ratio test for interaction term)
g: PT: Hypothyroidism
h: auto-SCT was not a treatment option
i: auto-SCT failure
auto-SCT: autologous Stem Cell Transplantation; CI: Confidence Interval; ECOG: Eastern Cooperative Oncology Group; n.a.: not applicable (when estimation not possible); PT: Preferred Term

Tabelle 4G-54: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für den Endpunkt Unerwünschte Ereignisse gesamt (SOC und PT) für die SOC „Erkrankungen des Gastrointestinaltrakts“ aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE 204[a]	Pembrolizumab			Brentuximab Vedotin			Pembrolizumab vs. Brentuximab Vedotin		
Adverse Events: SOC[g]	N[b]	Patients with Event n (%)	Median Time[c] in weeks [95 %-CI]	N[b]	Patients with Event n (%)	Median Time[c] in weeks [95 %-CI]	Hazard Ratio [95 %-CI][d]	p-Value[d,e]	p-Value for Interaction Test[f]
Gender									
Female	67	34 (50.7)	63.1 [23.4; -]	63	36 (57.1)	12.4 [8.3; -]	0.64 [0.40; 1.03]	0.068	0.735
Male	81	31 (38.3)	Not reached [36.4; -]	89	43 (48.3)	23.1 [15.6; -]	0.59 [0.37; 0.95]	0.029	
Age									

Study: KEYNOTE 204[a]	Pembrolizumab			Brentuximab Vedotin			Pembrolizumab vs. Brentuximab Vedotin		
Adverse Events: SOC[g]	N[b]	Patients with Event n (%)	Median Time[c] in weeks [95 %-CI]	N[b]	Patients with Event n (%)	Median Time[c] in weeks [95 %-CI]	Hazard Ratio [95 %-CI][d]	p-Value[d,e]	p-Value for Interaction Test[f]
<65	122	53 (43.4)	91.1 [36.4; -]	130	66 (50.8)	19.3 [12.4; -]	0.63 [0.43; 0.91]	0.014	0.670
≥65	26	12 (46.2)	54.4 [11.3; -]	22	13 (59.1)	8.4 [2.1; -]	0.49 [0.22; 1.10]	0.084	
ECOG performance status									
0	84	36 (42.9)	78.3 [36.3; -]	99	51 (51.5)	21.1 [11.6; -]	0.56 [0.36; 0.88]	0.011	0.825
1	63	28 (44.4)	91.1 [18.4; -]	53	28 (52.8)	16.1 [8.3; -]	0.65 [0.39; 1.11]	0.116	
Region									
EU	47	17 (36.2)	93.6 [54.4; -]	45	25 (55.6)	15.6 [5.7; -]	0.38 [0.20; 0.75]	0.005	0.148
Ex-EU	101	48 (47.5)	78.1 [23.6; -]	107	54 (50.5)	21.1 [12.4; -]	0.73 [0.49; 1.08]	0.114	
Disease status following first line therapy									
Primary refractory	60	27 (45.0)	72.4 [53.7; -]	62	30 (48.4)	18.9 [12.3; -]	0.58 [0.33; 1.00]	0.049	0.717
Relapsed < 12 months	41	21 (51.2)	36.3 [6.9; -]	42	25 (59.5)	13.9 [8.4; -]	0.72 [0.40; 1.31]	0.285	
Relapsed ≥ 12 months	47	17 (36.2)	Not reached [23.6; -]	48	24 (50.0)	19.3 [5.3; -]	0.55 [0.30; 1.04]	0.065	
Prior treatment									
One prior therapy[h]	27	12 (44.4)	Not reached [6.4; -]	27	13 (48.1)	19.3 [3.4; -]	0.73 [0.33; 1.62]	0.445	0.160
At least two prior therapies incl. auto-SCT[i]	55	22 (40.0)	93.6 [36.3; -]	56	34 (60.7)	10.2 [5.3; -]	0.43 [0.25; 0.76]	0.004	
At least two prior therapies excl. auto-SCT[h]	66	31 (47.0)	72.4 [20.0; -]	69	32 (46.4)	35.1 [15.9; -]	0.77 [0.47; 1.28]	0.313	
Prior treatment									
One prior therapy	27	12 (44.4)	Not reached [6.4; -]	27	13 (48.1)	19.3 [3.4; -]	0.73 [0.33; 1.62]	0.445	0.715
At least two prior therapies	121	53 (43.8)	78.3 [36.4; -]	125	66 (52.8)	18.9 [11.6; 48.9]	0.59 [0.41; 0.85]	0.005	

a: Database Cutoff Date: 16JAN2020
b: Number of patients: all-subjects-as-treated population
c: From product-limit (Kaplan-Meier) method
d: Based on Cox regression model with treatment as a covariate using Wald confidence interval
e: Two-sided p-value using Wald test (Score test in case of zero event in one treatment group)
f: Based on Cox regression model with treatment and subgroup as covariates, and treatment-by-subgroup interaction (p-value of likelihood ratio test for interaction term)
g: SOC: Gastrointestinal disorders
h: auto-SCT was not a treatment option
i: auto-SCT failure
auto-SCT: autologous Stem Cell Transplantation; CI: Confidence Interval; ECOG: Eastern Cooperative Oncology Group; SOC: System Organ Class

Tabelle 4G-55: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für den Endpunkt Unerwünschte Ereignisse gesamt (SOC und PT) für den PT „Verstopfung“ (SOC „Erkrankungen des Gastrointestinaltrakts“) aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE 204[a]	Pembrolizumab			Brentuximab Vedotin			Pembrolizumab vs. Brentuximab Vedotin		
Adverse Events: PT[g]	N[b]	Patients with Event n (%)	Median Time[c] in weeks [95 %-CI]	N[b]	Patients with Event n (%)	Median Time[c] in weeks [95 %-CI]	Hazard Ratio [95 %-CI][d]	p-Value[d,e]	p-Value for Interaction Test[f]
Gender									
Female	67	6 (9.0)	Not reached [-; -]	63	9 (14.3)	Not reached [-; -]	0.50 [0.17; 1.43]	0.195	0.783
Male	81	5 (6.2)	Not reached [-; -]	89	10 (11.2)	Not reached [54.1; -]	0.22 [0.06; 0.79]	0.020	
Age									
<65	122	9 (7.4)	Not reached [-; -]	130	14 (10.8)	Not reached [-; -]	0.40 [0.16; 0.97]	0.042	0.352
≥65	26	2 (7.7)	Not reached [-; -]	22	5 (22.7)	Not reached [-; -]	0.29 [0.06; 1.50]	0.140	
ECOG performance status									
0	84	7 (8.3)	Not reached [-; -]	99	12 (12.1)	Not reached [54.1; -]	0.30 [0.11; 0.85]	0.024	0.823
1	63	4 (6.3)	Not reached [-; -]	53	7 (13.2)	Not reached [-; -]	0.42 [0.12; 1.43]	0.163	
Region									
EU	47	2 (4.3)	Not reached [-; -]	45	7 (15.6)	Not reached [33.4; -]	0.22 [0.04; 1.08]	0.061	0.240
Ex-EU	101	9 (8.9)	Not reached [-; -]	107	12 (11.2)	Not reached [-; -]	0.47 [0.19; 1.18]	0.108	
Disease status following first line therapy									
Primary refractory	60	4 (6.7)	Not reached [-; -]	62	7 (11.3)	Not reached [36.0; -]	0.37 [0.10; 1.35]	0.131	0.263
Relapsed < 12 months	41	6 (14.6)	Not reached [-; -]	42	6 (14.3)	Not reached [54.1; -]	0.62 [0.19; 2.08]	0.439	
Relapsed ≥ 12 months	47	1 (2.1)	Not reached [-; -]	48	6 (12.5)	Not reached [-; -]	0.10 [0.01; 0.93]	0.043	
Prior treatment									
One prior therapy[h]	27	3 (11.1)	Not reached [-; -]	27	2 (7.4)	Not reached [-; -]	1.45 [0.24; 8.69]	0.684	0.401
At least two prior therapies incl. auto-SCT[i]	55	5 (9.1)	Not reached [-; -]	56	10 (17.9)	Not reached [-; -]	0.27 [0.08; 0.92]	0.037	
At least two prior therapies excl. auto-SCT[h]	66	3 (4.5)	Not reached [-; -]	69	7 (10.1)	Not reached [54.1; -]	0.26 [0.07; 1.07]	0.062	
Prior treatment									
One prior therapy	27	3 (11.1)	Not reached [-; -]	27	2 (7.4)	Not reached [-; -]	1.45 [0.24; 8.69]	0.684	0.193
At least two prior therapies	121	8 (6.6)	Not reached [-; -]	125	17 (13.6)	Not reached [-; -]	0.26 [0.11; 0.65]	0.004	

a: Database Cutoff Date: 16JAN2020
b: Number of patients: all-subjects-as-treated population
c: From product-limit (Kaplan-Meier) method
d: Based on Cox regression model with treatment as a covariate using Wald confidence interval
e: Two-sided p-value using Wald test (Score test in case of zero event in one treatment group)
f: Based on Cox regression model with treatment and subgroup as covariates, and treatment-by-subgroup interaction (p-value of likelihood ratio test for interaction term)

Study: KEYNOTE 204[a]	Pembrolizumab			Brentuximab Vedotin			Pembrolizumab vs. Brentuximab Vedotin		
Adverse Events: PT[g]	N[b]	Patients with Event n (%)	Median Time[c] in weeks [95 %-CI]	N[b]	Patients with Event n (%)	Median Time[c] in weeks [95 %-CI]	Hazard Ratio [95 %-CI][d]	p-Value[d,e]	p-Value for Interaction Test[f]
g: PT: Constipation									
h: auto-SCT was not a treatment option									
i: auto-SCT failure									
auto-SCT: autologous Stem Cell Transplantation; CI: Confidence Interval; ECOG: Eastern Cooperative Oncology Group; PT: Preferred Term									

Tabelle 4G-56: Subgruppenanalysen mit nicht signifikantem Interaktionstest ($p \geq 0,05$) für den Endpunkt Unerwünschte Ereignisse gesamt (SOC und PT) für den PT „Übelkeit“ (SOC „Erkrankungen des Gastrointestinaltrakts“) aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE 204[a]	Pembrolizumab			Brentuximab Vedotin			Pembrolizumab vs. Brentuximab Vedotin		
Adverse Events: PT[g]	N[b]	Patients with Event n (%)	Median Time[c] in weeks [95 %-CI]	N[b]	Patients with Event n (%)	Median Time[c] in weeks [95 %-CI]	Hazard Ratio [95 %-CI][d]	p-Value[d,e]	p-Value for Interaction Test[f]
Gender									
Female	67	11 (16.4)	Not reached [-; -]	63	13 (20.6)	Not reached [-; -]	0.61 [0.27; 1.39]	0.242	0.290
Male	81	10 (12.3)	Not reached [-; -]	89	24 (27.0)	Not reached [-; -]	0.33 [0.16; 0.69]	0.004	
Age									
<65	122	16 (13.1)	Not reached [-; -]	130	31 (23.8)	Not reached [-; -]	0.42 [0.23; 0.78]	0.006	0.852
≥65	26	5 (19.2)	Not reached [71.4; -]	22	6 (27.3)	Not reached [6.0; -]	0.33 [0.09; 1.27]	0.106	
ECOG performance status									
0	84	9 (10.7)	Not reached [-; -]	99	25 (25.3)	Not reached [-; -]	0.30 [0.14; 0.65]	0.002	0.180
1	63	12 (19.0)	Not reached [-; -]	53	12 (22.6)	Not reached [-; -]	0.66 [0.29; 1.48]	0.308	
Region									
EU	47	4 (8.5)	Not reached [-; -]	45	11 (24.4)	Not reached [-; -]	0.28 [0.09; 0.88]	0.030	0.321
Ex-EU	101	17 (16.8)	Not reached [-; -]	107	26 (24.3)	Not reached [-; -]	0.50 [0.27; 0.93]	0.029	
Disease status following first line therapy									
Primary refractory	60	7 (11.7)	Not reached [-; -]	62	15 (24.2)	Not reached [-; -]	0.35 [0.14; 0.86]	0.023	0.655
Relapsed < 12 months	41	8 (19.5)	Not reached [-; -]	42	11 (26.2)	Not reached [-; -]	0.64 [0.26; 1.61]	0.348	
Relapsed ≥ 12 months	47	6 (12.8)	Not reached [-; -]	48	11 (22.9)	Not reached [-; -]	0.37 [0.13; 1.02]	0.055	
Prior treatment									
One prior therapy[h]	27	4 (14.8)	Not reached [71.4; -]	27	8 (29.6)	Not reached [19.3; -]	0.32 [0.09; 1.10]	0.070	0.054
At least two prior therapies incl. auto-SCT[i]	55	3 (5.5)	Not reached [-; -]	56	14 (25.0)	Not reached [-; -]	0.17 [0.05; 0.60]	0.006	
At least two prior therapies excl. auto-	66	14 (21.2)	Not reached [-; -]	69	15 (21.7)	Not reached [-; -]	0.73 [0.35; 1.53]	0.407	

Study: KEYNOTE 204[a]	Pembrolizumab			Brentuximab Vedotin			Pembrolizumab vs. Brentuximab Vedotin		
Adverse Events: PT[g]	N[b]	Patients with Event n (%)	Median Time[c] in weeks [95 %-CI]	N[b]	Patients with Event n (%)	Median Time[c] in weeks [95 %-CI]	Hazard Ratio [95 %-CI][d]	p-Value[d,e]	p-Value for Interaction Test[f]
SCT[h]									
Prior treatment									
One prior therapy	27	4 (14.8)	Not reached [71.4; -]	27	8 (29.6)	Not reached [19.3; -]	0.32 [0.09; 1.10]	0.070	0.690
At least two prior therapies	121	17 (14.0)	Not reached [-; -]	125	29 (23.2)	Not reached [-; -]	0.46 [0.25; 0.85]	0.014	

a: Database Cutoff Date: 16JAN2020
b: Number of patients: all-subjects-as-treated population
c: From product-limit (Kaplan-Meier) method
d: Based on Cox regression model with treatment as a covariate using Wald confidence interval
e: Two-sided p-value using Wald test (Score test in case of zero event in one treatment group)
f: Based on Cox regression model with treatment and subgroup as covariates, and treatment-by-subgroup interaction (p-value of likelihood ratio test for interaction term)
g: PT: Nausea
h: auto-SCT was not a treatment option
i: auto-SCT failure
auto-SCT: autologous Stem Cell Transplantation; CI: Confidence Interval; ECOG: Eastern Cooperative Oncology Group; PT: Preferred Term

Tabelle 4G-57: Subgruppenanalysen mit nicht signifikantem Interaktionstest ($p \geq 0,05$) für den Endpunkt Unerwünschte Ereignisse gesamt (SOC und PT) für den PT „Harnwegsinfektion“ (SOC „Infektionen und parasitäre Erkrankungen“) aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE 204[a]	Pembrolizumab			Brentuximab Vedotin			Pembrolizumab vs. Brentuximab Vedotin		
Adverse Events: PT[g]	N[b]	Patients with Event n (%)	Median Time[c] in weeks [95 %-CI]	N[b]	Patients with Event n (%)	Median Time[c] in weeks [95 %-CI]	Hazard Ratio [95 %-CI][d]	p-Value[d,e]	p-Value for Interaction Test[f]
Gender									
Female	67	12 (17.9)	Not reached [-; -]	63	2 (3.2)	Not reached [-; -]	5.13 [1.14; 23.04]	0.033	0.353
Male	81	4 (4.9)	Not reached [-; -]	89	2 (2.2)	Not reached [52.0; -]	1.10 [0.19; 6.51]	0.913	
Age									
<65	122	11 (9.0)	Not reached [-; -]	130	3 (2.3)	Not reached [-; -]	2.87 [0.79; 10.47]	0.109	0.996
≥65	26	5 (19.2)	Not reached [-; -]	22	1 (4.5)	Not reached [-; -]	3.20 [0.36; 28.66]	0.299	
ECOG performance status									
0	84	9 (10.7)	Not reached [-; -]	99	3 (3.0)	Not reached [-; -]	2.11 [0.55; 8.06]	0.276	0.615
1	63	7 (11.1)	Not reached [-; -]	53	1 (1.9)	Not reached [-; -]	5.47 [0.67; 44.48]	0.112	
Region									
EU	47	7 (14.9)	Not reached [-; -]	45	2 (4.4)	Not reached [-; -]	2.52 [0.51; 12.32]	0.255	0.752
Ex-EU	101	9 (8.9)	Not reached [-; -]	107	2 (1.9)	Not reached [-; -]	3.33 [0.70; 15.75]	0.129	
Disease status following first line therapy									

Study: KEYNOTE 204[a]	Pembrolizumab			Brentuximab Vedotin			Pembrolizumab vs. Brentuximab Vedotin		
Adverse Events: PT[g]	N[b]	Patients with Event n (%)	Median Time[c] in weeks [95 %-CI]	N[b]	Patients with Event n (%)	Median Time[c] in weeks [95 %-CI]	Hazard Ratio [95 %-CI][d]	p-Value[d,e]	p-Value for Interaction Test[f]
Primary refractory	60	4 (6.7)	n.c.	62	2 (3.2)	n.c.	n.c.	n.c.	n.c.
Relapsed < 12 months	41	6 (14.6)	n.c.	42	0 (0.0)	n.c.	n.c.	n.c.	
Relapsed ≥ 12 months	47	6 (12.8)	n.c.	48	2 (4.2)	n.c.	n.c.	n.c.	
Prior treatment									
One prior therapy[h]	27	4 (14.8)	n.c.	27	1 (3.7)	n.c.	n.c.	n.c.	n.c.
At least two prior therapies incl. auto-SCT[i]	55	6 (10.9)	n.c.	56	1 (1.8)	n.c.	n.c.	n.c.	
At least two prior therapies excl. auto-SCT[h]	66	6 (9.1)	n.c.	69	2 (2.9)	n.c.	n.c.	n.c.	
Prior treatment									
One prior therapy	27	4 (14.8)	Not reached [-; -]	27	1 (3.7)	Not reached [-; -]	3.16 [0.34; 29.05]	0.309	0.982
At least two prior therapies	121	12 (9.9)	Not reached [-; -]	125	3 (2.4)	Not reached [-; -]	3.03 [0.84; 10.89]	0.090	

a: Database Cutoff Date: 16JAN2020
b: Number of patients: all-subjects-as-treated population
c: From product-limit (Kaplan-Meier) method
d: Based on Cox regression model with treatment as a covariate using Wald confidence interval
e: Two-sided p-value using Wald test (Score test in case of zero event in one treatment group)
f: Based on Cox regression model with treatment and subgroup as covariates, and treatment-by-subgroup interaction (p-value of likelihood ratio test for interaction term)
g: PT: Urinary tract infection
h: auto-SCT was not a treatment option
i: auto-SCT failure
auto-SCT: autologous Stem Cell Transplantation; CI: Confidence Interval; ECOG: Eastern Cooperative Oncology Group; n.c.: not calculated (at least 10 subjects per subgroup and at least 10 events in one of the subgroups necessary); PT: Preferred Term

Tabelle 4G-58: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für den Endpunkt Unerwünschte Ereignisse gesamt (SOC und PT) für den PT „Gewicht erniedrigt“ (SOC „Untersuchungen“) aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE 204[a]	Pembrolizumab			Brentuximab Vedotin			Pembrolizumab vs. Brentuximab Vedotin		
Adverse Events: PT[g]	N[b]	Patients with Event n (%)	Median Time[c] in weeks [95 %-CI]	N[b]	Patients with Event n (%)	Median Time[c] in weeks [95 %-CI]	Hazard Ratio [95 %-CI][d]	p-Value[d,e]	p-Value for Interaction Test[f]
Gender									
Female	67	3 (4.5)	n.c.	63	5 (7.9)	n.c.	n.c.	n.c.	n.c.
Male	81	2 (2.5)	n.c.	89	6 (6.7)	n.c.	n.c.	n.c.	
Age									
<65	122	3 (2.5)	Not reached [-; -]	130	9 (6.9)	Not reached [-; -]	0.24 [0.06; 0.91]	0.036	0.502
≥65	26	2 (7.7)	Not reached [-; -]	22	2 (9.1)	Not reached [28.3; -]	0.43 [0.06; 3.21]	0.413	
ECOG performance status									

Study: KEYNOTE 204[a]	Pembrolizumab			Brentuximab Vedotin			Pembrolizumab vs. Brentuximab Vedotin		
Adverse Events: PT[g]	N[b]	Patients with Event n (%)	Median Time[c] in weeks [95 %-CI]	N[b]	Patients with Event n (%)	Median Time[c] in weeks [95 %-CI]	Hazard Ratio [95 %-CI][d]	p-Value[d,e]	p-Value for Interaction Test[f]
0	84	4 (4.8)	Not reached [-; -]	99	6 (6.1)	Not reached [-; -]	0.45 [0.12; 1.63]	0.225	0.207
1	63	1 (1.6)	Not reached [-; -]	53	5 (9.4)	Not reached [-; -]	0.13 [0.01; 1.10]	0.062	
Region									
EU	47	2 (4.3)	Not reached [-; -]	45	4 (8.9)	Not reached [-; -]	0.32 [0.06; 1.78]	0.192	0.953
Ex-EU	101	3 (3.0)	Not reached [-; -]	107	7 (6.5)	Not reached [-; -]	0.29 [0.07; 1.14]	0.076	
Disease status following first line therapy									
Primary refractory	60	1 (1.7)	n.c.	62	4 (6.5)	n.c.	n.c.	n.c.	n.c.
Relapsed < 12 months	41	1 (2.4)	n.c.	42	5 (11.9)	n.c.	n.c.	n.c.	
Relapsed ≥ 12 months	47	3 (6.4)	n.c.	48	2 (4.2)	n.c.	n.c.	n.c.	
Prior treatment									
One prior therapy[h]	27	2 (7.4)	n.c.	27	1 (3.7)	n.c.	n.c.	n.c.	n.c.
At least two prior therapies incl. auto-SCT[i]	55	1 (1.8)	n.c.	56	3 (5.4)	n.c.	n.c.	n.c.	
At least two prior therapies excl. auto-SCT[h]	66	2 (3.0)	n.c.	69	7 (10.1)	n.c.	n.c.	n.c.	
Prior treatment									
One prior therapy	27	2 (7.4)	Not reached [-; -]	27	1 (3.7)	Not reached [49.0; -]	0.82 [0.07; 9.09]	0.871	0.166
At least two prior therapies	121	3 (2.5)	Not reached [-; -]	125	10 (8.0)	Not reached [-; -]	0.22 [0.06; 0.81]	0.023	

a: Database Cutoff Date: 16JAN2020
b: Number of patients: all-subjects-as-treated population
c: From product-limit (Kaplan-Meier) method
d: Based on Cox regression model with treatment as a covariate using Wald confidence interval
e: Two-sided p-value using Wald test (Score test in case of zero event in one treatment group)
f: Based on Cox regression model with treatment and subgroup as covariates, and treatment-by-subgroup interaction (p-value of likelihood ratio test for interaction term)
g: PT: Weight decreased
h: auto-SCT was not a treatment option
i: auto-SCT failure
auto-SCT: autologous Stem Cell Transplantation; CI: Confidence Interval; ECOG: Eastern Cooperative Oncology Group; n.c.: not calculated (at least 10 subjects per subgroup and at least 10 events in one of the subgroups necessary); PT: Preferred Term

Tabelle 4G-59: Subgruppenanalysen mit nicht signifikantem Interaktionstest ($p \geq 0,05$) für den Endpunkt Unerwünschte Ereignisse gesamt (SOC und PT) für die SOC „Erkrankungen des Nervensystems“ aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE 204[a]	Pembrolizumab			Brentuximab Vedotin			Pembrolizumab vs. Brentuximab Vedotin		
Adverse Events: SOC[g]	N[b]	Patients with Event n (%)	Median Time[c] in weeks [95 %-CI]	N[b]	Patients with Event n (%)	Median Time[c] in weeks [95 %-CI]	Hazard Ratio [95 %-CI][d]	p-Value[d,e]	p-Value for Interaction Test[f]
Gender									

Study: KEYNOTE 204[a]	Pembrolizumab			Brentuximab Vedotin			Pembrolizumab vs. Brentuximab Vedotin		
Adverse Events: SOC[g]	N[b]	Patients with Event n (%)	Median Time[c] in weeks [95 %-CI]	N[b]	Patients with Event n (%)	Median Time[c] in weeks [95 %-CI]	Hazard Ratio [95 %-CI][d]	p-Value[d,e]	p-Value for Interaction Test[f]
Female	67	22 (32.8)	Not reached [56.0; -]	63	32 (50.8)	31.0 [18.3; 59.4]	0.37 [0.21; 0.66]	< 0.001	0.152
Male	81	17 (21.0)	Not reached [-; -]	89	45 (50.6)	25.9 [18.6; 30.1]	0.24 [0.14; 0.43]	< 0.001	
ECOG performance status									
0	84	19 (22.6)	Not reached [-; -]	99	54 (54.5)	25.9 [18.6; 31.0]	0.20 [0.12; 0.36]	< 0.001	0.067
1	63	20 (31.7)	Not reached [54.4; -]	53	23 (43.4)	24.6 [17.3; 65.7]	0.49 [0.26; 0.92]	0.026	
Region									
EU	47	11 (23.4)	Not reached [55.4; -]	45	21 (46.7)	24.3 [19.7; 92.0]	0.29 [0.14; 0.63]	0.002	0.906
Ex-EU	101	28 (27.7)	Not reached [-; -]	107	56 (52.3)	25.9 [18.3; 31.0]	0.30 [0.19; 0.48]	< 0.001	
Prior treatment									
One prior therapy[h]	27	9 (33.3)	Not reached [30.3; -]	27	14 (51.9)	23.0 [12.1; 65.7]	0.39 [0.17; 0.94]	0.035	0.170
At least two prior therapies incl. auto-SCT[i]	55	12 (21.8)	Not reached [-; -]	56	33 (58.9)	24.3 [12.1; 45.0]	0.16 [0.08; 0.33]	< 0.001	
At least two prior therapies excl. auto-SCT[h]	66	18 (27.3)	Not reached [54.4; -]	69	30 (43.5)	27.9 [18.6; -]	0.40 [0.22; 0.74]	0.004	
Prior treatment									
One prior therapy	27	9 (33.3)	Not reached [30.3; -]	27	14 (51.9)	23.0 [12.1; 65.7]	0.39 [0.17; 0.94]	0.035	0.466
At least two prior therapies	121	30 (24.8)	Not reached [-; -]	125	63 (50.4)	27.7 [21.7; 45.0]	0.27 [0.17; 0.42]	< 0.001	

a: Database Cutoff Date: 16JAN2020

b: Number of patients: all-subjects-as-treated population

c: From product-limit (Kaplan-Meier) method

d: Based on Cox regression model with treatment as a covariate using Wald confidence interval

e: Two-sided p-value using Wald test (Score test in case of zero event in one treatment group)

f: Based on Cox regression model with treatment and subgroup as covariates, and treatment-by-subgroup interaction (p-value of likelihood ratio test for interaction term)

g: SOC: Nervous system disorders

h: auto-SCT was not a treatment option

i: auto-SCT failure

auto-SCT: autologous Stem Cell Transplantation; CI: Confidence Interval; ECOG: Eastern Cooperative Oncology Group; SOC: System Organ Class

Tabelle 4G-60: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für den Endpunkt Unerwünschte Ereignisse gesamt (SOC und PT) für den PT „Periphere Neuropathie“ (SOC „Erkrankungen des Nervensystems“) aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE 204[a]	Pembrolizumab			Brentuximab Vedotin			Pembrolizumab vs. Brentuximab Vedotin		
Adverse Events: PT[g]	N[b]	Patients with Event n (%)	Median Time[c] in weeks [95 %-CI]	N[b]	Patients with Event n (%)	Median Time[c] in weeks [95 %-CI]	Hazard Ratio [95 %-CI][d]	p-Value[d,e]	p-Value for Interaction Test[f]
Gender									
Female	67	3 (4.5)	Not reached [-; -]	63	11 (17.5)	Not reached [46.3; -]	0.17 [0.05; 0.61]	0.007	0.707
Male	81	3 (3.7)	Not reached [-; -]	89	17 (19.1)	Not reached [38.4; -]	0.11 [0.03; 0.40]	< 0.001	
Age									
<65	122	5 (4.1)	Not reached [-; -]	130	23 (17.7)	Not reached [46.4; -]	0.14 [0.05; 0.38]	< 0.001	0.676
≥65	26	1 (3.8)	Not reached [-; -]	22	5 (22.7)	31.0 [30.1; -]	0.09 [0.01; 0.85]	0.035	
ECOG performance status									
0	84	2 (2.4)	Not reached [-; -]	99	22 (22.2)	Not reached [45.0; -]	0.05 [0.01; 0.22]	< 0.001	0.054
1	63	4 (6.3)	Not reached [-; -]	53	6 (11.3)	Not reached [-; -]	0.50 [0.14; 1.77]	0.281	
Region									
EU	47	1 (2.1)	Not reached [-; -]	45	7 (15.6)	Not reached [45.0; -]	0.10 [0.01; 0.80]	0.030	0.607
Ex-EU	101	5 (5.0)	Not reached [-; -]	107	21 (19.6)	Not reached [46.3; -]	0.15 [0.06; 0.41]	< 0.001	
Disease status following first line therapy									
Primary refractory	60	3 (5.0)	Not reached [-; -]	62	8 (12.9)	Not reached [30.1; -]	0.22 [0.06; 0.87]	0.031	0.621
Relapsed < 12 months	41	1 (2.4)	Not reached [-; -]	42	10 (23.8)	Not reached [45.0; -]	0.06 [0.01; 0.46]	0.007	
Relapsed ≥ 12 months	47	2 (4.3)	Not reached [-; -]	48	10 (20.8)	Not reached [38.4; -]	0.15 [0.03; 0.69]	0.015	
Prior treatment									
One prior therapy[h]	27	1 (3.7)	Not reached [-; -]	27	6 (22.2)	Not reached [23.1; -]	0.11 [0.01; 0.97]	0.047	0.057
At least two prior therapies incl. auto-SCT[i]	55	1 (1.8)	Not reached [-; -]	56	16 (28.6)	46.4 [45.0; -]	0.03 [0.00; 0.24]	< 0.001	
At least two prior therapies excl. auto-SCT[h]	66	4 (6.1)	Not reached [-; -]	69	6 (8.7)	Not reached [-; -]	0.51 [0.14; 1.85]	0.304	
Prior treatment									
One prior therapy	27	1 (3.7)	Not reached [-; -]	27	6 (22.2)	Not reached [23.1; -]	0.11 [0.01; 0.97]	0.047	0.699
At least two prior therapies	121	5 (4.1)	Not reached [-; -]	125	22 (17.6)	Not reached [46.3; -]	0.14 [0.05; 0.37]	< 0.001	

a: Database Cutoff Date: 16JAN2020
b: Number of patients: all-subjects-as-treated population
c: From product-limit (Kaplan-Meier) method
d: Based on Cox regression model with treatment as a covariate using Wald confidence interval
e: Two-sided p-value using Wald test (Score test in case of zero event in one treatment group)
f: Based on Cox regression model with treatment and subgroup as covariates, and treatment-by-subgroup interaction (p-value of likelihood ratio test for interaction term)

Study: KEYNOTE 204[a]	Pembrolizumab			Brentuximab Vedotin			Pembrolizumab vs. Brentuximab Vedotin		
Adverse Events: PT[g]	N[b]	Patients with Event n (%)	Median Time[c] in weeks [95 %-CI]	N[b]	Patients with Event n (%)	Median Time[c] in weeks [95 %-CI]	Hazard Ratio [95 %-CI][d]	p-Value[d,e]	p-Value for Interaction Test[f]
g: PT: Neuropathy peripheral									
h: auto-SCT was not a treatment option									
i: auto-SCT failure									
auto-SCT: autologous Stem Cell Transplantation; CI: Confidence Interval; ECOG: Eastern Cooperative Oncology Group; PT: Preferred Term									

Tabelle 4G-61: Subgruppenanalysen mit nicht signifikantem Interaktionstest ($p \geq 0,05$) für den Endpunkt Unerwünschte Ereignisse gesamt (SOC und PT) für den PT „Paraesthesie“ (SOC „Erkrankungen des Nervensystems“) aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE 204[a]	Pembrolizumab			Brentuximab Vedotin			Pembrolizumab vs. Brentuximab Vedotin		
Adverse Events: PT[g]	N[b]	Patients with Event n (%)	Median Time[c] in weeks [95 %-CI]	N[b]	Patients with Event n (%)	Median Time[c] in weeks [95 %-CI]	Hazard Ratio [95 %-CI][d]	p-Value[d,e]	p-Value for Interaction Test[f]
Gender									
Female	67	3 (4.5)	Not reached [-; -]	63	2 (3.2)	Not reached [92.0; -]	0.71 [0.11; 4.58]	0.719	0.281
Male	81	4 (4.9)	Not reached [-; -]	89	8 (9.0)	Not reached [54.9; -]	0.22 [0.06; 0.89]	0.034	
Age									
<65	122	7 (5.7)	Not reached [-; -]	130	9 (6.9)	Not reached [92.0; -]	0.40 [0.14; 1.14]	0.087	0.240
≥65	26	0 (0.0)	Not reached [-; -]	22	1 (4.5)	Not reached [-; -]	n.a. [n.a.; n.a.]	0.214	
ECOG performance status									
0	84	5 (6.0)	Not reached [-; -]	99	8 (8.1)	Not reached [54.9; -]	0.28 [0.08; 0.99]	0.048	0.670
1	63	2 (3.2)	Not reached [-; -]	53	2 (3.8)	Not reached [-; -]	0.49 [0.07; 3.60]	0.480	
Region									
EU	47	3 (6.4)	Not reached [-; -]	45	8 (17.8)	92.0 [-; -]	0.20 [0.05; 0.83]	0.026	0.103
Ex-EU	101	4 (4.0)	Not reached [-; -]	107	2 (1.9)	Not reached [-; -]	0.63 [0.11; 3.72]	0.610	
Disease status following first line therapy									
Primary refractory	60	4 (6.7)	n.c.	62	1 (1.6)	n.c.	n.c.	n.c.	n.c.
Relapsed < 12 months	41	2 (4.9)	n.c.	42	4 (9.5)	n.c.	n.c.	n.c.	
Relapsed ≥ 12 months	47	1 (2.1)	n.c.	48	5 (10.4)	n.c.	n.c.	n.c.	
Prior treatment									
One prior therapy[h]	27	1 (3.7)	n.c.	27	2 (7.4)	n.c.	n.c.	n.c.	n.c.
At least two prior therapies incl. auto-SCT[i]	55	2 (3.6)	n.c.	56	5 (8.9)	n.c.	n.c.	n.c.	
At least two prior therapies excl. auto-SCT[h]	66	4 (6.1)	n.c.	69	3 (4.3)	n.c.	n.c.	n.c.	

Study: KEYNOTE 204[a]	Pembrolizumab			Brentuximab Vedotin			Pembrolizumab vs. Brentuximab Vedotin		
Adverse Events: PT[g]	N[b]	Patients with Event n (%)	Median Time[c] in weeks [95 %-CI]	N[b]	Patients with Event n (%)	Median Time[c] in weeks [95 %-CI]	Hazard Ratio [95 %-CI][d]	p-Value[d,e]	p-Value for Interaction Test[f]
Prior treatment									
One prior therapy	27	1 (3.7)	Not reached [-; -]	27	2 (7.4)	Not reached [-; -]	0.36 [0.03; 4.08]	0.411	0.882
At least two prior therapies	121	6 (5.0)	Not reached [-; -]	125	8 (6.4)	Not reached [92.0; -]	0.29 [0.09; 0.94]	0.039	

a: Database Cutoff Date: 16JAN2020
b: Number of patients: all-subjects-as-treated population
c: From product-limit (Kaplan-Meier) method
d: Based on Cox regression model with treatment as a covariate using Wald confidence interval
e: Two-sided p-value using Wald test (Score test in case of zero event in one treatment group)
f: Based on Cox regression model with treatment and subgroup as covariates, and treatment-by-subgroup interaction (p-value of likelihood ratio test for interaction term)
g: PT: Paraesthesia
h: auto-SCT was not a treatment option
i: auto-SCT failure
auto-SCT: autologous Stem Cell Transplantation; CI: Confidence Interval; ECOG: Eastern Cooperative Oncology Group; n.a.: not applicable (when estimation not possible); n.c.: not calculated (at least 10 subjects per subgroup and at least 10 events in one of the subgroups necessary); PT: Preferred Term

Tabelle 4G-62: Subgruppenanalysen mit nicht signifikantem Interaktionstest ($p \geq 0,05$) für den Endpunkt Unerwünschte Ereignisse gesamt (SOC und PT) für den PT „Periphere sensorische Neuropathie“ (SOC „Erkrankungen des Nervensystems“) aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE 204[a]	Pembrolizumab			Brentuximab Vedotin			Pembrolizumab vs. Brentuximab Vedotin		
Adverse Events: PT[g]	N[b]	Patients with Event n (%)	Median Time[c] in weeks [95 %-CI]	N[b]	Patients with Event n (%)	Median Time[c] in weeks [95 %-CI]	Hazard Ratio [95 %-CI][d]	p-Value[d,e]	p-Value for Interaction Test[f]
Gender									
Female	67	2 (3.0)	Not reached [-; -]	63	5 (7.9)	Not reached [59.4; -]	0.26 [0.05; 1.38]	0.113	0.328
Male	81	2 (2.5)	Not reached [-; -]	89	16 (18.0)	Not reached [47.6; -]	0.09 [0.02; 0.39]	0.001	
ECOG performance status									
0	84	1 (1.2)	Not reached [-; -]	99	14 (14.1)	Not reached [-; -]	0.05 [0.01; 0.41]	0.005	0.181
1	63	3 (4.8)	Not reached [-; -]	53	7 (13.2)	Not reached [59.4; -]	0.28 [0.07; 1.10]	0.069	
Disease status following first line therapy									
Primary refractory	60	3 (5.0)	n.c.	62	6 (9.7)	n.c.	n.c.	n.c.	n.c.
Relapsed < 12 months	41	0 (0.0)	n.c.	42	7 (16.7)	n.c.	n.c.	n.c.	
Relapsed ≥ 12 months	47	1 (2.1)	n.c.	48	8 (16.7)	n.c.	n.c.	n.c.	
Prior treatment									
One prior therapy[h]	27	1 (3.7)	Not reached [-; -]	27	4 (14.8)	Not reached [23.0; -]	0.13 [0.01; 1.21]	0.074	0.717
At least two prior therapies incl. auto-SCT[i]	55	1 (1.8)	Not reached [-; -]	56	9 (16.1)	Not reached [47.6; -]	0.07 [0.01; 0.58]	0.014	

Study: KEYNOTE 204[a]	Pembrolizumab			Brentuximab Vedotin			Pembrolizumab vs. Brentuximab Vedotin		
Adverse Events: PT[g]	N[b]	Patients with Event n (%)	Median Time[c] in weeks [95 %-CI]	N[b]	Patients with Event n (%)	Median Time[c] in weeks [95 %-CI]	Hazard Ratio [95 %-CI][d]	p-Value[d,e]	p-Value for Interaction Test[f]
At least two prior therapies excl. auto-SCT[h]	66	2 (3.0)	Not reached [-; -]	69	8 (11.6)	Not reached [59.4; -]	0.21 [0.04; 0.99]	0.048	
Prior treatment									
One prior therapy	27	1 (3.7)	Not reached [-; -]	27	4 (14.8)	Not reached [23.0; -]	0.13 [0.01; 1.21]	0.074	0.838
At least two prior therapies	121	3 (2.5)	Not reached [-; -]	125	17 (13.6)	Not reached [-; -]	0.13 [0.04; 0.45]	0.001	

a: Database Cutoff Date: 16JAN2020

b: Number of patients: all-subjects-as-treated population

c: From product-limit (Kaplan-Meier) method

d: Based on Cox regression model with treatment as a covariate using Wald confidence interval

e: Two-sided p-value using Wald test (Score test in case of zero event in one treatment group)

f: Based on Cox regression model with treatment and subgroup as covariates, and treatment-by-subgroup interaction (p-value of likelihood ratio test for interaction term)

g: PT: Peripheral sensory neuropathy

h: auto-SCT was not a treatment option

i: auto-SCT failure

auto-SCT: autologous Stem Cell Transplantation; CI: Confidence Interval; ECOG: Eastern Cooperative Oncology Group; n.c.: not calculated (at least 10 subjects per subgroup and at least 10 events in one of the subgroups necessary); PT: Preferred Term

Tabelle 4G-63: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für den Endpunkt Unerwünschte Ereignisse gesamt (SOC und PT) für die SOC „Psychiatrische Erkrankungen“ aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE 204[a]	**Pembrolizumab**			**Brentuximab Vedotin**			**Pembrolizumab vs. Brentuximab Vedotin**		
Adverse Events: SOC[g]	**N[b]**	**Patients with Event n (%)**	**Median Time[c] in weeks [95 %-CI]**	**N[b]**	**Patients with Event n (%)**	**Median Time[c] in weeks [95 %-CI]**	**Hazard Ratio [95 %-CI][d]**	**p-Value[d,e]**	**p-Value for Interaction Test[f]**
Gender									
Female	67	11 (16.4)	Not reached [-; -]	63	10 (15.9)	Not reached [-; -]	0.69 [0.29; 1.65]	0.405	0.330
Male	81	10 (12.3)	Not reached [-; -]	89	17 (19.1)	Not reached [-; -]	0.47 [0.21; 1.05]	0.065	
Age									
<65	122	18 (14.8)	Not reached [-; -]	130	21 (16.2)	Not reached [-; -]	0.64 [0.33; 1.21]	0.171	0.296
≥65	26	3 (11.5)	Not reached [48.1; -]	22	6 (27.3)	Not reached [19.3; -]	0.27 [0.06; 1.17]	0.080	
ECOG performance status									
0	84	10 (11.9)	Not reached [-; -]	99	20 (20.2)	Not reached [-; -]	0.39 [0.18; 0.85]	0.017	0.125
1	63	11 (17.5)	Not reached [-; -]	53	7 (13.2)	Not reached [-; -]	0.95 [0.36; 2.51]	0.924	
Region									
EU	47	6 (12.8)	Not reached [99.6; -]	45	9 (20.0)	Not reached [27.1; -]	0.37 [0.12; 1.09]	0.071	0.491
Ex-EU	101	15 (14.9)	Not reached [-; -]	107	18 (16.8)	Not reached [-; -]	0.66 [0.33; 1.32]	0.238	
Disease status following first line therapy									
Primary refractory	60	8 (13.3)	Not reached [99.6; -]	62	9 (14.5)	Not reached [32.1; -]	0.57 [0.21; 1.54]	0.270	0.825
Relapsed < 12 months	41	7 (17.1)	Not reached [-; -]	42	8 (19.0)	Not reached [-; -]	0.71 [0.25; 1.98]	0.511	
Relapsed ≥ 12 months	47	6 (12.8)	Not reached [-; -]	48	10 (20.8)	Not reached [-; -]	0.43 [0.15; 1.21]	0.108	
Prior treatment									
One prior therapy[h]	27	4 (14.8)	Not reached [-; -]	27	5 (18.5)	Not reached [27.1; -]	0.64 [0.17; 2.42]	0.513	0.809
At least two prior therapies incl. auto-SCT[i]	55	10 (18.2)	Not reached [-; -]	56	14 (25.0)	Not reached [32.1; -]	0.41 [0.17; 0.95]	0.038	
At least two prior therapies excl. auto-SCT[h]	66	7 (10.6)	Not reached [-; -]	69	8 (11.6)	Not reached [-; -]	0.72 [0.26; 2.04]	0.542	
Prior treatment									
One prior therapy	27	4 (14.8)	Not reached [-; -]	27	5 (18.5)	Not reached [27.1; -]	0.64 [0.17; 2.42]	0.513	0.924
At least two prior therapies	121	17 (14.0)	Not reached [-; -]	125	22 (17.6)	Not reached [-; -]	0.52 [0.27; 1.01]	0.053	

a: Database Cutoff Date: 16JAN2020
b: Number of patients: all-subjects-as-treated population
c: From product-limit (Kaplan-Meier) method
d: Based on Cox regression model with treatment as a covariate using Wald confidence interval
e: Two-sided p-value using Wald test (Score test in case of zero event in one treatment group)
f: Based on Cox regression model with treatment and subgroup as covariates, and treatment-by-subgroup interaction (p-value of likelihood ratio test for interaction term)
g: SOC: Psychiatric disorders

Study: KEYNOTE 204[a]	Pembrolizumab			Brentuximab Vedotin			Pembrolizumab vs. Brentuximab Vedotin		
Adverse Events: SOC[g]	N[b]	Patients with Event n (%)	Median Time[c] in weeks [95 %-CI]	N[b]	Patients with Event n (%)	Median Time[c] in weeks [95 %-CI]	Hazard Ratio [95 %-CI][d]	p-Value[d,e]	p-Value for Interaction Test[f]
h: auto-SCT was not a treatment option									
i: auto-SCT failure									
auto-SCT: autologous Stem Cell Transplantation; CI: Confidence Interval; ECOG: Eastern Cooperative Oncology Group; SOC: System Organ Class									

Nicht-schwere unerwünschte Ereignisse (CTCAE-Grad 1-2) (SOC und PT)

Tabelle 4G-64: Subgruppenanalysen mit nicht signifikantem Interaktionstest ($p \geq 0,05$) für den Endpunkt Nicht-schwere unerwünschte Ereignisse (CTCAE-Grad 1-2) (SOC und PT) für die SOC „Erkrankungen des Blutes und des Lymphsystems“ aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE 204[a]	Pembrolizumab			Brentuximab Vedotin			Pembrolizumab vs. Brentuximab Vedotin		
Non-Severe Adverse Events (CTCAE-Grade 1-2): SOC[g]	N[b]	Patients with Event n (%)	Median Time[c] in weeks [95 %-CI]	N[b]	Patients with Event n (%)	Median Time[c] in weeks [95 %-CI]	Hazard Ratio [95 %-CI][d]	p-Value[d,e]	p-Value for Interaction Test[f]
Gender									
Female	67	9 (13.4)	Not reached [-; -]	63	13 (20.6)	Not reached [-; -]	0.45 [0.19; 1.09]	0.076	0.885
Male	81	9 (11.1)	Not reached [-; -]	89	14 (15.7)	Not reached [47.6; -]	0.40 [0.16; 0.97]	0.042	
Age									
<65	122	17 (13.9)	Not reached [-; -]	130	25 (19.2)	Not reached [-; -]	0.48 [0.26; 0.91]	0.023	0.604
≥65	26	1 (3.8)	Not reached [75.1; -]	22	2 (9.1)	Not reached [-; -]	n.a. [n.a.; n.a.]	0.996	
ECOG performance status									
0	84	9 (10.7)	Not reached [-; -]	99	19 (19.2)	Not reached [47.6; -]	0.31 [0.14; 0.73]	0.007	0.301
1	63	9 (14.3)	Not reached [-; -]	53	8 (15.1)	Not reached [-; -]	0.68 [0.26; 1.80]	0.437	
Region									
EU	47	5 (10.6)	Not reached [95.6; -]	45	9 (20.0)	Not reached [-; -]	0.32 [0.10; 1.01]	0.053	0.533
Ex-EU	101	13 (12.9)	Not reached [-; -]	107	18 (16.8)	Not reached [-; -]	0.50 [0.24; 1.04]	0.064	
Disease status following first line therapy									
Primary refractory	60	7 (11.7)	Not reached [95.6; -]	62	5 (8.1)	Not reached [-; -]	0.87 [0.26; 2.89]	0.819	0.384
Relapsed < 12 months	41	5 (12.2)	Not reached [-; -]	42	10 (23.8)	Not reached [42.1; -]	0.34 [0.11; 1.03]	0.057	
Relapsed ≥ 12 months	47	6 (12.8)	Not reached [-; -]	48	12 (25.0)	Not reached [31.1; -]	0.35 [0.13; 0.94]	0.038	
Prior treatment									
One prior therapy[h]	27	2 (7.4)	Not reached [75.1; -]	27	4 (14.8)	Not reached [-; -]	0.32 [0.06; 1.86]	0.206	0.662
At least two prior	55	7	Not reached	56	12	Not reached	0.29	0.016	

Study: KEYNOTE 204[a]	Pembrolizumab			Brentuximab Vedotin			Pembrolizumab vs. Brentuximab Vedotin		
Non-Severe Adverse Events (CTCAE-Grade 1-2): SOC[g]	N[b]	Patients with Event n (%)	Median Time[c] in weeks [95 %-CI]	N[b]	Patients with Event n (%)	Median Time[c] in weeks [95 %-CI]	Hazard Ratio [95 %-CI][d]	p-Value[d,e]	p-Value for Interaction Test[f]
therapies incl. auto-SCT[i]		(12.7)	[-; -]		(21.4)	[42.1; -]	[0.11; 0.80]		
At least two prior therapies excl. auto-SCT[h]	66	9 (13.6)	Not reached [-; -]	69	11 (15.9)	Not reached [-; -]	0.65 [0.27; 1.60]	0.351	
Prior treatment									
One prior therapy	27	2 (7.4)	Not reached [75.1; -]	27	4 (14.8)	Not reached [-; -]	0.32 [0.06; 1.86]	0.206	0.689
At least two prior therapies	121	16 (13.2)	Not reached [-; -]	125	23 (18.4)	Not reached [47.6; -]	0.46 [0.24; 0.89]	0.021	

a: Database Cutoff Date: 16JAN2020
b: Number of patients: all-subjects-as-treated population
c: From product-limit (Kaplan-Meier) method
d: Based on Cox regression model with treatment as a covariate using Wald confidence interval
e: Two-sided p-value using Wald test (Score test in case of zero event in one treatment group)
f: Based on Cox regression model with treatment and subgroup as covariates, and treatment-by-subgroup interaction (p-value of likelihood ratio test for interaction term)
g: SOC: Blood and lymphatic system disorders
h: auto-SCT was not a treatment option
i: auto-SCT failure
auto-SCT: autologous Stem Cell Transplantation; CI: Confidence Interval; CTCAE: Common Terminology Criteria for Adverse Events; ECOG: Eastern Cooperative Oncology Group; n.a.: not applicable (when estimation not possible); SOC: System Organ Class

Tabelle 4G-65: Subgruppenanalysen mit nicht signifikantem Interaktionstest ($p \geq 0,05$) für den Endpunkt Nicht-schwere unerwünschte Ereignisse (CTCAE-Grad 1-2) (SOC und PT) für die SOC „Endokrine Erkrankungen“ aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE 204[a]	Pembrolizumab			Brentuximab Vedotin			Pembrolizumab vs. Brentuximab Vedotin		
Non-Severe Adverse Events (CTCAE-Grade 1-2): SOC[g]	N[b]	Patients with Event n (%)	Median Time[c] in weeks [95 %-CI]	N[b]	Patients with Event n (%)	Median Time[c] in weeks [95 %-CI]	Hazard Ratio [95 %-CI][d]	p-Value[d,e]	p-Value for Interaction Test[f]
Gender									
Female	67	15 (22.4)	Not reached [105.9; -]	63	2 (3.2)	Not reached [56.9; -]	5.14 [1.16; 22.80]	0.031	0.548
Male	81	15 (18.5)	Not reached [-; -]	89	4 (4.5)	Not reached [-; -]	3.93 [1.30; 11.87]	0.015	
Age									
<65	122	21 (17.2)	Not reached [-; -]	130	6 (4.6)	Not reached [92.0; -]	2.91 [1.16; 7.29]	0.023	0.052
≥65	26	9 (34.6)	Not reached [13.4; -]	22	0 (0.0)	Not reached [-; -]	n.a. [n.a.; n.a.]	0.007	
ECOG performance status									
0	84	16 (19.0)	Not reached [-; -]	99	5 (5.1)	Not reached [92.0; -]	3.48 [1.27; 9.57]	0.016	0.255
1	63	14 (22.2)	Not reached [105.9; -]	53	1 (1.9)	Not reached [56.9; -]	8.76 [1.14; 67.11]	0.037	
Region									
EU	47	9 (19.1)	Not reached [-; -]	45	0 (0.0)	Not reached [-; -]	n.a. [n.a.; n.a.]	0.007	0.056
Ex-EU	101	21 (20.8)	Not reached [-; -]	107	6 (5.6)	Not reached [92.0; -]	3.04 [1.21; 7.61]	0.018	

Study: KEYNOTE 204[a]	Pembrolizumab			Brentuximab Vedotin			Pembrolizumab vs. Brentuximab Vedotin		
Non-Severe Adverse Events (CTCAE-Grade 1-2): SOC[g]	N[b]	Patients with Event n (%)	Median Time[c] in weeks [95 %-CI]	N[b]	Patients with Event n (%)	Median Time[c] in weeks [95 %-CI]	Hazard Ratio [95 %-CI][d]	p-Value[d,e]	p-Value for Interaction Test[f]
Disease status following first line therapy									
Primary refractory	60	13 (21.7)	Not reached [-; -]	62	2 (3.2)	Not reached [-; -]	6.12 [1.37; 27.30]	0.017	0.774
Relapsed < 12 months	41	7 (17.1)	Not reached [105.9; -]	42	1 (2.4)	Not reached [56.9; -]	5.18 [0.62; 43.07]	0.128	
Relapsed ≥ 12 months	47	10 (21.3)	Not reached [-; -]	48	3 (6.3)	Not reached [92.0; -]	2.82 [0.77; 10.39]	0.119	
Prior treatment									
One prior therapy[h]	27	7 (25.9)	Not reached [-; -]	27	1 (3.7)	Not reached [92.0; -]	7.53 [0.93; 61.21]	0.059	0.877
At least two prior therapies incl. auto-SCT[i]	55	10 (18.2)	Not reached [-; -]	56	2 (3.6)	Not reached [-; -]	4.10 [0.89; 18.81]	0.070	
At least two prior therapies excl. auto-SCT[h]	66	13 (19.7)	Not reached [105.9; -]	69	3 (4.3)	Not reached [56.9; -]	3.65 [1.02; 12.98]	0.046	
Prior treatment									
One prior therapy	27	7 (25.9)	Not reached [-; -]	27	1 (3.7)	Not reached [92.0; -]	7.53 [0.93; 61.21]	0.059	0.603
At least two prior therapies	121	23 (19.0)	Not reached [-; -]	125	5 (4.0)	Not reached [-; -]	3.70 [1.39; 9.84]	0.009	

a: Database Cutoff Date: 16JAN2020
b: Number of patients: all-subjects-as-treated population
c: From product-limit (Kaplan-Meier) method
d: Based on Cox regression model with treatment as a covariate using Wald confidence interval
e: Two-sided p-value using Wald test (Score test in case of zero event in one treatment group)
f: Based on Cox regression model with treatment and subgroup as covariates, and treatment-by-subgroup interaction (p-value of likelihood ratio test for interaction term)
g: SOC: Endocrine disorders
h: auto-SCT was not a treatment option
i: auto-SCT failure
auto-SCT: autologous Stem Cell Transplantation; CI: Confidence Interval; CTCAE: Common Terminology Criteria for Adverse Events; ECOG: Eastern Cooperative Oncology Group; n.a.: not applicable (when estimation not possible); SOC: System Organ Class

Tabelle 4G-66: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für den Endpunkt Nicht-schwere unerwünschte Ereignisse (CTCAE-Grad 1-2) (SOC und PT) für den PT „Hypothyreose“ (SOC „Endokrine Erkrankungen“) aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE 204[a]	Pembrolizumab			Brentuximab Vedotin			Pembrolizumab vs. Brentuximab Vedotin		
Non-Severe Adverse Events (CTCAE-Grade 1-2): PT[g]	N[b]	Patients with Event n (%)	Median Time[c] in weeks [95 %-CI]	N[b]	Patients with Event n (%)	Median Time[c] in weeks [95 %-CI]	Hazard Ratio [95 %-CI][d]	p-Value[d,e]	p-Value for Interaction Test[f]
Gender									
Female	67	13 (19.4)	Not reached [-; -]	63	2 (3.2)	Not reached [56.9; -]	3.98 [0.88; 17.97]	0.072	0.762
Male	81	15 (18.5)	Not reached [-; -]	89	2 (2.2)	Not reached [-; -]	7.70 [1.76; 33.70]	0.007	
Age									
<65	122	20 (16.4)	Not reached [-; -]	130	4 (3.1)	Not reached [92.0; -]	4.00 [1.35; 11.83]	0.012	0.133

Study: KEYNOTE 204[a]	Pembrolizumab			Brentuximab Vedotin			Pembrolizumab vs. Brentuximab Vedotin		
Non-Severe Adverse Events (CTCAE-Grade 1-2): PT[g]	N[b]	Patients with Event n (%)	Median Time[c] in weeks [95 %-CI]	N[b]	Patients with Event n (%)	Median Time[c] in weeks [95 %-CI]	Hazard Ratio [95 %-CI][d]	p-Value[d,e]	p-Value for Interaction Test[f]
≥65	26	8 (30.8)	Not reached [21.1; -]	22	0 (0.0)	Not reached [-; -]	n.a. [n.a.; n.a.]	0.016	
ECOG performance status									
0	84	16 (19.0)	Not reached [-; -]	99	3 (3.0)	Not reached [92.0; -]	5.63 [1.63; 19.44]	0.006	0.672
1	63	12 (19.0)	Not reached [105.9; -]	53	1 (1.9)	Not reached [56.9; -]	6.71 [0.86; 52.19]	0.069	
Region									
EU	47	8 (17.0)	Not reached [-; -]	45	0 (0.0)	Not reached [-; -]	n.a. [n.a.; n.a.]	0.014	0.130
Ex-EU	101	20 (19.8)	Not reached [-; -]	107	4 (3.7)	Not reached [92.0; -]	4.15 [1.40; 12.27]	0.010	
Disease status following first line therapy									
Primary refractory	60	11 (18.3)	Not reached [-; -]	62	0 (0.0)	Not reached [-; -]	n.a. [n.a.; n.a.]	0.002	0.154
Relapsed < 12 months	41	7 (17.1)	Not reached [105.9; -]	42	1 (2.4)	Not reached [56.9; -]	5.07 [0.61; 42.15]	0.133	
Relapsed ≥ 12 months	47	10 (21.3)	Not reached [-; -]	48	3 (6.3)	Not reached [92.0; -]	2.79 [0.76; 10.29]	0.123	
Prior treatment									
One prior therapy[h]	27	5 (18.5)	Not reached [-; -]	27	1 (3.7)	Not reached [92.0; -]	4.86 [0.57; 41.59]	0.149	0.620
At least two prior therapies incl. auto-SCT[i]	55	10 (18.2)	Not reached [-; -]	56	2 (3.6)	Not reached [-; -]	4.03 [0.88; 18.50]	0.073	
At least two prior therapies excl. auto-SCT[h]	66	13 (19.7)	Not reached [105.9; -]	69	1 (1.4)	Not reached [56.9; -]	10.97 [1.42; 84.60]	0.022	
Prior treatment									
One prior therapy	27	5 (18.5)	Not reached [-; -]	27	1 (3.7)	Not reached [92.0; -]	4.86 [0.57; 41.59]	0.149	0.754
At least two prior therapies	121	23 (19.0)	Not reached [-; -]	125	3 (2.4)	Not reached [-; -]	6.12 [1.82; 20.56]	0.003	

a: Database Cutoff Date: 16JAN2020
b: Number of patients: all-subjects-as-treated population
c: From product-limit (Kaplan-Meier) method
d: Based on Cox regression model with treatment as a covariate using Wald confidence interval
e: Two-sided p-value using Wald test (Score test in case of zero event in one treatment group)
f: Based on Cox regression model with treatment and subgroup as covariates, and treatment-by-subgroup interaction (p-value of likelihood ratio test for interaction term)
g: PT: Hypothyroidism
h: auto-SCT was not a treatment option
i: auto-SCT failure
auto-SCT: autologous Stem Cell Transplantation; CI: Confidence Interval; CTCAE: Common Terminology Criteria for Adverse Events; ECOG: Eastern Cooperative Oncology Group; n.a.: not applicable (when estimation not possible); PT: Preferred Term

Tabelle 4G-67: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für den Endpunkt Nicht-schwere unerwünschte Ereignisse (CTCAE-Grad 1-2) (SOC und PT) für die SOC „Erkrankungen des Gastrointestinaltrakts“ aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE 204[a]	Pembrolizumab			Brentuximab Vedotin			Pembrolizumab vs. Brentuximab Vedotin		
Non-Severe Adverse Events (CTCAE-Grade 1-2): SOC[g]	N[b]	Patients with Event n (%)	Median Time[c] in weeks [95 %-CI]	N[b]	Patients with Event n (%)	Median Time[c] in weeks [95 %-CI]	Hazard Ratio [95 %-CI][d]	p-Value[d,e]	p-Value for Interaction Test[f]
Gender									
Female	67	34 (50.7)	69.7 [23.6; 93.6]	63	36 (57.1)	12.4 [8.3; -]	0.64 [0.39; 1.03]	0.063	0.850
Male	81	31 (38.3)	Not reached [36.4; -]	89	41 (46.1)	23.1 [15.6; -]	0.63 [0.39; 1.01]	0.055	
Age									
<65	122	53 (43.4)	78.3 [53.7; -]	130	66 (50.8)	19.3 [12.4; -]	0.62 [0.43; 0.90]	0.013	0.999
≥65	26	12 (46.2)	54.4 [11.3; -]	22	11 (50.0)	11.1 [2.1; -]	0.61 [0.26; 1.41]	0.249	
ECOG performance status									
0	84	36 (42.9)	78.3 [36.4; -]	99	50 (50.5)	21.1 [11.6; -]	0.57 [0.37; 0.89]	0.014	0.764
1	63	28 (44.4)	91.1 [18.4; -]	53	27 (50.9)	16.1 [8.4; -]	0.68 [0.40; 1.16]	0.157	
Region									
EU	47	17 (36.2)	93.6 [54.4; -]	45	25 (55.6)	15.6 [5.7; -]	0.38 [0.20; 0.75]	0.005	0.123
Ex-EU	101	48 (47.5)	78.1 [26.7; -]	107	52 (48.6)	23.1 [13.1; -]	0.76 [0.51; 1.13]	0.168	
Disease status following first line therapy									
Primary refractory	60	27 (45.0)	72.4 [53.7; 93.6]	62	28 (45.2)	27.1 [12.4; -]	0.62 [0.35; 1.08]	0.090	0.651
Relapsed < 12 months	41	21 (51.2)	36.3 [6.9; -]	42	25 (59.5)	13.9 [8.4; -]	0.72 [0.40; 1.31]	0.285	
Relapsed ≥ 12 months	47	17 (36.2)	Not reached [23.6; -]	48	24 (50.0)	19.3 [5.3; -]	0.55 [0.30; 1.04]	0.065	
Prior treatment									
One prior therapy[h]	27	12 (44.4)	Not reached [6.4; -]	27	13 (48.1)	19.3 [3.4; -]	0.73 [0.33; 1.62]	0.445	0.115
At least two prior therapies incl. auto-SCT[i]	55	22 (40.0)	93.6 [36.3; -]	56	34 (60.7)	10.2 [5.3; -]	0.43 [0.25; 0.76]	0.004	
At least two prior therapies excl. auto-SCT[h]	66	31 (47.0)	69.7 [20.0; -]	69	30 (43.5)	48.9 [16.1; -]	0.83 [0.50; 1.38]	0.466	
Prior treatment									
One prior therapy	27	12 (44.4)	Not reached [6.4; -]	27	13 (48.1)	19.3 [3.4; -]	0.73 [0.33; 1.62]	0.445	0.757
At least two prior therapies	121	53 (43.8)	78.3 [53.7; -]	125	64 (51.2)	18.9 [12.1; -]	0.61 [0.42; 0.88]	0.009	

a: Database Cutoff Date: 16JAN2020
b: Number of patients: all-subjects-as-treated population
c: From product-limit (Kaplan-Meier) method
d: Based on Cox regression model with treatment as a covariate using Wald confidence interval
e: Two-sided p-value using Wald test (Score test in case of zero event in one treatment group)
f: Based on Cox regression model with treatment and subgroup as covariates, and treatment-by-subgroup interaction (p-value of likelihood ratio test for interaction term)

g: SOC: Gastrointestinal disorders
h: auto-SCT was not a treatment option
i: auto-SCT failure
auto-SCT: autologous Stem Cell Transplantation; CI: Confidence Interval; CTCAE: Common Terminology Criteria for Adverse Events; ECOG: Eastern Cooperative Oncology Group; SOC: System Organ Class

Tabelle 4G-68: Subgruppenanalysen mit nicht signifikantem Interaktionstest ($p \geq 0,05$) für den Endpunkt Nicht-schwere unerwünschte Ereignisse (CTCAE-Grad 1-2) (SOC und PT) für den PT „Abdominalschmerz“ (SOC „Erkrankungen des Gastrointestinaltrakts“) aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE 204[a]	**Pembrolizumab**			**Brentuximab Vedotin**			**Pembrolizumab vs. Brentuximab Vedotin**		
Non-Severe Adverse Events (CTCAE-Grade 1-2): PT[g]	**N[b]**	**Patients with Event n (%)**	**Median Time[c] in weeks [95 %-CI]**	**N[b]**	**Patients with Event n (%)**	**Median Time[c] in weeks [95 %-CI]**	**Hazard Ratio [95 %-CI][d]**	**p-Value[d,e]**	**p-Value for Interaction Test[f]**
Gender									
Female	67	5 (7.5)	Not reached [-; -]	63	9 (14.3)	Not reached [-; -]	0.35 [0.11; 1.07]	0.065	0.661
Male	81	4 (4.9)	Not reached [-; -]	89	6 (6.7)	Not reached [-; -]	0.43 [0.11; 1.68]	0.225	
Age									
<65	122	8 (6.6)	Not reached [-; -]	130	12 (9.2)	Not reached [-; -]	0.43 [0.17; 1.10]	0.078	0.423
≥65	26	1 (3.8)	Not reached [-; -]	22	3 (13.6)	Not reached [-; -]	0.27 [0.03; 2.59]	0.256	
ECOG performance status									
0	84	5 (6.0)	Not reached [-; -]	99	9 (9.1)	Not reached [-; -]	0.36 [0.11; 1.18]	0.091	0.999
1	63	4 (6.3)	Not reached [-; -]	53	6 (11.3)	Not reached [57.1; -]	0.40 [0.11; 1.46]	0.166	
Region									
EU	47	2 (4.3)	Not reached [-; -]	45	4 (8.9)	Not reached [-; -]	0.47 [0.09; 2.54]	0.377	0.762
Ex-EU	101	7 (6.9)	Not reached [-; -]	107	11 (10.3)	Not reached [-; -]	0.38 [0.14; 1.04]	0.059	
Disease status following first line therapy									
Primary refractory	60	4 (6.7)	Not reached [-; -]	62	3 (4.8)	Not reached [57.1; -]	0.44 [0.08; 2.39]	0.343	0.333
Relapsed < 12 months	41	4 (9.8)	Not reached [-; -]	42	7 (16.7)	Not reached [-; -]	0.42 [0.12; 1.52]	0.187	
Relapsed ≥ 12 months	47	1 (2.1)	Not reached [-; -]	48	5 (10.4)	Not reached [-; -]	0.19 [0.02; 1.59]	0.124	
Prior treatment									
One prior therapy[h]	27	0 (0.0)	Not reached [-; -]	27	2 (7.4)	Not reached [-; -]	n.a. [n.a.; n.a.]	0.118	0.366
At least two prior therapies incl. auto-SCT[i]	55	5 (9.1)	Not reached [-; -]	56	7 (12.5)	Not reached [-; -]	0.39 [0.11; 1.35]	0.136	
At least two prior therapies excl. auto-SCT[h]	66	4 (6.1)	Not reached [-; -]	69	6 (8.7)	Not reached [57.1; -]	0.49 [0.13; 1.82]	0.287	
Prior treatment									
One prior therapy	27	0 (0.0)	Not reached [-; -]	27	2 (7.4)	Not reached [-; -]	n.a. [n.a.; n.a.]	0.118	0.159
At least two prior therapies	121	9 (7.4)	Not reached [-; -]	125	13 (10.4)	Not reached [-; -]	0.45 [0.18; 1.10]	0.079	

Study: KEYNOTE 204[a]	Pembrolizumab			Brentuximab Vedotin			Pembrolizumab vs. Brentuximab Vedotin		
Non-Severe Adverse Events (CTCAE-Grade 1-2): PT[g]	N[b]	Patients with Event n (%)	Median Time[c] in weeks [95 %-CI]	N[b]	Patients with Event n (%)	Median Time[c] in weeks [95 %-CI]	Hazard Ratio [95 %-CI][d]	p-Value[d,e]	p-Value for Interaction Test[f]

a: Database Cutoff Date: 16JAN2020
b: Number of patients: all-subjects-as-treated population
c: From product-limit (Kaplan-Meier) method
d: Based on Cox regression model with treatment as a covariate using Wald confidence interval
e: Two-sided p-value using Wald test (Score test in case of zero event in one treatment group)
f: Based on Cox regression model with treatment and subgroup as covariates, and treatment-by-subgroup interaction (p-value of likelihood ratio test for interaction term)
g: PT: Abdominal pain
h: auto-SCT was not a treatment option
i: auto-SCT failure
auto-SCT: autologous Stem Cell Transplantation; CI: Confidence Interval; CTCAE: Common Terminology Criteria for Adverse Events; ECOG: Eastern Cooperative Oncology Group; n.a.: not applicable (when estimation not possible); PT: Preferred Term

Tabelle 4G-69: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für den Endpunkt Nicht-schwere unerwünschte Ereignisse (CTCAE-Grad 1-2) (SOC und PT) für den PT „Verstopfung“ (SOC „Erkrankungen des Gastrointestinaltrakts“)aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE 204[a]	Pembrolizumab			Brentuximab Vedotin			Pembrolizumab vs. Brentuximab Vedotin		
Non-Severe Adverse Events (CTCAE-Grade 1-2): PT[g]	N[b]	Patients with Event n (%)	Median Time[c] in weeks [95 %-CI]	N[b]	Patients with Event n (%)	Median Time[c] in weeks [95 %-CI]	Hazard Ratio [95 %-CI][d]	p-Value[d,e]	p-Value for Interaction Test[f]
Gender									
Female	67	6 (9.0)	Not reached [-; -]	63	9 (14.3)	Not reached [-; -]	0.50 [0.17; 1.43]	0.195	0.783
Male	81	5 (6.2)	Not reached [-; -]	89	10 (11.2)	Not reached [54.1; -]	0.22 [0.06; 0.79]	0.020	
Age									
<65	122	9 (7.4)	Not reached [-; -]	130	14 (10.8)	Not reached [-; -]	0.40 [0.16; 0.97]	0.042	0.352
≥65	26	2 (7.7)	Not reached [-; -]	22	5 (22.7)	Not reached [-; -]	0.29 [0.06; 1.50]	0.140	
ECOG performance status									
0	84	7 (8.3)	Not reached [-; -]	99	12 (12.1)	Not reached [54.1; -]	0.30 [0.11; 0.85]	0.024	0.823
1	63	4 (6.3)	Not reached [-; -]	53	7 (13.2)	Not reached [-; -]	0.42 [0.12; 1.43]	0.163	
Region									
EU	47	2 (4.3)	Not reached [-; -]	45	7 (15.6)	Not reached [33.4; -]	0.22 [0.04; 1.08]	0.061	0.240
Ex-EU	101	9 (8.9)	Not reached [-; -]	107	12 (11.2)	Not reached [-; -]	0.47 [0.19; 1.18]	0.108	
Disease status following first line therapy									
Primary refractory	60	4 (6.7)	Not reached [-; -]	62	7 (11.3)	Not reached [36.0; -]	0.37 [0.10; 1.35]	0.131	0.263
Relapsed < 12 months	41	6 (14.6)	Not reached [-; -]	42	6 (14.3)	Not reached [54.1; -]	0.62 [0.19; 2.08]	0.439	
Relapsed ≥ 12 months	47	1 (2.1)	Not reached [-; -]	48	6 (12.5)	Not reached [-; -]	0.10 [0.01; 0.93]	0.043	

Study: KEYNOTE 204[a]	Pembrolizumab			Brentuximab Vedotin			Pembrolizumab vs. Brentuximab Vedotin		
Non-Severe Adverse Events (CTCAE-Grade 1-2): PT[g]	N[b]	Patients with Event n (%)	Median Time[c] in weeks [95 %-CI]	N[b]	Patients with Event n (%)	Median Time[c] in weeks [95 %-CI]	Hazard Ratio [95 %-CI][d]	p-Value[d,e]	p-Value for Interaction Test[f]
Prior treatment									
One prior therapy[h]	27	3 (11.1)	Not reached [-; -]	27	2 (7.4)	Not reached [-; -]	1.45 [0.24; 8.69]	0.684	0.401
At least two prior therapies incl. auto-SCT[i]	55	5 (9.1)	Not reached [-; -]	56	10 (17.9)	Not reached [-; -]	0.27 [0.08; 0.92]	0.037	
At least two prior therapies excl. auto-SCT[h]	66	3 (4.5)	Not reached [-; -]	69	7 (10.1)	Not reached [54.1; -]	0.26 [0.07; 1.07]	0.062	
Prior treatment									
One prior therapy	27	3 (11.1)	Not reached [-; -]	27	2 (7.4)	Not reached [-; -]	1.45 [0.24; 8.69]	0.684	0.193
At least two prior therapies	121	8 (6.6)	Not reached [-; -]	125	17 (13.6)	Not reached [-; -]	0.26 [0.11; 0.65]	0.004	

a: Database Cutoff Date: 16JAN2020
b: Number of patients: all-subjects-as-treated population
c: From product-limit (Kaplan-Meier) method
d: Based on Cox regression model with treatment as a covariate using Wald confidence interval
e: Two-sided p-value using Wald test (Score test in case of zero event in one treatment group)
f: Based on Cox regression model with treatment and subgroup as covariates, and treatment-by-subgroup interaction (p-value of likelihood ratio test for interaction term)
g: PT: Constipation
h: auto-SCT was not a treatment option
i: auto-SCT failure
auto-SCT: autologous Stem Cell Transplantation; CI: Confidence Interval; CTCAE: Common Terminology Criteria for Adverse Events; ECOG: Eastern Cooperative Oncology Group; PT: Preferred Term

Tabelle 4G-70: Subgruppenanalysen mit nicht signifikantem Interaktionstest ($p \geq 0,05$) für den Endpunkt Unerwünschte Ereignisse gesamt (SOC und PT) für den PT „Übelkeit“ (SOC „Erkrankungen des Gastrointestinaltrakts“) aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE 204[a]	Pembrolizumab			Brentuximab Vedotin			Pembrolizumab vs. Brentuximab Vedotin		
Non-Severe Adverse Events (CTCAE-Grade 1-2): PT[g]	N[b]	Patients with Event n (%)	Median Time[c] in weeks [95 %-CI]	N[b]	Patients with Event n (%)	Median Time[c] in weeks [95 %-CI]	Hazard Ratio [95 %-CI][d]	p-Value[d,e]	p-Value for Interaction Test[f]
Gender									
Female	67	11 (16.4)	Not reached [-; -]	63	13 (20.6)	Not reached [-; -]	0.61 [0.27; 1.39]	0.242	0.336
Male	81	10 (12.3)	Not reached [-; -]	89	23 (25.8)	Not reached [-; -]	0.34 [0.16; 0.73]	0.006	
Age									
<65	122	16 (13.1)	Not reached [-; -]	130	30 (23.1)	Not reached [-; -]	0.44 [0.24; 0.81]	0.009	0.895
≥65	26	5 (19.2)	Not reached [71.4; -]	22	6 (27.3)	Not reached [6.0; -]	0.33 [0.09; 1.27]	0.106	
ECOG performance status									
0	84	9 (10.7)	Not reached [-; -]	99	24 (24.2)	Not reached [-; -]	0.31 [0.14; 0.68]	0.003	0.211
1	63	12 (19.0)	Not reached [-; -]	53	12 (22.6)	Not reached [-; -]	0.66 [0.29; 1.48]	0.308	

Study: KEYNOTE 204[a]	Pembrolizumab			Brentuximab Vedotin			Pembrolizumab vs. Brentuximab Vedotin		
Non-Severe Adverse Events (CTCAE-Grade 1-2): PT[g]	N[b]	Patients with Event n (%)	Median Time[c] in weeks [95 %-CI]	N[b]	Patients with Event n (%)	Median Time[c] in weeks [95 %-CI]	Hazard Ratio [95 %-CI][d]	p-Value[d,e]	p-Value for Interaction Test[f]
Region									
EU	47	4 (8.5)	Not reached [-; -]	45	11 (24.4)	Not reached [-; -]	0.28 [0.09; 0.88]	0.030	0.288
Ex-EU	101	17 (16.8)	Not reached [-; -]	107	25 (23.4)	Not reached [-; -]	0.52 [0.28; 0.98]	0.042	
Disease status following first line therapy									
Primary refractory	60	7 (11.7)	Not reached [-; -]	62	15 (24.2)	Not reached [-; -]	0.35 [0.14; 0.86]	0.023	0.552
Relapsed < 12 months	41	8 (19.5)	Not reached [-; -]	42	10 (23.8)	Not reached [-; -]	0.71 [0.28; 1.82]	0.478	
Relapsed ≥ 12 months	47	6 (12.8)	Not reached [-; -]	48	11 (22.9)	Not reached [-; -]	0.37 [0.13; 1.02]	0.055	
Prior treatment									
One prior therapy	27	4 (14.8)	Not reached [71.4; -]	27	8 (29.6)	Not reached [19.3; -]	0.32 [0.09; 1.10]	0.070	0.646
At least two prior therapies	121	17 (14.0)	Not reached [-; -]	125	28 (22.4)	Not reached [-; -]	0.48 [0.26; 0.89]	0.020	

a: Database Cutoff Date: 16JAN2020

b: Number of patients: all-subjects-as-treated population

c: From product-limit (Kaplan-Meier) method

d: Based on Cox regression model with treatment as a covariate using Wald confidence interval

e: Two-sided p-value using Wald test (Score test in case of zero event in one treatment group)

f: Based on Cox regression model with treatment and subgroup as covariates, and treatment-by-subgroup interaction (p-value of likelihood ratio test for interaction term)

g: PT: Nausea

CI: Confidence Interval; CTCAE: Common Terminology Criteria for Adverse Events; ECOG: Eastern Cooperative Oncology Group; PT: Preferred Term

Tabelle 4G-71: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für den Endpunkt Nicht-schwere unerwünschte Ereignisse (CTCAE-Grad 1-2) (SOC und PT) für den PT „Erbrechen“ (SOC „Erkrankungen des Gastrointestinaltrakts“) aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE 204[a]	Pembrolizumab			Brentuximab Vedotin			Pembrolizumab vs. Brentuximab Vedotin		
Non-Severe Adverse Events (CTCAE-Grade 1-2): PT[g]	N[b]	Patients with Event n (%)	Median Time[c] in weeks [95 %-CI]	N[b]	Patients with Event n (%)	Median Time[c] in weeks [95 %-CI]	Hazard Ratio [95 %-CI][d]	p-Value[d,e]	p-Value for Interaction Test[f]
Gender									
Female	67	12 (17.9)	Not reached [-; -]	63	14 (22.2)	Not reached [-; -]	0.68 [0.31; 1.48]	0.335	0.363
Male	81	7 (8.6)	Not reached [-; -]	89	16 (18.0)	Not reached [-; -]	0.39 [0.16; 0.96]	0.040	
Age									
<65	122	15 (12.3)	Not reached [-; -]	130	26 (20.0)	Not reached [-; -]	0.51 [0.27; 0.96]	0.038	0.724
≥65	26	4 (15.4)	Not reached [-; -]	22	4 (18.2)	Not reached [-; -]	0.72 [0.18; 2.89]	0.646	
ECOG performance status									
0	84	13 (15.5)	Not reached [-; -]	99	17 (17.2)	Not reached [-; -]	0.73 [0.35; 1.52]	0.403	0.148
1	63	6 (9.5)	Not reached [-; -]	53	13 (24.5)	Not reached [-; -]	0.32 [0.12; 0.85]	0.023	
Region									
EU	47	5 (10.6)	Not reached [-; -]	45	9 (20.0)	Not reached [-; -]	0.46 [0.15; 1.37]	0.163	0.689
Ex-EU	101	14 (13.9)	Not reached [-; -]	107	21 (19.6)	Not reached [-; -]	0.57 [0.29; 1.13]	0.110	
Disease status following first line therapy									
Primary refractory	60	6 (10.0)	Not reached [-; -]	62	14 (22.6)	Not reached [-; -]	0.30 [0.11; 0.81]	0.018	0.169
Relapsed < 12 months	41	9 (22.0)	Not reached [-; -]	42	8 (19.0)	Not reached [-; -]	1.11 [0.43; 2.89]	0.823	
Relapsed ≥ 12 months	47	4 (8.5)	Not reached [-; -]	48	8 (16.7)	Not reached [-; -]	0.43 [0.13; 1.42]	0.165	
Prior treatment									
One prior therapy[h]	27	3 (11.1)	Not reached [-; -]	27	3 (11.1)	Not reached [-; -]	0.81 [0.16; 4.02]	0.795	0.602
At least two prior therapies incl. auto-SCT[i]	55	7 (12.7)	Not reached [-; -]	56	15 (26.8)	Not reached [-; -]	0.40 [0.16; 0.99]	0.048	
At least two prior therapies excl. auto-SCT[h]	66	9 (13.6)	Not reached [-; -]	69	12 (17.4)	Not reached [-; -]	0.64 [0.27; 1.52]	0.311	
Prior treatment									
One prior therapy	27	3 (11.1)	Not reached [-; -]	27	3 (11.1)	Not reached [-; -]	0.81 [0.16; 4.02]	0.795	0.551
At least two prior therapies	121	16 (13.2)	Not reached [-; -]	125	27 (21.6)	Not reached [-; -]	0.51 [0.27; 0.95]	0.033	

a: Database Cutoff Date: 16JAN2020
b: Number of patients: all-subjects-as-treated population
c: From product-limit (Kaplan-Meier) method
d: Based on Cox regression model with treatment as a covariate using Wald confidence interval
e: Two-sided p-value using Wald test (Score test in case of zero event in one treatment group)
f: Based on Cox regression model with treatment and subgroup as covariates, and treatment-by-subgroup interaction (p-value of likelihood ratio test for interaction term)

Study: KEYNOTE 204[a]	Pembrolizumab			Brentuximab Vedotin			Pembrolizumab vs. Brentuximab Vedotin		
Non-Severe Adverse Events (CTCAE-Grade 1-2): PT[g]	N[b]	Patients with Event n (%)	Median Time[c] in weeks [95 %-CI]	N[b]	Patients with Event n (%)	Median Time[c] in weeks [95 %-CI]	Hazard Ratio [95 %-CI][d]	p-Value[d,e]	p-Value for Interaction Test[f]
g: PT: Vomiting									
h: auto-SCT was not a treatment option									
i: auto-SCT failure									
auto-SCT: autologous Stem Cell Transplantation; CI: Confidence Interval; CTCAE: Common Terminology Criteria for Adverse Events; ECOG: Eastern Cooperative Oncology Group; PT: Preferred Term									

Tabelle 4G-72: Subgruppenanalysen mit nicht signifikantem Interaktionstest ($p \geq 0,05$) für den Endpunkt Nicht-schwere unerwünschte Ereignisse (CTCAE-Grad 1-2) (SOC und PT) für den PT „Harnwegsinfektion“ (SOC „Infektionen und parasitäre Erkrankungen“) aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE 204[a]	Pembrolizumab			Brentuximab Vedotin			Pembrolizumab vs. Brentuximab Vedotin		
Non-Severe Adverse Events (CTCAE-Grade 1-2): PT[g]	N[b]	Patients with Event n (%)	Median Time[c] in weeks [95 %-CI]	N[b]	Patients with Event n (%)	Median Time[c] in weeks [95 %-CI]	Hazard Ratio [95 %-CI][d]	p-Value[d,e]	p-Value for Interaction Test[f]
Gender									
Female	67	12 (17.9)	Not reached [-; -]	63	2 (3.2)	Not reached [-; -]	5.13 [1.14; 23.04]	0.033	0.780
Male	81	4 (4.9)	Not reached [-; -]	89	1 (1.1)	Not reached [-; -]	2.70 [0.29; 25.29]	0.385	
Age									
<65	122	11 (9.0)	Not reached [-; -]	130	2 (1.5)	Not reached [-; -]	4.59 [1.01; 20.93]	0.049	0.773
≥65	26	5 (19.2)	Not reached [-; -]	22	1 (4.5)	Not reached [-; -]	3.20 [0.36; 28.66]	0.299	
ECOG performance status									
0	84	9 (10.7)	Not reached [-; -]	99	2 (2.0)	Not reached [-; -]	3.46 [0.73; 16.39]	0.118	0.882
1	63	7 (11.1)	Not reached [-; -]	53	1 (1.9)	Not reached [-; -]	5.47 [0.67; 44.48]	0.112	
Region									
EU	47	7 (14.9)	Not reached [-; -]	45	2 (4.4)	Not reached [-; -]	2.52 [0.51; 12.32]	0.255	0.410
Ex-EU	101	9 (8.9)	Not reached [-; -]	107	1 (0.9)	Not reached [-; -]	7.24 [0.91; 57.82]	0.062	
Disease status following first line therapy									
Primary refractory	60	4 (6.7)	n.c.	62	1 (1.6)	n.c.	n.c.	n.c.	n.c.
Relapsed < 12 months	41	6 (14.6)	n.c.	42	0 (0.0)	n.c.	n.c.	n.c.	
Relapsed ≥ 12 months	47	6 (12.8)	n.c.	48	2 (4.2)	n.c.	n.c.	n.c.	
Prior treatment									
One prior therapy[h]	27	4 (14.8)	n.c.	27	1 (3.7)	n.c.	n.c.	n.c.	n.c.
At least two prior therapies incl. auto-SCT[i]	55	6 (10.9)	n.c.	56	1 (1.8)	n.c.	n.c.	n.c.	
At least two prior therapies excl. auto-	66	6 (9.1)	n.c.	69	1 (1.4)	n.c.	n.c.	n.c.	

Study: KEYNOTE 204[a]	Pembrolizumab			Brentuximab Vedotin			Pembrolizumab vs. Brentuximab Vedotin		
Non-Severe Adverse Events (CTCAE-Grade 1-2): PT[g]	N[b]	Patients with Event n (%)	Median Time[c] in weeks [95 %-CI]	N[b]	Patients with Event n (%)	Median Time[c] in weeks [95 %-CI]	Hazard Ratio [95 %-CI][d]	p-Value[d,e]	p-Value for Interaction Test[f]
SCT[h]									
Prior treatment									
One prior therapy	27	4 (14.8)	Not reached [-; -]	27	1 (3.7)	Not reached [-; -]	3.16 [0.34; 29.05]	0.309	0.748
At least two prior therapies	121	12 (9.9)	Not reached [-; -]	125	2 (1.6)	Not reached [-; -]	4.83 [1.07; 21.77]	0.041	

a: Database Cutoff Date: 16JAN2020
b: Number of patients: all-subjects-as-treated population
c: From product-limit (Kaplan-Meier) method
d: Based on Cox regression model with treatment as a covariate using Wald confidence interval
e: Two-sided p-value using Wald test (Score test in case of zero event in one treatment group)
f: Based on Cox regression model with treatment and subgroup as covariates, and treatment-by-subgroup interaction (p-value of likelihood ratio test for interaction term)
g: PT: Urinary tract infection
h: auto-SCT was not a treatment option
i: auto-SCT failure
auto-SCT: autologous Stem Cell Transplantation; CI: Confidence Interval; CTCAE: Common Terminology Criteria for Adverse Events; ECOG: Eastern Cooperative Oncology Group; n.c.: not calculated (at least 10 subjects per subgroup and at least 10 events in one of the subgroups necessary); PT: Preferred Term

Tabelle 4G-73: Subgruppenanalysen mit nicht signifikantem Interaktionstest ($p \geq 0,05$) für den Endpunkt Nicht-schwere unerwünschte Ereignisse (CTCAE-Grad 1-2) (SOC und PT) für den PT „Gewicht erniedrigt“ (SOC „Untersuchungen“) aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE 204[a]	Pembrolizumab			Brentuximab Vedotin			Pembrolizumab vs. Brentuximab Vedotin		
Non-Severe Adverse Events (CTCAE-Grade 1-2): PT[g]	N[b]	Patients with Event n (%)	Median Time[c] in weeks [95 %-CI]	N[b]	Patients with Event n (%)	Median Time[c] in weeks [95 %-CI]	Hazard Ratio [95 %-CI][d]	p-Value[d,e]	p-Value for Interaction Test[f]
Gender									
Female	67	3 (4.5)	n.c.	63	5 (7.9)	n.c.	n.c.	n.c.	n.c.
Male	81	2 (2.5)	n.c.	89	6 (6.7)	n.c.	n.c.	n.c.	
Age									
<65	122	3 (2.5)	Not reached [-; -]	130	9 (6.9)	Not reached [-; -]	0.24 [0.06; 0.91]	0.036	0.502
≥65	26	2 (7.7)	Not reached [-; -]	22	2 (9.1)	Not reached [28.3; -]	0.43 [0.06; 3.21]	0.413	
ECOG performance status									
0	84	4 (4.8)	Not reached [-; -]	99	6 (6.1)	Not reached [-; -]	0.45 [0.12; 1.63]	0.225	0.207
1	63	1 (1.6)	Not reached [-; -]	53	5 (9.4)	Not reached [-; -]	0.13 [0.01; 1.10]	0.062	
Region									
EU	47	2 (4.3)	Not reached [-; -]	45	4 (8.9)	Not reached [-; -]	0.32 [0.06; 1.78]	0.192	0.953
Ex-EU	101	3 (3.0)	Not reached [-; -]	107	7 (6.5)	Not reached [-; -]	0.29 [0.07; 1.14]	0.076	

Disease status following first line therapy									
Primary refractory	60	1 (1.7)	n.c.	62	4 (6.5)	n.c.	n.c.	n.c.	n.c.
Relapsed < 12 months	41	1 (2.4)	n.c.	42	5 (11.9)	n.c.	n.c.	n.c.	
Relapsed ≥ 12 months	47	3 (6.4)	n.c.	48	2 (4.2)	n.c.	n.c.	n.c.	
Prior treatment									
One prior therapy[h]	27	2 (7.4)	n.c.	27	1 (3.7)	n.c.	n.c.	n.c.	n.c.
At least two prior therapies incl. auto-SCT[i]	55	1 (1.8)	n.c.	56	3 (5.4)	n.c.	n.c.	n.c.	
At least two prior therapies excl. auto-SCT[h]	66	2 (3.0)	n.c.	69	7 (10.1)	n.c.	n.c.	n.c.	
Prior treatment									
One prior therapy	27	2 (7.4)	Not reached [-; -]	27	1 (3.7)	Not reached [49.0; -]	0.82 [0.07; 9.09]	0.871	0.166
At least two prior therapies	121	3 (2.5)	Not reached [-; -]	125	10 (8.0)	Not reached [-; -]	0.22 [0.06; 0.81]	0.023	

a: Database Cutoff Date: 16JAN2020
b: Number of patients: all-subjects-as-treated population
c: From product-limit (Kaplan-Meier) method
d: Based on Cox regression model with treatment as a covariate using Wald confidence interval
e: Two-sided p-value using Wald test (Score test in case of zero event in one treatment group)
f: Based on Cox regression model with treatment and subgroup as covariates, and treatment-by-subgroup interaction (p-value of likelihood ratio test for interaction term)
g: PT: Weight decreased
h: auto-SCT was not a treatment option
i: auto-SCT failure
auto-SCT: autologous Stem Cell Transplantation; CI: Confidence Interval; CTCAE: Common Terminology Criteria for Adverse Events; ECOG: Eastern Cooperative Oncology Group; n.c.: not calculated (at least 10 subjects per subgroup and at least 10 events in one of the subgroups necessary); PT: Preferred Term

Tabelle 4G-74: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für den Endpunkt Nicht-schwere unerwünschte Ereignisse (CTCAE-Grad 1-2) (SOC und PT) für die SOC „Erkrankungen des Nervensystems“ aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE 204[a]	**Pembrolizumab**			**Brentuximab Vedotin**			**Pembrolizumab vs. Brentuximab Vedotin**		
Non-Severe Adverse Events (CTCAE-Grade 1-2): SOC[g]	**N[b]**	**Patients with Event n (%)**	**Median Time[c] in weeks [95 %-CI]**	**N[b]**	**Patients with Event n (%)**	**Median Time[c] in weeks [95 %-CI]**	**Hazard Ratio [95 %-CI][d]**	**p-Value[d,e]**	**p-Value for Interaction Test[f]**
Gender									
Female	67	20 (29.9)	Not reached [76.7; -]	63	29 (46.0)	45.0 [21.7; 65.7]	0.39 [0.21; 0.70]	0.002	0.255
Male	81	16 (19.8)	Not reached [-; -]	89	40 (44.9)	27.9 [22.1; 45.1]	0.29 [0.16; 0.53]	< 0.001	
ECOG performance status									
0	84	18 (21.4)	Not reached [-; -]	99	47 (47.5)	30.1 [22.1; 45.1]	0.26 [0.15; 0.45]	< 0.001	0.195
1	63	18 (28.6)	Not reached [76.7; -]	53	22 (41.5)	59.4 [17.3; -]	0.47 [0.25; 0.90]	0.024	
Region									
EU	47	11 (23.4)	Not reached [55.4; -]	45	18 (40.0)	45.0 [22.7; 92.0]	0.38 [0.17; 0.82]	0.014	0.585
Ex-EU	101	25	Not reached	107	51	27.9	0.32	< 0.001	

Study: KEYNOTE 204[a]	Pembrolizumab			Brentuximab Vedotin			Pembrolizumab vs. Brentuximab Vedotin		
Non-Severe Adverse Events (CTCAE-Grade 1-2): SOC[g]	N[b]	Patients with Event n (%)	Median Time[c] in weeks [95 %-CI]	N[b]	Patients with Event n (%)	Median Time[c] in weeks [95 %-CI]	Hazard Ratio [95 %-CI][d]	p-Value[d,e]	p-Value for Interaction Test[f]
		(24.8)	[-; -]		(47.7)	[21.7; 45.1]	[0.19; 0.52]		
Disease status following first line therapy									
Primary refractory	60	16 (26.7)	Not reached [76.7; -]	62	20 (32.3)	59.4 [24.6; 59.4]	0.52 [0.26; 1.04]	0.066	0.281
Relapsed < 12 months	41	9 (22.0)	Not reached [-; -]	42	25 (59.5)	27.7 [10.1; 45.1]	0.27 [0.12; 0.59]	< 0.001	
Relapsed ≥ 12 months	47	11 (23.4)	Not reached [55.4; -]	48	24 (50.0)	24.3 [16.1; 65.7]	0.24 [0.12; 0.51]	< 0.001	
Prior treatment									
One prior therapy[h]	27	9 (33.3)	Not reached [30.3; -]	27	11 (40.7)	31.0 [17.3; -]	0.55 [0.22; 1.37]	0.199	0.224
At least two prior therapies incl. auto-SCT[i]	55	12 (21.8)	Not reached [-; -]	56	30 (53.6)	25.9 [16.1; 45.1]	0.21 [0.10; 0.42]	< 0.001	
At least two prior therapies excl. auto-SCT[h]	66	15 (22.7)	Not reached [-; -]	69	28 (40.6)	30.1 [21.7; -]	0.38 [0.20; 0.73]	0.003	
Prior treatment									
One prior therapy	27	9 (33.3)	Not reached [30.3; -]	27	11 (40.7)	31.0 [17.3; -]	0.55 [0.22; 1.37]	0.199	0.183
At least two prior therapies	121	27 (22.3)	Not reached [-; -]	125	58 (46.4)	29.3 [22.7; 45.1]	0.28 [0.18; 0.46]	< 0.001	

a: Database Cutoff Date: 16JAN2020

b: Number of patients: all-subjects-as-treated population

c: From product-limit (Kaplan-Meier) method

d: Based on Cox regression model with treatment as a covariate using Wald confidence interval

e: Two-sided p-value using Wald test (Score test in case of zero event in one treatment group)

f: Based on Cox regression model with treatment and subgroup as covariates, and treatment-by-subgroup interaction (p-value of likelihood ratio test for interaction term)

g: SOC: Nervous system disorders

h: auto-SCT was not a treatment option

i: auto-SCT failure

auto-SCT: autologous Stem Cell Transplantation; CI: Confidence Interval; CTCAE: Common Terminology Criteria for Adverse Events; ECOG: Eastern Cooperative Oncology Group; SOC: System Organ Class

Tabelle 4G-75: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für den Endpunkt Nicht-schwere unerwünschte Ereignisse (CTCAE-Grad 1-2) (SOC und PT) für den PT „Periphere Neuropathie“ (SOC „Erkrankungen des Nervensystems“) aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE 204[a]	**Pembrolizumab**			**Brentuximab Vedotin**			**Pembrolizumab vs. Brentuximab Vedotin**		
Non-Severe Adverse Events (CTCAE-Grade 1-2): PT[g]	**N[b]**	**Patients with Event n (%)**	**Median Time[c] in weeks [95 %-CI]**	**N[b]**	**Patients with Event n (%)**	**Median Time[c] in weeks [95 %-CI]**	**Hazard Ratio [95 %-CI][d]**	**p-Value[d,e]**	**p-Value for Interaction Test[f]**
Gender									
Female	67	3 (4.5)	Not reached [-; -]	63	10 (15.9)	Not reached [46.4; -]	0.18 [0.05; 0.67]	0.011	0.590
Male	81	2 (2.5)	Not reached [-; -]	89	13 (14.6)	Not reached [45.1; -]	0.10 [0.02; 0.46]	0.003	
Age									
<65	122	4 (3.3)	Not reached [-; -]	130	21 (16.2)	Not reached [46.4; -]	0.12 [0.04; 0.36]	< 0.001	0.660
≥65	26	1 (3.8)	Not reached [-; -]	22	2 (9.1)	Not reached [30.1; -]	0.27 [0.02; 3.32]	0.305	
ECOG performance status									
0	84	2 (2.4)	Not reached [-; -]	99	18 (18.2)	Not reached [45.1; -]	0.06 [0.01; 0.27]	< 0.001	0.151
1	63	3 (4.8)	Not reached [-; -]	53	5 (9.4)	Not reached [-; -]	0.48 [0.11; 2.01]	0.314	
Region									
EU	47	1 (2.1)	Not reached [-; -]	45	6 (13.3)	Not reached [45.0; -]	0.13 [0.01; 1.07]	0.058	0.715
Ex-EU	101	4 (4.0)	Not reached [-; -]	107	17 (15.9)	Not reached [46.4; -]	0.14 [0.05; 0.43]	< 0.001	
Disease status following first line therapy									
Primary refractory	60	2 (3.3)	Not reached [-; -]	62	7 (11.3)	Not reached [-; -]	0.16 [0.03; 0.81]	0.027	0.765
Relapsed < 12 months	41	1 (2.4)	Not reached [-; -]	42	9 (21.4)	Not reached [45.1; -]	0.07 [0.01; 0.53]	0.010	
Relapsed ≥ 12 months	47	2 (4.3)	Not reached [-; -]	48	7 (14.6)	Not reached [-; -]	0.22 [0.04; 1.08]	0.062	
Prior treatment									
One prior therapy[h]	27	1 (3.7)	Not reached [-; -]	27	2 (7.4)	Not reached [-; -]	0.51 [0.05; 5.58]	0.578	0.083
At least two prior therapies incl. auto-SCT[i]	55	1 (1.8)	Not reached [-; -]	56	16 (28.6)	46.4 [45.0; -]	0.03 [0.00; 0.24]	< 0.001	
At least two prior therapies excl. auto-SCT[h]	66	3 (4.5)	Not reached [-; -]	69	5 (7.2)	Not reached [-; -]	0.43 [0.10; 1.86]	0.259	
Prior treatment									
One prior therapy	27	1 (3.7)	Not reached [-; -]	27	2 (7.4)	Not reached [-; -]	0.51 [0.05; 5.58]	0.578	0.525
At least two prior therapies	121	4 (3.3)	Not reached [-; -]	125	21 (16.8)	Not reached [46.3; -]	0.11 [0.04; 0.33]	< 0.001	

a: Database Cutoff Date: 16JAN2020
b: Number of patients: all-subjects-as-treated population
c: From product-limit (Kaplan-Meier) method
d: Based on Cox regression model with treatment as a covariate using Wald confidence interval
e: Two-sided p-value using Wald test (Score test in case of zero event in one treatment group)
f: Based on Cox regression model with treatment and subgroup as covariates, and treatment-by-subgroup interaction (p-value of likelihood ratio test for interaction term)

Study: KEYNOTE 204[a]	Pembrolizumab			Brentuximab Vedotin			Pembrolizumab vs. Brentuximab Vedotin		
Non-Severe Adverse Events (CTCAE-Grade 1-2): PT[g]	N[b]	Patients with Event n (%)	Median Time[c] in weeks [95 %-CI]	N[b]	Patients with Event n (%)	Median Time[c] in weeks [95 %-CI]	Hazard Ratio [95 %-CI][d]	p-Value[d,e]	p-Value for Interaction Test[f]
g: PT: Neuropathy peripheral									
h: auto-SCT was not a treatment option									
i: auto-SCT failure									
auto-SCT: autologous Stem Cell Transplantation; CI: Confidence Interval; CTCAE: Common Terminology Criteria for Adverse Events; ECOG: Eastern Cooperative Oncology Group; PT: Preferred Term									

Tabelle 4G-76: Subgruppenanalysen mit nicht signifikantem Interaktionstest ($p \geq 0,05$) für den Endpunkt Nicht-schwere unerwünschte Ereignisse (CTCAE-Grad 1-2) (SOC und PT) für den PT „Periphere sensorische Neuropathie“ (SOC „Erkrankungen des Nervensystems“) aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE 204[a]	Pembrolizumab			Brentuximab Vedotin			Pembrolizumab vs. Brentuximab Vedotin		
Non-Severe Adverse Events (CTCAE-Grade 1-2): PT[g]	N[b]	Patients with Event n (%)	Median Time[c] in weeks [95 %-CI]	N[b]	Patients with Event n (%)	Median Time[c] in weeks [95 %-CI]	Hazard Ratio [95 %-CI][d]	p-Value[d,e]	p-Value for Interaction Test[f]
Gender									
Female	67	2 (3.0)	Not reached [-; -]	63	5 (7.9)	Not reached [59.4; -]	0.26 [0.05; 1.38]	0.113	0.397
Male	81	2 (2.5)	Not reached [-; -]	89	14 (15.7)	Not reached [-; -]	0.11 [0.03; 0.51]	0.004	
ECOG performance status									
0	84	1 (1.2)	Not reached [-; -]	99	12 (12.1)	Not reached [-; -]	0.07 [0.01; 0.56]	0.012	0.247
1	63	3 (4.8)	Not reached [-; -]	53	7 (13.2)	Not reached [59.4; -]	0.28 [0.07; 1.10]	0.069	
Disease status following first line therapy									
Primary refractory	60	3 (5.0)	n.c.	62	6 (9.7)	n.c.	n.c.	n.c.	n.c.
Relapsed < 12 months	41	0 (0.0)	n.c.	42	6 (14.3)	n.c.	n.c.	n.c.	
Relapsed ≥ 12 months	47	1 (2.1)	n.c.	48	7 (14.6)	n.c.	n.c.	n.c.	
Prior treatment									
One prior therapy[h]	27	1 (3.7)	Not reached [-; -]	27	3 (11.1)	Not reached [31.0; -]	0.18 [0.02; 1.82]	0.148	0.748
At least two prior therapies incl. auto-SCT[i]	55	1 (1.8)	Not reached [-; -]	56	8 (14.3)	Not reached [-; -]	0.10 [0.01; 0.79]	0.029	
At least two prior therapies excl. auto-SCT[h]	66	2 (3.0)	Not reached [-; -]	69	8 (11.6)	Not reached [59.4; -]	0.21 [0.04; 0.99]	0.048	
Prior treatment									
One prior therapy	27	1 (3.7)	Not reached [-; -]	27	3 (11.1)	Not reached [31.0; -]	0.18 [0.02; 1.82]	0.148	0.696
At least two prior therapies	121	3 (2.5)	Not reached [-; -]	125	16 (12.8)	Not reached [-; -]	0.15 [0.04; 0.51]	0.003	
a: Database Cutoff Date: 16JAN2020									
b: Number of patients: all-subjects-as-treated population									
c: From product-limit (Kaplan-Meier) method									
d: Based on Cox regression model with treatment as a covariate using Wald confidence interval									
e: Two-sided p-value using Wald test (Score test in case of zero event in one treatment group)									

Study: KEYNOTE 204[a]	Pembrolizumab			Brentuximab Vedotin			Pembrolizumab vs. Brentuximab Vedotin		
Non-Severe Adverse Events (CTCAE-Grade 1-2): PT[g]	N[b]	Patients with Event n (%)	Median Time[c] in weeks [95 %-CI]	N[b]	Patients with Event n (%)	Median Time[c] in weeks [95 %-CI]	Hazard Ratio [95 %-CI][d]	p-Value[d,e]	p-Value for Interaction Test[f]

f: Based on Cox regression model with treatment and subgroup as covariates, and treatment-by-subgroup interaction (p-value of likelihood ratio test for interaction term)

g: PT: Peripheral sensory neuropathy

h: auto-SCT was not a treatment option

i: auto-SCT failure

auto-SCT: autologous Stem Cell Transplantation; CI: Confidence Interval; CTCAE: Common Terminology Criteria for Adverse Events; ECOG: Eastern Cooperative Oncology Group; n.c.: not calculated (at least 10 subjects per subgroup and at least 10 events in one of the subgroups necessary); PT: Preferred Term

Schwere unerwünschte Ereignisse (CTCAE-Grad 3-5) (SOC und PT)

Tabelle 4G-77: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für den Endpunkt Schwere unerwünschte Ereignisse (CTCAE-Grad 3-5) (SOC und PT) für die SOC „Erkrankungen des Blutes und des Lymphsystems“ aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE 204[a]	**Pembrolizumab**			**Brentuximab Vedotin**			**Pembrolizumab vs. Brentuximab Vedotin**		
Severe Adverse Events (CTCAE-Grade 3-5): SOC[g]	**N[b]**	**Patients with Event n (%)**	**Median Time[c] in weeks [95 %-CI]**	**N[b]**	**Patients with Event n (%)**	**Median Time[c] in weeks [95 %-CI]**	**Hazard Ratio [95 %-CI][d]**	**p-Value[d,e]**	**p-Value for Interaction Test[f]**
Gender									
Female	67	9 (13.4)	Not reached [-; -]	63	9 (14.3)	Not reached [-; -]	0.67 [0.26; 1.75]	0.416	0.331
Male	81	5 (6.2)	Not reached [-; -]	89	12 (13.5)	Not reached [-; -]	0.36 [0.12; 1.01]	0.053	
Age									
<65	122	13 (10.7)	Not reached [-; -]	130	20 (15.4)	Not reached [-; -]	0.50 [0.24; 1.02]	0.057	0.873
≥65	26	1 (3.8)	Not reached [-; -]	22	1 (4.5)	Not reached [-; -]	0.70 [0.04; 11.30]	0.804	
ECOG performance status									
0	84	6 (7.1)	Not reached [-; -]	99	16 (16.2)	Not reached [-; -]	0.33 [0.13; 0.85]	0.022	0.108
1	63	8 (12.7)	Not reached [-; -]	53	5 (9.4)	Not reached [-; -]	0.96 [0.30; 3.00]	0.937	
Region									
EU	47	4 (8.5)	Not reached [-; -]	45	4 (8.9)	Not reached [-; -]	0.59 [0.14; 2.45]	0.466	0.577
Ex-EU	101	10 (9.9)	Not reached [-; -]	107	17 (15.9)	Not reached [-; -]	0.47 [0.21; 1.05]	0.064	
Prior treatment									
One prior therapy[h]	27	0 (0.0)	Not reached [-; -]	27	2 (7.4)	Not reached [-; -]	n.a. [n.a.; n.a.]	0.118	0.304
At least two prior therapies incl. auto-SCT[i]	55	6 (10.9)	Not reached [-; -]	56	6 (10.7)	Not reached [-; -]	0.71 [0.22; 2.27]	0.559	
At least two prior therapies excl. auto-SCT[h]	66	8 (12.1)	Not reached [106.3; -]	69	13 (18.8)	Not reached [-; -]	0.48 [0.20; 1.19]	0.114	
Prior treatment									
One prior therapy	27	0 (0.0)	Not reached [-; -]	27	2 (7.4)	Not reached [-; -]	n.a. [n.a.; n.a.]	0.118	0.147
At least two prior therapies	121	14 (11.6)	Not reached [-; -]	125	19 (15.2)	Not reached [-; -]	0.55 [0.27; 1.12]	0.101	

a: Database Cutoff Date: 16JAN2020

b: Number of patients: all-subjects-as-treated population

c: From product-limit (Kaplan-Meier) method

d: Based on Cox regression model with treatment as a covariate using Wald confidence interval

e: Two-sided p-value using Wald test (Score test in case of zero event in one treatment group)

f: Based on Cox regression model with treatment and subgroup as covariates, and treatment-by-subgroup interaction (p-value of likelihood ratio test for interaction term)

g: SOC: Blood and lymphatic system disorders

h: auto-SCT was not a treatment option

i: auto-SCT failure

auto-SCT: autologous Stem Cell Transplantation; CI: Confidence Interval; CTCAE: Common Terminology Criteria for Adverse Events; ECOG: Eastern Cooperative Oncology Group; n.a.: not applicable (when estimation not possible); SOC: System Organ Class

Tabelle 4G-78: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für den Endpunkt Schwere unerwünschte Ereignisse (CTCAE-Grad 3-5) (SOC und PT) für den PT „Neutropenie“ (SOC „Erkrankungen des Blutes und des Lymphsystems“) aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE 204[a]	**Pembrolizumab**			**Brentuximab Vedotin**			**Pembrolizumab vs. Brentuximab Vedotin**		
Severe Adverse Events (CTCAE-Grade 3-5): PT[g]	**N[b]**	**Patients with Event n (%)**	**Median Time[c] in weeks [95 %-CI]**	**N[b]**	**Patients with Event n (%)**	**Median Time[c] in weeks [95 %-CI]**	**Hazard Ratio [95 %-CI][d]**	**p-Value[d,e]**	**p-Value for Interaction Test[f]**
Gender									
Female	67	3 (4.5)	Not reached [-; -]	63	8 (12.7)	Not reached [-; -]	0.23 [0.06; 0.92]	0.038	0.738
Male	81	1 (1.2)	Not reached [-; -]	89	5 (5.6)	Not reached [-; -]	0.19 [0.02; 1.65]	0.132	
Age									
<65	122	4 (3.3)	Not reached [-; -]	130	12 (9.2)	Not reached [-; -]	0.25 [0.08; 0.80]	0.020	0.427
≥65	26	0 (0.0)	Not reached [-; -]	22	1 (4.5)	Not reached [-; -]	n.a. [n.a.; n.a.]	0.261	
Region									
EU	47	0 (0.0)	Not reached [-; -]	45	3 (6.7)	Not reached [-; -]	n.a. [n.a.; n.a.]	0.057	0.174
Ex-EU	101	4 (4.0)	Not reached [-; -]	107	10 (9.3)	Not reached [-; -]	0.29 [0.09; 0.98]	0.046	
Disease status following first line therapy									
Primary refractory	60	3 (5.0)	n.c.	62	2 (3.2)	n.c.	n.c.	n.c.	n.c.
Relapsed < 12 months	41	1 (2.4)	n.c.	42	5 (11.9)	n.c.	n.c.	n.c.	
Relapsed ≥ 12 months	47	0 (0.0)	n.c.	48	6 (12.5)	n.c.	n.c.	n.c.	
Prior treatment									
One prior therapy[h]	27	0 (0.0)	Not reached [-; -]	27	1 (3.7)	Not reached [-; -]	n.a. [n.a.; n.a.]	0.317	0.092
At least two prior therapies incl. auto-SCT[i]	55	0 (0.0)	Not reached [-; -]	56	5 (8.9)	Not reached [-; -]	n.a. [n.a.; n.a.]	0.018	
At least two prior therapies excl. auto-SCT[h]	66	4 (6.1)	Not reached [-; -]	69	7 (10.1)	Not reached [45.0; -]	0.42 [0.12; 1.48]	0.177	
Prior treatment									
One prior therapy	27	0 (0.0)	Not reached [-; -]	27	1 (3.7)	Not reached [-; -]	n.a. [n.a.; n.a.]	0.317	0.477
At least two prior therapies	121	4 (3.3)	Not reached [-; -]	125	12 (9.6)	Not reached [-; -]	0.23 [0.07; 0.76]	0.016	

a: Database Cutoff Date: 16JAN2020

b: Number of patients: all-subjects-as-treated population

c: From product-limit (Kaplan-Meier) method

d: Based on Cox regression model with treatment as a covariate using Wald confidence interval

e: Two-sided p-value using Wald test (Score test in case of zero event in one treatment group)

f: Based on Cox regression model with treatment and subgroup as covariates, and treatment-by-subgroup interaction (p-value of likelihood ratio test for interaction term)

g: PT: Neutropenia

h: auto-SCT was not a treatment option

i: auto-SCT failure

auto-SCT: autologous Stem Cell Transplantation; CI: Confidence Interval; CTCAE: Common Terminology Criteria for Adverse Events; n.a.: not applicable (when estimation not possible); n.c.: not calculated (at least 10 subjects per subgroup and at least 10 events in one of the subgroups necessary); PT: Preferred Term

Tabelle 4G-79: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für den Endpunkt Schwere unerwünschte Ereignisse (CTCAE-Grad 3-5) (SOC und PT) für die SOC „Erkrankungen des Nervensystems“ aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE 204[a]	Pembrolizumab			Brentuximab Vedotin			Pembrolizumab vs. Brentuximab Vedotin		
Severe Adverse Events (CTCAE-Grade 3-5): SOC[g]	N[b]	Patients with Event n (%)	Median Time[c] in weeks [95 %-CI]	N[b]	Patients with Event n (%)	Median Time[c] in weeks [95 %-CI]	Hazard Ratio [95 %-CI][d]	p-Value[d,e]	p-Value for Interaction Test[f]
Gender									
Female	67	2 (3.0)	Not reached [-; -]	63	3 (4.8)	Not reached [-; -]	0.45 [0.07; 2.79]	0.394	0.402
Male	81	2 (2.5)	Not reached [-; -]	89	9 (10.1)	60.0 [49.6; -]	0.08 [0.02; 0.39]	0.002	
Age									
<65	122	3 (2.5)	Not reached [-; -]	130	8 (6.2)	Not reached [60.0; -]	0.16 [0.04; 0.63]	0.009	0.463
≥65	26	1 (3.8)	Not reached [-; -]	22	4 (18.2)	Not reached [31.0; -]	0.06 [0.01; 0.69]	0.024	
ECOG performance status									
0	84	1 (1.2)	Not reached [-; -]	99	9 (9.1)	Not reached [50.6; -]	0.04 [0.01; 0.34]	0.003	0.098
1	63	3 (4.8)	Not reached [-; -]	53	3 (5.7)	Not reached [40.7; -]	0.46 [0.09; 2.33]	0.348	
Region									
EU	47	0 (0.0)	Not reached [-; -]	45	4 (8.9)	Not reached [31.0; -]	n.a. [n.a.; n.a.]	0.003	0.070
Ex-EU	101	4 (4.0)	Not reached [-; -]	107	8 (7.5)	Not reached [60.0; -]	0.24 [0.07; 0.82]	0.023	
Disease status following first line therapy									
Primary refractory	60	3 (5.0)	n.c.	62	1 (1.6)	n.c.	n.c.	n.c.	n.c.
Relapsed < 12 months	41	0 (0.0)	n.c.	42	4 (9.5)	n.c.	n.c.	n.c.	
Relapsed ≥ 12 months	47	1 (2.1)	n.c.	48	7 (14.6)	n.c.	n.c.	n.c.	
Prior treatment									
One prior therapy[h]	27	0 (0.0)	n.c.	27	6 (22.2)	n.c.	n.c.	n.c.	n.c.
At least two prior therapies incl. auto-SCT[i]	55	0 (0.0)	n.c.	56	3 (5.4)	n.c.	n.c.	n.c.	
At least two prior therapies excl. auto-SCT[h]	66	4 (6.1)	n.c.	69	3 (4.3)	n.c.	n.c.	n.c.	

a: Database Cutoff Date: 16JAN2020

b: Number of patients: all-subjects-as-treated population

c: From product-limit (Kaplan-Meier) method

d: Based on Cox regression model with treatment as a covariate using Wald confidence interval

e: Two-sided p-value using Wald test (Score test in case of zero event in one treatment group)

f: Based on Cox regression model with treatment and subgroup as covariates, and treatment-by-subgroup interaction (p-value of likelihood ratio test for interaction term)

g: SOC: Nervous system disorders

h: auto-SCT was not a treatment option

i: auto-SCT failure

auto-SCT: autologous Stem Cell Transplantation; CI: Confidence Interval; CTCAE: Common Terminology Criteria for Adverse Events; ECOG: Eastern Cooperative Oncology Group; n.a.: not applicable (when estimation not possible); n.c.: not calculated (at least 10 subjects per subgroup and at least 10 events in one of the subgroups necessary); SOC: System Organ Class

Anhang 4-G5: Ergänzende Analysen zur Studie KEYNOTE 051

Im Folgenden werden ergänzend zu Abschnitt 4.3.2.3.3 ergänzende Analysen zur Studie KEYNOTE 051 dargestellt.

Alle Ergebnisse beziehen sich auf den Datenschnitt vom 10. Januar 2020 der KEYNOTE 051.

Anhang 4-G5.1: Ergänzende Analysen zum Endpunkt Objektive Ansprechrate und Komplette Remission

Tabelle 4G-80: Ergebnisse für den Endpunkt Objektive Ansprechrate und Komplette Remission (Lugano-Kriterien) – weitere Untersuchungen

Study: KEYNOTE 051[a]	**Pembrolizumab[b] N[c] = 22**	
Response Evaluation[d]	**n[e]**	**Percentage[e] [95 %-CI][f]**
Objective Response	14	63.64 [40.66; 82.80]
Complete Response	4	18.18 [5.19; 40.28]
Partial Response	10	45.45 [24.39; 67.79]
Stable Disease	6	27.27 [10.73; 50.22]
Progressive Disease	2	9.09 [1.12; 29.16]

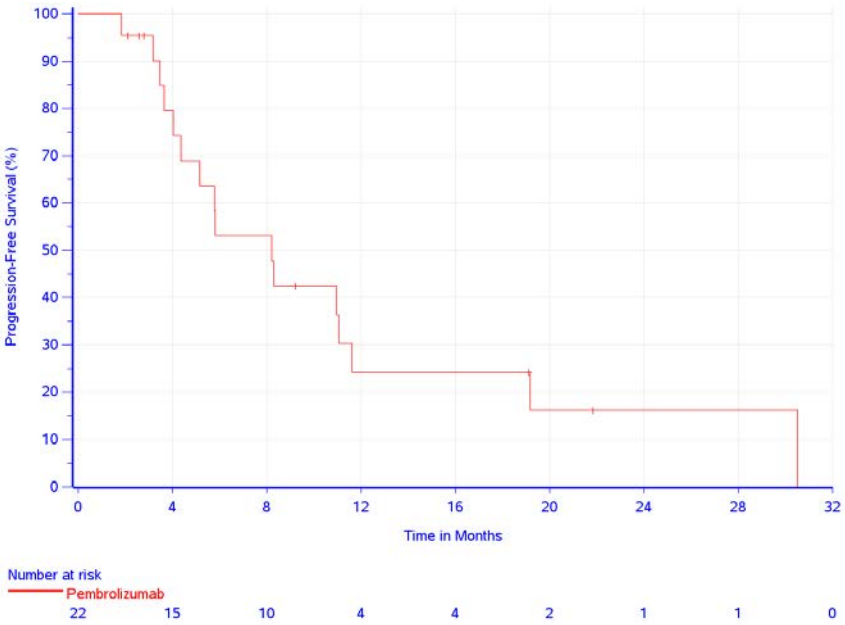
a: Database Cutoff Date: 10JAN2020
b: Dosing in pediatric patients 2 mg/kg (maximum dose = 200 mg) every 3 weeks
c: Number of patients: all-subjects-as-treated, rrcHL population
d: Responses are based on BICR assessments per Lugano
e: Subjects with event
f: Based on binomial exact confidence interval method for binomial data
BICR: Blinded Independent Central Review; CI: Confidence Interval; rrcHL: Relapsed/Refractory Hodgkin Lymphoma

Anhang 4-G5.2: Ergänzende Analysen zum Endpunkt Ergänzende Morbiditätsendpunkte

Tabelle 4G-81: Ergebnisse für den Endpunkt Progressionsfreies Überleben (Lugano-Kriterien) – weitere Untersuchungen

Study: KEYNOTE 051[a]	**Pembrolizumab[b]**						
	N[c]	**Patients with Event n (%)**	**Median Time[d] in Months [95%-CI]**	**Rate at Month 6[d] in % [95%-CI]**	**Rate at Month 12[d] in % [95%-CI]**	**Rate at Month 18[d] in % [95%-CI]**	**Rate at Month 24[d] in % [95%-CI]**
Progression-Free Survival (Lugano)[e]	22	16 (72.7)	8.2 [4.0; 11.6]	53.03 [29.05; 72.21]	24.24 [7.86; 45.40]	24.24 [7.86; 45.40]	16.16 [3.24; 37.96]

a: Database Cutoff Date: 10JAN2020
b: Dosing in pediatric patients 2 mg/kg (maximum dose = 200 mg) every 3 weeks
c: Number of patients: all-subjects-as-treated, rrcHL population
d: From product-limit (Kaplan-Meier) method
e: Progression-Free Survival analysis is based on BICR assessments per Lugano Criteria
BICR: Blinded Independent Central Review; CI: Confidence Interval; rrcHL: Relapsed/Refractory Hodgkin Lymphoma



Database Cutoff Date: 10JAN2020

Abbildung 4G- 30: Kaplan-Meier-Kurve für den Endpunkt Progressionsfreies Überleben (Lugano-Kriterien) – weitere Untersuchungen

Anhang 4-G5.3: Ergänzende Analysen zum Endpunkt Unerwünschte Ereignisse (gegliedert nach SOC und PT)

Tabelle 4G-82: Ergebnisse für Komplikationen nach einer allo-SZT (gegliedert nach PT) – weitere Untersuchungen

Study: KEYNOTE 051[a,b]	**Patients with Event n (%)**
Complications Post allo-SCT by PT[c,d]	**Pembrolizumab N[e]=2**
Patients with one or more adverse events	2 (100.0)
Chronic graft versus host disease	1 (50.0)
Cystitis haemorrhagic	1 (50.0)
Epstein-Barr virus infection	1 (50.0)
Febrile neutropenia	1 (50.0)
Mucosal inflammation	1 (50.0)
Systemic mycosis	1 (50.0)

a: Database Cutoff Date: 10JAN2020
b: MedDRA version 22.1 was applied
c: Adverse events on and after receiving allo-SCT
d: A specific adverse event appears on this report only if its incidence is > 0%
e: Number of patients: all-subjects-as-treated, Hodgkin lymphoma population who received allo-SCT after last dose
Dosing in pediatric patients 2 mg/kg (maximum dose = 200 mg) every 3 weeks
allo-SCT: allogeneic Stem Cell Transplantation; PT: Preferred Term

Anhang 4-G6: Hauptergebnisse des Datenschnitts vom 3. September 2018 der Studie KEYNOTE 051

Im Folgenden werden ergänzend zu Abschnitt 4.3.2.3. die Ergebnisse des Datenschnitts vom 3. September 2018 der Studie KEYNOTE 051 dargestellt. Da die Ergebnisse für die vorliegende Nutzenbewertung nicht zur Ableitung des Zusatznutzens herangezogen werden, werden ausschließlich die Hauptanalysen dargestellt.

Anhang 4-G6.1: Mortalität (Datenschnitt 3. September 2018, KEYNOTE 051)

Tabelle 4G-83: Ergebnisse für den Endpunkt Gesamtüberleben – weitere Untersuchungen (Datenschnitt 3. September 2018, KEYNOTE 051)

Study: KEYNOTE 051[a]	Pembrolizumab[b]						
	N[c]	Patients with Event n (%)	Median Time[d] in Months [95%-CI]	Rate at Month 6[d] in % [95%-CI]	Rate at Month 12[d] in % [95%-CI]	Rate at Month 18[d] in % [95%-CI]	Rate at Month 24[d] in % [95%-CI]
Overall Survival	18	0 (0.0)	Not reached [-; -]	100.00 [100.00; 100.00]	100.00 [100.00; 100.00]	100.00 [100.00; 100.00]	100.00 [100.00; 100.00]

a: Database Cutoff Date: 03SEP2018
b: Dosing in pediatric patients 2 mg/kg (maximum dose = 200 mg) every 3 weeks
c: Number of patients: all-subjects-as-treated, rrcHL population
d: From product-limit (Kaplan-Meier) method
CI: Confidence Interval; rrcHL: Relapsed/Refractory Hodgkin Lymphoma

Anhang 4-G6.2: Morbidität (Datenschnitt 3. September 2018, KEYNOTE 051)

B-Symptomatik (Datenschnitt 3. September 2018, KEYNOTE 051)

Tabelle 4G-84: Ergebnisse für den Rückgang der B-Symptomatik – weitere Untersuchungen (Datenschnitt 3. September 2018, KEYNOTE 051)

Study: KEYNOTE 051[a]	Pembrolizumab[b]
	N[c]=2
Resolution of B-Symptoms, n (%)	
Yes	1 (50.0)
No	0 (0.0)
Missing	1 (50.0)

a: Database Cutoff Date: 03SEP2018
b: Dosing in pediatric patients 2 mg/kg (maximum dose = 200 mg) every 3 weeks
c: Number of patients: all-subjects-as-treated, rrcHL population, with B-symtpoms at baseline
rrcHL: Relapsed/Refractory Hodgkin Lymphoma

Tabelle 4G-85: Ergebnisse für das Erstmalige Auftreten von B-Symptomen – weitere Untersuchungen (Datenschnitt 3. September 2018, KEYNOTE 051)

	Study: KEYNOTE 051[a] Pembrolizumab[b] N[c] = 16
Lymphoma B Symptoms[d], n (%)	
Yes	0
No	0
Missing	16 (100.0)

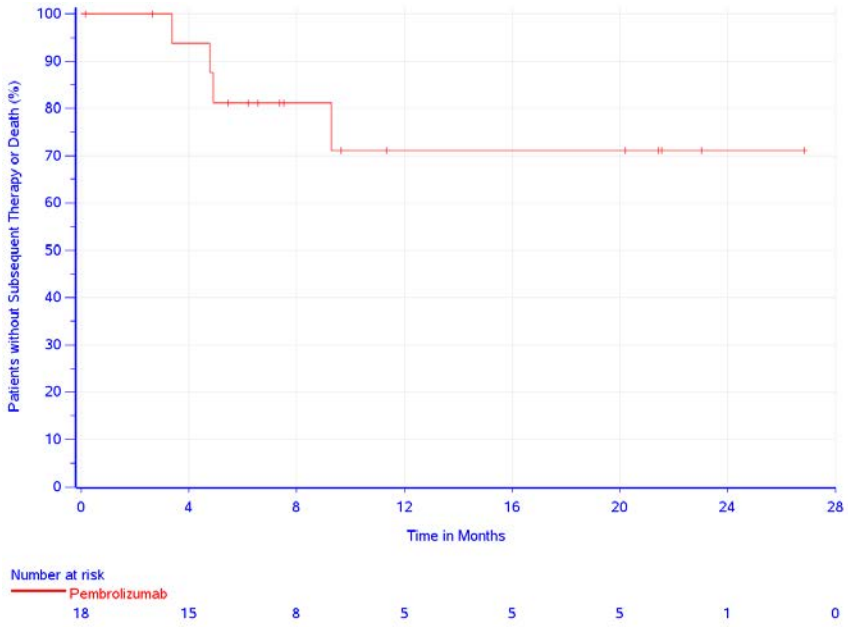
a: Database Cutoff Date: 03SEP2018

	Study: KEYNOTE 051[a] Pembrolizumab[b] N[c] = 16
Lymphoma B Symptoms[d], n (%)	
b: Dosing in pediatric patients 2 mg/kg (maximum dose = 200 mg) every 3 weeks c: Number of patients: all-subjects-as-treated, rrcHL population without B-symptoms at baseline d: First occurrence of Lymphoma B-Symptoms after the start of study drug rrcHL: Relapsed/Refractory Hodgkin Lymphoma	

Zeit bis zur ersten Folgetherapie oder Tod (Datenschnitt 3. September 2018, KEYNOTE 051)

Tabelle 4G-86: Ergebnisse für den Endpunkt Zeit bis zur ersten Folgetherapie oder Tod – weitere Untersuchungen (Datenschnitt 3. September 2018, KEYNOTE 051)

Study: KEYNOTE 051[a]	Pembrolizumab[b]						
	N[c]	Patients with Event n (%)	Median Time[d] in Months [95%-CI]	Rate at Month 6[d] in % [95%-CI]	Rate at Month 12[d] in % [95%-CI]	Rate at Month 18[d] in % [95%-CI]	Rate at Month 24[d] in % [95%-CI]
Time to First Subsequent Therapy or Death	18	4 (22.2)	Not reached [9.3; -]	81.25 [52.46; 93.54]	71.09 [38.38; 88.56]	71.09 [38.38; 88.56]	71.09 [38.38; 88.56]
a: Database Cutoff Date: 03SEP2018 b: Dosing in pediatric patients 2 mg/kg (maximum dose = 200 mg) every 3 weeks c: Number of patients: all-subjects-as-treated, rrcHL population d: From product-limit (Kaplan-Meier) method CI: Confidence Interval; rrcHL: Relapsed/Refractory Hodgkin Lymphoma							



Database Cutoff Date: 03SEP2018

Abbildung 4G- 31: Kaplan-Meier-Kurve für den Endpunkt Zeit bis zur ersten Folgetherapie oder Tod – weitere Untersuchungen (Datenschnitt 3. September 2018, KEYNOTE 051)

Rate an SZT als Folgetherapie (Datenschnitt 3. September 2018, KEYNOTE 051)

Tabelle 4G-87: Ergebnisse für den Endpunkt Rate an SZT als Folgetherapie – weitere Untersuchungen (Datenschnitt 3. September 2018, KEYNOTE 051)

Study: KEYNOTE 051[a]	**Pembrolizumab[b] N[c] = 18**	
Subsequent Transplant Type	**n[d]**	**Percentage[d] [95 %-CI][e]**
Subsequent SCT	2	11.11 [1.38; 34.71]
No Subsequent SCT	16	88.89 [65.29; 98.62]

a: Database Cutoff Date: 03SEP2018
b: Dosing in pediatric patients 2 mg/kg (maximum dose = 200 mg) every 3 weeks
c: Number of patients: all-subjects-as-treated, rrcHL population
d: Subjects with events
e: Based on binomial exact confidence interval method for binomial data
CI: Confidence Interval; SCT: Stem Cell Transplantation; rrcHL: Relapsed/Refractory Hodgkin Lymphoma

Objektive Ansprechrate und Komplette Remission (Datenschnitt 3. September 2018, KEYNOTE 051)

Tabelle 4G-88: Ergebnisse für den Endpunkt Objektive Ansprechrate und Komplette Remission – weitere Untersuchungen (Datenschnitt 3. September 2018, KEYNOTE 051)

Study: KEYNOTE 051[a]	**Pembrolizumab[b] N[c] = 18**	
Response Evaluation[d]	**n[e]**	**Percentage[e] [95 %-CI][f]**
Objective Response	9	50.00 [26.02; 73.98]
Complete Response	2	11.11 [1.38; 34.71]
Partial Response	7	38.89 [17.30; 64.25]
Stable Disease	3	16.67 [3.58; 41.42]
Progressive Disease	3	16.67 [3.58; 41.42]
No Assessment[g]	3	16.67 [3.58; 41.42]

a: Database Cutoff Date: 03SEP2018
b: Dosing in pediatric patients 2 mg/kg (maximum dose = 200 mg) every 3 weeks
c: Number of patients: all-subjects-as-treated, rrcHL population
d: Responses are based on investigator assessment per RECIST 1.1 with confirmed response
e: Subjects with event
f: Based on binomial exact confidence interval method for binomial data
g: Subjects who were enrolled under Amendment 7
CI: Confidence Interval; RECIST: Response Evaluation Criteria in Solid Tumors; rrcHL: Relapsed/Refractory Hodgkin Lymphoma

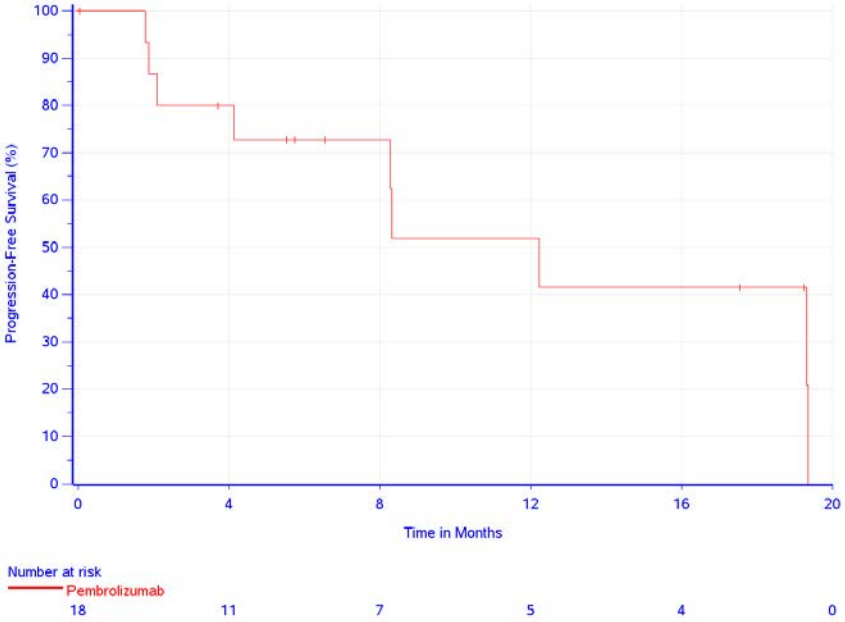
Ergänzende Morbiditätsendpunkte (Datenschnitt 3. September 2018, KEYNOTE 051)

Tabelle 4G-89: Ergebnisse für den Endpunkt Progressionsfreies Überleben – weitere Untersuchungen (Datenschnitt 3. September 2018, KEYNOTE 051)

Study: KEYNOTE 051[a]	**Pembrolizumab[b]**						
	N[c]	**Patients with Event n (%)**	**Median Time[d] in Months [95%-CI]**	**Rate at Month 6[d] in % [95%-CI]**	**Rate at Month 12[d] in % [95%-CI]**	**Rate at Month 18[d] in % [95%-CI]**	**Rate at Month 24[d] in % [95%-CI]**
Progression-Free Survival (Investigator)[e]	18	9 (50.0)	12.2 [2.1; 19.4]	72.73 [42.52; 88.82]	51.95 [21.22; 75.83]	41.56 [13.79; 67.76]	Not reached [-; -]

a: Database Cutoff Date: 03SEP2018
b: Dosing in pediatric patients 2 mg/kg (maximum dose = 200 mg) every 3 weeks

c: Number of patients: all-subjects-as-treated, rrcHL population
d: From product-limit (Kaplan-Meier) method
e: Progression-Free Survival analysis is based on investigator assessments per RECIST 1.1 criteria
CI: Confidence Interval; RECIST: Response Evaluation Criteria In Solid Tumors; rrcHL: Relapsed/Refractory Hodgkin Lymphoma



Database Cutoff Date: 03SEP2018

Abbildung 4G- 32: Kaplan-Meier-Kurve für den Endpunkt Progressionsfreies Überleben – weitere Untersuchungen (Datenschnitt 3. September 2018, KEYNOTE 051)

Anhang 4-G6.3: Nebenwirkungen (Datenschnitt 3. September 2018, KEYNOTE 051)

Tabelle 4G-90: Ergebnisse für den Endpunkt Unerwünschte Ereignisse Gesamtraten – weitere Untersuchungen (Datenschnitt 3. September 2018, KEYNOTE 051)

Study: KEYNOTE 051[a,b]	**Pembrolizumab**		
	N[c]	**Patients with Event n (%)**	**Median Time[d] in Weeks [95%-CI]**
Adverse Events	18	18 (100.0)	0.1 [0.1; 0.6]
Serious Adverse Events	18	2 (11.1)	Not reached [66.7; -]
Non-Severe Adverse Events (CTCAE-Grade 1-2)	18	18 (100.0)	0.1 [0.1; 0.6]
Severe Adverse Events (CTCAE-Grade 3-5)	18	4 (22.2)	Not reached [46.1; -]
Adverse Events Leading to Treatment Discontinuation	18	1 (5.6)	Not reached [66.7; -]

a: Database Cutoff Date: 03SEP2018
b: MedDRA version 21.0 was applied
c: Number of patients: all-subjects-as-treated population, Hodgkin lymphoma population
d: From product-limit (Kaplan-Meier) method
Dosing in pediatric patients 2 mg/kg (maximum dose = 200 mg) every 3 weeks
CI: Confidence Interval; CTCAE: Common Terminology Criteria for Adverse Events

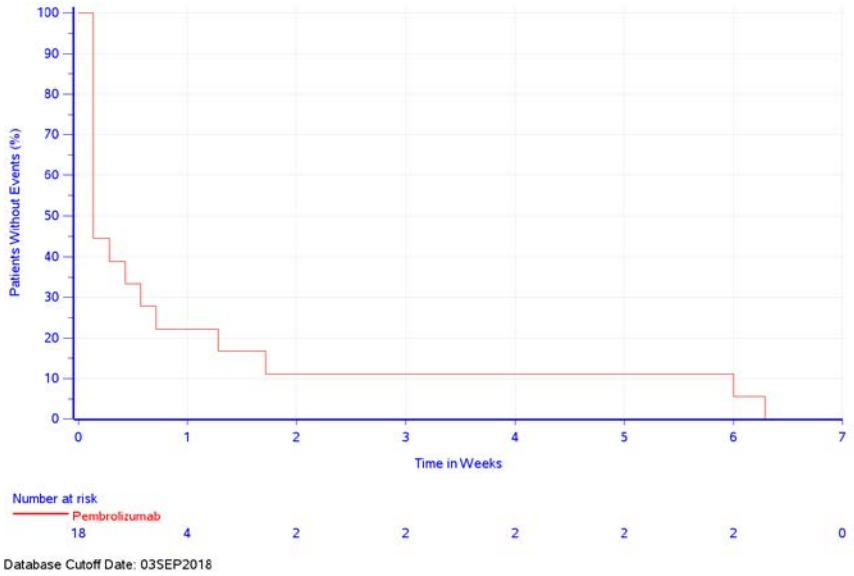


Abbildung 4G- 33: Kaplan-Meier-Kurve für den Endpunkt Unerwünschte Ereignisse gesamt in der Studie KEYNOTE 051 – weitere Untersuchungen (Datenschnitt 3. September 2018)

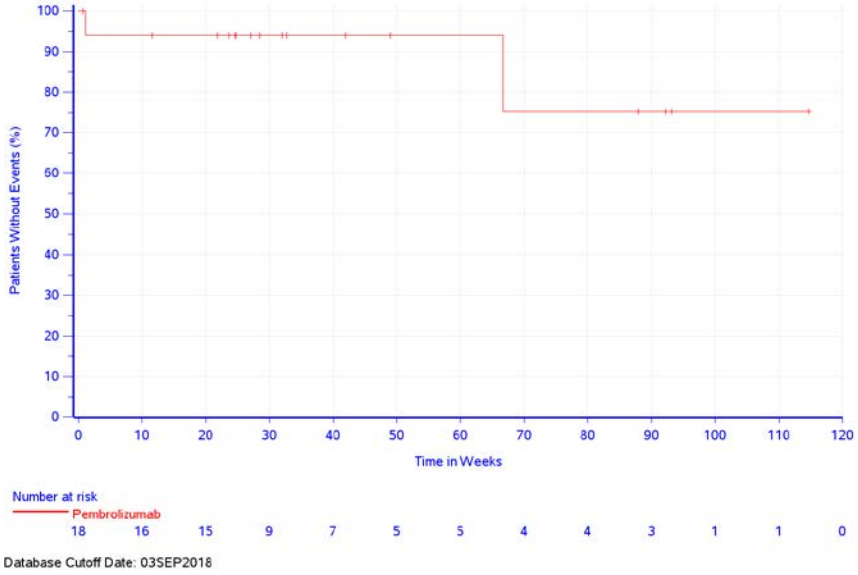


Abbildung 4G- 34: Kaplan-Meier-Kurve für den Endpunkt Schwerwiegende unerwünschte Ereignisse in der Studie KEYNOTE 051 – weitere Untersuchungen (Datenschnitt 3. September 2018)

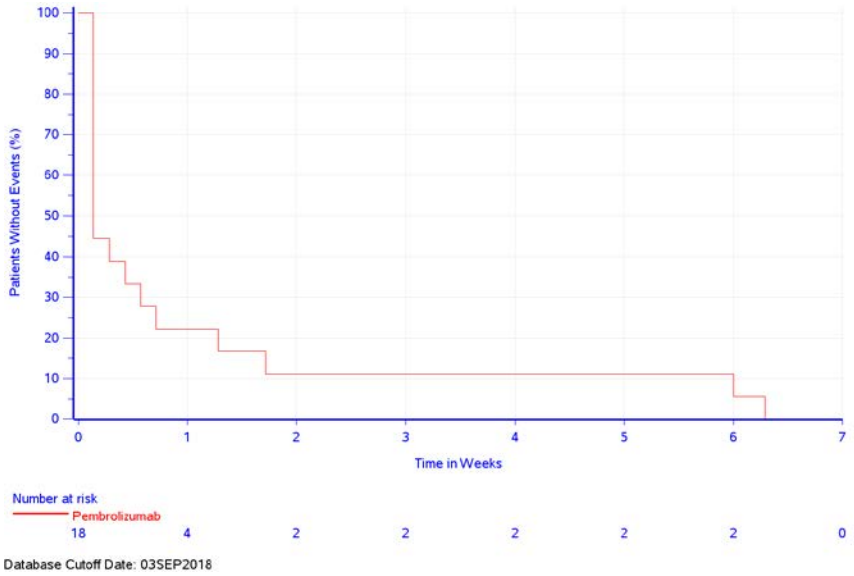


Abbildung 4G- 35: Kaplan-Meier-Kurve für den Endpunkt Nicht-schwere unerwünschte Ereignisse (CTCAE-Grad 1-2) in der Studie KEYNOTE 051 – weitere Untersuchungen (Datenschnitt 3. September 2018)

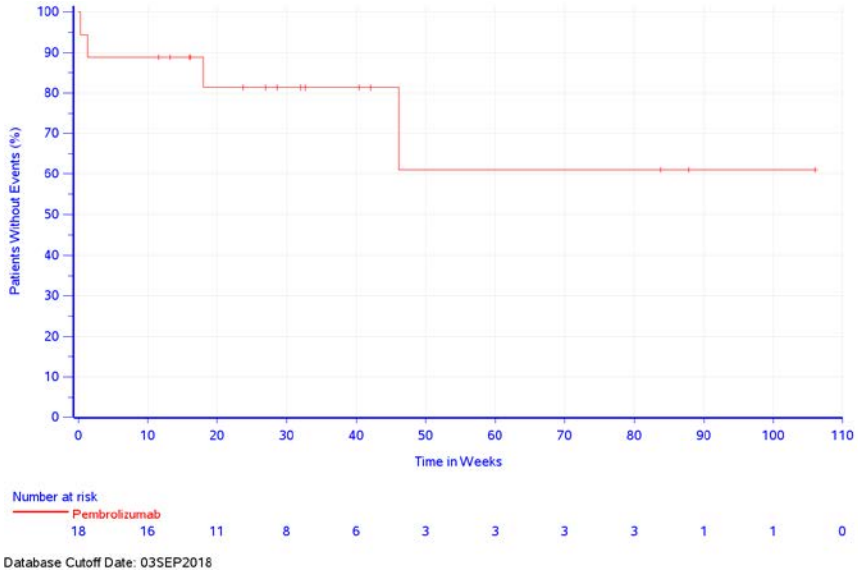


Abbildung 4G- 36: Kaplan-Meier-Kurve für den Endpunkt Schwere unerwünschte Ereignisse (CTCAE-Grad 3-5) in der Studie KEYNOTE 051 – weitere Untersuchungen (Datenschnitt 3. September 2018)

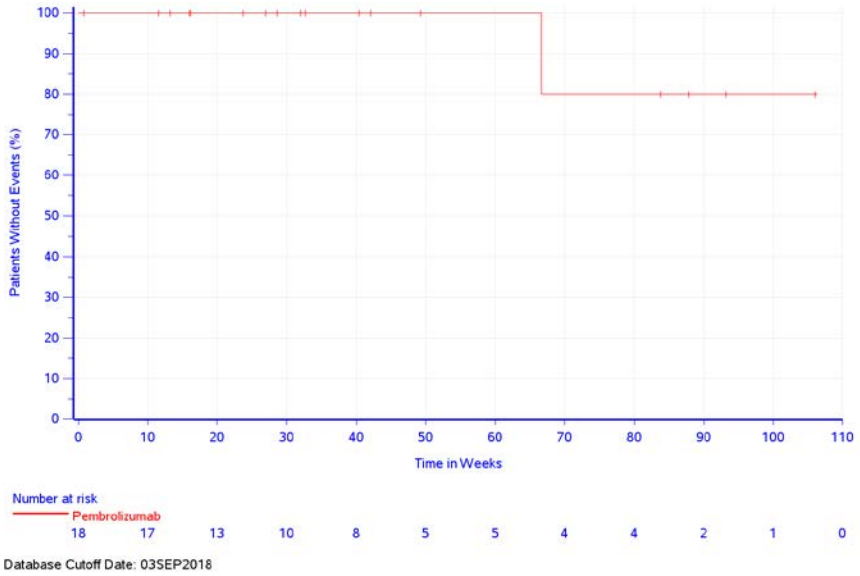


Abbildung 4G- 37: Kaplan-Meier-Kurve für den Endpunkt Therapieabbruch wegen unerwünschter Ereignisse in der Studie KEYNOTE 051 – weitere Untersuchungen (Datenschnitt 3. September 2018)

Anhang 4-G7: Definition der Immunvermittelten unerwünschten Ereignisse (AEOSI)

Im Folgenden wird ergänzend zu Abschnitt 4.3.1.3.1.3.3. bzw. Abschnitt 4.3.2.3.3.3.3. die Definition der Immunvermittelten unerwünschten Ereignisse (AEOSI) anhand der zugeordneten PT dargestellt.

Tabelle 4G-91: Definition der Immunvermittelten unerwünschten Ereignisse (AEOSI) anhand der zugeordneten PT in der Studie KEYNOTE 204 und in der Studie KEYNOTE 051

AEOSI	Preferred Terms	Immune-mediated (yes/no)
Pneumonitis	Acute interstitial pneumonitis, Autoimmune lung disease, Interstitial lung disease, Pneumonitis, Idiopathic pneumonia syndrome, Organising pneumonia, Immune-mediated pneumonitis	Yes
Colitis	Colitis, Colitis microscopic, Enterocolitis, Enterocolitis haemorrhagic, Necrotising colitis, Colitis erosive, Autoimmune colitis, Immune-mediated enterocolitis	Yes
Hepatitis	Hepatitis, Immune-mediated hepatitis, Autoimmune hepatitis, Hepatitis acute, Hepatitis fulminant, Drug-induced liver injury	Yes
Nephritis	Nephritis, Autoimmune nephritis, Chronic autoimmune glomerulonephritis, Fibrillary glomerulonephritis, Focal segmental glomerulosclerosis, Glomerulonephritis, Glomerulonephritis acute, Glomerulonephritis membranoproliferative, Glomerulonephritis membranous, Glomerulonephritis minimal lesion, Glomerulonephritis proliferative, Glomerulonephritis rapidly progressive, Mesangioproliferative glomerulonephritis, Nephritis haemorrhagic, Tubulointerstitial nephritis, Nephrotic syndrome, Immune-mediated nephritis	Yes
Adrenal Insufficiency	Adrenal insufficiency, Adrenocortical insufficiency acute, Secondary adrenocortical insufficiency, Primary adrenal insufficiency, Addison's disease	Yes
Hypophysitis	Hypophysitis, Hypopituitarism, Lymphocytic hypophysitis	Yes
Hyperthyroidism	Hyperthyroidism, Basedow's disease, Thyrotoxic crisis	Yes
Hypothyroidism	Hypothyroidism, Hypothyroidic goitre, Myxoedema, Myxoedema coma, Primary hypothyroidism, Autoimmune hypothyroidism, Immune-mediated hypothyroidism	Yes
Thyroiditis	Thyroid disorder, Thyroiditis, Autoimmune thyroiditis, Thyroiditis acute, Silent thyroiditis, Autoimmune thyroid disorder, Immune-mediated thyroiditis	Yes
Type 1 Diabetes Mellitus	Diabetic ketoacidosis, Diabetic ketoacidotic hyperglycaemic coma, Fulminant type 1 diabetes mellitus, Latent autoimmune diabetes in adults, Type 1 diabetes mellitus, Euglycaemic diabetic ketoacidosis, Diabetic ketosis, Ketosis-prone diabetes mellitus	Yes
Severe Skin Reactions Including Stevens-Johnson Syndrome	Dermatitis bullous, Dermatitis exfoliative, Dermatitis exfoliative generalised, Epidermal necrosis, Erythema multiforme, Exfoliative rash, Pemphigoid, Pemphigus,	Yes

AEOSI	Preferred Terms	Immune-mediated (yes/no)
(SJS) and Toxic Epidermal Necrolysis (TEN): or **Severe Skin (continued):** **If grade 3 or higher:**	Skin necrosis, Stevens-Johnson syndrome, Toxic epidermal necrolysis, Toxic skin eruption, SJS-TEN overlap Rash, Rash erythematous, Rash maculo-papular, Rash pruritic, Rash pustular, Pruritus, Pruritus genital, Lichen planus, Oral lichen planus	Yes
Uveitis	Iritis, Uveitis, Cyclitis, Autoimmune uveitis, Iridocyclitis, Vogt-Koyanagi-Harada disease, Chorioretinitis, Choroiditis, Immune-mediated uveitis	Yes
Pancreatitis	Pancreatitis, Autoimmune pancreatitis, Pancreatitis acute, Pancreatitis haemorrhagic, Pancreatitis necrotising, Immune-mediated pancreatitis	Yes
Myositis	Myositis, Necrotising myositis, Polymyositis, Immune-mediated myositis, Rhabdomyolysis, Myopathy, Dermatomyositis, Autoimmune myositis	Yes
Guillain-Barre Syndrome	Demyelinating polyneuropathy, Guillain-Barre syndrome, Axonal neuropathy, Multifocal motor neuropathy, Polyneuropathy idiopathic progressive, Miller Fisher syndrome, Subacute inflammatory demyelinating polyneuropathy	Yes
Myocarditis	Myocarditis, Autoimmune myocarditis, Hypersensitivity myocarditis, Immune-mediated myocarditis	Yes
Encephalitis	Encephalitis, Encephalitis autoimmune, Limbic encephalitis, Noninfective encephalitis, Immune-mediated encephalitis	Yes
Sarcoidosis	Sarcoidosis, Cutaneous sarcoidosis, Ocular sarcoidosis, Pulmonary sarcoidosis	Yes
Infusion Reactions	Hypersensitivity, Drug hypersensitivity, Anaphylactic reaction, Anaphylactoid reaction, Cytokine release syndrome, Serum sickness, Serum sickness-like reaction, Infusion related reaction, Infusion related hypersensitivity reaction	No
Myasthenic Syndrome	Myasthenic syndrome, Myasthenia gravis, Myasthenia gravis crisis, Ocular myasthenia	Yes
Myelitis	Myelitis, Myelitis transverse	Yes