Dokumentvorlage, Version vom 16.12.2021

Dossier zur Nutzenbewertung gemäß § 35a SGB V

Pembrolizumab (KEYTRUDA®)

MSD Sharp & Dohme GmbH

Modul 4 E

Behandlung von Tumoren mit MSI-H oder dMMR nach vorheriger Therapie bei Erwachsenen: Nicht resezierbares oder metastasierendes biliäres Karzinom

Medizinischer Nutzen und
medizinischer Zusatznutzen,
Patientengruppen mit therapeutisch
bedeutsamem Zusatznutzen

Stand: 18.07.2022

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Anhang 4-G1: Rücklaufquoten des EORTC QLQ-C30 und EQ-5D VAS

Im Folgenden werden ergänzend zu Abschnitt 4.3.2.3.3.2.1 die Rücklaufquoten des EORTC QLQ-C30 und die Rücklaufquoten des EQ-5D VAS dargestellt.

Alle Ergebnisse beziehen sich auf den Datenschnitt vom 05. Oktober 2020.

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

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

Study: KEYNOTE 158[a]		Pembrolizumab
Visit	EORTC QLQ-C30	N[b] = 22 n (%)
Baseline	Missing by Design	0 (0.0)
	Discontinued due to adverse event	0 (0.0)
	Discontinued due to clinical progression	0 (0.0)
	Discontinued due to complete response	0 (0.0)
	Discontinued due to progressive disease	0 (0.0)
	Subject died	0 (0.0)
	Visit not scheduled	0 (0.0)
	Expected to Complete Questionnaires[c]	22 (100.0)
	Not completed	1 (4.5)
	Not completed due to site staff error	0 (0.0)
	Subject refused for other reasons	0 (0.0)
	Other	1 (4.5)
	With visit, no record	0 (0.0)
	Completed	21 (95.5)
	Compliance (% in those expected to complete questionnaires)[d]	21 (95.5)
Week 3	Missing by Design	0 (0.0)
	Discontinued due to adverse event	0 (0.0)
	Discontinued due to clinical progression	0 (0.0)
	Discontinued due to complete response	0 (0.0)
	Discontinued due to progressive disease	0 (0.0)
	Subject died	0 (0.0)
	Visit not scheduled	0 (0.0)
	Expected to Complete Questionnaires[c]	22 (100.0)
	Not completed	1 (4.5)
	Not completed due to site staff error	0 (0.0)
	Subject refused for other reasons	0 (0.0)
	Other	1 (4.5)
	With visit, no record	0 (0.0)
	Completed	21 (95.5)
	Compliance (% in those expected to complete questionnaires)[d]	21 (95.5)
Week 6	Missing by Design	3 (13.6)
	Discontinued due to adverse event	0 (0.0)
	Discontinued due to clinical progression	0 (0.0)
	Discontinued due to complete response	0 (0.0)
	Discontinued due to progressive disease	0 (0.0)
	Subject died	1 (4.5)
	Visit not scheduled	2 (9.1)
	Expected to Complete Questionnaires[c]	19 (86.4)
	Not completed	2 (9.1)
	Not completed due to site staff error	0 (0.0)
	Subject refused for other reasons	0 (0.0)
	Other	2 (9.1)
	With visit, no record	0 (0.0)
	Completed	17 (77.3)
	Compliance (% in those expected to complete questionnaires)[d]	17 (89.5)

Week 9	Missing by Design	4 (18.2)
	Discontinued due to adverse event	0 (0.0)
	Discontinued due to clinical progression	2 (9.1)
	Discontinued due to complete response	0 (0.0)
	Discontinued due to progressive disease	0 (0.0)
	Subject died	0 (0.0)
	Visit not scheduled	2 (9.1)
	Expected to Complete Questionnaires[c]	18 (81.8)
	Not completed	0 (0.0)
	Not completed due to site staff error	0 (0.0)
	Subject refused for other reasons	0 (0.0)
	Other	0 (0.0)
	With visit, no record	0 (0.0)
	Completed	18 (81.8)
	Compliance (% in those expected to complete questionnaires)[d]	18 (100.0)
Week 18	Missing by Design	4 (18.2)
	Discontinued due to adverse event	1 (4.5)
	Discontinued due to clinical progression	2 (9.1)
	Discontinued due to complete response	0 (0.0)
	Discontinued due to progressive disease	1 (4.5)
	Subject died	0 (0.0)
	Visit not scheduled	0 (0.0)
	Expected to Complete Questionnaires[c]	18 (81.8)
	Not completed	1 (4.5)
	Not completed due to site staff error	0 (0.0)
	Subject refused for other reasons	0 (0.0)
	Other	1 (4.5)
	With visit, no record	0 (0.0)
	Completed	17 (77.3)
	Compliance (% in those expected to complete questionnaires)[d]	17 (94.4)
Week 27	Missing by Design	7 (31.8)
	Discontinued due to adverse event	1 (4.5)
	Discontinued due to clinical progression	3 (13.6)
	Discontinued due to complete response	0 (0.0)
	Discontinued due to progressive disease	3 (13.6)
	Subject died	0 (0.0)
	Visit not scheduled	0 (0.0)
	Expected to Complete Questionnaires[c]	15 (68.2)
	Not completed	3 (13.6)
	Not completed due to site staff error	1 (4.5)
	Subject refused for other reasons	1 (4.5)
	Other	0 (0.0)
	With visit, no record	1 (4.5)
	Completed	12 (54.5)
	Compliance (% in those expected to complete questionnaires)[d]	12 (80.0)
Week 39	Missing by Design	9 (40.9)
	Discontinued due to adverse event	1 (4.5)
	Discontinued due to clinical progression	5 (22.7)
	Discontinued due to complete response	0 (0.0)
	Discontinued due to progressive disease	3 (13.6)
	Subject died	0 (0.0)
	Visit not scheduled	0 (0.0)
	Expected to Complete Questionnaires[c]	13 (59.1)
	Not completed	2 (9.1)
	Not completed due to site staff error	1 (4.5)
	Subject refused for other reasons	0 (0.0)
	Other	1 (4.5)
	With visit, no record	0 (0.0)
	Completed	11 (50.0)
	Compliance (% in those expected to complete questionnaires)[d]	11 (84.6)
Week 51	Missing by Design	10 (45.5)

	Discontinued due to adverse event	1 (4.5)
	Discontinued due to clinical progression	5 (22.7)
	Discontinued due to complete response	0 (0.0)
	Discontinued due to progressive disease	3 (13.6)
	Subject died	1 (4.5)
	Visit not scheduled	0 (0.0)
	Expected to Complete Questionnaires[c]	12 (54.5)
	Not completed	3 (13.6)
	Not completed due to site staff error	1 (4.5)
	Subject refused for other reasons	1 (4.5)
	Other	0 (0.0)
	With visit, no record	1 (4.5)
	Completed	9 (40.9)
	Compliance (% in those expected to complete questionnaires)[d]	9 (75.0)
Week 63	Missing by Design	12 (54.5)
	Discontinued due to adverse event	2 (9.1)
	Discontinued due to clinical progression	6 (27.3)
	Discontinued due to complete response	0 (0.0)
	Discontinued due to progressive disease	4 (18.2)
	Subject died	0 (0.0)
	Visit not scheduled	0 (0.0)
	Expected to Complete Questionnaires[c]	10 (45.5)
	Not completed	2 (9.1)
	Not completed due to site staff error	1 (4.5)
	Subject refused for other reasons	0 (0.0)
	Other	0 (0.0)
	With visit, no record	1 (4.5)
	Completed	8 (36.4)
	Compliance (% in those expected to complete questionnaires)[d]	8 (80.0)
Week 75	Missing by Design	14 (63.6)
	Discontinued due to adverse event	2 (9.1)
	Discontinued due to clinical progression	6 (27.3)
	Discontinued due to complete response	1 (4.5)
	Discontinued due to progressive disease	5 (22.7)
	Subject died	0 (0.0)
	Visit not scheduled	0 (0.0)
	Expected to Complete Questionnaires[c]	8 (36.4)
	Not completed	0 (0.0)
	Not completed due to site staff error	0 (0.0)
	Subject refused for other reasons	0 (0.0)
	Other	0 (0.0)
	With visit, no record	0 (0.0)
	Completed	8 (36.4)
	Compliance (% in those expected to complete questionnaires)[d]	8 (100.0)
Week 87	Missing by Design	15 (68.2)
	Discontinued due to adverse event	2 (9.1)
	Discontinued due to clinical progression	6 (27.3)
	Discontinued due to complete response	1 (4.5)
	Discontinued due to progressive disease	6 (27.3)
	Subject died	0 (0.0)
	Visit not scheduled	0 (0.0)
	Expected to Complete Questionnaires[c]	7 (31.8)
	Not completed	1 (4.5)
	Not completed due to site staff error	0 (0.0)
	Subject refused for other reasons	0 (0.0)
	Other	1 (4.5)
	With visit, no record	0 (0.0)
	Completed	6 (27.3)
	Compliance (% in those expected to complete questionnaires)[d]	6 (85.7)
Week 99	Missing by Design	16 (72.7)
	Discontinued due to adverse event	2 (9.1)

	Discontinued due to clinical progression	6 (27.3)
	Discontinued due to complete response	1 (4.5)
	Discontinued due to progressive disease	7 (31.8)
	Subject died	0 (0.0)
	Visit not scheduled	0 (0.0)
	Expected to Complete Questionnaires[c]	6 (27.3)
	Not completed	1 (4.5)
	Not completed due to site staff error	0 (0.0)
	Subject refused for other reasons	0 (0.0)
	Other	0 (0.0)
	With visit, no record	1 (4.5)
	Completed	5 (22.7)
	Compliance (% in those expected to complete questionnaires)[d]	5 (83.3)
Week 111	Missing by Design	17 (77.3)
	Discontinued due to adverse event	3 (13.6)
	Discontinued due to clinical progression	6 (27.3)
	Discontinued due to complete response	1 (4.5)
	Discontinued due to progressive disease	7 (31.8)
	Subject died	0 (0.0)
	Visit not scheduled	0 (0.0)
	Expected to Complete Questionnaires[c]	5 (22.7)
	Not completed	1 (4.5)
	Not completed due to site staff error	1 (4.5)
	Subject refused for other reasons	0 (0.0)
	Other	0 (0.0)
	With visit, no record	0 (0.0)
	Completed	4 (18.2)
	Compliance (% in those expected to complete questionnaires)[d]	4 (80.0)

a: Database Cutoff Date: 05OCT2020

b: Number of participants: full-analysis-set population with MSI-H biliary carcinoma, at least one line of prior therapy

c: Expected to complete questionnaire includes all participants who do not have missing data due to a missing by design reason

d: Compliance is the proportion of participants who completed the PRO questionnaire among those who are expected to complete the questionnaire at each time point, excluding those missing by design. All the other percentages are defined as the proportion of participants in the analysis population (N)

EORTC QLQ-C30: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 items; MSI-H: Microsatellite Instability-High; PRO: Patient Reported Outcome

Anhang 4-G12: Rücklaufquoten des EQ-5D VAS

Tabelle 4G-2: Gründe für das Fehlen von Werten im EQ-5D VAS

Study: KEYNOTE 158[a]		**Pembrolizumab**
Visit	**EQ-5D-3L**	**N[b] = 22 n (%)**
Baseline	Missing by Design	0 (0.0)
	Discontinued due to adverse event	0 (0.0)
	Discontinued due to clinical progression	0 (0.0)
	Discontinued due to complete response	0 (0.0)
	Discontinued due to progressive disease	0 (0.0)
	Subject died	0 (0.0)
	Visit not scheduled	0 (0.0)
	Expected to Complete Questionnaires[c]	22 (100.0)
	Not completed	1 (4.5)
	Not completed due to site staff error	0 (0.0)
	Subject refused for other reasons	0 (0.0)
	Other	1 (4.5)
	With visit, no record	0 (0.0)
	Completed	21 (95.5)
	Compliance (% in those expected to complete questionnaires)[d]	21 (95.5)

Week 3	Missing by Design	0 (0.0)
	Discontinued due to adverse event	0 (0.0)
	Discontinued due to clinical progression	0 (0.0)
	Discontinued due to complete response	0 (0.0)
	Discontinued due to progressive disease	0 (0.0)
	Subject died	0 (0.0)
	Visit not scheduled	0 (0.0)
	Expected to Complete Questionnaires[c]	22 (100.0)
	Not completed	0 (0.0)
	Not completed due to site staff error	0 (0.0)
	Subject refused for other reasons	0 (0.0)
	Other	0 (0.0)
	With visit, no record	0 (0.0)
	Completed	22 (100.0)
	Compliance (% in those expected to complete questionnaires)[d]	22 (100.0)
Week 6	Missing by Design	3 (13.6)
	Discontinued due to adverse event	0 (0.0)
	Discontinued due to clinical progression	0 (0.0)
	Discontinued due to complete response	0 (0.0)
	Discontinued due to progressive disease	0 (0.0)
	Subject died	1 (4.5)
	Visit not scheduled	2 (9.1)
	Expected to Complete Questionnaires[c]	19 (86.4)
	Not completed	2 (9.1)
	Not completed due to site staff error	0 (0.0)
	Subject refused for other reasons	0 (0.0)
	Other	2 (9.1)
	With visit, no record	0 (0.0)
	Completed	17 (77.3)
	Compliance (% in those expected to complete questionnaires)[d]	17 (89.5)
Week 9	Missing by Design	4 (18.2)
	Discontinued due to adverse event	0 (0.0)
	Discontinued due to clinical progression	2 (9.1)
	Discontinued due to complete response	0 (0.0)
	Discontinued due to progressive disease	0 (0.0)
	Subject died	0 (0.0)
	Visit not scheduled	2 (9.1)
	Expected to Complete Questionnaires[c]	18 (81.8)
	Not completed	0 (0.0)
	Not completed due to site staff error	0 (0.0)
	Subject refused for other reasons	0 (0.0)
	Other	0 (0.0)
	With visit, no record	0 (0.0)
	Completed	18 (81.8)
	Compliance (% in those expected to complete questionnaires)[d]	18 (100.0)
Week 18	Missing by Design	4 (18.2)
	Discontinued due to adverse event	1 (4.5)
	Discontinued due to clinical progression	2 (9.1)
	Discontinued due to complete response	0 (0.0)
	Discontinued due to progressive disease	1 (4.5)
	Subject died	0 (0.0)
	Visit not scheduled	0 (0.0)
	Expected to Complete Questionnaires[c]	18 (81.8)
	Not completed	1 (4.5)
	Not completed due to site staff error	0 (0.0)
	Subject refused for other reasons	0 (0.0)
	Other	1 (4.5)
	With visit, no record	0 (0.0)
	Completed	17 (77.3)
	Compliance (% in those expected to complete questionnaires)[d]	17 (94.4)
Week 27	Missing by Design	7 (31.8)

	Discontinued due to adverse event	1 (4.5)
	Discontinued due to clinical progression	3 (13.6)
	Discontinued due to complete response	0 (0.0)
	Discontinued due to progressive disease	3 (13.6)
	Subject died	0 (0.0)
	Visit not scheduled	0 (0.0)
	Expected to Complete Questionnaires[c]	15 (68.2)
	Not completed	3 (13.6)
	Not completed due to site staff error	1 (4.5)
	Subject refused for other reasons	1 (4.5)
	Other	0 (0.0)
	With visit, no record	1 (4.5)
	Completed	12 (54.5)
	Compliance (% in those expected to complete questionnaires)[d]	12 (80.0)
Week 39	Missing by Design	9 (40.9)
	Discontinued due to adverse event	1 (4.5)
	Discontinued due to clinical progression	5 (22.7)
	Discontinued due to complete response	0 (0.0)
	Discontinued due to progressive disease	3 (13.6)
	Subject died	0 (0.0)
	Visit not scheduled	0 (0.0)
	Expected to Complete Questionnaires[c]	13 (59.1)
	Not completed	2 (9.1)
	Not completed due to site staff error	1 (4.5)
	Subject refused for other reasons	0 (0.0)
	Other	1 (4.5)
	With visit, no record	0 (0.0)
	Completed	11 (50.0)
	Compliance (% in those expected to complete questionnaires)[d]	11 (84.6)
Week 51	Missing by Design	10 (45.5)
	Discontinued due to adverse event	1 (4.5)
	Discontinued due to clinical progression	5 (22.7)
	Discontinued due to complete response	0 (0.0)
	Discontinued due to progressive disease	3 (13.6)
	Subject died	1 (4.5)
	Visit not scheduled	0 (0.0)
	Expected to Complete Questionnaires[c]	12 (54.5)
	Not completed	3 (13.6)
	Not completed due to site staff error	1 (4.5)
	Subject refused for other reasons	1 (4.5)
	Other	0 (0.0)
	With visit, no record	1 (4.5)
	Completed	9 (40.9)
	Compliance (% in those expected to complete questionnaires)[d]	9 (75.0)
Week 63	Missing by Design	12 (54.5)
	Discontinued due to adverse event	2 (9.1)
	Discontinued due to clinical progression	6 (27.3)
	Discontinued due to complete response	0 (0.0)
	Discontinued due to progressive disease	4 (18.2)
	Subject died	0 (0.0)
	Visit not scheduled	0 (0.0)
	Expected to Complete Questionnaires[c]	10 (45.5)
	Not completed	2 (9.1)
	Not completed due to site staff error	1 (4.5)
	Subject refused for other reasons	0 (0.0)
	Other	0 (0.0)
	With visit, no record	1 (4.5)
	Completed	8 (36.4)
	Compliance (% in those expected to complete questionnaires)[d]	8 (80.0)
Week 75	Missing by Design	14 (63.6)
	Discontinued due to adverse event	2 (9.1)

	Discontinued due to clinical progression	6 (27.3)
	Discontinued due to complete response	1 (4.5)
	Discontinued due to progressive disease	5 (22.7)
	Subject died	0 (0.0)
	Visit not scheduled	0 (0.0)
	Expected to Complete Questionnaires[c]	8 (36.4)
	Not completed	0 (0.0)
	Not completed due to site staff error	0 (0.0)
	Subject refused for other reasons	0 (0.0)
	Other	0 (0.0)
	With visit, no record	0 (0.0)
	Completed	8 (36.4)
	Compliance (% in those expected to complete questionnaires)[d]	8 (100.0)
Week 87	Missing by Design	15 (68.2)
	Discontinued due to adverse event	2 (9.1)
	Discontinued due to clinical progression	6 (27.3)
	Discontinued due to complete response	1 (4.5)
	Discontinued due to progressive disease	6 (27.3)
	Subject died	0 (0.0)
	Visit not scheduled	0 (0.0)
	Expected to Complete Questionnaires[c]	7 (31.8)
	Not completed	1 (4.5)
	Not completed due to site staff error	0 (0.0)
	Subject refused for other reasons	0 (0.0)
	Other	1 (4.5)
	With visit, no record	0 (0.0)
	Completed	6 (27.3)
	Compliance (% in those expected to complete questionnaires)[d]	6 (85.7)
Week 99	Missing by Design	16 (72.7)
	Discontinued due to adverse event	2 (9.1)
	Discontinued due to clinical progression	6 (27.3)
	Discontinued due to complete response	1 (4.5)
	Discontinued due to progressive disease	7 (31.8)
	Subject died	0 (0.0)
	Visit not scheduled	0 (0.0)
	Expected to Complete Questionnaires[c]	6 (27.3)
	Not completed	1 (4.5)
	Not completed due to site staff error	0 (0.0)
	Subject refused for other reasons	0 (0.0)
	Other	0 (0.0)
	With visit, no record	1 (4.5)
	Completed	5 (22.7)
	Compliance (% in those expected to complete questionnaires)[d]	5 (83.3)
Week 111	Missing by Design	17 (77.3)
	Discontinued due to adverse event	3 (13.6)
	Discontinued due to clinical progression	6 (27.3)
	Discontinued due to complete response	1 (4.5)
	Discontinued due to progressive disease	7 (31.8)
	Subject died	0 (0.0)
	Visit not scheduled	0 (0.0)
	Expected to Complete Questionnaires[c]	5 (22.7)
	Not completed	1 (4.5)
	Not completed due to site staff error	1 (4.5)
	Subject refused for other reasons	0 (0.0)
	Other	0 (0.0)
	With visit, no record	0 (0.0)
	Completed	4 (18.2)
	Compliance (% in those expected to complete questionnaires)[d]	4 (80.0)

a: Database Cutoff Date: 05OCT2020
b: Number of participants: full-analysis-set population with MSI-H biliary carcinoma, at least one line of prior therapy

c: Expected to complete questionnaire includes all participants who do not have missing data due to a missing by design reason
d: Compliance is the proportion of participants who completed the PRO questionnaire among those who are expected to complete the questionnaire at each time point, excluding those missing by design. All the other percentages are defined as the proportion of participants in the analysis population (N)
EQ-5D-3L: 3-level version of the EuroQol-5 Dimension of health questionnaire; MSI-H: Microsatellite Instability-High; PRO: Patient Reported Outcome

Anhang 4-G2: Definition der Immunvermittelten unerwünschten Ereignisse (AEOSI) anhand der zugeordneten PT

Die Definition der Immunvermittelten unerwünschten Ereignisse (AEOSI) anhand der zugeordneten PT in der Studie KEYNOTE 158 sind Anhang 4G des Moduls 4C (Magenkarzinom) zu entnehmen.