Dossier zur Nutzenbewertung gemäß § 35a SGB V

Pembrolizumab (KEYTRUDA®)

MSD Sharp & Dohme GmbH

Modul 4 A

Anhang 4-G: Weitere Ergebnisse

KEYTRUDA® ist in Kombination mit Gemcitabin und Cisplatin zur Erstlinienbehandlung des lokal fortgeschrittenen nicht resezierbaren oder metastasierenden biliären Karzinoms bei Erwachsenen angezeigt

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Anhang 4-G1: Rücklaufquoten des EORTC QLQ-C30, EORTC QLQ-BIL21 und EQ-5D VAS

Im Folgenden werden ergänzend zu Abschnitt 4.3.1.3.1.2.2 bzw. Abschnitt 4.3.1.3.1.3.1 die Rücklaufquoten des EORTC QLQ-C30, des EORTC QLQ-BIL21 und des EQ-5D VAS dargestellt.

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

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

Treatment Visit	Category	Pembrolizumab + Chemotherapy N=520		Placebo + Chemotherapy N=517	
		n	(%)	n	(%)
BASELINE	**Expected to Complete Questionnaires**	**520**	**(100.0)**	**515**	**(99.6)**
	Completed	489	(94.0)	496	(95.9)
	Compliance (% in those expected to complete questionnaires)	489	(94.0)	496	(96.3)
	Not completed	31	(6.0)	19	(3.7)
	Subject did not complete due to disease under study	1	(0.2)	0	(0.0)
	Not completed due to site staff error	13	(2.5)	5	(1.0)
	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 effects of treatment	0	(0.0)	0	(0.0)
	Subject refused for other reasons	2	(0.4)	1	(0.2)
	Other	7	(1.3)	9	(1.7)
	With visit, no record	8	(1.5)	4	(0.8)
	Missing by Design	**0**	**(0.0)**	**2**	**(0.4)**
	Discontinued due to adverse event	0	(0.0)	0	(0.0)
	Discontinued due to clinical progression	0	(0.0)	0	(0.0)
	Discontinued due to non-study anti-cancer therapy	0	(0.0)	0	(0.0)
	Discontinued due to physician decision	0	(0.0)	0	(0.0)

Treatment Visit	Category	Pembrolizumab + Chemotherapy N=520		Placebo + Chemotherapy N=517	
		n	(%)	n	(%)
BASELINE	Discontinued due to progressive disease	0	(0.0)	0	(0.0)
	Discontinued due to withdrawal by subject	0	(0.0)	0	(0.0)
	Completed study treatment	0	(0.0)	0	(0.0)
	Translation not available in subjects language	0	(0.0)	2	(0.4)
	Subject died	0	(0.0)	0	(0.0)
	Visit not reached	0	(0.0)	0	(0.0)
	Visit not scheduled	0	(0.0)	0	(0.0)
WEEK 3	**Expected to Complete Questionnaires**	**508**	**(97.7)**	**502**	**(97.1)**
	Completed	445	(85.6)	450	(87.0)
	Compliance (% in those expected to complete questionnaires)	445	(87.6)	450	(89.6)
	Not completed	63	(12.1)	52	(10.1)
	Subject did not complete due to disease under study	1	(0.2)	2	(0.4)
	Not completed due to site staff error	12	(2.3)	9	(1.7)
	Subject in hospital or hospice	2	(0.4)	1	(0.2)
	Subject was physically unable to complete	2	(0.4)	1	(0.2)
	Subject lost to follow-up/unable to contact	1	(0.2)	0	(0.0)
	Subject did not complete due to side effects of treatment	1	(0.2)	1	(0.2)
	Subject refused for other reasons	3	(0.6)	3	(0.6)

Treatment Visit	Category	Pembrolizumab + Chemotherapy N=520		Placebo + Chemotherapy N=517	
		n	(%)	n	(%)
WEEK 3	Other	15	(2.9)	13	(2.5)
	With visit, no record	26	(5.0)	22	(4.3)
	Missing by Design	**12**	**(2.3)**	**15**	**(2.9)**
	Discontinued due to adverse event	0	(0.0)	0	(0.0)
	Discontinued due to clinical progression	0	(0.0)	0	(0.0)
	Discontinued due to non-study anti-cancer therapy	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 withdrawal by subject	0	(0.0)	0	(0.0)
	Completed study treatment	0	(0.0)	0	(0.0)
	Translation not available in subjects language	1	(0.2)	1	(0.2)
	Subject died	4	(0.8)	10	(1.9)
	Visit not reached	0	(0.0)	0	(0.0)
	Visit not scheduled	7	(1.3)	4	(0.8)
WEEK 6	**Expected to Complete Questionnaires**	**479**	**(92.1)**	**477**	**(92.3)**
	Completed	419	(80.6)	434	(83.9)
	Compliance (% in those expected to complete questionnaires)	419	(87.5)	434	(91.0)
	Not completed	60	(11.5)	43	(8.3)

Treatment Visit	Category	Pembrolizumab + Chemotherapy N=520		Placebo + Chemotherapy N=517	
		n	(%)	n	(%)
WEEK 6	Subject did not complete due to disease under study	3	(0.6)	0	(0.0)
	Not completed due to site staff error	15	(2.9)	8	(1.5)
	Subject in hospital or hospice	3	(0.6)	0	(0.0)
	Subject was physically unable to complete	3	(0.6)	3	(0.6)
	Subject lost to follow-up/unable to contact	0	(0.0)	0	(0.0)
	Subject did not complete due to side effects of treatment	0	(0.0)	0	(0.0)
	Subject refused for other reasons	2	(0.4)	2	(0.4)
	Other	17	(3.3)	11	(2.1)
	With visit, no record	17	(3.3)	19	(3.7)
	Missing by Design	**41**	**(7.9)**	**40**	**(7.7)**
	Discontinued due to adverse event	7	(1.3)	9	(1.7)
	Discontinued due to clinical progression	2	(0.4)	5	(1.0)
	Discontinued due to non-study anti-cancer therapy	0	(0.0)	0	(0.0)
	Discontinued due to physician decision	1	(0.2)	0	(0.0)
	Discontinued due to progressive disease	7	(1.3)	5	(1.0)
	Discontinued due to withdrawal by subject	3	(0.6)	2	(0.4)
	Completed study treatment	0	(0.0)	0	(0.0)
	Translation not available in subjects language	0	(0.0)	1	(0.2)

Treatment Visit	Category	Pembrolizumab + Chemotherapy N=520		Placebo + Chemotherapy N=517	
		n	(%)	n	(%)
WEEK 6	Subject died	2	(0.4)	2	(0.4)
	Visit not reached	0	(0.0)	0	(0.0)
	Visit not scheduled	19	(3.7)	16	(3.1)
WEEK 9	**Expected to Complete Questionnaires**	**453**	**(87.1)**	**454**	**(87.8)**
	Completed	396	(76.2)	402	(77.8)
	Compliance (% in those expected to complete questionnaires)	396	(87.4)	402	(88.5)
	Not completed	57	(11.0)	52	(10.1)
	Subject did not complete due to disease under study	2	(0.4)	3	(0.6)
	Not completed due to site staff error	8	(1.5)	10	(1.9)
	Subject in hospital or hospice	3	(0.6)	0	(0.0)
	Subject was physically unable to complete	1	(0.2)	0	(0.0)
	Subject lost to follow-up/unable to contact	0	(0.0)	0	(0.0)
	Subject did not complete due to side effects of treatment	0	(0.0)	0	(0.0)
	Subject refused for other reasons	8	(1.5)	4	(0.8)
	Other	9	(1.7)	14	(2.7)
	With visit, no record	26	(5.0)	21	(4.1)
	Missing by Design	**67**	**(12.9)**	**63**	**(12.2)**
	Discontinued due to adverse event	11	(2.1)	15	(2.9)

Treatment Visit	Category	Pembrolizumab + Chemotherapy N=520		Placebo + Chemotherapy N=517	
		n	(%)	n	(%)
WEEK 9	Discontinued due to clinical progression	3	(0.6)	8	(1.5)
	Discontinued due to non-study anti-cancer therapy	0	(0.0)	0	(0.0)
	Discontinued due to physician decision	3	(0.6)	1	(0.2)
	Discontinued due to progressive disease	20	(3.8)	17	(3.3)
	Discontinued due to withdrawal by subject	5	(1.0)	8	(1.5)
	Completed study treatment	0	(0.0)	0	(0.0)
	Translation not available in subjects language	0	(0.0)	0	(0.0)
	Subject died	5	(1.0)	2	(0.4)
	Visit not reached	0	(0.0)	0	(0.0)
	Visit not scheduled	20	(3.8)	12	(2.3)
WEEK 12	**Expected to Complete Questionnaires**	**417**	**(80.2)**	**422**	**(81.6)**
	Completed	367	(70.6)	368	(71.2)
	Compliance (% in those expected to complete questionnaires)	367	(88.0)	368	(87.2)
	Not completed	50	(9.6)	54	(10.4)
	Subject did not complete due to disease under study	0	(0.0)	1	(0.2)
	Not completed due to site staff error	11	(2.1)	11	(2.1)
	Subject in hospital or hospice	0	(0.0)	1	(0.2)
	Subject was physically unable to complete	2	(0.4)	1	(0.2)

Treatment Visit	Category	Pembrolizumab + Chemotherapy N=520		Placebo + Chemotherapy N=517	
		n	(%)	n	(%)
WEEK 12	Subject lost to follow-up/unable to contact	0	(0.0)	0	(0.0)
	Subject did not complete due to side effects of treatment	0	(0.0)	1	(0.2)
	Subject refused for other reasons	3	(0.6)	3	(0.6)
	Other	13	(2.5)	5	(1.0)
	With visit, no record	21	(4.0)	31	(6.0)
	Missing by Design	**103**	**(19.8)**	**95**	**(18.4)**
	Discontinued due to adverse event	18	(3.5)	20	(3.9)
	Discontinued due to clinical progression	7	(1.3)	12	(2.3)
	Discontinued due to non-study anti-cancer therapy	1	(0.2)	0	(0.0)
	Discontinued due to physician decision	4	(0.8)	1	(0.2)
	Discontinued due to progressive disease	46	(8.8)	36	(7.0)
	Discontinued due to withdrawal by subject	7	(1.3)	10	(1.9)
	Completed study treatment	0	(0.0)	0	(0.0)
	Translation not available in subjects language	0	(0.0)	1	(0.2)
	Subject died	0	(0.0)	3	(0.6)
	Visit not reached	0	(0.0)	0	(0.0)
	Visit not scheduled	20	(3.8)	12	(2.3)
WEEK 15	**Expected to Complete Questionnaires**	**373**	**(71.7)**	**366**	**(70.8)**

Treatment Visit	Category	Pembrolizumab + Chemotherapy N=520		Placebo + Chemotherapy N=517	
		n	(%)	n	(%)
WEEK 15	Completed	340	(65.4)	342	(66.2)
	Compliance (% in those expected to complete questionnaires)	340	(91.2)	342	(93.4)
	Not completed	33	(6.3)	24	(4.6)
	Subject did not complete due to disease under study	3	(0.6)	2	(0.4)
	Not completed due to site staff error	9	(1.7)	6	(1.2)
	Subject in hospital or hospice	1	(0.2)	2	(0.4)
	Subject was physically unable to complete	1	(0.2)	0	(0.0)
	Subject lost to follow-up/unable to contact	0	(0.0)	0	(0.0)
	Subject did not complete due to side effects of treatment	0	(0.0)	2	(0.4)
	Subject refused for other reasons	2	(0.4)	1	(0.2)
	Other	6	(1.2)	6	(1.2)
	With visit, no record	11	(2.1)	5	(1.0)
	Missing by Design	**147**	**(28.3)**	**151**	**(29.2)**
	Discontinued due to adverse event	20	(3.8)	22	(4.3)
	Discontinued due to clinical progression	8	(1.5)	15	(2.9)
	Discontinued due to non-study anti-cancer therapy	1	(0.2)	0	(0.0)
	Discontinued due to physician decision	6	(1.2)	1	(0.2)
	Discontinued due to progressive disease	61	(11.7)	64	(12.4)

Treatment Visit	Category	Pembrolizumab + Chemotherapy N=520		Placebo + Chemotherapy N=517	
		n	(%)	n	(%)
WEEK 15	Discontinued due to withdrawal by subject	8	(1.5)	13	(2.5)
	Completed study treatment	0	(0.0)	0	(0.0)
	Translation not available in subjects language	0	(0.0)	1	(0.2)
	Subject died	3	(0.6)	4	(0.8)
	Visit not reached	0	(0.0)	0	(0.0)
	Visit not scheduled	40	(7.7)	31	(6.0)
WEEK 18	**Expected to Complete Questionnaires**	**343**	**(66.0)**	**329**	**(63.6)**
	Completed	320	(61.5)	315	(60.9)
	Compliance (% in those expected to complete questionnaires)	320	(93.3)	315	(95.7)
	Not completed	23	(4.4)	14	(2.7)
	Subject did not complete due to disease under study	1	(0.2)	1	(0.2)
	Not completed due to site staff error	6	(1.2)	3	(0.6)
	Subject in hospital or hospice	0	(0.0)	2	(0.4)
	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 effects of treatment	0	(0.0)	0	(0.0)
	Subject refused for other reasons	3	(0.6)	3	(0.6)
	Other	8	(1.5)	3	(0.6)

Treatment Visit	Category	Pembrolizumab + Chemotherapy N=520		Placebo + Chemotherapy N=517	
		n	(%)	n	(%)
WEEK 18	With visit, no record	5	(1.0)	2	(0.4)
	Missing by Design	**177**	**(34.0)**	**188**	**(36.4)**
	Discontinued due to adverse event	25	(4.8)	26	(5.0)
	Discontinued due to clinical progression	11	(2.1)	17	(3.3)
	Discontinued due to non-study anti-cancer therapy	1	(0.2)	0	(0.0)
	Discontinued due to physician decision	7	(1.3)	2	(0.4)
	Discontinued due to progressive disease	82	(15.8)	85	(16.4)
	Discontinued due to withdrawal by subject	11	(2.1)	15	(2.9)
	Completed study treatment	0	(0.0)	0	(0.0)
	Translation not available in subjects language	0	(0.0)	1	(0.2)
	Subject died	2	(0.4)	3	(0.6)
	Visit not reached	0	(0.0)	0	(0.0)
	Visit not scheduled	38	(7.3)	39	(7.5)
WEEK 21	**Expected to Complete Questionnaires**	**330**	**(63.5)**	**307**	**(59.4)**
	Completed	304	(58.5)	284	(54.9)
	Compliance (% in those expected to complete questionnaires)	304	(92.1)	284	(92.5)
	Not completed	26	(5.0)	23	(4.4)
	Subject did not complete due to disease under study	1	(0.2)	1	(0.2)

Treatment Visit	Category	Pembrolizumab + Chemotherapy N=520		Placebo + Chemotherapy N=517	
		n	(%)	n	(%)
WEEK 21	Not completed due to site staff error	6	(1.2)	7	(1.4)
	Subject in hospital or hospice	0	(0.0)	1	(0.2)
	Subject was physically unable to complete	2	(0.4)	0	(0.0)
	Subject lost to follow-up/unable to contact	0	(0.0)	0	(0.0)
	Subject did not complete due to side effects of treatment	0	(0.0)	0	(0.0)
	Subject refused for other reasons	2	(0.4)	2	(0.4)
	Other	9	(1.7)	10	(1.9)
	With visit, no record	6	(1.2)	2	(0.4)
	Missing by Design	**190**	**(36.5)**	**210**	**(40.6)**
	Discontinued due to adverse event	27	(5.2)	28	(5.4)
	Discontinued due to clinical progression	15	(2.9)	19	(3.7)
	Discontinued due to non-study anti-cancer therapy	1	(0.2)	0	(0.0)
	Discontinued due to physician decision	8	(1.5)	3	(0.6)
	Discontinued due to progressive disease	94	(18.1)	104	(20.1)
	Discontinued due to withdrawal by subject	13	(2.5)	16	(3.1)
	Completed study treatment	0	(0.0)	0	(0.0)
	Translation not available in subjects language	0	(0.0)	1	(0.2)
	Subject died	0	(0.0)	3	(0.6)

Treatment Visit	Category	Pembrolizumab + Chemotherapy N=520		Placebo + Chemotherapy N=517	
		n	(%)	n	(%)
WEEK 21	Visit not reached	0	(0.0)	0	(0.0)
	Visit not scheduled	32	(6.2)	36	(7.0)
WEEK 24	**Expected to Complete Questionnaires**	**304**	**(58.5)**	**281**	**(54.4)**
	Completed	284	(54.6)	264	(51.1)
	Compliance (% in those expected to complete questionnaires)	284	(93.4)	264	(94.0)
	Not completed	20	(3.8)	17	(3.3)
	Subject did not complete due to disease under study	1	(0.2)	2	(0.4)
	Not completed due to site staff error	12	(2.3)	5	(1.0)
	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 effects of treatment	0	(0.0)	0	(0.0)
	Subject refused for other reasons	1	(0.2)	2	(0.4)
	Other	4	(0.8)	6	(1.2)
	With visit, no record	2	(0.4)	2	(0.4)
	Missing by Design	**216**	**(41.5)**	**236**	**(45.6)**
	Discontinued due to adverse event	31	(6.0)	36	(7.0)
	Discontinued due to clinical progression	15	(2.9)	21	(4.1)

Treatment Visit	Category	Pembrolizumab + Chemotherapy N=520		Placebo + Chemotherapy N=517	
		n	(%)	n	(%)
WEEK 24	Discontinued due to non-study anti-cancer therapy	1	(0.2)	1	(0.2)
	Discontinued due to physician decision	8	(1.5)	4	(0.8)
	Discontinued due to progressive disease	113	(21.7)	115	(22.2)
	Discontinued due to withdrawal by subject	15	(2.9)	18	(3.5)
	Completed study treatment	0	(0.0)	0	(0.0)
	Translation not available in subjects language	0	(0.0)	0	(0.0)
	Subject died	1	(0.2)	5	(1.0)
	Visit not reached	0	(0.0)	0	(0.0)
	Visit not scheduled	32	(6.2)	36	(7.0)
WEEK 27	**Expected to Complete Questionnaires**	**294**	**(56.5)**	**274**	**(53.0)**
	Completed	279	(53.7)	256	(49.5)
	Compliance (% in those expected to complete questionnaires)	279	(94.9)	256	(93.4)
	Not completed	15	(2.9)	18	(3.5)
	Subject did not complete due to disease under study	1	(0.2)	2	(0.4)
	Not completed due to site staff error	4	(0.8)	4	(0.8)
	Subject in hospital or hospice	0	(0.0)	1	(0.2)
	Subject was physically unable to complete	0	(0.0)	3	(0.6)
	Subject lost to follow-up/unable to contact	0	(0.0)	0	(0.0)

Treatment Visit	Category	Pembrolizumab + Chemotherapy N=520		Placebo + Chemotherapy N=517	
		n	(%)	n	(%)
WEEK 27	Subject did not complete due to side effects of treatment	0	(0.0)	0	(0.0)
	Subject refused for other reasons	1	(0.2)	3	(0.6)
	Other	6	(1.2)	4	(0.8)
	With visit, no record	3	(0.6)	1	(0.2)
	Missing by Design	**226**	**(43.5)**	**243**	**(47.0)**
	Discontinued due to adverse event	36	(6.9)	37	(7.2)
	Discontinued due to clinical progression	18	(3.5)	22	(4.3)
	Discontinued due to non-study anti-cancer therapy	1	(0.2)	1	(0.2)
	Discontinued due to physician decision	10	(1.9)	4	(0.8)
	Discontinued due to progressive disease	127	(24.4)	143	(27.7)
	Discontinued due to withdrawal by subject	16	(3.1)	20	(3.9)
	Completed study treatment	0	(0.0)	0	(0.0)
	Translation not available in subjects language	0	(0.0)	1	(0.2)
	Subject died	4	(0.8)	1	(0.2)
	Visit not reached	0	(0.0)	0	(0.0)
	Visit not scheduled	14	(2.7)	14	(2.7)
WEEK 33	**Expected to Complete Questionnaires**	**271**	**(52.1)**	**237**	**(45.8)**
	Completed	235	(45.2)	205	(39.7)

Treatment Visit	Category	Pembrolizumab + Chemotherapy N=520		Placebo + Chemotherapy N=517	
		n	(%)	n	(%)
WEEK 33	Compliance (% in those expected to complete questionnaires)	235	(86.7)	205	(86.5)
	Not completed	36	(6.9)	32	(6.2)
	Subject did not complete due to disease under study	2	(0.4)	1	(0.2)
	Not completed due to site staff error	5	(1.0)	0	(0.0)
	Subject in hospital or hospice	1	(0.2)	0	(0.0)
	Subject was physically unable to complete	1	(0.2)	0	(0.0)
	Subject lost to follow-up/unable to contact	0	(0.0)	0	(0.0)
	Subject did not complete due to side effects of treatment	0	(0.0)	0	(0.0)
	Subject refused for other reasons	1	(0.2)	3	(0.6)
	Other	4	(0.8)	7	(1.4)
	With visit, no record	22	(4.2)	21	(4.1)
	Missing by Design	**249**	**(47.9)**	**280**	**(54.2)**
	Discontinued due to adverse event	40	(7.7)	39	(7.5)
	Discontinued due to clinical progression	22	(4.2)	24	(4.6)
	Discontinued due to non-study anti-cancer therapy	1	(0.2)	2	(0.4)
	Discontinued due to physician decision	12	(2.3)	6	(1.2)
	Discontinued due to progressive disease	149	(28.7)	177	(34.2)
	Discontinued due to withdrawal by subject	16	(3.1)	20	(3.9)

Treatment Visit	Category	Pembrolizumab + Chemotherapy N=520		Placebo + Chemotherapy N=517	
		n	(%)	n	(%)
WEEK 33	Completed study treatment	0	(0.0)	0	(0.0)
	Translation not available in subjects language	0	(0.0)	1	(0.2)
	Subject died	2	(0.4)	4	(0.8)
	Visit not reached	0	(0.0)	0	(0.0)
	Visit not scheduled	7	(1.3)	7	(1.4)
WEEK 39	**Expected to Complete Questionnaires**	**225**	**(43.3)**	**195**	**(37.7)**
	Completed	192	(36.9)	167	(32.3)
	Compliance (% in those expected to complete questionnaires)	192	(85.3)	167	(85.6)
	Not completed	33	(6.3)	28	(5.4)
	Subject did not complete due to disease under study	1	(0.2)	0	(0.0)
	Not completed due to site staff error	6	(1.2)	10	(1.9)
	Subject in hospital or hospice	1	(0.2)	1	(0.2)
	Subject was physically unable to complete	1	(0.2)	0	(0.0)
	Subject lost to follow-up/unable to contact	0	(0.0)	0	(0.0)
	Subject did not complete due to side effects of treatment	1	(0.2)	0	(0.0)
	Subject refused for other reasons	3	(0.6)	2	(0.4)
	Other	2	(0.4)	6	(1.2)
	With visit, no record	18	(3.5)	9	(1.7)

Treatment Visit	Category	Pembrolizumab + Chemotherapy N=520		Placebo + Chemotherapy N=517	
		n	(%)	n	(%)
WEEK 39	**Missing by Design**	**295**	**(56.7)**	**322**	**(62.3)**
	Discontinued due to adverse event	43	(8.3)	41	(7.9)
	Discontinued due to clinical progression	24	(4.6)	30	(5.8)
	Discontinued due to non-study anti-cancer therapy	1	(0.2)	2	(0.4)
	Discontinued due to physician decision	18	(3.5)	10	(1.9)
	Discontinued due to progressive disease	179	(34.4)	207	(40.0)
	Discontinued due to withdrawal by subject	19	(3.7)	22	(4.3)
	Completed study treatment	0	(0.0)	0	(0.0)
	Translation not available in subjects language	0	(0.0)	1	(0.2)
	Subject died	2	(0.4)	3	(0.6)
	Visit not reached	0	(0.0)	0	(0.0)
	Visit not scheduled	9	(1.7)	6	(1.2)
WEEK 45	**Expected to Complete Questionnaires**	**187**	**(36.0)**	**152**	**(29.4)**
	Completed	160	(30.8)	135	(26.1)
	Compliance (% in those expected to complete questionnaires)	160	(85.6)	135	(88.8)
	Not completed	27	(5.2)	17	(3.3)
	Subject did not complete due to disease under study	2	(0.4)	1	(0.2)
	Not completed due to site staff error	5	(1.0)	4	(0.8)

Treatment Visit	Category	Pembrolizumab + Chemotherapy N=520		Placebo + Chemotherapy N=517	
		n	(%)	n	(%)
WEEK 45	Subject in hospital or hospice	0	(0.0)	1	(0.2)
	Subject was physically unable to complete	0	(0.0)	1	(0.2)
	Subject lost to follow-up/unable to contact	0	(0.0)	0	(0.0)
	Subject did not complete due to side effects of treatment	0	(0.0)	0	(0.0)
	Subject refused for other reasons	1	(0.2)	2	(0.4)
	Other	5	(1.0)	1	(0.2)
	With visit, no record	14	(2.7)	7	(1.4)
	Missing by Design	**333**	**(64.0)**	**365**	**(70.6)**
	Discontinued due to adverse event	50	(9.6)	44	(8.5)
	Discontinued due to clinical progression	27	(5.2)	31	(6.0)
	Discontinued due to non-study anti-cancer therapy	1	(0.2)	3	(0.6)
	Discontinued due to physician decision	20	(3.8)	12	(2.3)
	Discontinued due to progressive disease	210	(40.4)	243	(47.0)
	Discontinued due to withdrawal by subject	20	(3.8)	22	(4.3)
	Completed study treatment	0	(0.0)	0	(0.0)
	Translation not available in subjects language	0	(0.0)	1	(0.2)
	Subject died	1	(0.2)	2	(0.4)
	Visit not reached	0	(0.0)	0	(0.0)

Treatment Visit	Category	Pembrolizumab + Chemotherapy N=520		Placebo + Chemotherapy N=517	
		n	(%)	n	(%)
WEEK 45	Visit not scheduled	4	(0.8)	7	(1.4)
WEEK 51	**Expected to Complete Questionnaires**	**154**	**(29.6)**	**122**	**(23.6)**
	Completed	136	(26.2)	109	(21.1)
	Compliance (% in those expected to complete questionnaires)	136	(88.3)	109	(89.3)
	Not completed	18	(3.5)	13	(2.5)
	Subject did not complete due to disease under study	0	(0.0)	0	(0.0)
	Not completed due to site staff error	4	(0.8)	3	(0.6)
	Subject in hospital or hospice	0	(0.0)	1	(0.2)
	Subject was physically unable to complete	0	(0.0)	0	(0.0)
	Subject lost to follow-up/unable to contact	1	(0.2)	0	(0.0)
	Subject did not complete due to side effects of treatment	0	(0.0)	0	(0.0)
	Subject refused for other reasons	2	(0.4)	2	(0.4)
	Other	7	(1.3)	5	(1.0)
	With visit, no record	4	(0.8)	2	(0.4)
	Missing by Design	**366**	**(70.4)**	**395**	**(76.4)**
	Discontinued due to adverse event	51	(9.8)	46	(8.9)
	Discontinued due to clinical progression	31	(6.0)	32	(6.2)
	Discontinued due to non-study anti-cancer therapy	1	(0.2)	3	(0.6)

Treatment Visit	Category	Pembrolizumab + Chemotherapy N=520		Placebo + Chemotherapy N=517	
		n	(%)	n	(%)
WEEK 51	Discontinued due to physician decision	23	(4.4)	13	(2.5)
	Discontinued due to progressive disease	236	(45.4)	274	(53.0)
	Discontinued due to withdrawal by subject	23	(4.4)	23	(4.4)
	Completed study treatment	0	(0.0)	0	(0.0)
	Translation not available in subjects language	0	(0.0)	1	(0.2)
	Subject died	1	(0.2)	1	(0.2)
	Visit not reached	0	(0.0)	0	(0.0)
	Visit not scheduled	0	(0.0)	2	(0.4)
WEEK 63	**Expected to Complete Questionnaires**	**109**	**(21.0)**	**101**	**(19.5)**
	Completed	45	(8.7)	43	(8.3)
	Compliance (% in those expected to complete questionnaires)	45	(41.3)	43	(42.6)
	Not completed	64	(12.3)	58	(11.2)
	Subject did not complete due to disease under study	0	(0.0)	0	(0.0)
	Not completed due to site staff error	4	(0.8)	2	(0.4)
	Subject in hospital or hospice	1	(0.2)	1	(0.2)
	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 effects of treatment	0	(0.0)	0	(0.0)

Treatment Visit	Category	Pembrolizumab + Chemotherapy N=520		Placebo + Chemotherapy N=517	
		n	(%)	n	(%)
WEEK 63	Subject refused for other reasons	2	(0.4)	0	(0.0)
	Other	3	(0.6)	2	(0.4)
	With visit, no record	54	(10.4)	53	(10.3)
	Missing by Design	**411**	**(79.0)**	**416**	**(80.5)**
	Discontinued due to adverse event	54	(10.4)	49	(9.5)
	Discontinued due to clinical progression	33	(6.3)	32	(6.2)
	Discontinued due to non-study anti-cancer therapy	2	(0.4)	4	(0.8)
	Discontinued due to physician decision	25	(4.8)	13	(2.5)
	Discontinued due to progressive disease	266	(51.2)	291	(56.3)
	Discontinued due to withdrawal by subject	27	(5.2)	23	(4.4)
	Completed study treatment	0	(0.0)	0	(0.0)
	Translation not available in subjects language	0	(0.0)	1	(0.2)
	Subject died	3	(0.6)	2	(0.4)
	Visit not reached	0	(0.0)	0	(0.0)
	Visit not scheduled	1	(0.2)	1	(0.2)
WEEK 75	**Expected to Complete Questionnaires**	**79**	**(15.2)**	**73**	**(14.1)**
	Completed	17	(3.3)	24	(4.6)
	Compliance (% in those expected to complete questionnaires)	17	(21.5)	24	(32.9)

Treatment Visit	Category	Pembrolizumab + Chemotherapy N=520		Placebo + Chemotherapy N=517	
		n	(%)	n	(%)
WEEK 75	Not completed	62	(11.9)	49	(9.5)
	Subject did not complete due to disease under study	1	(0.2)	1	(0.2)
	Not completed due to site staff error	1	(0.2)	2	(0.4)
	Subject in hospital or hospice	0	(0.0)	0	(0.0)
	Subject was physically unable to complete	1	(0.2)	1	(0.2)
	Subject lost to follow-up/unable to contact	0	(0.0)	0	(0.0)
	Subject did not complete due to side effects of treatment	0	(0.0)	0	(0.0)
	Subject refused for other reasons	0	(0.0)	0	(0.0)
	Other	2	(0.4)	0	(0.0)
	With visit, no record	57	(11.0)	45	(8.7)
	Missing by Design	**441**	**(84.8)**	**444**	**(85.9)**
	Discontinued due to adverse event	59	(11.3)	50	(9.7)
	Discontinued due to clinical progression	34	(6.5)	36	(7.0)
	Discontinued due to non-study anti-cancer therapy	3	(0.6)	5	(1.0)
	Discontinued due to physician decision	26	(5.0)	13	(2.5)
	Discontinued due to progressive disease	288	(55.4)	314	(60.7)
	Discontinued due to withdrawal by subject	27	(5.2)	23	(4.4)
	Completed study treatment	0	(0.0)	0	(0.0)

Treatment Visit	Category	Pembrolizumab + Chemotherapy N=520		Placebo + Chemotherapy N=517	
		n	(%)	n	(%)
WEEK 75	Translation not available in subjects language	0	(0.0)	0	(0.0)
	Subject died	3	(0.6)	2	(0.4)
	Visit not reached	1	(0.2)	1	(0.2)
	Visit not scheduled	0	(0.0)	0	(0.0)
WEEK 87	**Expected to Complete Questionnaires**	**60**	**(11.5)**	**44**	**(8.5)**
	Completed	7	(1.3)	8	(1.5)
	Compliance (% in those expected to complete questionnaires)	7	(11.7)	8	(18.2)
	Not completed	53	(10.2)	36	(7.0)
	Subject did not complete due to disease under study	1	(0.2)	0	(0.0)
	Not completed due to site staff error	0	(0.0)	1	(0.2)
	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 effects of treatment	0	(0.0)	0	(0.0)
	Subject refused for other reasons	1	(0.2)	0	(0.0)
	Other	2	(0.4)	0	(0.0)
	With visit, no record	49	(9.4)	35	(6.8)
	Missing by Design	**460**	**(88.5)**	**473**	**(91.5)**

Treatment Visit	Category	Pembrolizumab + Chemotherapy N=520		Placebo + Chemotherapy N=517	
		n	(%)	n	(%)
WEEK 87	Discontinued due to adverse event	61	(11.7)	54	(10.4)
	Discontinued due to clinical progression	35	(6.7)	37	(7.2)
	Discontinued due to non-study anti-cancer therapy	3	(0.6)	5	(1.0)
	Discontinued due to physician decision	28	(5.4)	13	(2.5)
	Discontinued due to progressive disease	303	(58.3)	337	(65.2)
	Discontinued due to withdrawal by subject	27	(5.2)	24	(4.6)
	Completed study treatment	0	(0.0)	0	(0.0)
	Translation not available in subjects language	0	(0.0)	0	(0.0)
	Subject died	2	(0.4)	0	(0.0)
	Visit not reached	1	(0.2)	3	(0.6)
	Visit not scheduled	0	(0.0)	0	(0.0)
WEEK 99	**Expected to Complete Questionnaires**	**37**	**(7.1)**	**29**	**(5.6)**
	Completed	7	(1.3)	6	(1.2)
	Compliance (% in those expected to complete questionnaires)	7	(18.9)	6	(20.7)
	Not completed	30	(5.8)	23	(4.4)
	Subject did not complete due to disease under study	0	(0.0)	0	(0.0)
	Not completed due to site staff error	0	(0.0)	1	(0.2)
	Subject in hospital or hospice	0	(0.0)	0	(0.0)

Treatment Visit	Category	Pembrolizumab + Chemotherapy N=520		Placebo + Chemotherapy N=517	
		n	(%)	n	(%)
WEEK 99	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 effects of treatment	0	(0.0)	0	(0.0)
	Subject refused for other reasons	0	(0.0)	0	(0.0)
	Other	1	(0.2)	1	(0.2)
	With visit, no record	29	(5.6)	21	(4.1)
	Missing by Design	**483**	**(92.9)**	**488**	**(94.4)**
	Discontinued due to adverse event	64	(12.3)	56	(10.8)
	Discontinued due to clinical progression	35	(6.7)	38	(7.4)
	Discontinued due to non-study anti-cancer therapy	3	(0.6)	6	(1.2)
	Discontinued due to physician decision	28	(5.4)	14	(2.7)
	Discontinued due to progressive disease	312	(60.0)	340	(65.8)
	Discontinued due to withdrawal by subject	28	(5.4)	24	(4.6)
	Completed study treatment	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)
	Visit not reached	13	(2.5)	10	(1.9)
	Visit not scheduled	0	(0.0)	0	(0.0)

Treatment Visit	Category	Pembrolizumab + Chemotherapy N=520		Placebo + Chemotherapy N=517	
		n	(%)	n	(%)
WEEK 111	**Expected to Complete Questionnaires**	**26**	**(5.0)**	**16**	**(3.1)**
	Completed	9	(1.7)	11	(2.1)
	Compliance (% in those expected to complete questionnaires)	9	(34.6)	11	(68.8)
	Not completed	17	(3.3)	5	(1.0)
	Subject did not complete due to disease under study	0	(0.0)	0	(0.0)
	Not completed due to site staff error	2	(0.4)	0	(0.0)
	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	1	(0.2)	0	(0.0)
	Subject did not complete due to side effects of treatment	0	(0.0)	0	(0.0)
	Subject refused for other reasons	0	(0.0)	0	(0.0)
	Other	0	(0.0)	0	(0.0)
	With visit, no record	14	(2.7)	5	(1.0)
	Missing by Design	**494**	**(95.0)**	**501**	**(96.9)**
	Discontinued due to adverse event	65	(12.5)	57	(11.0)
	Discontinued due to clinical progression	35	(6.7)	39	(7.5)
	Discontinued due to non-study anti-cancer therapy	3	(0.6)	6	(1.2)
	Discontinued due to physician decision	28	(5.4)	14	(2.7)

Treatment Visit	Category	Pembrolizumab + Chemotherapy N=520		Placebo + Chemotherapy N=517	
		n	(%)	n	(%)
WEEK 111	Discontinued due to progressive disease	318	(61.2)	342	(66.2)
	Discontinued due to withdrawal by subject	28	(5.4)	24	(4.6)
	Completed study treatment	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)
	Visit not reached	17	(3.3)	19	(3.7)
	Visit not scheduled	0	(0.0)	0	(0.0)
WEEK 123	**Expected to Complete Questionnaires**	**8**	**(1.5)**	**3**	**(0.6)**
	Completed	3	(0.6)	1	(0.2)
	Compliance (% in those expected to complete questionnaires)	3	(37.5)	1	(33.3)
	Not completed	5	(1.0)	2	(0.4)
	Subject did not complete due to disease under study	0	(0.0)	0	(0.0)
	Not completed due to site staff error	0	(0.0)	0	(0.0)
	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 effects of treatment	0	(0.0)	0	(0.0)
	Subject refused for other reasons	0	(0.0)	0	(0.0)

Treatment Visit	Category	Pembrolizumab + Chemotherapy N=520		Placebo + Chemotherapy N=517	
		n	(%)	n	(%)
WEEK 123	Other	0	(0.0)	0	(0.0)
	With visit, no record	5	(1.0)	2	(0.4)
	Missing by Design	**512**	**(98.5)**	**514**	**(99.4)**
	Discontinued due to adverse event	65	(12.5)	57	(11.0)
	Discontinued due to clinical progression	35	(6.7)	39	(7.5)
	Discontinued due to non-study anti-cancer therapy	3	(0.6)	6	(1.2)
	Discontinued due to physician decision	29	(5.6)	16	(3.1)
	Discontinued due to progressive disease	319	(61.3)	345	(66.7)
	Discontinued due to withdrawal by subject	28	(5.4)	24	(4.6)
	Completed study treatment	10	(1.9)	6	(1.2)
	Translation not available in subjects language	0	(0.0)	0	(0.0)
	Subject died	0	(0.0)	0	(0.0)
	Visit not reached	23	(4.4)	21	(4.1)
	Visit not scheduled	0	(0.0)	0	(0.0)
WEEK 135	**Expected to Complete Questionnaires**	**3**	**(0.6)**	**1**	**(0.2)**
	Completed	1	(0.2)	0	(0.0)
	Compliance (% in those expected to complete questionnaires)	1	(33.3)	0	(0.0)
	Not completed	2	(0.4)	1	(0.2)

Treatment Visit	Category	Pembrolizumab + Chemotherapy N=520		Placebo + Chemotherapy N=517	
		n	(%)	n	(%)
WEEK 135	Subject did not complete due to disease under study	0	(0.0)	0	(0.0)
	Not completed due to site staff error	0	(0.0)	0	(0.0)
	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 effects of treatment	0	(0.0)	0	(0.0)
	Subject refused for other reasons	0	(0.0)	0	(0.0)
	Other	0	(0.0)	0	(0.0)
	With visit, no record	2	(0.4)	1	(0.2)
	Missing by Design	**517**	**(99.4)**	**516**	**(99.8)**
	Discontinued due to adverse event	65	(12.5)	57	(11.0)
	Discontinued due to clinical progression	35	(6.7)	39	(7.5)
	Discontinued due to non-study anti-cancer therapy	3	(0.6)	6	(1.2)
	Discontinued due to physician decision	29	(5.6)	16	(3.1)
	Discontinued due to progressive disease	319	(61.3)	346	(66.9)
	Discontinued due to withdrawal by subject	28	(5.4)	24	(4.6)
	Completed study treatment	13	(2.5)	6	(1.2)
	Translation not available in subjects language	0	(0.0)	0	(0.0)

Treatment Visit	Category	Pembrolizumab + Chemotherapy N=520		Placebo + Chemotherapy N=517	
		n	(%)	n	(%)
WEEK 135	Subject died	0	(0.0)	0	(0.0)
	Visit not reached	25	(4.8)	22	(4.3)
	Visit not scheduled	0	(0.0)	0	(0.0)
WEEK 147	**Expected to Complete Questionnaires**	**2**	**(0.4)**	**0**	**(0.0)**
	Completed	0	(0.0)	0	(0.0)
	Compliance (% in those expected to complete questionnaires)	0	(0.0)	0	(0.0)
	Not completed	2	(0.4)	0	(0.0)
	Subject did not complete due to disease under study	0	(0.0)	0	(0.0)
	Not completed due to site staff error	0	(0.0)	0	(0.0)
	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 effects of treatment	0	(0.0)	0	(0.0)
	Subject refused for other reasons	0	(0.0)	0	(0.0)
	Other	0	(0.0)	0	(0.0)
	With visit, no record	2	(0.4)	0	(0.0)
	Missing by Design	**518**	**(99.6)**	**517**	**(100.0)**
	Discontinued due to adverse event	65	(12.5)	57	(11.0)

Treatment Visit	Category	Pembrolizumab + Chemotherapy N=520		Placebo + Chemotherapy N=517	
		n	(%)	n	(%)
WEEK 147	Discontinued due to clinical progression	35	(6.7)	39	(7.5)
	Discontinued due to non-study anti-cancer therapy	3	(0.6)	6	(1.2)
	Discontinued due to physician decision	29	(5.6)	16	(3.1)
	Discontinued due to progressive disease	320	(61.5)	346	(66.9)
	Discontinued due to withdrawal by subject	28	(5.4)	24	(4.6)
	Completed study treatment	13	(2.5)	6	(1.2)
	Translation not available in subjects language	0	(0.0)	0	(0.0)
	Subject died	0	(0.0)	0	(0.0)
	Visit not reached	25	(4.8)	23	(4.4)
	Visit not scheduled	0	(0.0)	0	(0.0)
WEEK 159	**Expected to Complete Questionnaires**	**2**	**(0.4)**	**0**	**(0.0)**
	Completed	0	(0.0)	0	(0.0)
	Compliance (% in those expected to complete questionnaires)	0	(0.0)	0	(0.0)
	Not completed	2	(0.4)	0	(0.0)
	Subject did not complete due to disease under study	0	(0.0)	0	(0.0)
	Not completed due to site staff error	0	(0.0)	0	(0.0)
	Subject in hospital or hospice	0	(0.0)	0	(0.0)
	Subject was physically unable to complete	0	(0.0)	0	(0.0)

Treatment Visit	Category	Pembrolizumab + Chemotherapy N=520		Placebo + Chemotherapy N=517	
		n	(%)	n	(%)
WEEK 159	Subject lost to follow-up/unable to contact	0	(0.0)	0	(0.0)
	Subject did not complete due to side effects of treatment	0	(0.0)	0	(0.0)
	Subject refused for other reasons	0	(0.0)	0	(0.0)
	Other	0	(0.0)	0	(0.0)
	With visit, no record	2	(0.4)	0	(0.0)
	Missing by Design	**518**	**(99.6)**	**517**	**(100.0)**
	Discontinued due to adverse event	65	(12.5)	57	(11.0)
	Discontinued due to clinical progression	35	(6.7)	39	(7.5)
	Discontinued due to non-study anti-cancer therapy	3	(0.6)	6	(1.2)
	Discontinued due to physician decision	29	(5.6)	16	(3.1)
	Discontinued due to progressive disease	320	(61.5)	346	(66.9)
	Discontinued due to withdrawal by subject	28	(5.4)	24	(4.6)
	Completed study treatment	13	(2.5)	6	(1.2)
	Translation not available in subjects language	0	(0.0)	0	(0.0)
	Subject died	0	(0.0)	0	(0.0)
	Visit not reached	25	(4.8)	23	(4.4)

Treatment Visit	Category	Pembrolizumab + Chemotherapy N=520 n	(%)	Placebo + Chemotherapy N=517 n	(%)
WEEK 159	Visit not scheduled	0	(0.0)	0	(0.0)

Expected to complete questionnaire includes all patients who do not have missing data due to a missing by design reason.

Compliance is the proportion of patients who completed the PRO questionnaire among those who are **expected to complete the questionnaire** at this time point, excluding those missing by design. All the other categories are defined as the proportion of patients in the analysis population (N).

Missing by design includes: adverse event, death, discontinuation, translations not available, and no visit scheduled.

Database Cutoff Date: 15DEC2022

Anhang 4-G1.2: Rücklaufquoten des EORTC QLQ-BIL21

Tabelle 4G-2: Gründe für das Fehlen von Werten im EORTC QLQ-BIL21

Treatment Visit	Category	Pembrolizumab + Chemotherapy N=520		Placebo + Chemotherapy N=516	
		n	(%)	n	(%)
BASELINE	**Expected to Complete Questionnaires**	**520**	**(100.0)**	**514**	**(99.6)**
	Completed	482	(92.7)	490	(95.0)
	Compliance (% in those expected to complete questionnaires)	482	(92.7)	490	(95.3)
	Not completed	38	(7.3)	24	(4.7)
	Subject did not complete due to disease under study	1	(0.2)	1	(0.2)
	Not completed due to site staff error	15	(2.9)	7	(1.4)
	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 effects of treatment	0	(0.0)	0	(0.0)
	Subject refused for other reasons	3	(0.6)	1	(0.2)
	Other	11	(2.1)	11	(2.1)
	With visit, no record	8	(1.5)	4	(0.8)
	Missing by Design	**0**	**(0.0)**	**2**	**(0.4)**
	Discontinued due to adverse event	0	(0.0)	0	(0.0)
	Discontinued due to clinical progression	0	(0.0)	0	(0.0)
	Discontinued due to non-study anti-cancer therapy	0	(0.0)	0	(0.0)
	Discontinued due to physician decision	0	(0.0)	0	(0.0)

Treatment Visit	Category	Pembrolizumab + Chemotherapy N=520		Placebo + Chemotherapy N=516	
		n	(%)	n	(%)
BASELINE	Discontinued due to progressive disease	0	(0.0)	0	(0.0)
	Discontinued due to withdrawal by subject	0	(0.0)	0	(0.0)
	Completed study treatment	0	(0.0)	0	(0.0)
	Translation not available in subjects language	0	(0.0)	2	(0.4)
	Subject died	0	(0.0)	0	(0.0)
	Visit not reached	0	(0.0)	0	(0.0)
	Visit not scheduled	0	(0.0)	0	(0.0)
WEEK 3	**Expected to Complete Questionnaires**	**508**	**(97.7)**	**502**	**(97.3)**
	Completed	444	(85.4)	448	(86.8)
	Compliance (% in those expected to complete questionnaires)	444	(87.4)	448	(89.2)
	Not completed	64	(12.3)	54	(10.5)
	Subject did not complete due to disease under study	1	(0.2)	2	(0.4)
	Not completed due to site staff error	12	(2.3)	9	(1.7)
	Subject in hospital or hospice	2	(0.4)	1	(0.2)
	Subject was physically unable to complete	2	(0.4)	1	(0.2)
	Subject lost to follow-up/unable to contact	1	(0.2)	0	(0.0)
	Subject did not complete due to side effects of treatment	1	(0.2)	1	(0.2)
	Subject refused for other reasons	3	(0.6)	3	(0.6)

Treatment Visit	Category	Pembrolizumab + Chemotherapy N=520		Placebo + Chemotherapy N=516	
		n	(%)	n	(%)
WEEK 3	Other	16	(3.1)	15	(2.9)
	With visit, no record	26	(5.0)	22	(4.3)
	Missing by Design	**12**	**(2.3)**	**14**	**(2.7)**
	Discontinued due to adverse event	0	(0.0)	0	(0.0)
	Discontinued due to clinical progression	0	(0.0)	0	(0.0)
	Discontinued due to non-study anti-cancer therapy	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 withdrawal by subject	0	(0.0)	0	(0.0)
	Completed study treatment	0	(0.0)	0	(0.0)
	Translation not available in subjects language	1	(0.2)	1	(0.2)
	Subject died	4	(0.8)	9	(1.7)
	Visit not reached	0	(0.0)	0	(0.0)
	Visit not scheduled	7	(1.3)	4	(0.8)
WEEK 6	**Expected to Complete Questionnaires**	**478**	**(91.9)**	**477**	**(92.4)**
	Completed	415	(79.8)	428	(82.9)
	Compliance (% in those expected to complete questionnaires)	415	(86.8)	428	(89.7)
	Not completed	63	(12.1)	49	(9.5)

Treatment Visit	Category	Pembrolizumab + Chemotherapy N=520		Placebo + Chemotherapy N=516	
		n	(%)	n	(%)
WEEK 6	Subject did not complete due to disease under study	3	(0.6)	0	(0.0)
	Not completed due to site staff error	18	(3.5)	11	(2.1)
	Subject in hospital or hospice	3	(0.6)	0	(0.0)
	Subject was physically unable to complete	3	(0.6)	3	(0.6)
	Subject lost to follow-up/unable to contact	0	(0.0)	0	(0.0)
	Subject did not complete due to side effects of treatment	0	(0.0)	0	(0.0)
	Subject refused for other reasons	2	(0.4)	2	(0.4)
	Other	17	(3.3)	14	(2.7)
	With visit, no record	17	(3.3)	19	(3.7)
	Missing by Design	**42**	**(8.1)**	**39**	**(7.6)**
	Discontinued due to adverse event	7	(1.3)	8	(1.6)
	Discontinued due to clinical progression	2	(0.4)	5	(1.0)
	Discontinued due to non-study anti-cancer therapy	0	(0.0)	0	(0.0)
	Discontinued due to physician decision	1	(0.2)	0	(0.0)
	Discontinued due to progressive disease	7	(1.3)	5	(1.0)
	Discontinued due to withdrawal by subject	3	(0.6)	2	(0.4)
	Completed study treatment	0	(0.0)	0	(0.0)
	Translation not available in subjects language	0	(0.0)	1	(0.2)

Treatment Visit	Category	Pembrolizumab + Chemotherapy N=520		Placebo + Chemotherapy N=516	
		n	(%)	n	(%)
WEEK 6	Subject died	3	(0.6)	2	(0.4)
	Visit not reached	0	(0.0)	0	(0.0)
	Visit not scheduled	19	(3.7)	16	(3.1)
WEEK 9	**Expected to Complete Questionnaires**	**453**	**(87.1)**	**454**	**(88.0)**
	Completed	393	(75.6)	399	(77.3)
	Compliance (% in those expected to complete questionnaires)	393	(86.8)	399	(87.9)
	Not completed	60	(11.5)	55	(10.7)
	Subject did not complete due to disease under study	3	(0.6)	3	(0.6)
	Not completed due to site staff error	9	(1.7)	11	(2.1)
	Subject in hospital or hospice	3	(0.6)	0	(0.0)
	Subject was physically unable to complete	1	(0.2)	0	(0.0)
	Subject lost to follow-up/unable to contact	0	(0.0)	0	(0.0)
	Subject did not complete due to side effects of treatment	0	(0.0)	0	(0.0)
	Subject refused for other reasons	9	(1.7)	4	(0.8)
	Other	9	(1.7)	16	(3.1)
	With visit, no record	26	(5.0)	21	(4.1)
	Missing by Design	**67**	**(12.9)**	**62**	**(12.0)**
	Discontinued due to adverse event	11	(2.1)	14	(2.7)

Treatment Visit	Category	Pembrolizumab + Chemotherapy N=520		Placebo + Chemotherapy N=516	
		n	(%)	n	(%)
WEEK 9	Discontinued due to clinical progression	3	(0.6)	8	(1.6)
	Discontinued due to non-study anti-cancer therapy	0	(0.0)	0	(0.0)
	Discontinued due to physician decision	3	(0.6)	1	(0.2)
	Discontinued due to progressive disease	20	(3.8)	17	(3.3)
	Discontinued due to withdrawal by subject	5	(1.0)	8	(1.6)
	Completed study treatment	0	(0.0)	0	(0.0)
	Translation not available in subjects language	0	(0.0)	0	(0.0)
	Subject died	5	(1.0)	2	(0.4)
	Visit not reached	0	(0.0)	0	(0.0)
	Visit not scheduled	20	(3.8)	12	(2.3)
WEEK 12	**Expected to Complete Questionnaires**	**417**	**(80.2)**	**422**	**(81.8)**
	Completed	367	(70.6)	367	(71.1)
	Compliance (% in those expected to complete questionnaires)	367	(88.0)	367	(87.0)
	Not completed	50	(9.6)	55	(10.7)
	Subject did not complete due to disease under study	0	(0.0)	1	(0.2)
	Not completed due to site staff error	12	(2.3)	12	(2.3)
	Subject in hospital or hospice	0	(0.0)	1	(0.2)
	Subject was physically unable to complete	2	(0.4)	1	(0.2)

Treatment Visit	Category	Pembrolizumab + Chemotherapy N=520		Placebo + Chemotherapy N=516	
		n	(%)	n	(%)
WEEK 12	Subject lost to follow-up/unable to contact	0	(0.0)	0	(0.0)
	Subject did not complete due to side effects of treatment	0	(0.0)	1	(0.2)
	Subject refused for other reasons	2	(0.4)	3	(0.6)
	Other	13	(2.5)	5	(1.0)
	With visit, no record	21	(4.0)	31	(6.0)
	Missing by Design	**103**	**(19.8)**	**94**	**(18.2)**
	Discontinued due to adverse event	18	(3.5)	19	(3.7)
	Discontinued due to clinical progression	7	(1.3)	12	(2.3)
	Discontinued due to non-study anti-cancer therapy	1	(0.2)	0	(0.0)
	Discontinued due to physician decision	4	(0.8)	1	(0.2)
	Discontinued due to progressive disease	46	(8.8)	36	(7.0)
	Discontinued due to withdrawal by subject	7	(1.3)	10	(1.9)
	Completed study treatment	0	(0.0)	0	(0.0)
	Translation not available in subjects language	0	(0.0)	1	(0.2)
	Subject died	0	(0.0)	3	(0.6)
	Visit not reached	0	(0.0)	0	(0.0)
	Visit not scheduled	20	(3.8)	12	(2.3)
WEEK 15	**Expected to Complete Questionnaires**	**373**	**(71.7)**	**366**	**(70.9)**

Treatment Visit	Category	Pembrolizumab + Chemotherapy N=520		Placebo + Chemotherapy N=516	
		n	(%)	n	(%)
WEEK 15	Completed	337	(64.8)	339	(65.7)
	Compliance (% in those expected to complete questionnaires)	337	(90.3)	339	(92.6)
	Not completed	36	(6.9)	27	(5.2)
	Subject did not complete due to disease under study	3	(0.6)	2	(0.4)
	Not completed due to site staff error	10	(1.9)	7	(1.4)
	Subject in hospital or hospice	1	(0.2)	2	(0.4)
	Subject was physically unable to complete	1	(0.2)	0	(0.0)
	Subject lost to follow-up/unable to contact	0	(0.0)	0	(0.0)
	Subject did not complete due to side effects of treatment	0	(0.0)	2	(0.4)
	Subject refused for other reasons	3	(0.6)	1	(0.2)
	Other	7	(1.3)	8	(1.6)
	With visit, no record	11	(2.1)	5	(1.0)
	Missing by Design	**147**	**(28.3)**	**150**	**(29.1)**
	Discontinued due to adverse event	20	(3.8)	21	(4.1)
	Discontinued due to clinical progression	8	(1.5)	15	(2.9)
	Discontinued due to non-study anti-cancer therapy	1	(0.2)	0	(0.0)
	Discontinued due to physician decision	6	(1.2)	1	(0.2)
	Discontinued due to progressive disease	61	(11.7)	64	(12.4)

Treatment Visit	Category	Pembrolizumab + Chemotherapy N=520		Placebo + Chemotherapy N=516	
		n	(%)	n	(%)
WEEK 15	Discontinued due to withdrawal by subject	8	(1.5)	13	(2.5)
	Completed study treatment	0	(0.0)	0	(0.0)
	Translation not available in subjects language	0	(0.0)	1	(0.2)
	Subject died	3	(0.6)	4	(0.8)
	Visit not reached	0	(0.0)	0	(0.0)
	Visit not scheduled	40	(7.7)	31	(6.0)
WEEK 18	**Expected to Complete Questionnaires**	**343**	**(66.0)**	**329**	**(63.8)**
	Completed	320	(61.5)	315	(61.0)
	Compliance (% in those expected to complete questionnaires)	320	(93.3)	315	(95.7)
	Not completed	23	(4.4)	14	(2.7)
	Subject did not complete due to disease under study	1	(0.2)	1	(0.2)
	Not completed due to site staff error	6	(1.2)	3	(0.6)
	Subject in hospital or hospice	0	(0.0)	2	(0.4)
	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 effects of treatment	0	(0.0)	0	(0.0)
	Subject refused for other reasons	3	(0.6)	3	(0.6)
	Other	8	(1.5)	3	(0.6)

Treatment Visit	Category	Pembrolizumab + Chemotherapy N=520		Placebo + Chemotherapy N=516	
		n	(%)	n	(%)
WEEK 18	With visit, no record	5	(1.0)	2	(0.4)
	Missing by Design	**177**	**(34.0)**	**187**	**(36.2)**
	Discontinued due to adverse event	25	(4.8)	25	(4.8)
	Discontinued due to clinical progression	11	(2.1)	17	(3.3)
	Discontinued due to non-study anti-cancer therapy	1	(0.2)	0	(0.0)
	Discontinued due to physician decision	7	(1.3)	2	(0.4)
	Discontinued due to progressive disease	82	(15.8)	85	(16.5)
	Discontinued due to withdrawal by subject	11	(2.1)	15	(2.9)
	Completed study treatment	0	(0.0)	0	(0.0)
	Translation not available in subjects language	0	(0.0)	1	(0.2)
	Subject died	2	(0.4)	3	(0.6)
	Visit not reached	0	(0.0)	0	(0.0)
	Visit not scheduled	38	(7.3)	39	(7.6)
WEEK 21	**Expected to Complete Questionnaires**	**330**	**(63.5)**	**307**	**(59.5)**
	Completed	301	(57.9)	282	(54.7)
	Compliance (% in those expected to complete questionnaires)	301	(91.2)	282	(91.9)
	Not completed	29	(5.6)	25	(4.8)
	Subject did not complete due to disease under study	1	(0.2)	2	(0.4)

Treatment Visit	Category	Pembrolizumab + Chemotherapy N=520		Placebo + Chemotherapy N=516	
		n	(%)	n	(%)
WEEK 21	Not completed due to site staff error	7	(1.3)	7	(1.4)
	Subject in hospital or hospice	0	(0.0)	1	(0.2)
	Subject was physically unable to complete	2	(0.4)	0	(0.0)
	Subject lost to follow-up/unable to contact	0	(0.0)	0	(0.0)
	Subject did not complete due to side effects of treatment	0	(0.0)	0	(0.0)
	Subject refused for other reasons	2	(0.4)	2	(0.4)
	Other	11	(2.1)	11	(2.1)
	With visit, no record	6	(1.2)	2	(0.4)
	Missing by Design	**190**	**(36.5)**	**209**	**(40.5)**
	Discontinued due to adverse event	27	(5.2)	27	(5.2)
	Discontinued due to clinical progression	15	(2.9)	19	(3.7)
	Discontinued due to non-study anti-cancer therapy	1	(0.2)	0	(0.0)
	Discontinued due to physician decision	8	(1.5)	3	(0.6)
	Discontinued due to progressive disease	94	(18.1)	104	(20.2)
	Discontinued due to withdrawal by subject	13	(2.5)	16	(3.1)
	Completed study treatment	0	(0.0)	0	(0.0)
	Translation not available in subjects language	0	(0.0)	1	(0.2)
	Subject died	0	(0.0)	3	(0.6)

Treatment Visit	Category	Pembrolizumab + Chemotherapy N=520		Placebo + Chemotherapy N=516	
		n	(%)	n	(%)
WEEK 21	Visit not reached	0	(0.0)	0	(0.0)
	Visit not scheduled	32	(6.2)	36	(7.0)
WEEK 24	**Expected to Complete Questionnaires**	**304**	**(58.5)**	**281**	**(54.5)**
	Completed	283	(54.4)	263	(51.0)
	Compliance (% in those expected to complete questionnaires)	283	(93.1)	263	(93.6)
	Not completed	21	(4.0)	18	(3.5)
	Subject did not complete due to disease under study	1	(0.2)	2	(0.4)
	Not completed due to site staff error	12	(2.3)	5	(1.0)
	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 effects of treatment	0	(0.0)	0	(0.0)
	Subject refused for other reasons	1	(0.2)	2	(0.4)
	Other	5	(1.0)	7	(1.4)
	With visit, no record	2	(0.4)	2	(0.4)
	Missing by Design	**216**	**(41.5)**	**235**	**(45.5)**
	Discontinued due to adverse event	31	(6.0)	35	(6.8)
	Discontinued due to clinical progression	15	(2.9)	21	(4.1)

Treatment Visit	Category	Pembrolizumab + Chemotherapy N=520		Placebo + Chemotherapy N=516	
		n	(%)	n	(%)
WEEK 24	Discontinued due to non-study anti-cancer therapy	1	(0.2)	1	(0.2)
	Discontinued due to physician decision	8	(1.5)	4	(0.8)
	Discontinued due to progressive disease	113	(21.7)	115	(22.3)
	Discontinued due to withdrawal by subject	15	(2.9)	18	(3.5)
	Completed study treatment	0	(0.0)	0	(0.0)
	Translation not available in subjects language	0	(0.0)	0	(0.0)
	Subject died	1	(0.2)	5	(1.0)
	Visit not reached	0	(0.0)	0	(0.0)
	Visit not scheduled	32	(6.2)	36	(7.0)
WEEK 27	**Expected to Complete Questionnaires**	**294**	**(56.5)**	**274**	**(53.1)**
	Completed	277	(53.3)	256	(49.6)
	Compliance (% in those expected to complete questionnaires)	277	(94.2)	256	(93.4)
	Not completed	17	(3.3)	18	(3.5)
	Subject did not complete due to disease under study	1	(0.2)	2	(0.4)
	Not completed due to site staff error	5	(1.0)	4	(0.8)
	Subject in hospital or hospice	0	(0.0)	1	(0.2)
	Subject was physically unable to complete	0	(0.0)	3	(0.6)
	Subject lost to follow-up/unable to contact	0	(0.0)	0	(0.0)

Treatment Visit	Category	Pembrolizumab + Chemotherapy N=520		Placebo + Chemotherapy N=516	
		n	(%)	n	(%)
WEEK 27	Subject did not complete due to side effects of treatment	0	(0.0)	0	(0.0)
	Subject refused for other reasons	1	(0.2)	3	(0.6)
	Other	7	(1.3)	4	(0.8)
	With visit, no record	3	(0.6)	1	(0.2)
	Missing by Design	**226**	**(43.5)**	**242**	**(46.9)**
	Discontinued due to adverse event	36	(6.9)	36	(7.0)
	Discontinued due to clinical progression	18	(3.5)	22	(4.3)
	Discontinued due to non-study anti-cancer therapy	1	(0.2)	1	(0.2)
	Discontinued due to physician decision	10	(1.9)	4	(0.8)
	Discontinued due to progressive disease	127	(24.4)	143	(27.7)
	Discontinued due to withdrawal by subject	16	(3.1)	20	(3.9)
	Completed study treatment	0	(0.0)	0	(0.0)
	Translation not available in subjects language	0	(0.0)	1	(0.2)
	Subject died	4	(0.8)	1	(0.2)
	Visit not reached	0	(0.0)	0	(0.0)
	Visit not scheduled	14	(2.7)	14	(2.7)
WEEK 33	**Expected to Complete Questionnaires**	**271**	**(52.1)**	**237**	**(45.9)**
	Completed	235	(45.2)	203	(39.3)

Treatment Visit	Category	Pembrolizumab + Chemotherapy N=520		Placebo + Chemotherapy N=516	
		n	(%)	n	(%)
WEEK 33	Compliance (% in those expected to complete questionnaires)	235	(86.7)	203	(85.7)
	Not completed	36	(6.9)	34	(6.6)
	Subject did not complete due to disease under study	2	(0.4)	1	(0.2)
	Not completed due to site staff error	5	(1.0)	2	(0.4)
	Subject in hospital or hospice	1	(0.2)	0	(0.0)
	Subject was physically unable to complete	1	(0.2)	0	(0.0)
	Subject lost to follow-up/unable to contact	0	(0.0)	0	(0.0)
	Subject did not complete due to side effects of treatment	0	(0.0)	0	(0.0)
	Subject refused for other reasons	1	(0.2)	3	(0.6)
	Other	4	(0.8)	7	(1.4)
	With visit, no record	22	(4.2)	21	(4.1)
	Missing by Design	**249**	**(47.9)**	**279**	**(54.1)**
	Discontinued due to adverse event	40	(7.7)	38	(7.4)
	Discontinued due to clinical progression	22	(4.2)	24	(4.7)
	Discontinued due to non-study anti-cancer therapy	1	(0.2)	2	(0.4)
	Discontinued due to physician decision	12	(2.3)	6	(1.2)
	Discontinued due to progressive disease	149	(28.7)	177	(34.3)
	Discontinued due to withdrawal by subject	16	(3.1)	20	(3.9)

Treatment Visit	Category	Pembrolizumab + Chemotherapy N=520		Placebo + Chemotherapy N=516	
		n	(%)	n	(%)
WEEK 33	Completed study treatment	0	(0.0)	0	(0.0)
	Translation not available in subjects language	0	(0.0)	1	(0.2)
	Subject died	2	(0.4)	4	(0.8)
	Visit not reached	0	(0.0)	0	(0.0)
	Visit not scheduled	7	(1.3)	7	(1.4)
WEEK 39	**Expected to Complete Questionnaires**	**225**	**(43.3)**	**195**	**(37.8)**
	Completed	192	(36.9)	167	(32.4)
	Compliance (% in those expected to complete questionnaires)	192	(85.3)	167	(85.6)
	Not completed	33	(6.3)	28	(5.4)
	Subject did not complete due to disease under study	1	(0.2)	0	(0.0)
	Not completed due to site staff error	6	(1.2)	10	(1.9)
	Subject in hospital or hospice	1	(0.2)	1	(0.2)
	Subject was physically unable to complete	1	(0.2)	0	(0.0)
	Subject lost to follow-up/unable to contact	0	(0.0)	0	(0.0)
	Subject did not complete due to side effects of treatment	1	(0.2)	0	(0.0)
	Subject refused for other reasons	3	(0.6)	2	(0.4)
	Other	2	(0.4)	6	(1.2)
	With visit, no record	18	(3.5)	9	(1.7)

Treatment Visit	Category	Pembrolizumab + Chemotherapy N=520		Placebo + Chemotherapy N=516	
		n	(%)	n	(%)
WEEK 39	**Missing by Design**	**295**	**(56.7)**	**321**	**(62.2)**
	Discontinued due to adverse event	43	(8.3)	40	(7.8)
	Discontinued due to clinical progression	24	(4.6)	30	(5.8)
	Discontinued due to non-study anti-cancer therapy	1	(0.2)	2	(0.4)
	Discontinued due to physician decision	18	(3.5)	10	(1.9)
	Discontinued due to progressive disease	179	(34.4)	207	(40.1)
	Discontinued due to withdrawal by subject	19	(3.7)	22	(4.3)
	Completed study treatment	0	(0.0)	0	(0.0)
	Translation not available in subjects language	0	(0.0)	1	(0.2)
	Subject died	2	(0.4)	3	(0.6)
	Visit not reached	0	(0.0)	0	(0.0)
	Visit not scheduled	9	(1.7)	6	(1.2)
WEEK 45	**Expected to Complete Questionnaires**	**187**	**(36.0)**	**152**	**(29.5)**
	Completed	160	(30.8)	135	(26.2)
	Compliance (% in those expected to complete questionnaires)	160	(85.6)	135	(88.8)
	Not completed	27	(5.2)	17	(3.3)
	Subject did not complete due to disease under study	2	(0.4)	1	(0.2)
	Not completed due to site staff error	5	(1.0)	4	(0.8)

Treatment Visit	Category	Pembrolizumab + Chemotherapy N=520		Placebo + Chemotherapy N=516	
		n	(%)	n	(%)
WEEK 45	Subject in hospital or hospice	0	(0.0)	1	(0.2)
	Subject was physically unable to complete	0	(0.0)	1	(0.2)
	Subject lost to follow-up/unable to contact	0	(0.0)	0	(0.0)
	Subject did not complete due to side effects of treatment	0	(0.0)	0	(0.0)
	Subject refused for other reasons	1	(0.2)	2	(0.4)
	Other	5	(1.0)	1	(0.2)
	With visit, no record	14	(2.7)	7	(1.4)
	Missing by Design	**333**	**(64.0)**	**364**	**(70.5)**
	Discontinued due to adverse event	50	(9.6)	43	(8.3)
	Discontinued due to clinical progression	27	(5.2)	31	(6.0)
	Discontinued due to non-study anti-cancer therapy	1	(0.2)	3	(0.6)
	Discontinued due to physician decision	20	(3.8)	12	(2.3)
	Discontinued due to progressive disease	210	(40.4)	243	(47.1)
	Discontinued due to withdrawal by subject	20	(3.8)	22	(4.3)
	Completed study treatment	0	(0.0)	0	(0.0)
	Translation not available in subjects language	0	(0.0)	1	(0.2)
	Subject died	1	(0.2)	2	(0.4)
	Visit not reached	0	(0.0)	0	(0.0)

Treatment Visit	Category	Pembrolizumab + Chemotherapy N=520		Placebo + Chemotherapy N=516	
		n	(%)	n	(%)
WEEK 45	Visit not scheduled	4	(0.8)	7	(1.4)
WEEK 51	**Expected to Complete Questionnaires**	**154**	**(29.6)**	**122**	**(23.6)**
	Completed	135	(26.0)	109	(21.1)
	Compliance (% in those expected to complete questionnaires)	135	(87.7)	109	(89.3)
	Not completed	19	(3.7)	13	(2.5)
	Subject did not complete due to disease under study	0	(0.0)	0	(0.0)
	Not completed due to site staff error	5	(1.0)	3	(0.6)
	Subject in hospital or hospice	0	(0.0)	1	(0.2)
	Subject was physically unable to complete	0	(0.0)	0	(0.0)
	Subject lost to follow-up/unable to contact	1	(0.2)	0	(0.0)
	Subject did not complete due to side effects of treatment	0	(0.0)	0	(0.0)
	Subject refused for other reasons	2	(0.4)	2	(0.4)
	Other	7	(1.3)	5	(1.0)
	With visit, no record	4	(0.8)	2	(0.4)
	Missing by Design	**366**	**(70.4)**	**394**	**(76.4)**
	Discontinued due to adverse event	51	(9.8)	45	(8.7)
	Discontinued due to clinical progression	31	(6.0)	32	(6.2)
	Discontinued due to non-study anti-cancer therapy	1	(0.2)	3	(0.6)

Treatment Visit	Category	Pembrolizumab + Chemotherapy N=520		Placebo + Chemotherapy N=516	
		n	(%)	n	(%)
WEEK 51	Discontinued due to physician decision	23	(4.4)	13	(2.5)
	Discontinued due to progressive disease	236	(45.4)	274	(53.1)
	Discontinued due to withdrawal by subject	23	(4.4)	23	(4.5)
	Completed study treatment	0	(0.0)	0	(0.0)
	Translation not available in subjects language	0	(0.0)	1	(0.2)
	Subject died	1	(0.2)	1	(0.2)
	Visit not reached	0	(0.0)	0	(0.0)
	Visit not scheduled	0	(0.0)	2	(0.4)
WEEK 63	**Expected to Complete Questionnaires**	**109**	**(21.0)**	**101**	**(19.6)**
	Completed	45	(8.7)	43	(8.3)
	Compliance (% in those expected to complete questionnaires)	45	(41.3)	43	(42.6)
	Not completed	64	(12.3)	58	(11.2)
	Subject did not complete due to disease under study	0	(0.0)	0	(0.0)
	Not completed due to site staff error	4	(0.8)	2	(0.4)
	Subject in hospital or hospice	1	(0.2)	1	(0.2)
	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 effects of treatment	0	(0.0)	0	(0.0)

Treatment Visit	Category	Pembrolizumab + Chemotherapy N=520		Placebo + Chemotherapy N=516	
		n	(%)	n	(%)
WEEK 63	Subject refused for other reasons	2	(0.4)	0	(0.0)
	Other	3	(0.6)	2	(0.4)
	With visit, no record	54	(10.4)	53	(10.3)
	Missing by Design	**411**	**(79.0)**	**415**	**(80.4)**
	Discontinued due to adverse event	54	(10.4)	48	(9.3)
	Discontinued due to clinical progression	33	(6.3)	32	(6.2)
	Discontinued due to non-study anti-cancer therapy	2	(0.4)	4	(0.8)
	Discontinued due to physician decision	25	(4.8)	13	(2.5)
	Discontinued due to progressive disease	266	(51.2)	291	(56.4)
	Discontinued due to withdrawal by subject	27	(5.2)	23	(4.5)
	Completed study treatment	0	(0.0)	0	(0.0)
	Translation not available in subjects language	0	(0.0)	1	(0.2)
	Subject died	3	(0.6)	2	(0.4)
	Visit not reached	0	(0.0)	0	(0.0)
	Visit not scheduled	1	(0.2)	1	(0.2)
WEEK 75	**Expected to Complete Questionnaires**	**79**	**(15.2)**	**73**	**(14.1)**
	Completed	17	(3.3)	24	(4.7)
	Compliance (% in those expected to complete questionnaires)	17	(21.5)	24	(32.9)

Treatment Visit	Category	Pembrolizumab + Chemotherapy N=520		Placebo + Chemotherapy N=516	
		n	(%)	n	(%)
WEEK 75	Not completed	62	(11.9)	49	(9.5)
	Subject did not complete due to disease under study	1	(0.2)	1	(0.2)
	Not completed due to site staff error	1	(0.2)	2	(0.4)
	Subject in hospital or hospice	0	(0.0)	0	(0.0)
	Subject was physically unable to complete	1	(0.2)	1	(0.2)
	Subject lost to follow-up/unable to contact	0	(0.0)	0	(0.0)
	Subject did not complete due to side effects of treatment	0	(0.0)	0	(0.0)
	Subject refused for other reasons	0	(0.0)	0	(0.0)
	Other	2	(0.4)	0	(0.0)
	With visit, no record	57	(11.0)	45	(8.7)
	Missing by Design	**441**	**(84.8)**	**443**	**(85.9)**
	Discontinued due to adverse event	59	(11.3)	49	(9.5)
	Discontinued due to clinical progression	34	(6.5)	36	(7.0)
	Discontinued due to non-study anti-cancer therapy	3	(0.6)	5	(1.0)
	Discontinued due to physician decision	26	(5.0)	13	(2.5)
	Discontinued due to progressive disease	288	(55.4)	314	(60.9)
	Discontinued due to withdrawal by subject	27	(5.2)	23	(4.5)
	Completed study treatment	0	(0.0)	0	(0.0)

Treatment Visit	Category	Pembrolizumab + Chemotherapy N=520		Placebo + Chemotherapy N=516	
		n	(%)	n	(%)
WEEK 75	Translation not available in subjects language	0	(0.0)	0	(0.0)
	Subject died	3	(0.6)	2	(0.4)
	Visit not reached	1	(0.2)	1	(0.2)
	Visit not scheduled	0	(0.0)	0	(0.0)
WEEK 87	**Expected to Complete Questionnaires**	**60**	**(11.5)**	**44**	**(8.5)**
	Completed	7	(1.3)	8	(1.6)
	Compliance (% in those expected to complete questionnaires)	7	(11.7)	8	(18.2)
	Not completed	53	(10.2)	36	(7.0)
	Subject did not complete due to disease under study	1	(0.2)	0	(0.0)
	Not completed due to site staff error	0	(0.0)	1	(0.2)
	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 effects of treatment	0	(0.0)	0	(0.0)
	Subject refused for other reasons	1	(0.2)	0	(0.0)
	Other	2	(0.4)	0	(0.0)
	With visit, no record	49	(9.4)	35	(6.8)
	Missing by Design	**460**	**(88.5)**	**472**	**(91.5)**

Treatment Visit	Category	Pembrolizumab + Chemotherapy N=520		Placebo + Chemotherapy N=516	
		n	(%)	n	(%)
WEEK 87	Discontinued due to adverse event	61	(11.7)	53	(10.3)
	Discontinued due to clinical progression	35	(6.7)	37	(7.2)
	Discontinued due to non-study anti-cancer therapy	3	(0.6)	5	(1.0)
	Discontinued due to physician decision	28	(5.4)	13	(2.5)
	Discontinued due to progressive disease	303	(58.3)	337	(65.3)
	Discontinued due to withdrawal by subject	27	(5.2)	24	(4.7)
	Completed study treatment	0	(0.0)	0	(0.0)
	Translation not available in subjects language	0	(0.0)	0	(0.0)
	Subject died	2	(0.4)	0	(0.0)
	Visit not reached	1	(0.2)	3	(0.6)
	Visit not scheduled	0	(0.0)	0	(0.0)
WEEK 99	**Expected to Complete Questionnaires**	**37**	**(7.1)**	**29**	**(5.6)**
	Completed	7	(1.3)	6	(1.2)
	Compliance (% in those expected to complete questionnaires)	7	(18.9)	6	(20.7)
	Not completed	30	(5.8)	23	(4.5)
	Subject did not complete due to disease under study	0	(0.0)	0	(0.0)
	Not completed due to site staff error	0	(0.0)	1	(0.2)
	Subject in hospital or hospice	0	(0.0)	0	(0.0)

Treatment Visit	Category	Pembrolizumab + Chemotherapy N=520		Placebo + Chemotherapy N=516	
		n	(%)	n	(%)
WEEK 99	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 effects of treatment	0	(0.0)	0	(0.0)
	Subject refused for other reasons	0	(0.0)	0	(0.0)
	Other	1	(0.2)	1	(0.2)
	With visit, no record	29	(5.6)	21	(4.1)
	Missing by Design	**483**	**(92.9)**	**487**	**(94.4)**
	Discontinued due to adverse event	64	(12.3)	55	(10.7)
	Discontinued due to clinical progression	35	(6.7)	38	(7.4)
	Discontinued due to non-study anti-cancer therapy	3	(0.6)	6	(1.2)
	Discontinued due to physician decision	28	(5.4)	14	(2.7)
	Discontinued due to progressive disease	312	(60.0)	340	(65.9)
	Discontinued due to withdrawal by subject	28	(5.4)	24	(4.7)
	Completed study treatment	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)
	Visit not reached	13	(2.5)	10	(1.9)
	Visit not scheduled	0	(0.0)	0	(0.0)

Treatment Visit	Category	Pembrolizumab + Chemotherapy N=520		Placebo + Chemotherapy N=516	
		n	(%)	n	(%)
WEEK 111	**Expected to Complete Questionnaires**	**26**	**(5.0)**	**16**	**(3.1)**
	Completed	9	(1.7)	11	(2.1)
	Compliance (% in those expected to complete questionnaires)	9	(34.6)	11	(68.8)
	Not completed	17	(3.3)	5	(1.0)
	Subject did not complete due to disease under study	0	(0.0)	0	(0.0)
	Not completed due to site staff error	2	(0.4)	0	(0.0)
	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	1	(0.2)	0	(0.0)
	Subject did not complete due to side effects of treatment	0	(0.0)	0	(0.0)
	Subject refused for other reasons	0	(0.0)	0	(0.0)
	Other	0	(0.0)	0	(0.0)
	With visit, no record	14	(2.7)	5	(1.0)
	Missing by Design	**494**	**(95.0)**	**500**	**(96.9)**
	Discontinued due to adverse event	65	(12.5)	56	(10.9)
	Discontinued due to clinical progression	35	(6.7)	39	(7.6)
	Discontinued due to non-study anti-cancer therapy	3	(0.6)	6	(1.2)
	Discontinued due to physician decision	28	(5.4)	14	(2.7)

Treatment Visit	Category	Pembrolizumab + Chemotherapy N=520		Placebo + Chemotherapy N=516	
		n	(%)	n	(%)
WEEK 111	Discontinued due to progressive disease	318	(61.2)	342	(66.3)
	Discontinued due to withdrawal by subject	28	(5.4)	24	(4.7)
	Completed study treatment	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)
	Visit not reached	17	(3.3)	19	(3.7)
	Visit not scheduled	0	(0.0)	0	(0.0)
WEEK 123	**Expected to Complete Questionnaires**	**8**	**(1.5)**	**3**	**(0.6)**
	Completed	3	(0.6)	1	(0.2)
	Compliance (% in those expected to complete questionnaires)	3	(37.5)	1	(33.3)
	Not completed	5	(1.0)	2	(0.4)
	Subject did not complete due to disease under study	0	(0.0)	0	(0.0)
	Not completed due to site staff error	0	(0.0)	0	(0.0)
	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 effects of treatment	0	(0.0)	0	(0.0)
	Subject refused for other reasons	0	(0.0)	0	(0.0)

Treatment Visit	Category	Pembrolizumab + Chemotherapy N=520		Placebo + Chemotherapy N=516	
		n	(%)	n	(%)
WEEK 123	Other	0	(0.0)	0	(0.0)
	With visit, no record	5	(1.0)	2	(0.4)
	Missing by Design	**512**	**(98.5)**	**513**	**(99.4)**
	Discontinued due to adverse event	65	(12.5)	56	(10.9)
	Discontinued due to clinical progression	35	(6.7)	39	(7.6)
	Discontinued due to non-study anti-cancer therapy	3	(0.6)	6	(1.2)
	Discontinued due to physician decision	29	(5.6)	16	(3.1)
	Discontinued due to progressive disease	319	(61.3)	345	(66.9)
	Discontinued due to withdrawal by subject	28	(5.4)	24	(4.7)
	Completed study treatment	10	(1.9)	6	(1.2)
	Translation not available in subjects language	0	(0.0)	0	(0.0)
	Subject died	0	(0.0)	0	(0.0)
	Visit not reached	23	(4.4)	21	(4.1)
	Visit not scheduled	0	(0.0)	0	(0.0)
WEEK 135	**Expected to Complete Questionnaires**	**3**	**(0.6)**	**1**	**(0.2)**
	Completed	1	(0.2)	0	(0.0)
	Compliance (% in those expected to complete questionnaires)	1	(33.3)	0	(0.0)
	Not completed	2	(0.4)	1	(0.2)

Treatment Visit	Category	Pembrolizumab + Chemotherapy N=520		Placebo + Chemotherapy N=516	
		n	(%)	n	(%)
WEEK 135	Subject did not complete due to disease under study	0	(0.0)	0	(0.0)
	Not completed due to site staff error	0	(0.0)	0	(0.0)
	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 effects of treatment	0	(0.0)	0	(0.0)
	Subject refused for other reasons	0	(0.0)	0	(0.0)
	Other	0	(0.0)	0	(0.0)
	With visit, no record	2	(0.4)	1	(0.2)
	Missing by Design	**517**	**(99.4)**	**515**	**(99.8)**
	Discontinued due to adverse event	65	(12.5)	56	(10.9)
	Discontinued due to clinical progression	35	(6.7)	39	(7.6)
	Discontinued due to non-study anti-cancer therapy	3	(0.6)	6	(1.2)
	Discontinued due to physician decision	29	(5.6)	16	(3.1)
	Discontinued due to progressive disease	319	(61.3)	346	(67.1)
	Discontinued due to withdrawal by subject	28	(5.4)	24	(4.7)
	Completed study treatment	13	(2.5)	6	(1.2)
	Translation not available in subjects language	0	(0.0)	0	(0.0)

Treatment Visit	Category	Pembrolizumab + Chemotherapy N=520		Placebo + Chemotherapy N=516	
		n	(%)	n	(%)
WEEK 135	Subject died	0	(0.0)	0	(0.0)
	Visit not reached	25	(4.8)	22	(4.3)
	Visit not scheduled	0	(0.0)	0	(0.0)
WEEK 147	**Expected to Complete Questionnaires**	**2**	**(0.4)**	**0**	**(0.0)**
	Completed	0	(0.0)	0	(0.0)
	Compliance (% in those expected to complete questionnaires)	0	(0.0)	0	(0.0)
	Not completed	2	(0.4)	0	(0.0)
	Subject did not complete due to disease under study	0	(0.0)	0	(0.0)
	Not completed due to site staff error	0	(0.0)	0	(0.0)
	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 effects of treatment	0	(0.0)	0	(0.0)
	Subject refused for other reasons	0	(0.0)	0	(0.0)
	Other	0	(0.0)	0	(0.0)
	With visit, no record	2	(0.4)	0	(0.0)
	Missing by Design	**518**	**(99.6)**	**516**	**(100.0)**
	Discontinued due to adverse event	65	(12.5)	56	(10.9)

Treatment Visit	Category	Pembrolizumab + Chemotherapy N=520		Placebo + Chemotherapy N=516	
		n	(%)	n	(%)
WEEK 147	Discontinued due to clinical progression	35	(6.7)	39	(7.6)
	Discontinued due to non-study anti-cancer therapy	3	(0.6)	6	(1.2)
	Discontinued due to physician decision	29	(5.6)	16	(3.1)
	Discontinued due to progressive disease	320	(61.5)	346	(67.1)
	Discontinued due to withdrawal by subject	28	(5.4)	24	(4.7)
	Completed study treatment	13	(2.5)	6	(1.2)
	Translation not available in subjects language	0	(0.0)	0	(0.0)
	Subject died	0	(0.0)	0	(0.0)
	Visit not reached	25	(4.8)	23	(4.5)
	Visit not scheduled	0	(0.0)	0	(0.0)
WEEK 159	**Expected to Complete Questionnaires**	**2**	**(0.4)**	**0**	**(0.0)**
	Completed	0	(0.0)	0	(0.0)
	Compliance (% in those expected to complete questionnaires)	0	(0.0)	0	(0.0)
	Not completed	2	(0.4)	0	(0.0)
	Subject did not complete due to disease under study	0	(0.0)	0	(0.0)
	Not completed due to site staff error	0	(0.0)	0	(0.0)
	Subject in hospital or hospice	0	(0.0)	0	(0.0)
	Subject was physically unable to complete	0	(0.0)	0	(0.0)

Treatment Visit	Category	Pembrolizumab + Chemotherapy N=520		Placebo + Chemotherapy N=516	
		n	(%)	n	(%)
WEEK 159	Subject lost to follow-up/unable to contact	0	(0.0)	0	(0.0)
	Subject did not complete due to side effects of treatment	0	(0.0)	0	(0.0)
	Subject refused for other reasons	0	(0.0)	0	(0.0)
	Other	0	(0.0)	0	(0.0)
	With visit, no record	2	(0.4)	0	(0.0)
	Missing by Design	**518**	**(99.6)**	**516**	**(100.0)**
	Discontinued due to adverse event	65	(12.5)	56	(10.9)
	Discontinued due to clinical progression	35	(6.7)	39	(7.6)
	Discontinued due to non-study anti-cancer therapy	3	(0.6)	6	(1.2)
	Discontinued due to physician decision	29	(5.6)	16	(3.1)
	Discontinued due to progressive disease	320	(61.5)	346	(67.1)
	Discontinued due to withdrawal by subject	28	(5.4)	24	(4.7)
	Completed study treatment	13	(2.5)	6	(1.2)
	Translation not available in subjects language	0	(0.0)	0	(0.0)
	Subject died	0	(0.0)	0	(0.0)
	Visit not reached	25	(4.8)	23	(4.5)

		Pembrolizumab + Chemotherapy N=520		Placebo + Chemotherapy N=516	
Treatment Visit	Category	n	(%)	n	(%)
WEEK 159	Visit not scheduled	0	(0.0)	0	(0.0)

Expected to complete questionnaire includes all patients who do not have missing data due to a missing by design reason.

Compliance is the proportion of patients who completed the PRO questionnaire among those who are **expected to complete the questionnaire** at this time point, excluding those missing by design. All the other categories are defined as the proportion of patients in the analysis population (N).

Missing by design includes: adverse event, death, discontinuation, translations not available, and no visit scheduled.

Database Cutoff Date: 15DEC2022

Anhang 4-G1.3: Rücklaufquoten des EQ-5D VAS

Tabelle 4G-3: Gründe für das Fehlen von Werten in der EQ-5D VAS

Treatment Visit	Category	Pembrolizumab + Chemotherapy N=520		Placebo + Chemotherapy N=517	
		n	(%)	n	(%)
BASELINE	**Expected to Complete Questionnaires**	**520**	**(100.0)**	**515**	**(99.6)**
	Completed	491	(94.4)	500	(96.7)
	Compliance (% in those expected to complete questionnaires)	491	(94.4)	500	(97.1)
	Not completed	29	(5.6)	15	(2.9)
	Subject did not complete due to disease under study	1	(0.2)	0	(0.0)
	Not completed due to site staff error	11	(2.1)	5	(1.0)
	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 effects of treatment	0	(0.0)	0	(0.0)
	Subject refused for other reasons	2	(0.4)	0	(0.0)
	Other	7	(1.3)	6	(1.2)
	With visit, no record	8	(1.5)	4	(0.8)
	Missing by Design	**0**	**(0.0)**	**2**	**(0.4)**
	Discontinued due to adverse event	0	(0.0)	0	(0.0)
	Discontinued due to clinical progression	0	(0.0)	0	(0.0)
	Discontinued due to non-study anti-cancer therapy	0	(0.0)	0	(0.0)
	Discontinued due to physician decision	0	(0.0)	0	(0.0)

Treatment Visit	Category	Pembrolizumab + Chemotherapy N=520		Placebo + Chemotherapy N=517	
		n	(%)	n	(%)
BASELINE	Discontinued due to progressive disease	0	(0.0)	0	(0.0)
	Discontinued due to withdrawal by subject	0	(0.0)	0	(0.0)
	Completed study treatment	0	(0.0)	0	(0.0)
	Translation not available in subjects language	0	(0.0)	2	(0.4)
	Subject died	0	(0.0)	0	(0.0)
	Visit not reached	0	(0.0)	0	(0.0)
	Visit not scheduled	0	(0.0)	0	(0.0)
WEEK 3	**Expected to Complete Questionnaires**	**508**	**(97.7)**	**502**	**(97.1)**
	Completed	449	(86.3)	456	(88.2)
	Compliance (% in those expected to complete questionnaires)	449	(88.4)	456	(90.8)
	Not completed	59	(11.3)	46	(8.9)
	Subject did not complete due to disease under study	1	(0.2)	2	(0.4)
	Not completed due to site staff error	11	(2.1)	7	(1.4)
	Subject in hospital or hospice	2	(0.4)	1	(0.2)
	Subject was physically unable to complete	2	(0.4)	1	(0.2)
	Subject lost to follow-up/unable to contact	1	(0.2)	0	(0.0)
	Subject did not complete due to side effects of treatment	1	(0.2)	0	(0.0)
	Subject refused for other reasons	3	(0.6)	1	(0.2)

Treatment Visit	Category	Pembrolizumab + Chemotherapy N=520		Placebo + Chemotherapy N=517	
		n	(%)	n	(%)
WEEK 3	Other	12	(2.3)	12	(2.3)
	With visit, no record	26	(5.0)	22	(4.3)
	Missing by Design	**12**	**(2.3)**	**15**	**(2.9)**
	Discontinued due to adverse event	0	(0.0)	0	(0.0)
	Discontinued due to clinical progression	0	(0.0)	0	(0.0)
	Discontinued due to non-study anti-cancer therapy	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 withdrawal by subject	0	(0.0)	0	(0.0)
	Completed study treatment	0	(0.0)	0	(0.0)
	Translation not available in subjects language	1	(0.2)	1	(0.2)
	Subject died	4	(0.8)	10	(1.9)
	Visit not reached	0	(0.0)	0	(0.0)
	Visit not scheduled	7	(1.3)	4	(0.8)
WEEK 6	**Expected to Complete Questionnaires**	**478**	**(91.9)**	**477**	**(92.3)**
	Completed	423	(81.3)	435	(84.1)
	Compliance (% in those expected to complete questionnaires)	423	(88.5)	435	(91.2)
	Not completed	55	(10.6)	42	(8.1)

Treatment Visit	Category	Pembrolizumab + Chemotherapy N=520		Placebo + Chemotherapy N=517	
		n	(%)	n	(%)
WEEK 6	Subject did not complete due to disease under study	3	(0.6)	0	(0.0)
	Not completed due to site staff error	14	(2.7)	8	(1.5)
	Subject in hospital or hospice	3	(0.6)	0	(0.0)
	Subject was physically unable to complete	3	(0.6)	3	(0.6)
	Subject lost to follow-up/unable to contact	0	(0.0)	0	(0.0)
	Subject did not complete due to side effects of treatment	0	(0.0)	0	(0.0)
	Subject refused for other reasons	2	(0.4)	2	(0.4)
	Other	13	(2.5)	10	(1.9)
	With visit, no record	17	(3.3)	19	(3.7)
	Missing by Design	**42**	**(8.1)**	**40**	**(7.7)**
	Discontinued due to adverse event	7	(1.3)	9	(1.7)
	Discontinued due to clinical progression	2	(0.4)	5	(1.0)
	Discontinued due to non-study anti-cancer therapy	0	(0.0)	0	(0.0)
	Discontinued due to physician decision	1	(0.2)	0	(0.0)
	Discontinued due to progressive disease	7	(1.3)	5	(1.0)
	Discontinued due to withdrawal by subject	3	(0.6)	2	(0.4)
	Completed study treatment	0	(0.0)	0	(0.0)
	Translation not available in subjects language	0	(0.0)	1	(0.2)

Treatment Visit	Category	Pembrolizumab + Chemotherapy N=520		Placebo + Chemotherapy N=517	
		n	(%)	n	(%)
WEEK 6	Subject died	3	(0.6)	2	(0.4)
	Visit not reached	0	(0.0)	0	(0.0)
	Visit not scheduled	19	(3.7)	16	(3.1)
WEEK 9	**Expected to Complete Questionnaires**	**453**	**(87.1)**	**454**	**(87.8)**
	Completed	395	(76.0)	405	(78.3)
	Compliance (% in those expected to complete questionnaires)	395	(87.2)	405	(89.2)
	Not completed	58	(11.2)	49	(9.5)
	Subject did not complete due to disease under study	2	(0.4)	3	(0.6)
	Not completed due to site staff error	8	(1.5)	10	(1.9)
	Subject in hospital or hospice	3	(0.6)	0	(0.0)
	Subject was physically unable to complete	1	(0.2)	0	(0.0)
	Subject lost to follow-up/unable to contact	0	(0.0)	0	(0.0)
	Subject did not complete due to side effects of treatment	0	(0.0)	0	(0.0)
	Subject refused for other reasons	7	(1.3)	4	(0.8)
	Other	11	(2.1)	11	(2.1)
	With visit, no record	26	(5.0)	21	(4.1)
	Missing by Design	**67**	**(12.9)**	**63**	**(12.2)**
	Discontinued due to adverse event	11	(2.1)	15	(2.9)

Treatment Visit	Category	Pembrolizumab + Chemotherapy N=520		Placebo + Chemotherapy N=517	
		n	(%)	n	(%)
WEEK 9	Discontinued due to clinical progression	3	(0.6)	8	(1.5)
	Discontinued due to non-study anti-cancer therapy	0	(0.0)	0	(0.0)
	Discontinued due to physician decision	3	(0.6)	1	(0.2)
	Discontinued due to progressive disease	20	(3.8)	17	(3.3)
	Discontinued due to withdrawal by subject	5	(1.0)	8	(1.5)
	Completed study treatment	0	(0.0)	0	(0.0)
	Translation not available in subjects language	0	(0.0)	0	(0.0)
	Subject died	5	(1.0)	2	(0.4)
	Visit not reached	0	(0.0)	0	(0.0)
	Visit not scheduled	20	(3.8)	12	(2.3)
WEEK 12	**Expected to Complete Questionnaires**	**417**	**(80.2)**	**422**	**(81.6)**
	Completed	369	(71.0)	367	(71.0)
	Compliance (% in those expected to complete questionnaires)	369	(88.5)	367	(87.0)
	Not completed	48	(9.2)	55	(10.6)
	Subject did not complete due to disease under study	0	(0.0)	1	(0.2)
	Not completed due to site staff error	11	(2.1)	11	(2.1)
	Subject in hospital or hospice	0	(0.0)	1	(0.2)
	Subject was physically unable to complete	2	(0.4)	1	(0.2)

Treatment Visit	Category	Pembrolizumab + Chemotherapy N=520		Placebo + Chemotherapy N=517	
		n	(%)	n	(%)
WEEK 12	Subject lost to follow-up/unable to contact	0	(0.0)	0	(0.0)
	Subject did not complete due to side effects of treatment	0	(0.0)	1	(0.2)
	Subject refused for other reasons	2	(0.4)	3	(0.6)
	Other	12	(2.3)	6	(1.2)
	With visit, no record	21	(4.0)	31	(6.0)
	Missing by Design	**103**	**(19.8)**	**95**	**(18.4)**
	Discontinued due to adverse event	18	(3.5)	20	(3.9)
	Discontinued due to clinical progression	7	(1.3)	12	(2.3)
	Discontinued due to non-study anti-cancer therapy	1	(0.2)	0	(0.0)
	Discontinued due to physician decision	4	(0.8)	1	(0.2)
	Discontinued due to progressive disease	46	(8.8)	36	(7.0)
	Discontinued due to withdrawal by subject	7	(1.3)	10	(1.9)
	Completed study treatment	0	(0.0)	0	(0.0)
	Translation not available in subjects language	0	(0.0)	1	(0.2)
	Subject died	0	(0.0)	3	(0.6)
	Visit not reached	0	(0.0)	0	(0.0)
	Visit not scheduled	20	(3.8)	12	(2.3)
WEEK 15	**Expected to Complete Questionnaires**	**373**	**(71.7)**	**366**	**(70.8)**

Treatment Visit	Category	Pembrolizumab + Chemotherapy N=520		Placebo + Chemotherapy N=517	
		n	(%)	n	(%)
WEEK 15	Completed	340	(65.4)	344	(66.5)
	Compliance (% in those expected to complete questionnaires)	340	(91.2)	344	(94.0)
	Not completed	33	(6.3)	22	(4.3)
	Subject did not complete due to disease under study	3	(0.6)	2	(0.4)
	Not completed due to site staff error	9	(1.7)	5	(1.0)
	Subject in hospital or hospice	1	(0.2)	2	(0.4)
	Subject was physically unable to complete	1	(0.2)	0	(0.0)
	Subject lost to follow-up/unable to contact	0	(0.0)	0	(0.0)
	Subject did not complete due to side effects of treatment	0	(0.0)	2	(0.4)
	Subject refused for other reasons	2	(0.4)	1	(0.2)
	Other	6	(1.2)	5	(1.0)
	With visit, no record	11	(2.1)	5	(1.0)
	Missing by Design	**147**	**(28.3)**	**151**	**(29.2)**
	Discontinued due to adverse event	20	(3.8)	22	(4.3)
	Discontinued due to clinical progression	8	(1.5)	15	(2.9)
	Discontinued due to non-study anti-cancer therapy	1	(0.2)	0	(0.0)
	Discontinued due to physician decision	6	(1.2)	1	(0.2)
	Discontinued due to progressive disease	61	(11.7)	64	(12.4)

Treatment Visit	Category	Pembrolizumab + Chemotherapy N=520		Placebo + Chemotherapy N=517	
		n	(%)	n	(%)
WEEK 15	Discontinued due to withdrawal by subject	8	(1.5)	13	(2.5)
	Completed study treatment	0	(0.0)	0	(0.0)
	Translation not available in subjects language	0	(0.0)	1	(0.2)
	Subject died	3	(0.6)	4	(0.8)
	Visit not reached	0	(0.0)	0	(0.0)
	Visit not scheduled	40	(7.7)	31	(6.0)
WEEK 18	**Expected to Complete Questionnaires**	**343**	**(66.0)**	**329**	**(63.6)**
	Completed	321	(61.7)	316	(61.1)
	Compliance (% in those expected to complete questionnaires)	321	(93.6)	316	(96.0)
	Not completed	22	(4.2)	13	(2.5)
	Subject did not complete due to disease under study	1	(0.2)	1	(0.2)
	Not completed due to site staff error	6	(1.2)	3	(0.6)
	Subject in hospital or hospice	0	(0.0)	2	(0.4)
	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 effects of treatment	0	(0.0)	0	(0.0)
	Subject refused for other reasons	3	(0.6)	2	(0.4)
	Other	7	(1.3)	3	(0.6)

Treatment Visit	Category	Pembrolizumab + Chemotherapy N=520		Placebo + Chemotherapy N=517	
		n	(%)	n	(%)
WEEK 18	With visit, no record	5	(1.0)	2	(0.4)
	Missing by Design	**177**	**(34.0)**	**188**	**(36.4)**
	Discontinued due to adverse event	25	(4.8)	26	(5.0)
	Discontinued due to clinical progression	11	(2.1)	17	(3.3)
	Discontinued due to non-study anti-cancer therapy	1	(0.2)	0	(0.0)
	Discontinued due to physician decision	7	(1.3)	2	(0.4)
	Discontinued due to progressive disease	82	(15.8)	85	(16.4)
	Discontinued due to withdrawal by subject	11	(2.1)	15	(2.9)
	Completed study treatment	0	(0.0)	0	(0.0)
	Translation not available in subjects language	0	(0.0)	1	(0.2)
	Subject died	2	(0.4)	3	(0.6)
	Visit not reached	0	(0.0)	0	(0.0)
	Visit not scheduled	38	(7.3)	39	(7.5)
WEEK 21	**Expected to Complete Questionnaires**	**330**	**(63.5)**	**307**	**(59.4)**
	Completed	306	(58.8)	284	(54.9)
	Compliance (% in those expected to complete questionnaires)	306	(92.7)	284	(92.5)
	Not completed	24	(4.6)	23	(4.4)
	Subject did not complete due to disease under study	1	(0.2)	1	(0.2)

Treatment Visit	Category	Pembrolizumab + Chemotherapy N=520		Placebo + Chemotherapy N=517	
		n	(%)	n	(%)
WEEK 21	Not completed due to site staff error	5	(1.0)	7	(1.4)
	Subject in hospital or hospice	0	(0.0)	1	(0.2)
	Subject was physically unable to complete	2	(0.4)	0	(0.0)
	Subject lost to follow-up/unable to contact	0	(0.0)	0	(0.0)
	Subject did not complete due to side effects of treatment	0	(0.0)	0	(0.0)
	Subject refused for other reasons	2	(0.4)	2	(0.4)
	Other	8	(1.5)	10	(1.9)
	With visit, no record	6	(1.2)	2	(0.4)
	Missing by Design	**190**	**(36.5)**	**210**	**(40.6)**
	Discontinued due to adverse event	27	(5.2)	28	(5.4)
	Discontinued due to clinical progression	15	(2.9)	19	(3.7)
	Discontinued due to non-study anti-cancer therapy	1	(0.2)	0	(0.0)
	Discontinued due to physician decision	8	(1.5)	3	(0.6)
	Discontinued due to progressive disease	94	(18.1)	104	(20.1)
	Discontinued due to withdrawal by subject	13	(2.5)	16	(3.1)
	Completed study treatment	0	(0.0)	0	(0.0)
	Translation not available in subjects language	0	(0.0)	1	(0.2)
	Subject died	0	(0.0)	3	(0.6)

Treatment Visit	Category	Pembrolizumab + Chemotherapy N=520		Placebo + Chemotherapy N=517	
		n	(%)	n	(%)
WEEK 21	Visit not reached	0	(0.0)	0	(0.0)
	Visit not scheduled	32	(6.2)	36	(7.0)
WEEK 24	**Expected to Complete Questionnaires**	**304**	**(58.5)**	**281**	**(54.4)**
	Completed	285	(54.8)	264	(51.1)
	Compliance (% in those expected to complete questionnaires)	285	(93.8)	264	(94.0)
	Not completed	19	(3.7)	17	(3.3)
	Subject did not complete due to disease under study	1	(0.2)	2	(0.4)
	Not completed due to site staff error	11	(2.1)	5	(1.0)
	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 effects of treatment	0	(0.0)	0	(0.0)
	Subject refused for other reasons	1	(0.2)	2	(0.4)
	Other	4	(0.8)	6	(1.2)
	With visit, no record	2	(0.4)	2	(0.4)
	Missing by Design	**216**	**(41.5)**	**236**	**(45.6)**
	Discontinued due to adverse event	31	(6.0)	36	(7.0)
	Discontinued due to clinical progression	15	(2.9)	21	(4.1)

Treatment Visit	Category	Pembrolizumab + Chemotherapy N=520		Placebo + Chemotherapy N=517	
		n	(%)	n	(%)
WEEK 24	Discontinued due to non-study anti-cancer therapy	1	(0.2)	1	(0.2)
	Discontinued due to physician decision	8	(1.5)	4	(0.8)
	Discontinued due to progressive disease	113	(21.7)	115	(22.2)
	Discontinued due to withdrawal by subject	15	(2.9)	18	(3.5)
	Completed study treatment	0	(0.0)	0	(0.0)
	Translation not available in subjects language	0	(0.0)	0	(0.0)
	Subject died	1	(0.2)	5	(1.0)
	Visit not reached	0	(0.0)	0	(0.0)
	Visit not scheduled	32	(6.2)	36	(7.0)
WEEK 27	**Expected to Complete Questionnaires**	**294**	**(56.5)**	**274**	**(53.0)**
	Completed	279	(53.7)	257	(49.7)
	Compliance (% in those expected to complete questionnaires)	279	(94.9)	257	(93.8)
	Not completed	15	(2.9)	17	(3.3)
	Subject did not complete due to disease under study	1	(0.2)	2	(0.4)
	Not completed due to site staff error	4	(0.8)	3	(0.6)
	Subject in hospital or hospice	0	(0.0)	1	(0.2)
	Subject was physically unable to complete	0	(0.0)	3	(0.6)
	Subject lost to follow-up/unable to contact	0	(0.0)	0	(0.0)

Treatment Visit	Category	Pembrolizumab + Chemotherapy N=520		Placebo + Chemotherapy N=517	
		n	(%)	n	(%)
WEEK 27	Subject did not complete due to side effects of treatment	0	(0.0)	0	(0.0)
	Subject refused for other reasons	1	(0.2)	3	(0.6)
	Other	6	(1.2)	4	(0.8)
	With visit, no record	3	(0.6)	1	(0.2)
	Missing by Design	**226**	**(43.5)**	**243**	**(47.0)**
	Discontinued due to adverse event	36	(6.9)	37	(7.2)
	Discontinued due to clinical progression	18	(3.5)	22	(4.3)
	Discontinued due to non-study anti-cancer therapy	1	(0.2)	1	(0.2)
	Discontinued due to physician decision	10	(1.9)	4	(0.8)
	Discontinued due to progressive disease	127	(24.4)	143	(27.7)
	Discontinued due to withdrawal by subject	16	(3.1)	20	(3.9)
	Completed study treatment	0	(0.0)	0	(0.0)
	Translation not available in subjects language	0	(0.0)	1	(0.2)
	Subject died	4	(0.8)	1	(0.2)
	Visit not reached	0	(0.0)	0	(0.0)
	Visit not scheduled	14	(2.7)	14	(2.7)
WEEK 33	**Expected to Complete Questionnaires**	**271**	**(52.1)**	**237**	**(45.8)**
	Completed	235	(45.2)	205	(39.7)

Treatment Visit	Category	Pembrolizumab + Chemotherapy N=520		Placebo + Chemotherapy N=517	
		n	(%)	n	(%)
WEEK 33	Compliance (% in those expected to complete questionnaires)	235	(86.7)	205	(86.5)
	Not completed	36	(6.9)	32	(6.2)
	Subject did not complete due to disease under study	2	(0.4)	1	(0.2)
	Not completed due to site staff error	5	(1.0)	0	(0.0)
	Subject in hospital or hospice	1	(0.2)	0	(0.0)
	Subject was physically unable to complete	1	(0.2)	0	(0.0)
	Subject lost to follow-up/unable to contact	0	(0.0)	0	(0.0)
	Subject did not complete due to side effects of treatment	0	(0.0)	0	(0.0)
	Subject refused for other reasons	1	(0.2)	3	(0.6)
	Other	4	(0.8)	7	(1.4)
	With visit, no record	22	(4.2)	21	(4.1)
	Missing by Design	**249**	**(47.9)**	**280**	**(54.2)**
	Discontinued due to adverse event	40	(7.7)	39	(7.5)
	Discontinued due to clinical progression	22	(4.2)	24	(4.6)
	Discontinued due to non-study anti-cancer therapy	1	(0.2)	2	(0.4)
	Discontinued due to physician decision	12	(2.3)	6	(1.2)
	Discontinued due to progressive disease	149	(28.7)	177	(34.2)
	Discontinued due to withdrawal by subject	16	(3.1)	20	(3.9)

Treatment Visit	Category	Pembrolizumab + Chemotherapy N=520		Placebo + Chemotherapy N=517	
		n	(%)	n	(%)
WEEK 33	Completed study treatment	0	(0.0)	0	(0.0)
	Translation not available in subjects language	0	(0.0)	1	(0.2)
	Subject died	2	(0.4)	4	(0.8)
	Visit not reached	0	(0.0)	0	(0.0)
	Visit not scheduled	7	(1.3)	7	(1.4)
WEEK 39	**Expected to Complete Questionnaires**	**225**	**(43.3)**	**195**	**(37.7)**
	Completed	192	(36.9)	167	(32.3)
	Compliance (% in those expected to complete questionnaires)	192	(85.3)	167	(85.6)
	Not completed	33	(6.3)	28	(5.4)
	Subject did not complete due to disease under study	1	(0.2)	0	(0.0)
	Not completed due to site staff error	6	(1.2)	10	(1.9)
	Subject in hospital or hospice	1	(0.2)	1	(0.2)
	Subject was physically unable to complete	1	(0.2)	0	(0.0)
	Subject lost to follow-up/unable to contact	0	(0.0)	0	(0.0)
	Subject did not complete due to side effects of treatment	1	(0.2)	0	(0.0)
	Subject refused for other reasons	3	(0.6)	2	(0.4)
	Other	2	(0.4)	6	(1.2)
	With visit, no record	18	(3.5)	9	(1.7)

Treatment Visit	Category	Pembrolizumab + Chemotherapy N=520		Placebo + Chemotherapy N=517	
		n	(%)	n	(%)
WEEK 39	**Missing by Design**	**295**	**(56.7)**	**322**	**(62.3)**
	Discontinued due to adverse event	43	(8.3)	41	(7.9)
	Discontinued due to clinical progression	24	(4.6)	30	(5.8)
	Discontinued due to non-study anti-cancer therapy	1	(0.2)	2	(0.4)
	Discontinued due to physician decision	18	(3.5)	10	(1.9)
	Discontinued due to progressive disease	179	(34.4)	207	(40.0)
	Discontinued due to withdrawal by subject	19	(3.7)	22	(4.3)
	Completed study treatment	0	(0.0)	0	(0.0)
	Translation not available in subjects language	0	(0.0)	1	(0.2)
	Subject died	2	(0.4)	3	(0.6)
	Visit not reached	0	(0.0)	0	(0.0)
	Visit not scheduled	9	(1.7)	6	(1.2)
WEEK 45	**Expected to Complete Questionnaires**	**187**	**(36.0)**	**152**	**(29.4)**
	Completed	161	(31.0)	137	(26.5)
	Compliance (% in those expected to complete questionnaires)	161	(86.1)	137	(90.1)
	Not completed	26	(5.0)	15	(2.9)
	Subject did not complete due to disease under study	2	(0.4)	0	(0.0)
	Not completed due to site staff error	4	(0.8)	3	(0.6)

Treatment Visit	Category	Pembrolizumab + Chemotherapy N=520		Placebo + Chemotherapy N=517	
		n	(%)	n	(%)
WEEK 45	Subject in hospital or hospice	0	(0.0)	1	(0.2)
	Subject was physically unable to complete	0	(0.0)	1	(0.2)
	Subject lost to follow-up/unable to contact	0	(0.0)	0	(0.0)
	Subject did not complete due to side effects of treatment	0	(0.0)	0	(0.0)
	Subject refused for other reasons	1	(0.2)	2	(0.4)
	Other	5	(1.0)	1	(0.2)
	With visit, no record	14	(2.7)	7	(1.4)
	Missing by Design	**333**	**(64.0)**	**365**	**(70.6)**
	Discontinued due to adverse event	50	(9.6)	44	(8.5)
	Discontinued due to clinical progression	27	(5.2)	31	(6.0)
	Discontinued due to non-study anti-cancer therapy	1	(0.2)	3	(0.6)
	Discontinued due to physician decision	20	(3.8)	12	(2.3)
	Discontinued due to progressive disease	210	(40.4)	243	(47.0)
	Discontinued due to withdrawal by subject	20	(3.8)	22	(4.3)
	Completed study treatment	0	(0.0)	0	(0.0)
	Translation not available in subjects language	0	(0.0)	1	(0.2)
	Subject died	1	(0.2)	2	(0.4)
	Visit not reached	0	(0.0)	0	(0.0)

Treatment Visit	Category	Pembrolizumab + Chemotherapy N=520		Placebo + Chemotherapy N=517	
		n	(%)	n	(%)
WEEK 45	Visit not scheduled	4	(0.8)	7	(1.4)
WEEK 51	**Expected to Complete Questionnaires**	**154**	**(29.6)**	**122**	**(23.6)**
	Completed	136	(26.2)	109	(21.1)
	Compliance (% in those expected to complete questionnaires)	136	(88.3)	109	(89.3)
	Not completed	18	(3.5)	13	(2.5)
	Subject did not complete due to disease under study	0	(0.0)	0	(0.0)
	Not completed due to site staff error	4	(0.8)	3	(0.6)
	Subject in hospital or hospice	0	(0.0)	1	(0.2)
	Subject was physically unable to complete	0	(0.0)	0	(0.0)
	Subject lost to follow-up/unable to contact	1	(0.2)	0	(0.0)
	Subject did not complete due to side effects of treatment	0	(0.0)	0	(0.0)
	Subject refused for other reasons	2	(0.4)	2	(0.4)
	Other	7	(1.3)	5	(1.0)
	With visit, no record	4	(0.8)	2	(0.4)
	Missing by Design	**366**	**(70.4)**	**395**	**(76.4)**
	Discontinued due to adverse event	51	(9.8)	46	(8.9)
	Discontinued due to clinical progression	31	(6.0)	32	(6.2)
	Discontinued due to non-study anti-cancer therapy	1	(0.2)	3	(0.6)

Treatment Visit	Category	Pembrolizumab + Chemotherapy N=520		Placebo + Chemotherapy N=517	
		n	(%)	n	(%)
WEEK 51	Discontinued due to physician decision	23	(4.4)	13	(2.5)
	Discontinued due to progressive disease	236	(45.4)	274	(53.0)
	Discontinued due to withdrawal by subject	23	(4.4)	23	(4.4)
	Completed study treatment	0	(0.0)	0	(0.0)
	Translation not available in subjects language	0	(0.0)	1	(0.2)
	Subject died	1	(0.2)	1	(0.2)
	Visit not reached	0	(0.0)	0	(0.0)
	Visit not scheduled	0	(0.0)	2	(0.4)
WEEK 63	**Expected to Complete Questionnaires**	**109**	**(21.0)**	**101**	**(19.5)**
	Completed	45	(8.7)	43	(8.3)
	Compliance (% in those expected to complete questionnaires)	45	(41.3)	43	(42.6)
	Not completed	64	(12.3)	58	(11.2)
	Subject did not complete due to disease under study	0	(0.0)	0	(0.0)
	Not completed due to site staff error	4	(0.8)	2	(0.4)
	Subject in hospital or hospice	1	(0.2)	1	(0.2)
	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 effects of treatment	0	(0.0)	0	(0.0)

Treatment Visit	Category	Pembrolizumab + Chemotherapy N=520		Placebo + Chemotherapy N=517	
		n	(%)	n	(%)
WEEK 63	Subject refused for other reasons	2	(0.4)	0	(0.0)
	Other	3	(0.6)	2	(0.4)
	With visit, no record	54	(10.4)	53	(10.3)
	Missing by Design	**411**	**(79.0)**	**416**	**(80.5)**
	Discontinued due to adverse event	54	(10.4)	49	(9.5)
	Discontinued due to clinical progression	33	(6.3)	32	(6.2)
	Discontinued due to non-study anti-cancer therapy	2	(0.4)	4	(0.8)
	Discontinued due to physician decision	25	(4.8)	13	(2.5)
	Discontinued due to progressive disease	266	(51.2)	291	(56.3)
	Discontinued due to withdrawal by subject	27	(5.2)	23	(4.4)
	Completed study treatment	0	(0.0)	0	(0.0)
	Translation not available in subjects language	0	(0.0)	1	(0.2)
	Subject died	3	(0.6)	2	(0.4)
	Visit not reached	0	(0.0)	0	(0.0)
	Visit not scheduled	1	(0.2)	1	(0.2)
WEEK 75	**Expected to Complete Questionnaires**	**79**	**(15.2)**	**73**	**(14.1)**
	Completed	17	(3.3)	24	(4.6)
	Compliance (% in those expected to complete questionnaires)	17	(21.5)	24	(32.9)

Treatment Visit	Category	Pembrolizumab + Chemotherapy N=520		Placebo + Chemotherapy N=517	
		n	(%)	n	(%)
WEEK 75	Not completed	62	(11.9)	49	(9.5)
	Subject did not complete due to disease under study	1	(0.2)	1	(0.2)
	Not completed due to site staff error	1	(0.2)	2	(0.4)
	Subject in hospital or hospice	0	(0.0)	0	(0.0)
	Subject was physically unable to complete	1	(0.2)	1	(0.2)
	Subject lost to follow-up/unable to contact	0	(0.0)	0	(0.0)
	Subject did not complete due to side effects of treatment	0	(0.0)	0	(0.0)
	Subject refused for other reasons	0	(0.0)	0	(0.0)
	Other	2	(0.4)	0	(0.0)
	With visit, no record	57	(11.0)	45	(8.7)
	Missing by Design	**441**	**(84.8)**	**444**	**(85.9)**
	Discontinued due to adverse event	59	(11.3)	50	(9.7)
	Discontinued due to clinical progression	34	(6.5)	36	(7.0)
	Discontinued due to non-study anti-cancer therapy	3	(0.6)	5	(1.0)
	Discontinued due to physician decision	26	(5.0)	13	(2.5)
	Discontinued due to progressive disease	288	(55.4)	314	(60.7)
	Discontinued due to withdrawal by subject	27	(5.2)	23	(4.4)
	Completed study treatment	0	(0.0)	0	(0.0)

Treatment Visit	Category	Pembrolizumab + Chemotherapy N=520		Placebo + Chemotherapy N=517	
		n	(%)	n	(%)
WEEK 75	Translation not available in subjects language	0	(0.0)	0	(0.0)
	Subject died	3	(0.6)	2	(0.4)
	Visit not reached	1	(0.2)	1	(0.2)
	Visit not scheduled	0	(0.0)	0	(0.0)
WEEK 87	**Expected to Complete Questionnaires**	**60**	**(11.5)**	**44**	**(8.5)**
	Completed	7	(1.3)	8	(1.5)
	Compliance (% in those expected to complete questionnaires)	7	(11.7)	8	(18.2)
	Not completed	53	(10.2)	36	(7.0)
	Subject did not complete due to disease under study	1	(0.2)	0	(0.0)
	Not completed due to site staff error	0	(0.0)	1	(0.2)
	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 effects of treatment	0	(0.0)	0	(0.0)
	Subject refused for other reasons	1	(0.2)	0	(0.0)
	Other	2	(0.4)	0	(0.0)
	With visit, no record	49	(9.4)	35	(6.8)
	Missing by Design	**460**	**(88.5)**	**473**	**(91.5)**

Treatment Visit	Category	Pembrolizumab + Chemotherapy N=520		Placebo + Chemotherapy N=517	
		n	(%)	n	(%)
WEEK 87	Discontinued due to adverse event	61	(11.7)	54	(10.4)
	Discontinued due to clinical progression	35	(6.7)	37	(7.2)
	Discontinued due to non-study anti-cancer therapy	3	(0.6)	5	(1.0)
	Discontinued due to physician decision	28	(5.4)	13	(2.5)
	Discontinued due to progressive disease	303	(58.3)	337	(65.2)
	Discontinued due to withdrawal by subject	27	(5.2)	24	(4.6)
	Completed study treatment	0	(0.0)	0	(0.0)
	Translation not available in subjects language	0	(0.0)	0	(0.0)
	Subject died	2	(0.4)	0	(0.0)
	Visit not reached	1	(0.2)	3	(0.6)
	Visit not scheduled	0	(0.0)	0	(0.0)
WEEK 99	**Expected to Complete Questionnaires**	**37**	**(7.1)**	**29**	**(5.6)**
	Completed	7	(1.3)	6	(1.2)
	Compliance (% in those expected to complete questionnaires)	7	(18.9)	6	(20.7)
	Not completed	30	(5.8)	23	(4.4)
	Subject did not complete due to disease under study	0	(0.0)	0	(0.0)
	Not completed due to site staff error	0	(0.0)	1	(0.2)
	Subject in hospital or hospice	0	(0.0)	0	(0.0)

Treatment Visit	Category	Pembrolizumab + Chemotherapy N=520		Placebo + Chemotherapy N=517	
		n	(%)	n	(%)
WEEK 99	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 effects of treatment	0	(0.0)	0	(0.0)
	Subject refused for other reasons	0	(0.0)	0	(0.0)
	Other	1	(0.2)	1	(0.2)
	With visit, no record	29	(5.6)	21	(4.1)
	Missing by Design	**483**	**(92.9)**	**488**	**(94.4)**
	Discontinued due to adverse event	64	(12.3)	56	(10.8)
	Discontinued due to clinical progression	35	(6.7)	38	(7.4)
	Discontinued due to non-study anti-cancer therapy	3	(0.6)	6	(1.2)
	Discontinued due to physician decision	28	(5.4)	14	(2.7)
	Discontinued due to progressive disease	312	(60.0)	340	(65.8)
	Discontinued due to withdrawal by subject	28	(5.4)	24	(4.6)
	Completed study treatment	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)
	Visit not reached	13	(2.5)	10	(1.9)
	Visit not scheduled	0	(0.0)	0	(0.0)

Treatment Visit	Category	Pembrolizumab + Chemotherapy N=520		Placebo + Chemotherapy N=517	
		n	(%)	n	(%)
WEEK 111	**Expected to Complete Questionnaires**	**26**	**(5.0)**	**16**	**(3.1)**
	Completed	9	(1.7)	11	(2.1)
	Compliance (% in those expected to complete questionnaires)	9	(34.6)	11	(68.8)
	Not completed	17	(3.3)	5	(1.0)
	Subject did not complete due to disease under study	0	(0.0)	0	(0.0)
	Not completed due to site staff error	2	(0.4)	0	(0.0)
	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	1	(0.2)	0	(0.0)
	Subject did not complete due to side effects of treatment	0	(0.0)	0	(0.0)
	Subject refused for other reasons	0	(0.0)	0	(0.0)
	Other	0	(0.0)	0	(0.0)
	With visit, no record	14	(2.7)	5	(1.0)
	Missing by Design	**494**	**(95.0)**	**501**	**(96.9)**
	Discontinued due to adverse event	65	(12.5)	57	(11.0)
	Discontinued due to clinical progression	35	(6.7)	39	(7.5)
	Discontinued due to non-study anti-cancer therapy	3	(0.6)	6	(1.2)
	Discontinued due to physician decision	28	(5.4)	14	(2.7)

Treatment Visit	Category	Pembrolizumab + Chemotherapy N=520		Placebo + Chemotherapy N=517	
		n	(%)	n	(%)
WEEK 111	Discontinued due to progressive disease	318	(61.2)	342	(66.2)
	Discontinued due to withdrawal by subject	28	(5.4)	24	(4.6)
	Completed study treatment	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)
	Visit not reached	17	(3.3)	19	(3.7)
	Visit not scheduled	0	(0.0)	0	(0.0)
WEEK 123	**Expected to Complete Questionnaires**	**8**	**(1.5)**	**3**	**(0.6)**
	Completed	3	(0.6)	1	(0.2)
	Compliance (% in those expected to complete questionnaires)	3	(37.5)	1	(33.3)
	Not completed	5	(1.0)	2	(0.4)
	Subject did not complete due to disease under study	0	(0.0)	0	(0.0)
	Not completed due to site staff error	0	(0.0)	0	(0.0)
	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 effects of treatment	0	(0.0)	0	(0.0)
	Subject refused for other reasons	0	(0.0)	0	(0.0)

Treatment Visit	Category	Pembrolizumab + Chemotherapy N=520		Placebo + Chemotherapy N=517	
		n	(%)	n	(%)
WEEK 123	Other	0	(0.0)	0	(0.0)
	With visit, no record	5	(1.0)	2	(0.4)
	Missing by Design	**512**	**(98.5)**	**514**	**(99.4)**
	Discontinued due to adverse event	65	(12.5)	57	(11.0)
	Discontinued due to clinical progression	35	(6.7)	39	(7.5)
	Discontinued due to non-study anti-cancer therapy	3	(0.6)	6	(1.2)
	Discontinued due to physician decision	29	(5.6)	16	(3.1)
	Discontinued due to progressive disease	319	(61.3)	345	(66.7)
	Discontinued due to withdrawal by subject	28	(5.4)	24	(4.6)
	Completed study treatment	10	(1.9)	6	(1.2)
	Translation not available in subjects language	0	(0.0)	0	(0.0)
	Subject died	0	(0.0)	0	(0.0)
	Visit not reached	23	(4.4)	21	(4.1)
	Visit not scheduled	0	(0.0)	0	(0.0)
WEEK 135	**Expected to Complete Questionnaires**	**3**	**(0.6)**	**1**	**(0.2)**
	Completed	1	(0.2)	0	(0.0)
	Compliance (% in those expected to complete questionnaires)	1	(33.3)	0	(0.0)
	Not completed	2	(0.4)	1	(0.2)

Treatment Visit	Category	Pembrolizumab + Chemotherapy N=520		Placebo + Chemotherapy N=517	
		n	(%)	n	(%)
WEEK 135	Subject did not complete due to disease under study	0	(0.0)	0	(0.0)
	Not completed due to site staff error	0	(0.0)	0	(0.0)
	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 effects of treatment	0	(0.0)	0	(0.0)
	Subject refused for other reasons	0	(0.0)	0	(0.0)
	Other	0	(0.0)	0	(0.0)
	With visit, no record	2	(0.4)	1	(0.2)
	Missing by Design	**517**	**(99.4)**	**516**	**(99.8)**
	Discontinued due to adverse event	65	(12.5)	57	(11.0)
	Discontinued due to clinical progression	35	(6.7)	39	(7.5)
	Discontinued due to non-study anti-cancer therapy	3	(0.6)	6	(1.2)
	Discontinued due to physician decision	29	(5.6)	16	(3.1)
	Discontinued due to progressive disease	319	(61.3)	346	(66.9)
	Discontinued due to withdrawal by subject	28	(5.4)	24	(4.6)
	Completed study treatment	13	(2.5)	6	(1.2)
	Translation not available in subjects language	0	(0.0)	0	(0.0)

Treatment Visit	Category	Pembrolizumab + Chemotherapy N=520		Placebo + Chemotherapy N=517	
		n	(%)	n	(%)
WEEK 135	Subject died	0	(0.0)	0	(0.0)
	Visit not reached	25	(4.8)	22	(4.3)
	Visit not scheduled	0	(0.0)	0	(0.0)
WEEK 147	**Expected to Complete Questionnaires**	**2**	**(0.4)**	**0**	**(0.0)**
	Completed	0	(0.0)	0	(0.0)
	Compliance (% in those expected to complete questionnaires)	0	(0.0)	0	(0.0)
	Not completed	2	(0.4)	0	(0.0)
	Subject did not complete due to disease under study	0	(0.0)	0	(0.0)
	Not completed due to site staff error	0	(0.0)	0	(0.0)
	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 effects of treatment	0	(0.0)	0	(0.0)
	Subject refused for other reasons	0	(0.0)	0	(0.0)
	Other	0	(0.0)	0	(0.0)
	With visit, no record	2	(0.4)	0	(0.0)
	Missing by Design	**518**	**(99.6)**	**517**	**(100.0)**
	Discontinued due to adverse event	65	(12.5)	57	(11.0)

Treatment Visit	Category	Pembrolizumab + Chemotherapy N=520		Placebo + Chemotherapy N=517	
		n	(%)	n	(%)
WEEK 147	Discontinued due to clinical progression	35	(6.7)	39	(7.5)
	Discontinued due to non-study anti-cancer therapy	3	(0.6)	6	(1.2)
	Discontinued due to physician decision	29	(5.6)	16	(3.1)
	Discontinued due to progressive disease	320	(61.5)	346	(66.9)
	Discontinued due to withdrawal by subject	28	(5.4)	24	(4.6)
	Completed study treatment	13	(2.5)	6	(1.2)
	Translation not available in subjects language	0	(0.0)	0	(0.0)
	Subject died	0	(0.0)	0	(0.0)
	Visit not reached	25	(4.8)	23	(4.4)
	Visit not scheduled	0	(0.0)	0	(0.0)
WEEK 159	**Expected to Complete Questionnaires**	**2**	**(0.4)**	**0**	**(0.0)**
	Completed	0	(0.0)	0	(0.0)
	Compliance (% in those expected to complete questionnaires)	0	(0.0)	0	(0.0)
	Not completed	2	(0.4)	0	(0.0)
	Subject did not complete due to disease under study	0	(0.0)	0	(0.0)
	Not completed due to site staff error	0	(0.0)	0	(0.0)
	Subject in hospital or hospice	0	(0.0)	0	(0.0)
	Subject was physically unable to complete	0	(0.0)	0	(0.0)

Treatment Visit	Category	Pembrolizumab + Chemotherapy N=520		Placebo + Chemotherapy N=517	
		n	(%)	n	(%)
WEEK 159	Subject lost to follow-up/unable to contact	0	(0.0)	0	(0.0)
	Subject did not complete due to side effects of treatment	0	(0.0)	0	(0.0)
	Subject refused for other reasons	0	(0.0)	0	(0.0)
	Other	0	(0.0)	0	(0.0)
	With visit, no record	2	(0.4)	0	(0.0)
	Missing by Design	**518**	**(99.6)**	**517**	**(100.0)**
	Discontinued due to adverse event	65	(12.5)	57	(11.0)
	Discontinued due to clinical progression	35	(6.7)	39	(7.5)
	Discontinued due to non-study anti-cancer therapy	3	(0.6)	6	(1.2)
	Discontinued due to physician decision	29	(5.6)	16	(3.1)
	Discontinued due to progressive disease	320	(61.5)	346	(66.9)
	Discontinued due to withdrawal by subject	28	(5.4)	24	(4.6)
	Completed study treatment	13	(2.5)	6	(1.2)
	Translation not available in subjects language	0	(0.0)	0	(0.0)
	Subject died	0	(0.0)	0	(0.0)
	Visit not reached	25	(4.8)	23	(4.4)

Treatment Visit	Category	Pembrolizumab + Chemotherapy N=520 n	(%)	Placebo + Chemotherapy N=517 n	(%)
WEEK 159	Visit not scheduled	0	(0.0)	0	(0.0)

Expected to complete questionnaire includes all patients who do not have missing data due to a missing by design reason.

Compliance is the proportion of patients who completed the PRO questionnaire among those who are **expected to complete the questionnaire** at this time point, excluding those missing by design. All the other categories are defined as the proportion of patients in the analysis population (N).

Missing by design includes: adverse event, death, discontinuation, translations not available, and no visit scheduled.

Database Cutoff Date: 15DEC2022

Anhang 4-G2: Deskriptive Kennzahlen des EORTC QLQ-C30, EORTC QLQ-BIL21 und EQ-5D VAS im Studienverlauf

Anhang 4-G2.1: EORTC QLQ-C30 im Studienverlauf

Symptomskala Erschöpfung

Tabelle 4G-4: EORTC QLQ-C30 Erschöpfung im Studienverlauf

EORTC QLQ-C30 Erschöpfung	Studie: KEYNOTE 966[a]	
	Pembrolizumab + Chemotherapie[b] N[c]= 520	Placebo + Chemotherapie[b] N[c]= 517
Baseline		
N[d]	489	496
Mittelwert (SD)	29,5 (22,3)	29,8 (24,2)
Median (Q1; Q3)	33,3 (11,1; 44,4)	33,3 (11,1; 44,4)
Min, Max	0,0; 100,0	0,0; 100,0
Woche 3		
N[d]	445	450
Mittelwert (SD)	33,8 (24,0)	33,6 (24,0)
Median (Q1; Q3)	33,3 (22,2; 44,4)	33,3 (22,2; 44,4)
Min, Max	0,0; 100,0	0,0; 100,0
Woche 6		
N[d]	419	434
Mittelwert (SD)	33,2 (22,5)	32,4 (23,3)
Median (Q1; Q3)	33,3 (22,2; 44,4)	33,3 (22,2; 44,4)
Min, Max	0,0; 100,0	0,0; 100,0
Woche 9		
N[d]	396	402
Mittelwert (SD)	33,3 (21,1)	32,7 (23,9)
Median (Q1; Q3)	33,3 (22,2; 44,4)	33,3 (22,2; 44,4)
Min, Max	0,0; 100,0	0,0; 100,0
Woche 12		
N[d]	367	368
Mittelwert (SD)	31,7 (21,1)	32,1 (21,3)
Median (Q1; Q3)	33,3 (22,2; 33,3)	33,3 (22,2; 44,4)
Min, Max	0,0; 100,0	0,0; 100,0
Woche 15		
N[d]	340	342
Mittelwert (SD)	32,5 (22,7)	29,9 (21,8)
Median (Q1; Q3)	33,3 (22,2; 44,4)	33,3 (11,1; 33,3)
Min, Max	0,0; 100,0	0,0; 100,0
Woche 18		
N[d]	320	315
Mittelwert (SD)	32,1 (23,4)	32,0 (21,2)
Median (Q1; Q3)	33,3 (11,1; 44,4)	33,3 (22,2; 44,4)
Min, Max	0,0; 100,0	0,0; 100,0
Woche 21		
N[d]	304	284

EORTC QLQ-C30 Erschöpfung	Studie: KEYNOTE 966[a]	
	Pembrolizumab + Chemotherapie[b] N[c]= 520	Placebo + Chemotherapie[b] N[c]= 517
Mittelwert (SD)	31,9 (23,0)	30,8 (21,5)
Median (Q1; Q3)	33,3 (16,7; 44,4)	33,3 (11,1; 38,9)
Min, Max	0,0; 100,0	0,0; 100,0
Woche 24		
N[d]	284	264
Mittelwert (SD)	33,1 (23,4)	32,2 (24,6)
Median (Q1; Q3)	33,3 (22,2; 44,4)	33,3 (11,1; 44,4)
Min, Max	0,0; 100,0	0,0; 100,0
Woche 27		
N[d]	279	256
Mittelwert (SD)	29,5 (22,1)	29,1 (22,1)
Median (Q1; Q3)	33,3 (11,1; 33,3)	33,3 (11,1; 33,3)
Min, Max	0,0; 100,0	0,0; 100,0
Woche 33		
N[d]	235	205
Mittelwert (SD)	29,6 (21,6)	28,6 (21,5)
Median (Q1; Q3)	33,3 (11,1; 33,3)	33,3 (11,1; 33,3)
Min, Max	0,0; 100,0	0,0; 100,0
Woche 39		
N[d]	192	167
Mittelwert (SD)	30,8 (22,1)	29,9 (23,1)
Median (Q1; Q3)	33,3 (11,1; 33,3)	33,3 (11,1; 33,3)
Min, Max	0,0; 88,9	0,0; 100,0
Woche 45		
N[d]	160	135
Mittelwert (SD)	29,3 (22,0)	29,1 (24,4)
Median (Q1; Q3)	33,3 (11,1; 38,9)	33,3 (11,1; 44,4)
Min, Max	0,0; 100,0	0,0; 100,0
Woche 51		
N[d]	136	109
Mittelwert (SD)	31,1 (24,4)	29,9 (26,4)
Median (Q1; Q3)	33,3 (11,1; 44,4)	22,2 (11,1; 44,4)
Min, Max	0,0; 100,0	0,0; 100,0
Woche 63		
N[d]	45	43
Mittelwert (SD)	35,3 (29,3)	32,8 (20,6)
Median (Q1; Q3)	33,3 (11,1; 44,4)	33,3 (22,2; 44,4)
Min, Max	0,0; 100,0	0,0; 88,9
Woche 75		
N[d]	17	24
Mittelwert (SD)	41,2 (29,1)	38,4 (27,6)
Median (Q1; Q3)	33,3 (22,2; 55,6)	33,3 (16,7; 50,0)
Min, Max	0,0; 100,0	0,0; 100,0
Woche 87		
N[d]	7	8
Mittelwert (SD)	38,1 (35,6)	58,3 (37,9)
Median (Q1; Q3)	33,3 (11,1; 66,7)	50,0 (33,3; 100,0)

EORTC QLQ-C30 Erschöpfung	Studie: KEYNOTE 966[a]	
	Pembrolizumab + Chemotherapie[b] N[c]= 520	Placebo + Chemotherapie[b] N[c]= 517
Min, Max	0,0; 100,0	0,0; 100,0
Woche 99		
N[d]	7	6
Mittelwert (SD)	47,6 (37,2)	20,4 (24,8)
Median (Q1; Q3)	44,4 (11,1; 88,9)	16,7 (0,0; 22,2)
Min, Max	0,0; 100,0	0,0; 66,7
Woche 111		
N[d]	9	11
Mittelwert (SD)	22,2 (24,8)	25,3 (25,9)
Median (Q1; Q3)	11,1 (0,0; 33,3)	22,2 (0,0; 44,4)
Min, Max	0,0; 66,7	0,0; 66,7
Woche 123		
N[d]	3	1
Mittelwert (SD)	22,2 (19,2)	33,3 (-)
Median (Q1; Q3)	33,3 (0,0; 33,3)	33,3 (33,3; 33,3)
Min, Max	0,0; 33,3	33,3; 33,3
Woche 135		
N[d]	1	0
Mittelwert (SD)	0,0 (-)	- (-)
Median (Q1; Q3)	0,0 (0,0; 0,0)	- (-; -)
Min, Max	0,0; 0,0	-; -

a: Datenschnitt: 15. Dezember 2022
b: Chemotherapie: Gemcitabin + Cisplatin
c: Anzahl der Patient:innen: Full-Analysis-Set Population
d: Anzahl der Beobachtungen zu jedem Zeitpunkt
EORTC QLQ-C30: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Core 30; Max: Maximum; Min: Minimum; Q1: Erstes Quartil; Q3: Drittes Quartil; SD: Standardabweichung

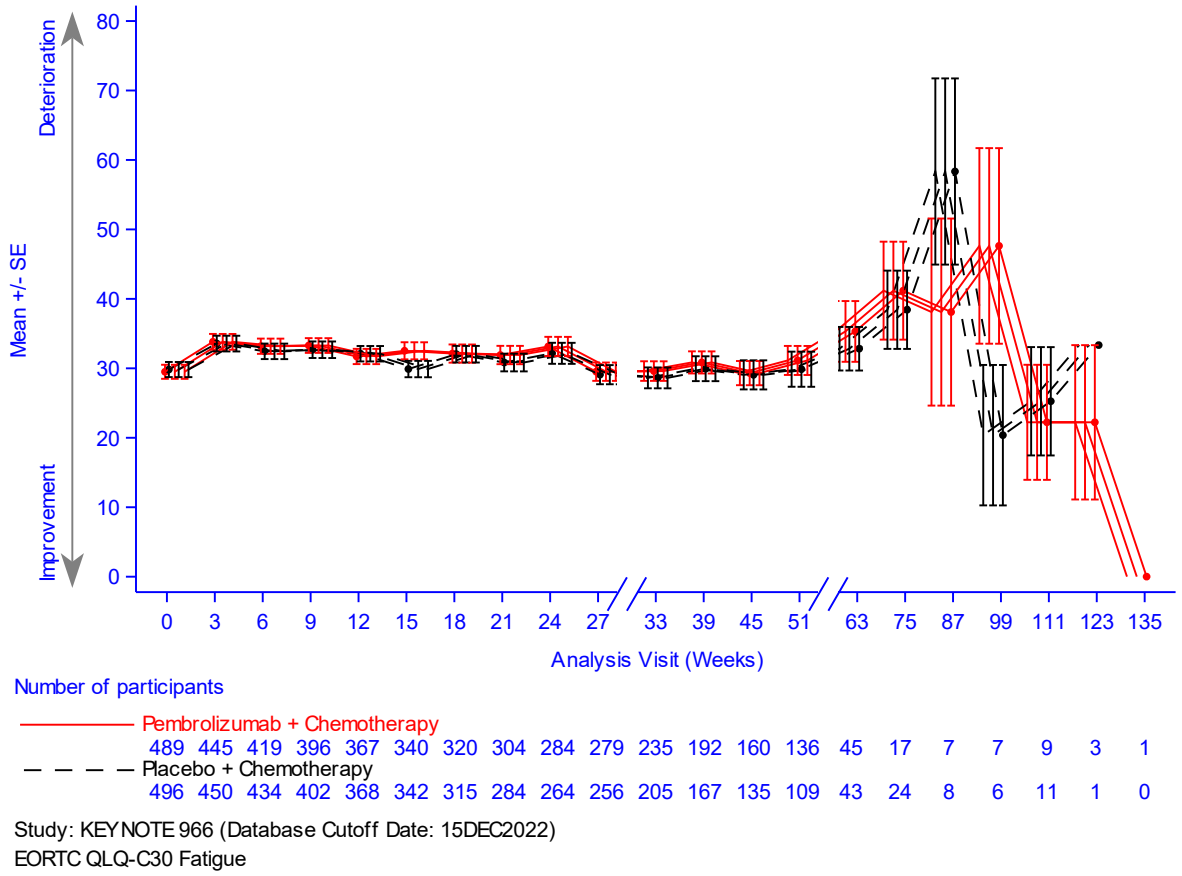


Abbildung 4G-1: EORTC QLQ-C30 Erschöpfung im Studienverlauf

Symptomskala Übelkeit und Erbrechen

Tabelle 4G-5: EORTC QLQ-C30 Übelkeit und Erbrechen im Studienverlauf

EORTC QLQ-C30 Übelkeit und Erbrechen	Studie: KEYNOTE 966[a]	
	Pembrolizumab + Chemotherapie[b] N[c]= 520	Placebo + Chemotherapie[b] N[c]= 517
Baseline		
N[d]	489	496
Mittelwert (SD)	9,0 (17,4)	9,6 (17,7)
Median (Q1; Q3)	0,0 (0,0; 16,7)	0,0 (0,0; 16,7)
Min, Max	0,0; 100,0	0,0; 100,0
Woche 3		
N[d]	445	450
Mittelwert (SD)	13,3 (19,9)	13,3 (20,2)
Median (Q1; Q3)	0,0 (0,0; 16,7)	0,0 (0,0; 16,7)
Min, Max	0,0; 100,0	0,0; 100,0
Woche 6		
N[d]	419	434
Mittelwert (SD)	12,1 (17,1)	14,1 (20,3)
Median (Q1; Q3)	0,0 (0,0; 16,7)	0,0 (0,0; 16,7)
Min, Max	0,0; 100,0	0,0; 100,0
Woche 9		
N[d]	396	402
Mittelwert (SD)	12,0 (16,5)	12,6 (17,2)
Median (Q1; Q3)	0,0 (0,0; 16,7)	0,0 (0,0; 16,7)
Min, Max	0,0; 66,7	0,0; 83,3
Woche 12		
N[d]	367	368
Mittelwert (SD)	12,2 (16,7)	12,5 (17,1)
Median (Q1; Q3)	0,0 (0,0; 16,7)	0,0 (0,0; 16,7)
Min, Max	0,0; 83,3	0,0; 100,0
Woche 15		
N[d]	340	342
Mittelwert (SD)	12,4 (17,6)	11,9 (17,8)
Median (Q1; Q3)	0,0 (0,0; 16,7)	0,0 (0,0; 16,7)
Min, Max	0,0; 100,0	0,0; 100,0
Woche 18		
N[d]	320	315
Mittelwert (SD)	10,7 (17,8)	13,2 (19,9)
Median (Q1; Q3)	0,0 (0,0; 16,7)	0,0 (0,0; 16,7)
Min, Max	0,0; 100,0	0,0; 100,0
Woche 21		
N[d]	304	284
Mittelwert (SD)	12,5 (19,4)	12,8 (18,8)
Median (Q1; Q3)	0,0 (0,0; 16,7)	0,0 (0,0; 16,7)
Min, Max	0,0; 100,0	0,0; 100,0
Woche 24		
N[d]	284	264

EORTC QLQ-C30 Übelkeit und Erbrechen	Studie: KEYNOTE 966[a]	
	Pembrolizumab + Chemotherapie[b]	Placebo + Chemotherapie[b]
	N[c]= 520	N[c]= 517
Mittelwert (SD)	11,2 (17,5)	13,1 (19,0)
Median (Q1; Q3)	0,0 (0,0; 16,7)	0,0 (0,0; 16,7)
Min, Max	0,0; 100,0	0,0; 100,0
Woche 27		
N[d]	279	256
Mittelwert (SD)	8,5 (15,7)	9,6 (16,0)
Median (Q1; Q3)	0,0 (0,0; 16,7)	0,0 (0,0; 16,7)
Min, Max	0,0; 100,0	0,0; 100,0
Woche 33		
N[d]	235	205
Mittelwert (SD)	9,2 (16,3)	7,3 (13,6)
Median (Q1; Q3)	0,0 (0,0; 16,7)	0,0 (0,0; 16,7)
Min, Max	0,0; 100,0	0,0; 66,7
Woche 39		
N[d]	192	167
Mittelwert (SD)	9,5 (19,2)	8,0 (16,7)
Median (Q1; Q3)	0,0 (0,0; 16,7)	0,0 (0,0; 16,7)
Min, Max	0,0; 100,0	0,0; 100,0
Woche 45		
N[d]	160	135
Mittelwert (SD)	9,1 (14,8)	8,9 (16,3)
Median (Q1; Q3)	0,0 (0,0; 16,7)	0,0 (0,0; 16,7)
Min, Max	0,0; 83,3	0,0; 100,0
Woche 51		
N[d]	136	109
Mittelwert (SD)	8,9 (16,1)	7,2 (13,7)
Median (Q1; Q3)	0,0 (0,0; 16,7)	0,0 (0,0; 16,7)
Min, Max	0,0; 100,0	0,0; 66,7
Woche 63		
N[d]	45	43
Mittelwert (SD)	16,3 (27,6)	12,4 (21,5)
Median (Q1; Q3)	0,0 (0,0; 33,3)	0,0 (0,0; 16,7)
Min, Max	0,0; 100,0	0,0; 100,0
Woche 75		
N[d]	17	24
Mittelwert (SD)	12,7 (16,2)	12,5 (19,8)
Median (Q1; Q3)	0,0 (0,0; 16,7)	0,0 (0,0; 16,7)
Min, Max	0,0; 50,0	0,0; 83,3
Woche 87		
N[d]	7	8
Mittelwert (SD)	11,9 (18,5)	12,5 (23,1)
Median (Q1; Q3)	0,0 (0,0; 16,7)	0,0 (0,0; 16,7)
Min, Max	0,0; 50,0	0,0; 66,7
Woche 99		
N[d]	7	6
Mittelwert (SD)	14,3 (24,4)	11,1 (27,2)

EORTC QLQ-C30 Übelkeit und Erbrechen	Studie: KEYNOTE 966[a]	
	Pembrolizumab + Chemotherapie[b]	Placebo + Chemotherapie[b]
	N[c]= 520	N[c]= 517
Median (Q1; Q3)	0,0 (0,0; 16,7)	0,0 (0,0; 0,0)
Min, Max	0,0; 66,7	0,0; 66,7
Woche 111		
N[d]	9	11
Mittelwert (SD)	0,0 (0,0)	3,0 (10,1)
Median (Q1; Q3)	0,0 (0,0; 0,0)	0,0 (0,0; 0,0)
Min, Max	0,0; 0,0	0,0; 33,3
Woche 123		
N[d]	3	1
Mittelwert (SD)	5,6 (9,6)	0,0 (-)
Median (Q1; Q3)	0,0 (0,0; 16,7)	0,0 (0,0; 0,0)
Min, Max	0,0; 16,7	0,0; 0,0
Woche 135		
N[d]	1	0
Mittelwert (SD)	0,0 (-)	- (-)
Median (Q1; Q3)	0,0 (0,0; 0,0)	- (-; -)
Min, Max	0,0; 0,0	-; -

a: Datenschnitt: 15. Dezember 2022
b: Chemotherapie: Gemcitabin + Cisplatin
c: Anzahl der Patient:innen: Full-Analysis-Set Population
d: Anzahl der Beobachtungen zu jedem Zeitpunkt
EORTC QLQ-C30: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Core 30; Max: Maximum; Min: Minimum; Q1: Erstes Quartil; Q3: Drittes Quartil; SD: Standardabweichung

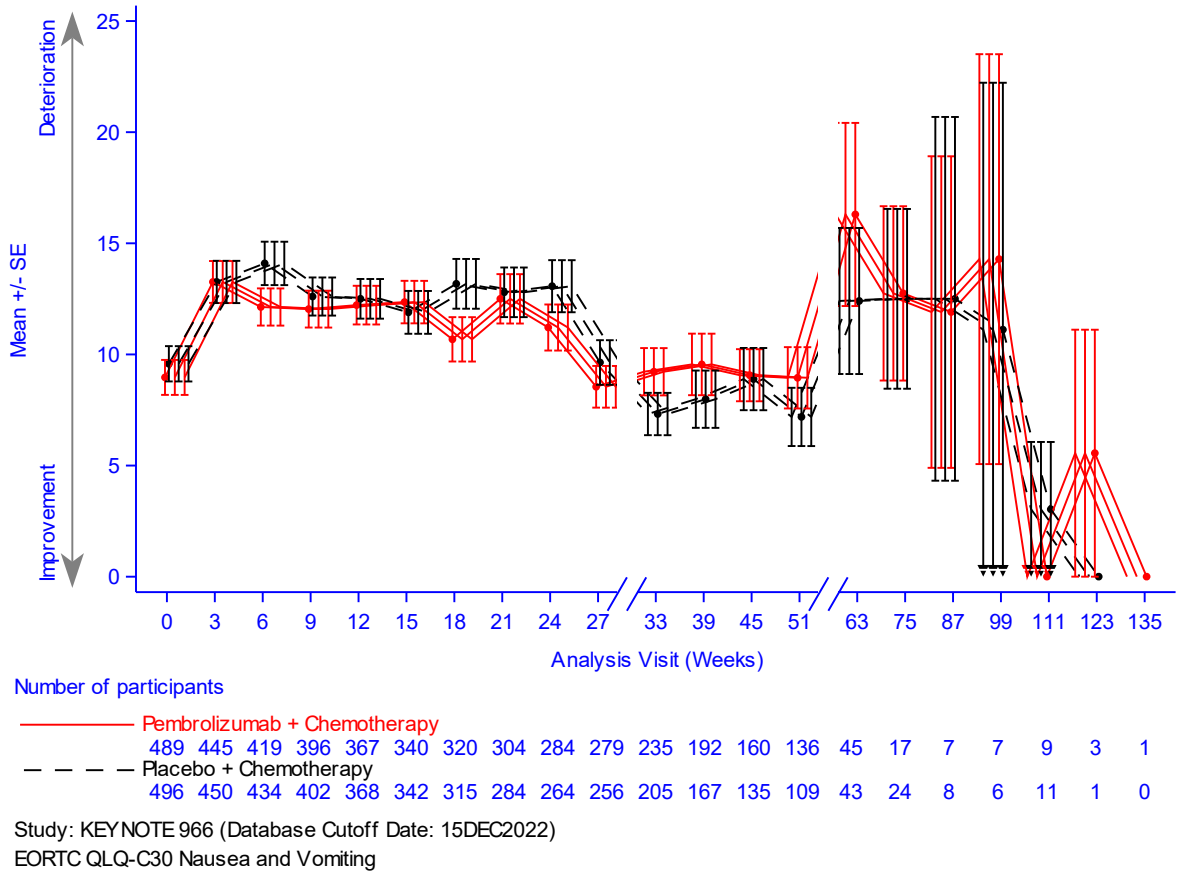


Abbildung 4G-2: EORTC QLQ-C30 Übelkeit und Erbrechen im Studienverlauf

Symptomskala Schmerzen

Tabelle 4G-6: EORTC QLQ-C30 Schmerzen im Studienverlauf

EORTC QLQ-C30 Schmerzen	Studie: KEYNOTE 966[a]	
	Pembrolizumab + Chemotherapie[b] N[c]= 520	Placebo + Chemotherapie[b] N[c]= 517
Baseline		
N[d]	489	496
Mittelwert (SD)	25,4 (24,0)	27,4 (25,8)
Median (Q1; Q3)	16,7 (0,0; 33,3)	16,7 (0,0; 33,3)
Min, Max	0,0; 100,0	0,0; 100,0
Woche 3		
N[d]	445	450
Mittelwert (SD)	21,7 (24,7)	22,1 (22,9)
Median (Q1; Q3)	16,7 (0,0; 33,3)	16,7 (0,0; 33,3)
Min, Max	0,0; 100,0	0,0; 100,0
Woche 6		
N[d]	419	434
Mittelwert (SD)	19,8 (22,7)	22,2 (24,4)
Median (Q1; Q3)	16,7 (0,0; 33,3)	16,7 (0,0; 33,3)
Min, Max	0,0; 100,0	0,0; 100,0
Woche 9		
N[d]	396	402
Mittelwert (SD)	18,9 (22,1)	20,3 (23,1)
Median (Q1; Q3)	16,7 (0,0; 33,3)	16,7 (0,0; 33,3)
Min, Max	0,0; 100,0	0,0; 100,0
Woche 12		
N[d]	367	368
Mittelwert (SD)	19,2 (21,0)	20,1 (21,7)
Median (Q1; Q3)	16,7 (0,0; 33,3)	16,7 (0,0; 33,3)
Min, Max	0,0; 100,0	0,0; 100,0
Woche 15		
N[d]	340	342
Mittelwert (SD)	18,3 (20,5)	18,4 (21,2)
Median (Q1; Q3)	16,7 (0,0; 33,3)	16,7 (0,0; 33,3)
Min, Max	0,0; 83,3	0,0; 100,0
Woche 18		
N[d]	320	315
Mittelwert (SD)	20,6 (24,3)	19,3 (21,8)
Median (Q1; Q3)	16,7 (0,0; 33,3)	16,7 (0,0; 33,3)
Min, Max	0,0; 100,0	0,0; 100,0
Woche 21		
N[d]	304	284
Mittelwert (SD)	20,5 (22,8)	19,7 (22,2)
Median (Q1; Q3)	16,7 (0,0; 33,3)	16,7 (0,0; 33,3)
Min, Max	0,0; 100,0	0,0; 100,0
Woche 24		
N[d]	284	264
Mittelwert (SD)	19,6 (22,5)	21,8 (24,1)

EORTC QLQ-C30 Schmerzen	Studie: KEYNOTE 966[a]	
	Pembrolizumab + Chemotherapie[b] N[c]= 520	Placebo + Chemotherapie[b] N[c]= 517
Median (Q1; Q3)	16,7 (0,0; 33,3)	16,7 (0,0; 33,3)
Min, Max	0,0; 100,0	0,0; 100,0
Woche 27		
N[d]	279	256
Mittelwert (SD)	17,7 (21,9)	21,2 (23,5)
Median (Q1; Q3)	16,7 (0,0; 33,3)	16,7 (0,0; 33,3)
Min, Max	0,0; 100,0	0,0; 100,0
Woche 33		
N[d]	235	205
Mittelwert (SD)	20,3 (23,4)	19,2 (20,7)
Median (Q1; Q3)	16,7 (0,0; 33,3)	16,7 (0,0; 33,3)
Min, Max	0,0; 100,0	0,0; 100,0
Woche 39		
N[d]	192	167
Mittelwert (SD)	19,4 (23,4)	23,3 (24,8)
Median (Q1; Q3)	16,7 (0,0; 33,3)	16,7 (0,0; 33,3)
Min, Max	0,0; 100,0	0,0; 100,0
Woche 45		
N[d]	160	135
Mittelwert (SD)	20,0 (22,4)	21,4 (25,3)
Median (Q1; Q3)	16,7 (0,0; 33,3)	16,7 (0,0; 33,3)
Min, Max	0,0; 100,0	0,0; 100,0
Woche 51		
N[d]	136	109
Mittelwert (SD)	18,8 (23,5)	24,0 (26,6)
Median (Q1; Q3)	16,7 (0,0; 33,3)	16,7 (0,0; 33,3)
Min, Max	0,0; 100,0	0,0; 100,0
Woche 63		
N[d]	45	43
Mittelwert (SD)	25,6 (28,8)	22,9 (25,2)
Median (Q1; Q3)	16,7 (0,0; 33,3)	16,7 (0,0; 33,3)
Min, Max	0,0; 100,0	0,0; 100,0
Woche 75		
N[d]	17	24
Mittelwert (SD)	33,3 (25,7)	34,0 (32,4)
Median (Q1; Q3)	33,3 (16,7; 33,3)	33,3 (0,0; 58,3)
Min, Max	0,0; 100,0	0,0; 100,0
Woche 87		
N[d]	7	8
Mittelwert (SD)	26,2 (35,8)	43,8 (38,8)
Median (Q1; Q3)	16,7 (0,0; 33,3)	33,3 (16,7; 75,0)
Min, Max	0,0; 100,0	0,0; 100,0
Woche 99		
N[d]	7	6
Mittelwert (SD)	26,2 (21,2)	5,6 (13,6)
Median (Q1; Q3)	33,3 (0,0; 50,0)	0,0 (0,0; 0,0)

EORTC QLQ-C30 Schmerzen	Studie: KEYNOTE 966[a]	
	Pembrolizumab + Chemotherapie[b] N[c]= 520	Placebo + Chemotherapie[b] N[c]= 517
Min, Max	0,0; 50,0	0,0; 33,3
Woche 111		
N[d]	9	11
Mittelwert (SD)	11,1 (33,3)	25,8 (31,1)
Median (Q1; Q3)	0,0 (0,0; 0,0)	16,7 (0,0; 50,0)
Min, Max	0,0; 100,0	0,0; 83,3
Woche 123		
N[d]	3	1
Mittelwert (SD)	0,0 (0,0)	0,0 (-)
Median (Q1; Q3)	0,0 (0,0; 0,0)	0,0 (0,0; 0,0)
Min, Max	0,0; 0,0	0,0; 0,0
Woche 135		
N[d]	1	0
Mittelwert (SD)	0,0 (-)	- (-)
Median (Q1; Q3)	0,0 (0,0; 0,0)	- (-; -)
Min, Max	0,0; 0,0	-; -

a: Datenschnitt: 15. Dezember 2022
b: Chemotherapie: Gemcitabin + Cisplatin
c: Anzahl der Patient:innen: Full-Analysis-Set Population
d: Anzahl der Beobachtungen zu jedem Zeitpunkt
EORTC QLQ-C30: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Core 30; Max: Maximum; Min: Minimum; Q1: Erstes Quartil; Q3: Drittes Quartil; SD: Standardabweichung

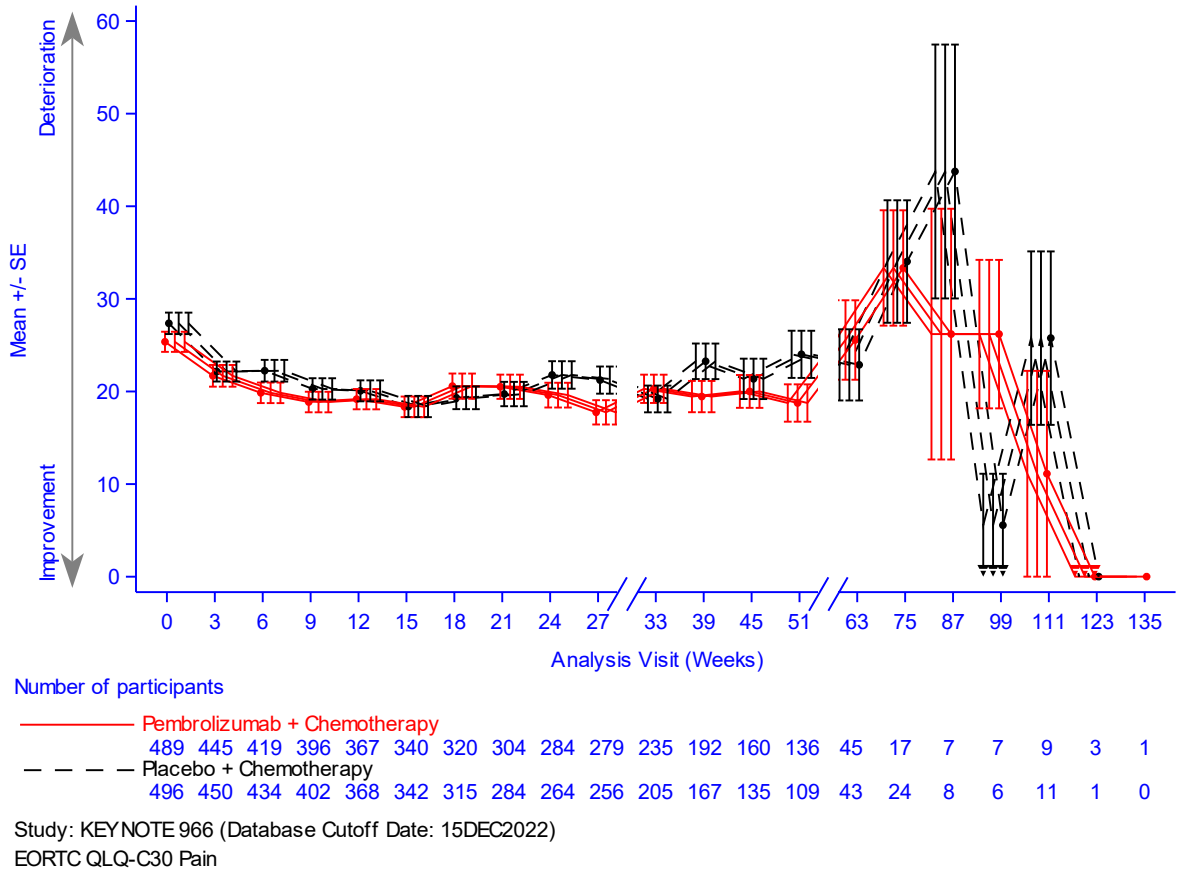


Abbildung 4G-3: EORTC QLQ-C30 Schmerzen im Studienverlauf

Symptomskala Dyspnoe

Tabelle 4G-7: EORTC QLQ-C30 Dyspnoe im Studienverlauf

EORTC QLQ-C30 Dyspnoe	Studie: KEYNOTE 966[a]	
	Pembrolizumab + Chemotherapie[b] N[c]= 520	Placebo + Chemotherapie[b] N[c]= 517
Baseline		
N[d]	489	496
Mittelwert (SD)	15,2 (21,8)	13,3 (21,4)
Median (Q1; Q3)	0,0 (0,0; 33,3)	0,0 (0,0; 33,3)
Min, Max	0,0; 100,0	0,0; 100,0
Woche 3		
N[d]	445	450
Mittelwert (SD)	17,9 (23,7)	16,1 (21,0)
Median (Q1; Q3)	0,0 (0,0; 33,3)	0,0 (0,0; 33,3)
Min, Max	0,0; 100,0	0,0; 100,0
Woche 6		
N[d]	419	434
Mittelwert (SD)	16,9 (21,8)	17,5 (24,5)
Median (Q1; Q3)	0,0 (0,0; 33,3)	0,0 (0,0; 33,3)
Min, Max	0,0; 100,0	0,0; 100,0
Woche 9		
N[d]	396	402
Mittelwert (SD)	16,6 (21,8)	16,0 (23,3)
Median (Q1; Q3)	0,0 (0,0; 33,3)	0,0 (0,0; 33,3)
Min, Max	0,0; 100,0	0,0; 100,0
Woche 12		
N[d]	367	368
Mittelwert (SD)	17,9 (22,5)	16,0 (21,9)
Median (Q1; Q3)	0,0 (0,0; 33,3)	0,0 (0,0; 33,3)
Min, Max	0,0; 100,0	0,0; 100,0
Woche 15		
N[d]	340	342
Mittelwert (SD)	18,7 (24,3)	16,7 (21,9)
Median (Q1; Q3)	0,0 (0,0; 33,3)	0,0 (0,0; 33,3)
Min, Max	0,0; 100,0	0,0; 100,0
Woche 18		
N[d]	320	315
Mittelwert (SD)	17,2 (23,7)	16,5 (20,8)
Median (Q1; Q3)	0,0 (0,0; 33,3)	0,0 (0,0; 33,3)
Min, Max	0,0; 100,0	0,0; 100,0
Woche 21		
N[d]	304	284
Mittelwert (SD)	20,6 (23,9)	17,5 (21,0)
Median (Q1; Q3)	0,0 (0,0; 33,3)	0,0 (0,0; 33,3)
Min, Max	0,0; 100,0	0,0; 100,0
Woche 24		
N[d]	284	264
Mittelwert (SD)	18,7 (23,3)	18,1 (23,2)

EORTC QLQ-C30 Dyspnoe	Studie: KEYNOTE 966[a]	
	Pembrolizumab + Chemotherapie[b] N[c]= 520	Placebo + Chemotherapie[b] N[c]= 517
Median (Q1; Q3)	0,0 (0,0; 33,3)	0,0 (0,0; 33,3)
Min, Max	0,0; 100,0	0,0; 100,0
Woche 27		
N[d]	279	256
Mittelwert (SD)	15,7 (22,0)	16,8 (22,7)
Median (Q1; Q3)	0,0 (0,0; 33,3)	0,0 (0,0; 33,3)
Min, Max	0,0; 100,0	0,0; 100,0
Woche 33		
N[d]	235	205
Mittelwert (SD)	15,2 (19,3)	16,7 (22,3)
Median (Q1; Q3)	0,0 (0,0; 33,3)	0,0 (0,0; 33,3)
Min, Max	0,0; 66,7	0,0; 100,0
Woche 39		
N[d]	192	167
Mittelwert (SD)	16,1 (21,8)	16,6 (21,9)
Median (Q1; Q3)	0,0 (0,0; 33,3)	0,0 (0,0; 33,3)
Min, Max	0,0; 100,0	0,0; 100,0
Woche 45		
N[d]	160	135
Mittelwert (SD)	16,0 (19,8)	18,0 (21,5)
Median (Q1; Q3)	0,0 (0,0; 33,3)	0,0 (0,0; 33,3)
Min, Max	0,0; 100,0	0,0; 66,7
Woche 51		
N[d]	136	109
Mittelwert (SD)	16,4 (24,3)	17,7 (22,9)
Median (Q1; Q3)	0,0 (0,0; 33,3)	0,0 (0,0; 33,3)
Min, Max	0,0; 100,0	0,0; 100,0
Woche 63		
N[d]	45	43
Mittelwert (SD)	20,0 (27,9)	18,6 (22,2)
Median (Q1; Q3)	0,0 (0,0; 33,3)	0,0 (0,0; 33,3)
Min, Max	0,0; 100,0	0,0; 66,7
Woche 75		
N[d]	17	24
Mittelwert (SD)	29,4 (30,9)	29,2 (26,6)
Median (Q1; Q3)	33,3 (0,0; 33,3)	33,3 (0,0; 33,3)
Min, Max	0,0; 100,0	0,0; 100,0
Woche 87		
N[d]	7	8
Mittelwert (SD)	33,3 (38,5)	25,0 (38,8)
Median (Q1; Q3)	33,3 (0,0; 66,7)	0,0 (0,0; 50,0)
Min, Max	0,0; 100,0	0,0; 100,0
Woche 99		
N[d]	7	6
Mittelwert (SD)	19,0 (17,8)	22,2 (17,2)
Median (Q1; Q3)	33,3 (0,0; 33,3)	33,3 (0,0; 33,3)

EORTC QLQ-C30 Dyspnoe	Studie: KEYNOTE 966[a]	
	Pembrolizumab + Chemotherapie[b] N[c]= 520	Placebo + Chemotherapie[b] N[c]= 517
Min, Max	0,0; 33,3	0,0; 33,3
Woche 111		
N[d]	9	11
Mittelwert (SD)	7,4 (14,7)	15,2 (17,4)
Median (Q1; Q3)	0,0 (0,0; 0,0)	0,0 (0,0; 33,3)
Min, Max	0,0; 33,3	0,0; 33,3
Woche 123		
N[d]	3	1
Mittelwert (SD)	33,3 (33,3)	0,0 (-)
Median (Q1; Q3)	33,3 (0,0; 66,7)	0,0 (0,0; 0,0)
Min, Max	0,0; 66,7	0,0; 0,0
Woche 135		
N[d]	1	0
Mittelwert (SD)	0,0 (-)	- (-)
Median (Q1; Q3)	0,0 (0,0; 0,0)	- (-; -)
Min, Max	0,0; 0,0	-; -

a: Datenschnitt: 15. Dezember 2022
b: Chemotherapie: Gemcitabin + Cisplatin
c: Anzahl der Patient:innen: Full-Analysis-Set Population
d: Anzahl der Beobachtungen zu jedem Zeitpunkt
EORTC QLQ-C30: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Core 30; Max: Maximum; Min: Minimum; Q1: Erstes Quartil; Q3: Drittes Quartil; SD: Standardabweichung

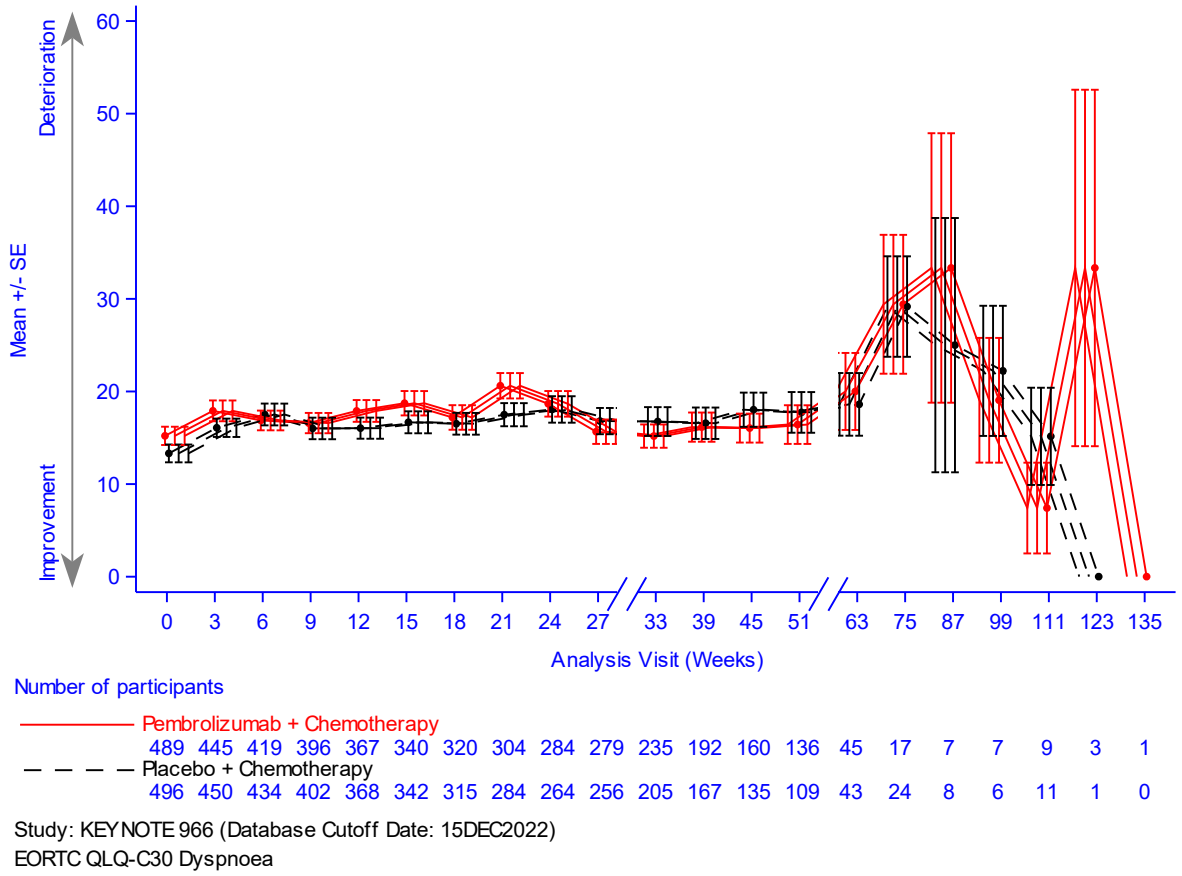


Abbildung 4G-4: EORTC QLQ-C30 Dyspnoe im Studienverlauf

Symptomskala Schlaflosigkeit

Tabelle 4G-8: EORTC QLQ-C30 Schlaflosigkeit im Studienverlauf

EORTC QLQ-C30 Schlaflosigkeit	Studie: KEYNOTE 966[a]	
	Pembrolizumab + Chemotherapie[b] N[c]= 520	Placebo + Chemotherapie[b] N[c]= 517
Baseline		
N[d]	489	496
Mittelwert (SD)	24,9 (27,7)	27,2 (30,4)
Median (Q1; Q3)	33,3 (0,0; 33,3)	33,3 (0,0; 33,3)
Min, Max	0,0; 100,0	0,0; 100,0
Woche 3		
N[d]	445	450
Mittelwert (SD)	25,5 (28,5)	24,7 (29,0)
Median (Q1; Q3)	33,3 (0,0; 33,3)	33,3 (0,0; 33,3)
Min, Max	0,0; 100,0	0,0; 100,0
Woche 6		
N[d]	419	434
Mittelwert (SD)	21,2 (26,7)	24,4 (28,2)
Median (Q1; Q3)	0,0 (0,0; 33,3)	33,3 (0,0; 33,3)
Min, Max	0,0; 100,0	0,0; 100,0
Woche 9		
N[d]	396	402
Mittelwert (SD)	20,2 (25,5)	21,2 (25,9)
Median (Q1; Q3)	0,0 (0,0; 33,3)	0,0 (0,0; 33,3)
Min, Max	0,0; 100,0	0,0; 100,0
Woche 12		
N[d]	367	368
Mittelwert (SD)	20,2 (24,6)	21,0 (24,6)
Median (Q1; Q3)	0,0 (0,0; 33,3)	0,0 (0,0; 33,3)
Min, Max	0,0; 100,0	0,0; 100,0
Woche 15		
N[d]	340	342
Mittelwert (SD)	19,8 (25,0)	20,3 (23,9)
Median (Q1; Q3)	0,0 (0,0; 33,3)	0,0 (0,0; 33,3)
Min, Max	0,0; 100,0	0,0; 100,0
Woche 18		
N[d]	320	315
Mittelwert (SD)	20,2 (25,3)	22,0 (23,7)
Median (Q1; Q3)	0,0 (0,0; 33,3)	33,3 (0,0; 33,3)
Min, Max	0,0; 100,0	0,0; 100,0
Woche 21		
N[d]	304	284
Mittelwert (SD)	20,1 (25,8)	20,2 (25,8)
Median (Q1; Q3)	0,0 (0,0; 33,3)	0,0 (0,0; 33,3)
Min, Max	0,0; 100,0	0,0; 100,0
Woche 24		
N[d]	284	264
Mittelwert (SD)	20,4 (25,5)	20,3 (24,4)

EORTC QLQ-C30 Schlaflosigkeit	Studie: KEYNOTE 966[a]	
	Pembrolizumab + Chemotherapie[b] N[c]= 520	Placebo + Chemotherapie[b] N[c]= 517
Median (Q1; Q3)	0,0 (0,0; 33,3)	0,0 (0,0; 33,3)
Min, Max	0,0; 100,0	0,0; 100,0
Woche 27		
N[d]	279	256
Mittelwert (SD)	17,1 (23,1)	19,3 (24,7)
Median (Q1; Q3)	0,0 (0,0; 33,3)	0,0 (0,0; 33,3)
Min, Max	0,0; 100,0	0,0; 100,0
Woche 33		
N[d]	235	205
Mittelwert (SD)	20,0 (26,0)	16,9 (22,0)
Median (Q1; Q3)	0,0 (0,0; 33,3)	0,0 (0,0; 33,3)
Min, Max	0,0; 100,0	0,0; 100,0
Woche 39		
N[d]	192	167
Mittelwert (SD)	21,2 (23,9)	21,6 (24,6)
Median (Q1; Q3)	33,3 (0,0; 33,3)	33,3 (0,0; 33,3)
Min, Max	0,0; 100,0	0,0; 100,0
Woche 45		
N[d]	160	135
Mittelwert (SD)	24,0 (25,9)	23,0 (28,6)
Median (Q1; Q3)	33,3 (0,0; 33,3)	0,0 (0,0; 33,3)
Min, Max	0,0; 100,0	0,0; 100,0
Woche 51		
N[d]	136	109
Mittelwert (SD)	20,1 (25,4)	22,0 (31,2)
Median (Q1; Q3)	0,0 (0,0; 33,3)	0,0 (0,0; 33,3)
Min, Max	0,0; 100,0	0,0; 100,0
Woche 63		
N[d]	45	43
Mittelwert (SD)	28,1 (31,7)	25,6 (25,0)
Median (Q1; Q3)	33,3 (0,0; 33,3)	33,3 (0,0; 33,3)
Min, Max	0,0; 100,0	0,0; 66,7
Woche 75		
N[d]	17	24
Mittelwert (SD)	37,3 (35,1)	36,1 (38,0)
Median (Q1; Q3)	33,3 (0,0; 66,7)	33,3 (0,0; 66,7)
Min, Max	0,0; 100,0	0,0; 100,0
Woche 87		
N[d]	7	8
Mittelwert (SD)	28,6 (40,5)	62,5 (27,8)
Median (Q1; Q3)	0,0 (0,0; 66,7)	66,7 (33,3; 83,3)
Min, Max	0,0; 100,0	33,3; 100,0
Woche 99		
N[d]	7	6
Mittelwert (SD)	19,0 (37,8)	11,1 (17,2)
Median (Q1; Q3)	0,0 (0,0; 33,3)	0,0 (0,0; 33,3)

EORTC QLQ-C30 Schlaflosigkeit	Studie: KEYNOTE 966[a]	
	Pembrolizumab + Chemotherapie[b] N[c]= 520	Placebo + Chemotherapie[b] N[c]= 517
Min, Max	0,0; 100,0	0,0; 33,3
Woche 111		
N[d]	9	11
Mittelwert (SD)	14,8 (33,8)	12,1 (22,5)
Median (Q1; Q3)	0,0 (0,0; 0,0)	0,0 (0,0; 33,3)
Min, Max	0,0; 100,0	0,0; 66,7
Woche 123		
N[d]	3	1
Mittelwert (SD)	0,0 (0,0)	33,3 (-)
Median (Q1; Q3)	0,0 (0,0; 0,0)	33,3 (33,3; 33,3)
Min, Max	0,0; 0,0	33,3; 33,3
Woche 135		
N[d]	1	0
Mittelwert (SD)	0,0 (-)	- (-)
Median (Q1; Q3)	0,0 (0,0; 0,0)	- (-; -)
Min, Max	0,0; 0,0	-; -

a: Datenschnitt: 15. Dezember 2022
b: Chemotherapie: Gemcitabin + Cisplatin
c: Anzahl der Patient:innen: Full-Analysis-Set Population
d: Anzahl der Beobachtungen zu jedem Zeitpunkt
EORTC QLQ-C30: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Core 30; Max: Maximum; Min: Minimum; Q1: Erstes Quartil; Q3: Drittes Quartil; SD: Standardabweichung

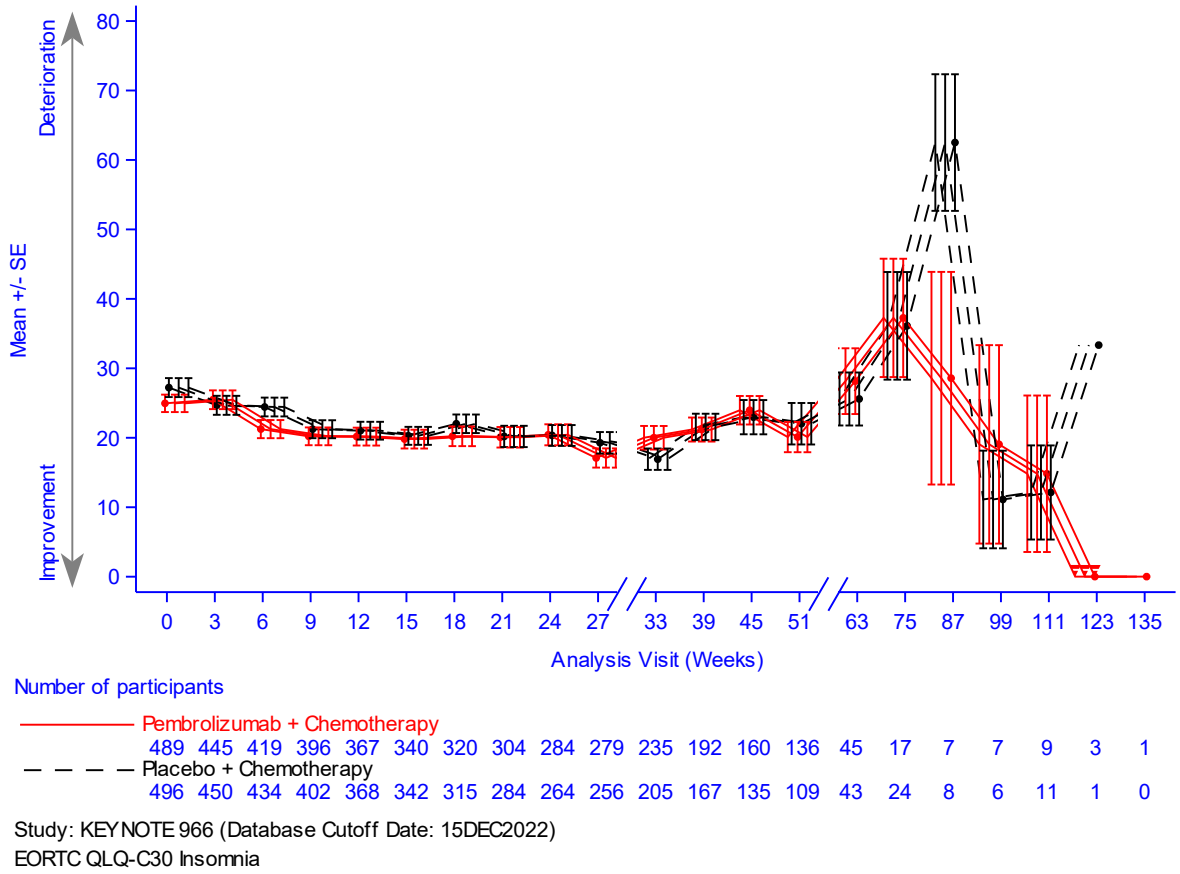


Abbildung 4G-5: EORTC QLQ-C30 Schlaflosigkeit im Studienverlauf

Symptomskala Appetitverlust

Tabelle 4G-9: EORTC QLQ-C30 Appetitverlust im Studienverlauf

EORTC QLQ-C30 Appetitverlust	Studie: KEYNOTE 966[a]	
	Pembrolizumab + Chemotherapie[b] N[c]= 520	Placebo + Chemotherapie[b] N[c]= 517
Baseline		
N[d]	489	496
Mittelwert (SD)	23,2 (28,5)	25,2 (30,8)
Median (Q1; Q3)	0,0 (0,0; 33,3)	0,0 (0,0; 33,3)
Min, Max	0,0; 100,0	0,0; 100,0
Woche 3		
N[d]	445	450
Mittelwert (SD)	25,1 (27,9)	25,0 (28,5)
Median (Q1; Q3)	33,3 (0,0; 33,3)	33,3 (0,0; 33,3)
Min, Max	0,0; 100,0	0,0; 100,0
Woche 6		
N[d]	419	434
Mittelwert (SD)	23,9 (27,4)	24,0 (28,6)
Median (Q1; Q3)	33,3 (0,0; 33,3)	0,0 (0,0; 33,3)
Min, Max	0,0; 100,0	0,0; 100,0
Woche 9		
N[d]	396	402
Mittelwert (SD)	22,2 (25,7)	22,8 (25,8)
Median (Q1; Q3)	33,3 (0,0; 33,3)	33,3 (0,0; 33,3)
Min, Max	0,0; 100,0	0,0; 100,0
Woche 12		
N[d]	367	368
Mittelwert (SD)	20,7 (23,9)	22,3 (25,7)
Median (Q1; Q3)	0,0 (0,0; 33,3)	33,3 (0,0; 33,3)
Min, Max	0,0; 100,0	0,0; 100,0
Woche 15		
N[d]	340	342
Mittelwert (SD)	22,7 (25,5)	19,0 (24,3)
Median (Q1; Q3)	33,3 (0,0; 33,3)	0,0 (0,0; 33,3)
Min, Max	0,0; 100,0	0,0; 100,0
Woche 18		
N[d]	320	315
Mittelwert (SD)	19,5 (26,6)	22,3 (25,2)
Median (Q1; Q3)	0,0 (0,0; 33,3)	33,3 (0,0; 33,3)
Min, Max	0,0; 100,0	0,0; 100,0
Woche 21		
N[d]	304	284
Mittelwert (SD)	20,7 (26,1)	20,5 (24,2)
Median (Q1; Q3)	0,0 (0,0; 33,3)	0,0 (0,0; 33,3)
Min, Max	0,0; 100,0	0,0; 100,0
Woche 24		
N[d]	284	264
Mittelwert (SD)	20,3 (23,7)	21,7 (26,2)

EORTC QLQ-C30 Appetitverlust	Studie: KEYNOTE 966[a]	
	Pembrolizumab + Chemotherapie[b] N[c]= 520	Placebo + Chemotherapie[b] N[c]= 517
Median (Q1; Q3)	0,0 (0,0; 33,3)	0,0 (0,0; 33,3)
Min, Max	0,0; 100,0	0,0; 100,0
Woche 27		
N[d]	279	256
Mittelwert (SD)	17,7 (24,3)	18,4 (23,9)
Median (Q1; Q3)	0,0 (0,0; 33,3)	0,0 (0,0; 33,3)
Min, Max	0,0; 100,0	0,0; 100,0
Woche 33		
N[d]	235	205
Mittelwert (SD)	18,2 (24,7)	17,4 (23,5)
Median (Q1; Q3)	0,0 (0,0; 33,3)	0,0 (0,0; 33,3)
Min, Max	0,0; 100,0	0,0; 100,0
Woche 39		
N[d]	192	167
Mittelwert (SD)	18,8 (26,1)	18,0 (25,8)
Median (Q1; Q3)	0,0 (0,0; 33,3)	0,0 (0,0; 33,3)
Min, Max	0,0; 100,0	0,0; 100,0
Woche 45		
N[d]	160	135
Mittelwert (SD)	16,5 (23,3)	18,0 (25,4)
Median (Q1; Q3)	0,0 (0,0; 33,3)	0,0 (0,0; 33,3)
Min, Max	0,0; 100,0	0,0; 100,0
Woche 51		
N[d]	136	109
Mittelwert (SD)	17,9 (26,9)	17,1 (28,9)
Median (Q1; Q3)	0,0 (0,0; 33,3)	0,0 (0,0; 33,3)
Min, Max	0,0; 100,0	0,0; 100,0
Woche 63		
N[d]	45	43
Mittelwert (SD)	19,3 (30,6)	20,2 (25,3)
Median (Q1; Q3)	0,0 (0,0; 33,3)	0,0 (0,0; 33,3)
Min, Max	0,0; 100,0	0,0; 100,0
Woche 75		
N[d]	17	24
Mittelwert (SD)	39,2 (31,7)	23,6 (30,3)
Median (Q1; Q3)	33,3 (33,3; 66,7)	16,7 (0,0; 33,3)
Min, Max	0,0; 100,0	0,0; 100,0
Woche 87		
N[d]	7	8
Mittelwert (SD)	33,3 (43,0)	37,5 (51,8)
Median (Q1; Q3)	0,0 (0,0; 66,7)	0,0 (0,0; 100,0)
Min, Max	0,0; 100,0	0,0; 100,0
Woche 99		
N[d]	7	6
Mittelwert (SD)	28,6 (40,5)	22,2 (40,4)
Median (Q1; Q3)	0,0 (0,0; 66,7)	0,0 (0,0; 33,3)

EORTC QLQ-C30 Appetitverlust	Studie: KEYNOTE 966[a]	
	Pembrolizumab + Chemotherapie[b] N[c]= 520	Placebo + Chemotherapie[b] N[c]= 517
Min, Max	0,0; 100,0	0,0; 100,0
Woche 111		
N[d]	9	11
Mittelwert (SD)	11,1 (16,7)	15,2 (17,4)
Median (Q1; Q3)	0,0 (0,0; 33,3)	0,0 (0,0; 33,3)
Min, Max	0,0; 33,3	0,0; 33,3
Woche 123		
N[d]	3	1
Mittelwert (SD)	11,1 (19,2)	0,0 (-)
Median (Q1; Q3)	0,0 (0,0; 33,3)	0,0 (0,0; 0,0)
Min, Max	0,0; 33,3	0,0; 0,0
Woche 135		
N[d]	1	0
Mittelwert (SD)	0,0 (-)	- (-)
Median (Q1; Q3)	0,0 (0,0; 0,0)	- (-; -)
Min, Max	0,0; 0,0	-; -

a: Datenschnitt: 15. Dezember 2022
b: Chemotherapie: Gemcitabin + Cisplatin
c: Anzahl der Patient:innen: Full-Analysis-Set Population
d: Anzahl der Beobachtungen zu jedem Zeitpunkt
EORTC QLQ-C30: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Core 30; Max: Maximum; Min: Minimum; Q1: Erstes Quartil; Q3: Drittes Quartil; SD: Standardabweichung

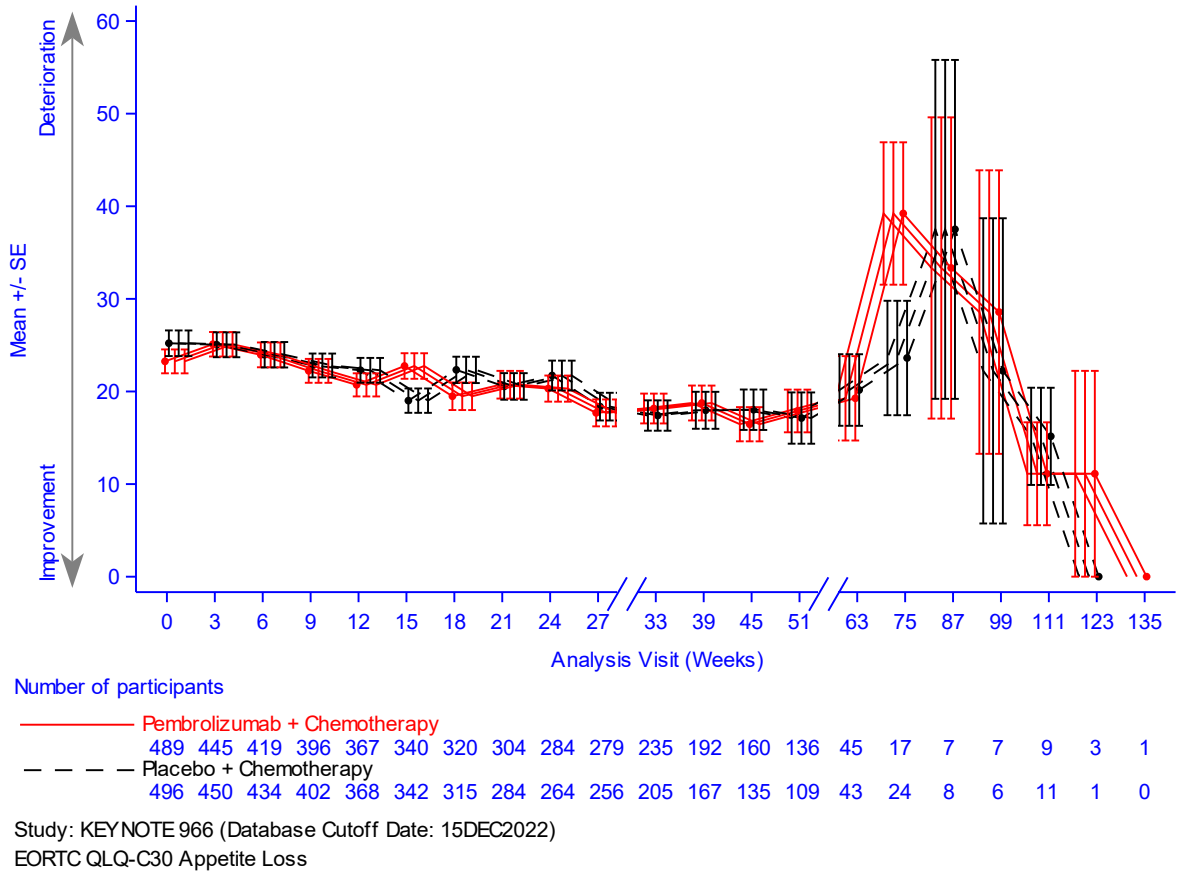


Abbildung 4G-6: EORTC QLQ-C30 Appetitverlust im Studienverlauf

Symptomskala Verstopfung

Tabelle 4G-10: EORTC QLQ-C30 Verstopfung im Studienverlauf

EORTC QLQ-C30 Verstopfung	Studie: KEYNOTE 966[a]	
	Pembrolizumab + Chemotherapie[b] N[c]= 520	Placebo + Chemotherapie[b] N[c]= 517
Baseline		
N[d]	489	496
Mittelwert (SD)	17,7 (26,7)	17,7 (26,4)
Median (Q1; Q3)	0,0 (0,0; 33,3)	0,0 (0,0; 33,3)
Min, Max	0,0; 100,0	0,0; 100,0
Woche 3		
N[d]	445	450
Mittelwert (SD)	24,2 (28,1)	23,6 (28,3)
Median (Q1; Q3)	33,3 (0,0; 33,3)	0,0 (0,0; 33,3)
Min, Max	0,0; 100,0	0,0; 100,0
Woche 6		
N[d]	419	434
Mittelwert (SD)	20,1 (25,9)	22,3 (27,9)
Median (Q1; Q3)	0,0 (0,0; 33,3)	0,0 (0,0; 33,3)
Min, Max	0,0; 100,0	0,0; 100,0
Woche 9		
N[d]	396	402
Mittelwert (SD)	18,9 (25,2)	19,4 (26,0)
Median (Q1; Q3)	0,0 (0,0; 33,3)	0,0 (0,0; 33,3)
Min, Max	0,0; 100,0	0,0; 100,0
Woche 12		
N[d]	367	368
Mittelwert (SD)	16,8 (22,7)	18,3 (24,9)
Median (Q1; Q3)	0,0 (0,0; 33,3)	0,0 (0,0; 33,3)
Min, Max	0,0; 100,0	0,0; 100,0
Woche 15		
N[d]	340	342
Mittelwert (SD)	16,0 (22,1)	17,5 (23,8)
Median (Q1; Q3)	0,0 (0,0; 33,3)	0,0 (0,0; 33,3)
Min, Max	0,0; 100,0	0,0; 100,0
Woche 18		
N[d]	320	315
Mittelwert (SD)	15,9 (21,6)	18,3 (25,7)
Median (Q1; Q3)	0,0 (0,0; 33,3)	0,0 (0,0; 33,3)
Min, Max	0,0; 100,0	0,0; 100,0
Woche 21		
N[d]	304	284
Mittelwert (SD)	18,3 (24,3)	15,8 (23,2)
Median (Q1; Q3)	0,0 (0,0; 33,3)	0,0 (0,0; 33,3)
Min, Max	0,0; 100,0	0,0; 100,0
Woche 24		
N[d]	284	264
Mittelwert (SD)	16,1 (22,3)	16,4 (23,4)

EORTC QLQ-C30 Verstopfung	Studie: KEYNOTE 966[a]	
	Pembrolizumab + Chemotherapie[b] N[c]= 520	Placebo + Chemotherapie[b] N[c]= 517
Median (Q1; Q3)	0,0 (0,0; 33,3)	0,0 (0,0; 33,3)
Min, Max	0,0; 100,0	0,0; 100,0
Woche 27		
N[d]	279	256
Mittelwert (SD)	13,5 (20,7)	14,7 (21,2)
Median (Q1; Q3)	0,0 (0,0; 33,3)	0,0 (0,0; 33,3)
Min, Max	0,0; 100,0	0,0; 100,0
Woche 33		
N[d]	235	205
Mittelwert (SD)	13,3 (21,8)	14,0 (21,9)
Median (Q1; Q3)	0,0 (0,0; 33,3)	0,0 (0,0; 33,3)
Min, Max	0,0; 100,0	0,0; 100,0
Woche 39		
N[d]	192	167
Mittelwert (SD)	16,0 (23,6)	13,2 (20,7)
Median (Q1; Q3)	0,0 (0,0; 33,3)	0,0 (0,0; 33,3)
Min, Max	0,0; 100,0	0,0; 100,0
Woche 45		
N[d]	160	135
Mittelwert (SD)	13,8 (21,6)	12,8 (21,2)
Median (Q1; Q3)	0,0 (0,0; 33,3)	0,0 (0,0; 33,3)
Min, Max	0,0; 100,0	0,0; 100,0
Woche 51		
N[d]	136	109
Mittelwert (SD)	13,7 (22,4)	16,8 (24,3)
Median (Q1; Q3)	0,0 (0,0; 33,3)	0,0 (0,0; 33,3)
Min, Max	0,0; 100,0	0,0; 100,0
Woche 63		
N[d]	45	43
Mittelwert (SD)	16,3 (28,1)	19,4 (20,9)
Median (Q1; Q3)	0,0 (0,0; 33,3)	33,3 (0,0; 33,3)
Min, Max	0,0; 100,0	0,0; 66,7
Woche 75		
N[d]	17	24
Mittelwert (SD)	29,4 (35,1)	20,8 (30,8)
Median (Q1; Q3)	33,3 (0,0; 33,3)	0,0 (0,0; 33,3)
Min, Max	0,0; 100,0	0,0; 100,0
Woche 87		
N[d]	7	8
Mittelwert (SD)	28,6 (35,6)	50,0 (47,1)
Median (Q1; Q3)	33,3 (0,0; 33,3)	50,0 (0,0; 100,0)
Min, Max	0,0; 100,0	0,0; 100,0
Woche 99		
N[d]	7	6
Mittelwert (SD)	23,8 (25,2)	11,1 (17,2)
Median (Q1; Q3)	33,3 (0,0; 33,3)	0,0 (0,0; 33,3)

EORTC QLQ-C30 Verstopfung	Studie: KEYNOTE 966[a]	
	Pembrolizumab + Chemotherapie[b] N[c]= 520	Placebo + Chemotherapie[b] N[c]= 517
Min, Max	0,0; 66,7	0,0; 33,3
Woche 111		
N[d]	9	11
Mittelwert (SD)	18,5 (33,8)	9,1 (15,6)
Median (Q1; Q3)	0,0 (0,0; 33,3)	0,0 (0,0; 33,3)
Min, Max	0,0; 100,0	0,0; 33,3
Woche 123		
N[d]	3	1
Mittelwert (SD)	0,0 (0,0)	0,0 (-)
Median (Q1; Q3)	0,0 (0,0; 0,0)	0,0 (0,0; 0,0)
Min, Max	0,0; 0,0	0,0; 0,0
Woche 135		
N[d]	1	0
Mittelwert (SD)	0,0 (-)	- (-)
Median (Q1; Q3)	0,0 (0,0; 0,0)	- (-; -)
Min, Max	0,0; 0,0	-; -

a: Datenschnitt: 15. Dezember 2022
b: Chemotherapie: Gemcitabin + Cisplatin
c: Anzahl der Patient:innen: Full-Analysis-Set Population
d: Anzahl der Beobachtungen zu jedem Zeitpunkt
EORTC QLQ-C30: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Core 30; Max: Maximum; Min: Minimum; Q1: Erstes Quartil; Q3: Drittes Quartil; SD: Standardabweichung

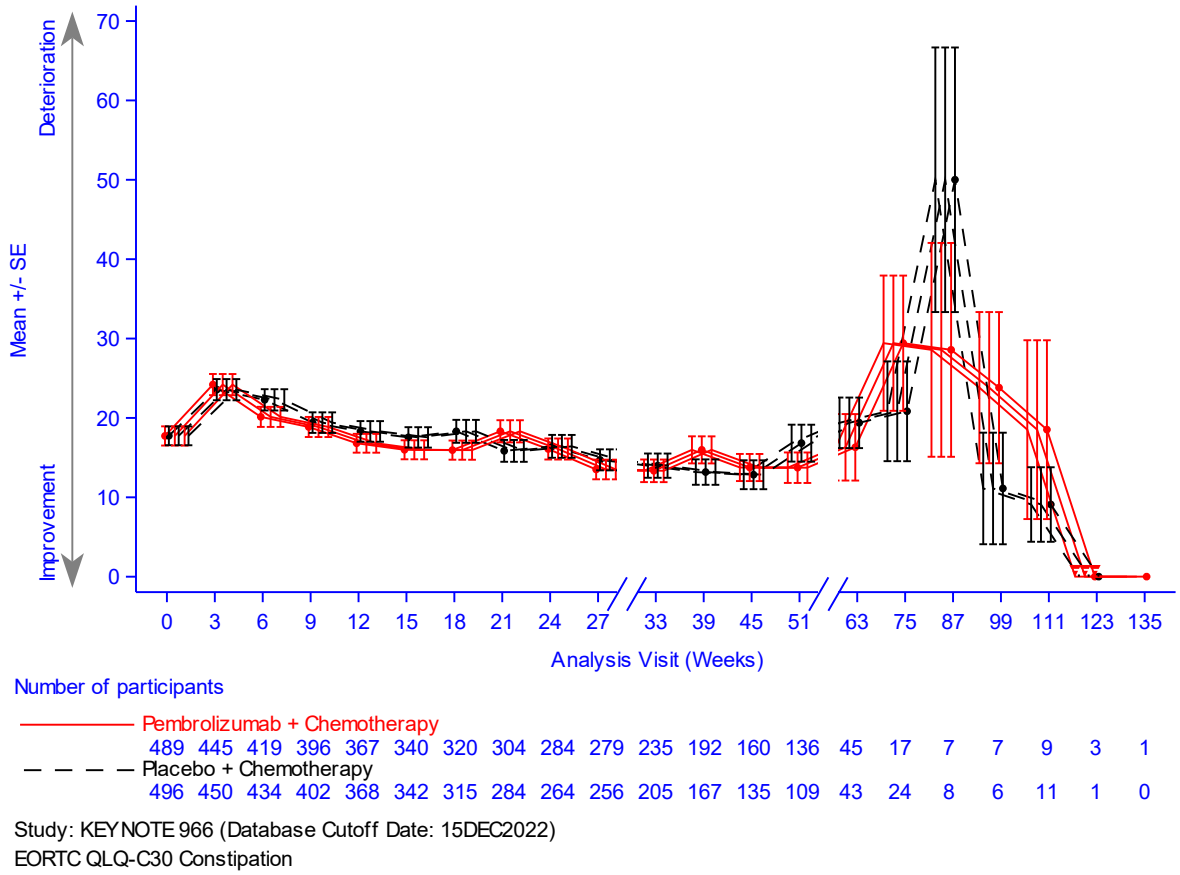


Abbildung 4G-7: EORTC QLQ-C30 Verstopfung im Studienverlauf

Symptomskala Diarrhö

Tabelle 4G-11: EORTC QLQ-C30 Diarrhö im Studienverlauf

EORTC QLQ-C30 Diarrhö	Studie: KEYNOTE 966[a]	
	Pembrolizumab + Chemotherapie[b] N[c]= 520	Placebo + Chemotherapie[b] N[c]= 517
Baseline		
N[d]	489	496
Mittelwert (SD)	6,1 (15,3)	6,5 (16,4)
Median (Q1; Q3)	0,0 (0,0; 0,0)	0,0 (0,0; 0,0)
Min, Max	0,0; 100,0	0,0; 100,0
Woche 3		
N[d]	445	450
Mittelwert (SD)	7,7 (17,7)	6,9 (16,6)
Median (Q1; Q3)	0,0 (0,0; 0,0)	0,0 (0,0; 0,0)
Min, Max	0,0; 100,0	0,0; 100,0
Woche 6		
N[d]	419	434
Mittelwert (SD)	6,4 (16,3)	6,1 (15,1)
Median (Q1; Q3)	0,0 (0,0; 0,0)	0,0 (0,0; 0,0)
Min, Max	0,0; 100,0	0,0; 100,0
Woche 9		
N[d]	396	402
Mittelwert (SD)	5,6 (14,9)	7,6 (17,4)
Median (Q1; Q3)	0,0 (0,0; 0,0)	0,0 (0,0; 0,0)
Min, Max	0,0; 100,0	0,0; 100,0
Woche 12		
N[d]	367	368
Mittelwert (SD)	6,4 (15,3)	6,8 (16,8)
Median (Q1; Q3)	0,0 (0,0; 0,0)	0,0 (0,0; 0,0)
Min, Max	0,0; 100,0	0,0; 100,0
Woche 15		
N[d]	340	342
Mittelwert (SD)	6,2 (15,3)	7,5 (17,5)
Median (Q1; Q3)	0,0 (0,0; 0,0)	0,0 (0,0; 0,0)
Min, Max	0,0; 100,0	0,0; 100,0
Woche 18		
N[d]	320	315
Mittelwert (SD)	6,5 (16,5)	8,8 (17,4)
Median (Q1; Q3)	0,0 (0,0; 0,0)	0,0 (0,0; 0,0)
Min, Max	0,0; 100,0	0,0; 100,0
Woche 21		
N[d]	304	284
Mittelwert (SD)	6,9 (15,3)	7,7 (16,7)
Median (Q1; Q3)	0,0 (0,0; 0,0)	0,0 (0,0; 0,0)
Min, Max	0,0; 66,7	0,0; 100,0
Woche 24		
N[d]	284	264
Mittelwert (SD)	5,9 (14,2)	7,3 (15,3)

EORTC QLQ-C30 Diarrhö	Studie: KEYNOTE 966[a]	
	Pembrolizumab + Chemotherapie[b] N[c]= 520	Placebo + Chemotherapie[b] N[c]= 517
Median (Q1; Q3)	0,0 (0,0; 0,0)	0,0 (0,0; 0,0)
Min, Max	0,0; 66,7	0,0; 66,7
Woche 27		
N[d]	279	256
Mittelwert (SD)	5,9 (14,2)	6,6 (15,2)
Median (Q1; Q3)	0,0 (0,0; 0,0)	0,0 (0,0; 0,0)
Min, Max	0,0; 66,7	0,0; 66,7
Woche 33		
N[d]	235	205
Mittelwert (SD)	5,8 (15,1)	7,6 (17,2)
Median (Q1; Q3)	0,0 (0,0; 0,0)	0,0 (0,0; 0,0)
Min, Max	0,0; 100,0	0,0; 100,0
Woche 39		
N[d]	192	167
Mittelwert (SD)	4,9 (12,7)	7,6 (18,2)
Median (Q1; Q3)	0,0 (0,0; 0,0)	0,0 (0,0; 0,0)
Min, Max	0,0; 66,7	0,0; 100,0
Woche 45		
N[d]	160	135
Mittelwert (SD)	6,9 (14,5)	8,9 (19,6)
Median (Q1; Q3)	0,0 (0,0; 0,0)	0,0 (0,0; 0,0)
Min, Max	0,0; 66,7	0,0; 100,0
Woche 51		
N[d]	136	109
Mittelwert (SD)	6,1 (15,3)	7,3 (21,9)
Median (Q1; Q3)	0,0 (0,0; 0,0)	0,0 (0,0; 0,0)
Min, Max	0,0; 100,0	0,0; 100,0
Woche 63		
N[d]	45	43
Mittelwert (SD)	5,9 (12,9)	12,4 (25,2)
Median (Q1; Q3)	0,0 (0,0; 0,0)	0,0 (0,0; 33,3)
Min, Max	0,0; 33,3	0,0; 100,0
Woche 75		
N[d]	17	24
Mittelwert (SD)	7,8 (14,6)	16,7 (27,8)
Median (Q1; Q3)	0,0 (0,0; 0,0)	0,0 (0,0; 33,3)
Min, Max	0,0; 33,3	0,0; 100,0
Woche 87		
N[d]	7	8
Mittelwert (SD)	0,0 (0,0)	20,8 (35,4)
Median (Q1; Q3)	0,0 (0,0; 0,0)	0,0 (0,0; 33,3)
Min, Max	0,0; 0,0	0,0; 100,0
Woche 99		
N[d]	7	6
Mittelwert (SD)	0,0 (0,0)	22,2 (40,4)
Median (Q1; Q3)	0,0 (0,0; 0,0)	0,0 (0,0; 33,3)

EORTC QLQ-C30 Diarrhö	Studie: KEYNOTE 966[a]	
	Pembrolizumab + Chemotherapie[b] N[c]= 520	Placebo + Chemotherapie[b] N[c]= 517
Min, Max	0,0; 0,0	0,0; 100,0
Woche 111		
N[d]	9	11
Mittelwert (SD)	7,4 (14,7)	3,0 (10,1)
Median (Q1; Q3)	0,0 (0,0; 0,0)	0,0 (0,0; 0,0)
Min, Max	0,0; 33,3	0,0; 33,3
Woche 123		
N[d]	3	1
Mittelwert (SD)	11,1 (19,2)	0,0 (-)
Median (Q1; Q3)	0,0 (0,0; 33,3)	0,0 (0,0; 0,0)
Min, Max	0,0; 33,3	0,0; 0,0
Woche 135		
N[d]	1	0
Mittelwert (SD)	0,0 (-)	- (-)
Median (Q1; Q3)	0,0 (0,0; 0,0)	- (-; -)
Min, Max	0,0; 0,0	-; -

a: Datenschnitt: 15. Dezember 2022
b: Chemotherapie: Gemcitabin + Cisplatin
c: Anzahl der Patient:innen: Full-Analysis-Set Population
d: Anzahl der Beobachtungen zu jedem Zeitpunkt
EORTC QLQ-C30: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Core 30; Max: Maximum; Min: Minimum; Q1: Erstes Quartil; Q3: Drittes Quartil; SD: Standardabweichung

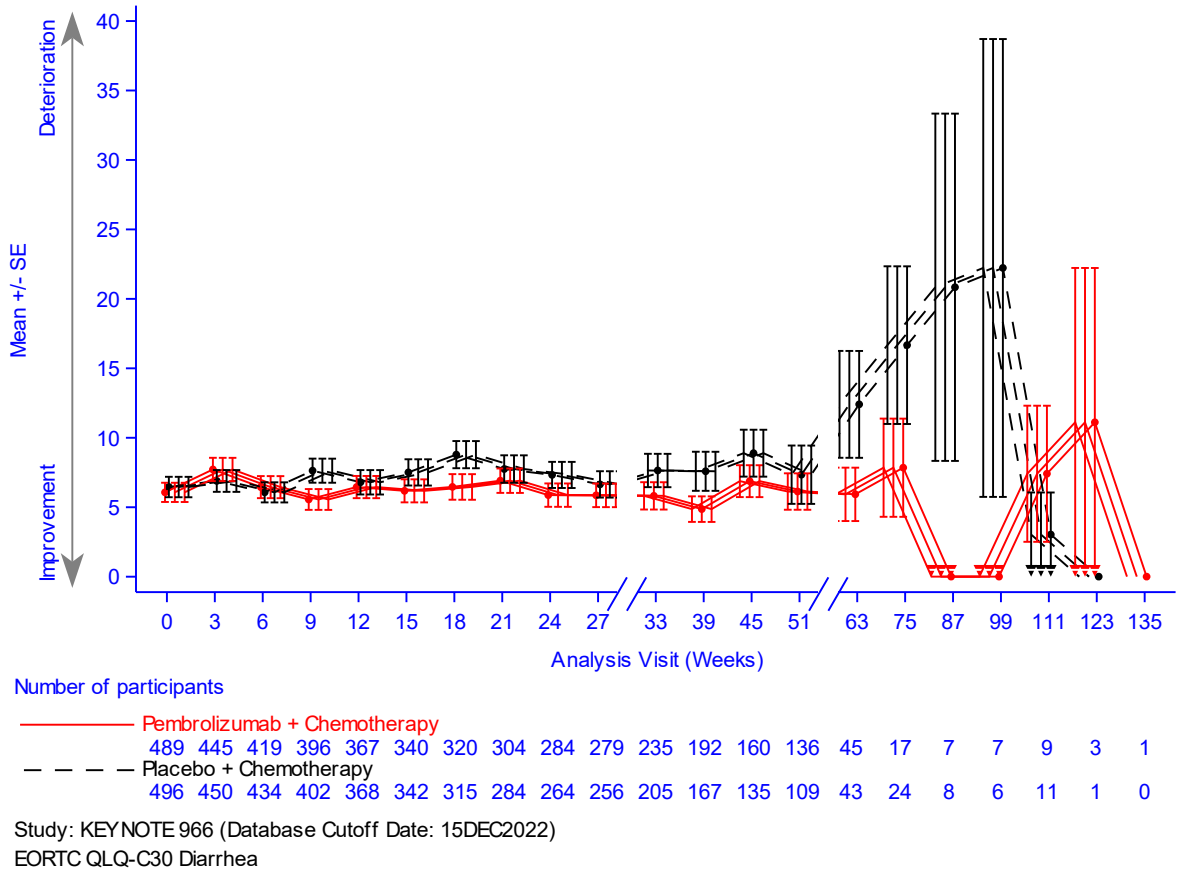


Abbildung 4G-8: EORTC QLQ-C30 Diarrhö im Studienverlauf

Anhang 4-G2.1: EORTC QLQ-BIL21 im Studienverlauf

Symptomskala Essen

Tabelle 4G-12: EORTC QLQ-BIL21 Essen im Studienverlauf

EORTC QLQ-BIL21 Schwierigkeiten bei der Nahrungsaufnahme	Studie: KEYNOTE 966[a]	
	Pembrolizumab + Chemotherapie[b] N[c]= 520	Placebo + Chemotherapie[b] N[c]= 516
Baseline		
N[d]	482	490
Mittelwert (SD)	16,7 (19,2)	19,4 (22,1)
Median (Q1; Q3)	8,3 (0,0; 25,0)	8,3 (0,0; 33,3)
Min, Max	0,0; 100,0	0,0; 100,0
Woche 3		
N[d]	444	448
Mittelwert (SD)	19,8 (21,5)	19,7 (20,2)
Median (Q1; Q3)	16,7 (0,0; 33,3)	16,7 (0,0; 25,0)
Min, Max	0,0; 100,0	0,0; 100,0
Woche 6		
N[d]	415	428
Mittelwert (SD)	19,6 (20,4)	19,4 (20,5)
Median (Q1; Q3)	16,7 (0,0; 33,3)	16,7 (0,0; 33,3)
Min, Max	0,0; 91,7	0,0; 100,0
Woche 9		
N[d]	393	399
Mittelwert (SD)	18,4 (19,2)	19,3 (20,3)
Median (Q1; Q3)	16,7 (0,0; 25,0)	16,7 (0,0; 33,3)
Min, Max	0,0; 100,0	0,0; 100,0
Woche 12		
N[d]	367	367
Mittelwert (SD)	16,7 (18,6)	18,8 (19,1)
Median (Q1; Q3)	8,3 (0,0; 25,0)	16,7 (0,0; 25,0)
Min, Max	0,0; 100,0	0,0; 100,0
Woche 15		
N[d]	337	339
Mittelwert (SD)	18,2 (18,6)	18,1 (18,0)
Median (Q1; Q3)	16,7 (0,0; 33,3)	16,7 (0,0; 33,3)
Min, Max	0,0; 91,7	0,0; 100,0
Woche 18		
N[d]	320	315
Mittelwert (SD)	17,5 (20,8)	19,0 (19,3)
Median (Q1; Q3)	8,3 (0,0; 25,0)	16,7 (0,0; 33,3)
Min, Max	0,0; 100,0	0,0; 100,0
Woche 21		
N[d]	301	282
Mittelwert (SD)	18,2 (21,1)	18,6 (18,6)
Median (Q1; Q3)	8,3 (0,0; 25,0)	16,7 (0,0; 33,3)
Min, Max	0,0; 100,0	0,0; 100,0

EORTC QLQ-BIL21 Schwierigkeiten bei der Nahrungsaufnahme	Studie: KEYNOTE 966[a]	
	Pembrolizumab + Chemotherapie[b] N[c]= 520	Placebo + Chemotherapie[b] N[c]= 516
Woche 24		
N[d]	283	263
Mittelwert (SD)	18,0 (19,3)	20,4 (19,4)
Median (Q1; Q3)	8,3 (0,0; 25,0)	16,7 (8,3; 33,3)
Min, Max	0,0; 83,3	0,0; 100,0
Woche 27		
N[d]	277	256
Mittelwert (SD)	14,6 (16,7)	17,1 (18,2)
Median (Q1; Q3)	8,3 (0,0; 25,0)	16,7 (0,0; 25,0)
Min, Max	0,0; 100,0	0,0; 100,0
Woche 33		
N[d]	235	203
Mittelwert (SD)	15,0 (17,6)	16,0 (17,7)
Median (Q1; Q3)	8,3 (0,0; 25,0)	8,3 (0,0; 25,0)
Min, Max	0,0; 91,7	0,0; 100,0
Woche 39		
N[d]	192	167
Mittelwert (SD)	15,6 (19,0)	16,6 (19,1)
Median (Q1; Q3)	8,3 (0,0; 25,0)	8,3 (0,0; 25,0)
Min, Max	0,0; 100,0	0,0; 83,3
Woche 45		
N[d]	160	135
Mittelwert (SD)	13,5 (15,0)	15,1 (18,6)
Median (Q1; Q3)	8,3 (0,0; 20,8)	8,3 (0,0; 25,0)
Min, Max	0,0; 75,0	0,0; 91,7
Woche 51		
N[d]	135	109
Mittelwert (SD)	15,2 (18,6)	13,7 (18,2)
Median (Q1; Q3)	8,3 (0,0; 25,0)	8,3 (0,0; 16,7)
Min, Max	0,0; 100,0	0,0; 91,7
Woche 63		
N[d]	45	43
Mittelwert (SD)	17,4 (24,5)	16,5 (16,9)
Median (Q1; Q3)	8,3 (0,0; 25,0)	8,3 (8,3; 25,0)
Min, Max	0,0; 100,0	0,0; 66,7
Woche 75		
N[d]	17	24
Mittelwert (SD)	27,5 (16,3)	29,9 (29,0)
Median (Q1; Q3)	25,0 (16,7; 41,7)	25,0 (0,0; 45,8)
Min, Max	0,0; 50,0	0,0; 100,0
Woche 87		
N[d]	7	8
Mittelwert (SD)	23,8 (37,1)	30,2 (30,8)
Median (Q1; Q3)	0,0 (0,0; 33,3)	12,5 (8,3; 62,5)
Min, Max	0,0; 100,0	0,0; 75,0
Woche 99		

EORTC QLQ-BIL21 Schwierigkeiten bei der Nahrungsaufnahme	Studie: KEYNOTE 966[a]	
	Pembrolizumab + Chemotherapie[b] N[c]= 520	Placebo + Chemotherapie[b] N[c]= 516
N[d]	7	6
Mittelwert (SD)	19,0 (19,7)	11,1 (19,5)
Median (Q1; Q3)	16,7 (0,0; 41,7)	4,2 (0,0; 8,3)
Min, Max	0,0; 50,0	0,0; 50,0
Woche 111		
N[d]	9	11
Mittelwert (SD)	7,4 (8,8)	11,4 (10,7)
Median (Q1; Q3)	8,3 (0,0; 8,3)	8,3 (0,0; 25,0)
Min, Max	0,0; 25,0	0,0; 25,0
Woche 123		
N[d]	3	1
Mittelwert (SD)	5,6 (4,8)	0,0 (-)
Median (Q1; Q3)	8,3 (0,0; 8,3)	0,0 (0,0; 0,0)
Min, Max	0,0; 8,3	0,0; 0,0
Woche 135		
N[d]	1	0
Mittelwert (SD)	0,0 (-)	- (-)
Median (Q1; Q3)	0,0 (0,0; 0,0)	- (-; -)
Min, Max	0,0; 0,0	-; -

a: Datenschnitt: 15. Dezember 2022
b: Chemotherapie: Gemcitabin + Cisplatin
c: Anzahl der Patient:innen: Full-Analysis-Set Population
d: Anzahl der Beobachtungen zu jedem Zeitpunkt
EORTC QLQ-BIL21: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Cholangiokarzinom und Gallenblasenkarzinom 21 Fragen; Max: Maximum; Min: Minimum; Q1: Erstes Quartil; Q3: Drittes Quartil; SD: Standardabweichung

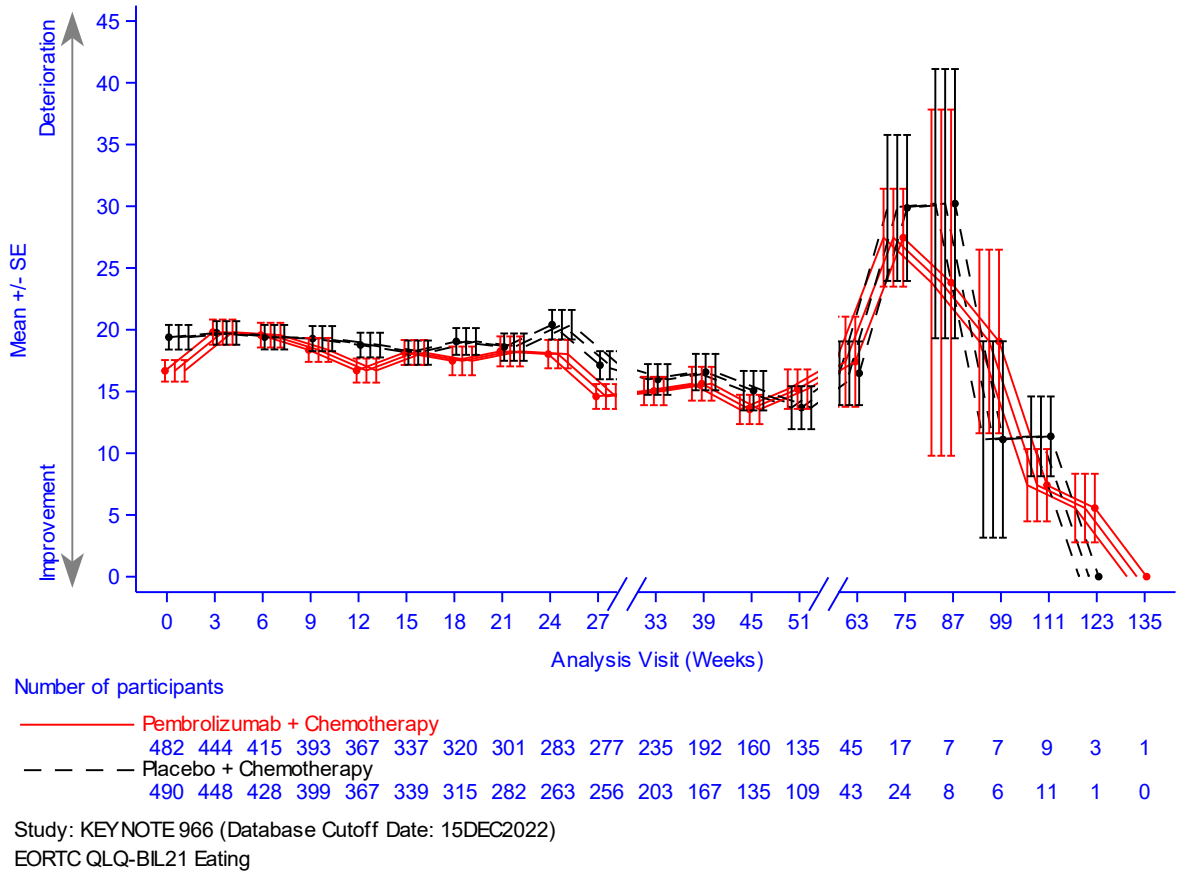


Abbildung 4G-9: EORTC QLQ-BIL21 Essen im Studienverlauf

Symptomskala Ikterus

Tabelle 4G-13: EORTC QLQ-BIL21 Ikterus im Studienverlauf

EORTC QLQ-BIL21 Gelbsucht	Studie: KEYNOTE 966[a]	
	Pembrolizumab + Chemotherapie[b] N[c]= 520	Placebo + Chemotherapie[b] N[c]= 516
Baseline		
N[d]	482	490
Mittelwert (SD)	6,0 (12,4)	6,3 (12,0)
Median (Q1; Q3)	0,0 (0,0; 11,1)	0,0 (0,0; 11,1)
Min, Max	0,0; 100,0	0,0; 100,0
Woche 3		
N[d]	444	448
Mittelwert (SD)	8,0 (13,0)	6,3 (11,2)
Median (Q1; Q3)	0,0 (0,0; 11,1)	0,0 (0,0; 11,1)
Min, Max	0,0; 88,9	0,0; 100,0
Woche 6		
N[d]	415	428
Mittelwert (SD)	6,5 (11,4)	5,9 (10,8)
Median (Q1; Q3)	0,0 (0,0; 11,1)	0,0 (0,0; 11,1)
Min, Max	0,0; 77,8	0,0; 66,7
Woche 9		
N[d]	393	399
Mittelwert (SD)	5,5 (10,5)	5,5 (10,1)
Median (Q1; Q3)	0,0 (0,0; 11,1)	0,0 (0,0; 11,1)
Min, Max	0,0; 77,8	0,0; 88,9
Woche 12		
N[d]	367	367
Mittelwert (SD)	6,1 (11,7)	5,7 (10,9)
Median (Q1; Q3)	0,0 (0,0; 11,1)	0,0 (0,0; 11,1)
Min, Max	0,0; 88,9	0,0; 88,9
Woche 15		
N[d]	337	339
Mittelwert (SD)	5,6 (10,0)	5,4 (10,4)
Median (Q1; Q3)	0,0 (0,0; 11,1)	0,0 (0,0; 11,1)
Min, Max	0,0; 66,7	0,0; 77,8
Woche 18		
N[d]	320	315
Mittelwert (SD)	5,9 (11,3)	5,5 (10,5)
Median (Q1; Q3)	0,0 (0,0; 11,1)	0,0 (0,0; 11,1)
Min, Max	0,0; 66,7	0,0; 77,8
Woche 21		
N[d]	301	282
Mittelwert (SD)	6,8 (13,1)	4,9 (9,0)
Median (Q1; Q3)	0,0 (0,0; 11,1)	0,0 (0,0; 11,1)
Min, Max	0,0; 100,0	0,0; 44,4
Woche 24		
N[d]	283	263
Mittelwert (SD)	6,5 (11,4)	4,7 (8,5)

EORTC QLQ-BIL21 Gelbsucht	Studie: KEYNOTE 966[a]	
	Pembrolizumab + Chemotherapie[b] N[c]= 520	Placebo + Chemotherapie[b] N[c]= 516
Median (Q1; Q3)	0,0 (0,0; 11,1)	0,0 (0,0; 11,1)
Min, Max	0,0; 66,7	0,0; 33,3
Woche 27		
N[d]	277	256
Mittelwert (SD)	5,8 (10,4)	5,5 (8,9)
Median (Q1; Q3)	0,0 (0,0; 11,1)	0,0 (0,0; 11,1)
Min, Max	0,0; 66,7	0,0; 33,3
Woche 33		
N[d]	235	203
Mittelwert (SD)	7,3 (13,0)	4,7 (9,0)
Median (Q1; Q3)	0,0 (0,0; 11,1)	0,0 (0,0; 11,1)
Min, Max	0,0; 100,0	0,0; 44,4
Woche 39		
N[d]	192	167
Mittelwert (SD)	6,5 (10,6)	5,6 (10,4)
Median (Q1; Q3)	0,0 (0,0; 11,1)	0,0 (0,0; 11,1)
Min, Max	0,0; 55,6	0,0; 77,8
Woche 45		
N[d]	160	135
Mittelwert (SD)	7,0 (10,2)	5,3 (9,4)
Median (Q1; Q3)	0,0 (0,0; 11,1)	0,0 (0,0; 11,1)
Min, Max	0,0; 44,4	0,0; 44,4
Woche 51		
N[d]	135	109
Mittelwert (SD)	6,2 (10,0)	5,8 (10,0)
Median (Q1; Q3)	0,0 (0,0; 11,1)	0,0 (0,0; 11,1)
Min, Max	0,0; 55,6	0,0; 44,4
Woche 63		
N[d]	45	43
Mittelwert (SD)	7,2 (13,6)	8,5 (13,0)
Median (Q1; Q3)	0,0 (0,0; 11,1)	0,0 (0,0; 11,1)
Min, Max	0,0; 66,7	0,0; 55,6
Woche 75		
N[d]	17	24
Mittelwert (SD)	8,5 (9,2)	15,3 (17,0)
Median (Q1; Q3)	11,1 (0,0; 11,1)	11,1 (0,0; 22,2)
Min, Max	0,0; 33,3	0,0; 55,6
Woche 87		
N[d]	7	8
Mittelwert (SD)	11,1 (24,8)	8,3 (7,9)
Median (Q1; Q3)	0,0 (0,0; 11,1)	11,1 (0,0; 11,1)
Min, Max	0,0; 66,7	0,0; 22,2
Woche 99		
N[d]	7	6
Mittelwert (SD)	6,3 (8,7)	3,7 (9,1)
Median (Q1; Q3)	0,0 (0,0; 11,1)	0,0 (0,0; 0,0)

EORTC QLQ-BIL21 Gelbsucht	Studie: KEYNOTE 966[a]	
	Pembrolizumab + Chemotherapie[b] N[c]= 520	Placebo + Chemotherapie[b] N[c]= 516
Min, Max	0,0; 22,2	0,0; 22,2
Woche 111		
N[d]	9	11
Mittelwert (SD)	9,9 (6,7)	6,1 (9,1)
Median (Q1; Q3)	11,1 (11,1; 11,1)	0,0 (0,0; 11,1)
Min, Max	0,0; 22,2	0,0; 22,2
Woche 123		
N[d]	3	1
Mittelwert (SD)	11,1 (0,0)	0,0 (-)
Median (Q1; Q3)	11,1 (11,1; 11,1)	0,0 (0,0; 0,0)
Min, Max	11,1; 11,1	0,0; 0,0
Woche 135		
N[d]	1	0
Mittelwert (SD)	0,0 (-)	- (-)
Median (Q1; Q3)	0,0 (0,0; 0,0)	- (-; -)
Min, Max	0,0; 0,0	-; -

a: Datenschnitt: 15. Dezember 2022
b: Chemotherapie: Gemcitabin + Cisplatin
c: Anzahl der Patient:innen: Full-Analysis-Set Population
d: Anzahl der Beobachtungen zu jedem Zeitpunkt
EORTC QLQ-BIL21: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Cholangiokarzinom und Gallenblasenkarzinom 21 Fragen; Max: Maximum; Min: Minimum; Q1: Erstes Quartil; Q3: Drittes Quartil; SD: Standardabweichung

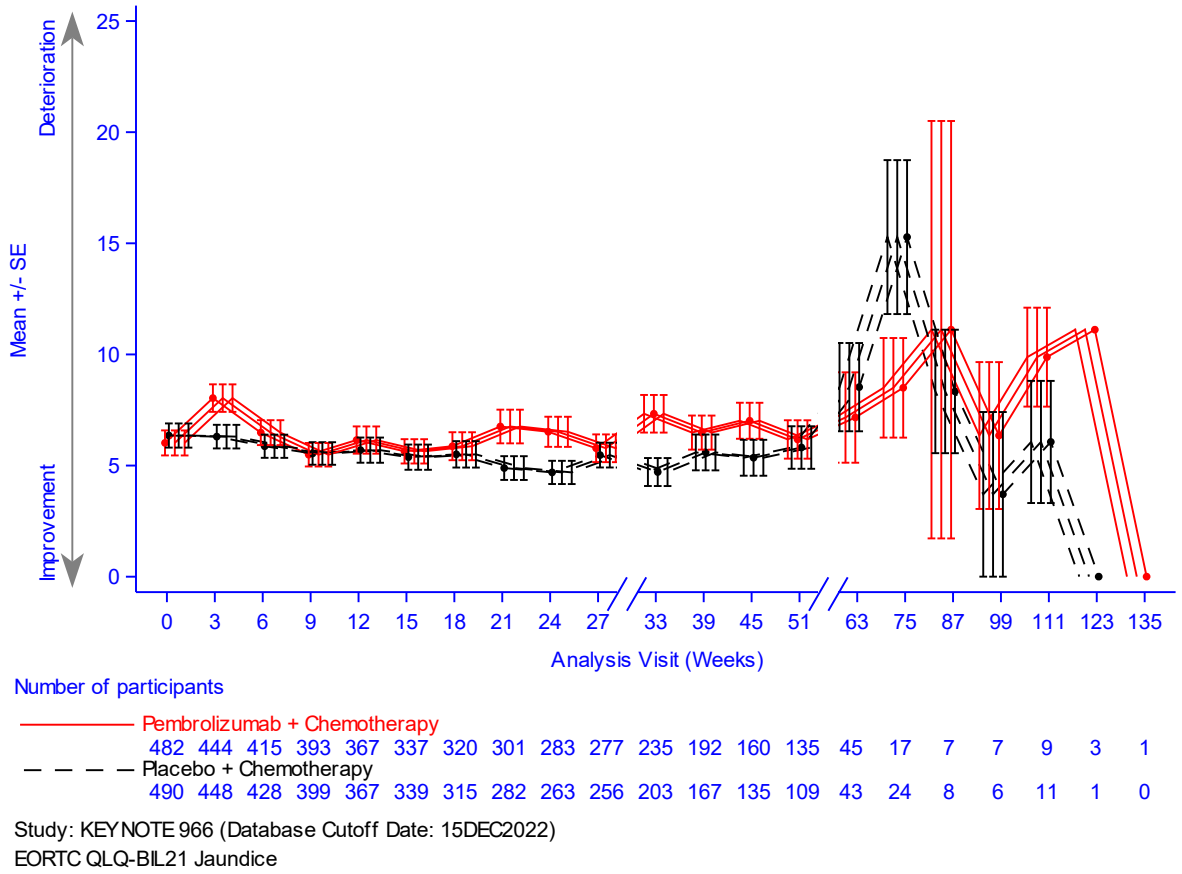


Abbildung 4G-10: EORTC QLQ-BIL21 Ikterus im Studienverlauf

Symptomskala Fatigue

Tabelle 4G-14: EORTC QLQ-BIL21 Fatigue im Studienverlauf

EORTC QLQ-BIL21 Fatigue	Studie: KEYNOTE 966[a]	
	Pembrolizumab + Chemotherapie[b] N[c]= 520	Placebo + Chemotherapie[b] N[c]= 516
Baseline		
N[d]	482	490
Mittelwert (SD)	29,3 (24,1)	31,3 (25,9)
Median (Q1; Q3)	33,3 (11,1; 33,3)	33,3 (11,1; 44,4)
Min, Max	0,0; 100,0	0,0; 100,0
Woche 3		
N[d]	444	448
Mittelwert (SD)	33,4 (25,7)	32,3 (25,5)
Median (Q1; Q3)	33,3 (11,1; 44,4)	33,3 (11,1; 44,4)
Min, Max	0,0; 100,0	0,0; 100,0
Woche 6		
N[d]	415	428
Mittelwert (SD)	32,1 (25,4)	31,6 (24,9)
Median (Q1; Q3)	33,3 (11,1; 44,4)	33,3 (11,1; 38,9)
Min, Max	0,0; 100,0	0,0; 100,0
Woche 9		
N[d]	393	399
Mittelwert (SD)	30,9 (23,1)	31,8 (25,7)
Median (Q1; Q3)	33,3 (11,1; 33,3)	33,3 (11,1; 44,4)
Min, Max	0,0; 100,0	0,0; 100,0
Woche 12		
N[d]	367	367
Mittelwert (SD)	29,8 (22,0)	31,0 (22,8)
Median (Q1; Q3)	33,3 (11,1; 33,3)	33,3 (11,1; 33,3)
Min, Max	0,0; 100,0	0,0; 100,0
Woche 15		
N[d]	337	339
Mittelwert (SD)	31,5 (23,5)	30,5 (23,0)
Median (Q1; Q3)	33,3 (11,1; 44,4)	33,3 (11,1; 33,3)
Min, Max	0,0; 100,0	0,0; 100,0
Woche 18		
N[d]	320	315
Mittelwert (SD)	31,4 (25,7)	32,0 (23,5)
Median (Q1; Q3)	33,3 (11,1; 44,4)	33,3 (11,1; 33,3)
Min, Max	0,0; 100,0	0,0; 100,0
Woche 21		
N[d]	301	282
Mittelwert (SD)	31,8 (25,0)	29,8 (22,5)
Median (Q1; Q3)	33,3 (11,1; 44,4)	33,3 (11,1; 33,3)
Min, Max	0,0; 100,0	0,0; 100,0
Woche 24		
N[d]	283	263
Mittelwert (SD)	31,4 (25,1)	32,3 (24,9)

EORTC QLQ-BIL21 Fatigue	Studie: KEYNOTE 966[a]	
	Pembrolizumab + Chemotherapie[b] N[c]= 520	Placebo + Chemotherapie[b] N[c]= 516
Median (Q1; Q3)	33,3 (11,1; 44,4)	33,3 (11,1; 44,4)
Min, Max	0,0; 100,0	0,0; 100,0
Woche 27		
N[d]	277	256
Mittelwert (SD)	28,3 (23,3)	29,1 (22,4)
Median (Q1; Q3)	33,3 (0,0; 33,3)	33,3 (11,1; 33,3)
Min, Max	0,0; 100,0	0,0; 100,0
Woche 33		
N[d]	235	203
Mittelwert (SD)	29,0 (23,2)	28,1 (22,6)
Median (Q1; Q3)	33,3 (11,1; 33,3)	33,3 (11,1; 33,3)
Min, Max	0,0; 100,0	0,0; 100,0
Woche 39		
N[d]	192	167
Mittelwert (SD)	30,7 (24,1)	29,3 (23,8)
Median (Q1; Q3)	33,3 (11,1; 38,9)	33,3 (11,1; 33,3)
Min, Max	0,0; 100,0	0,0; 100,0
Woche 45		
N[d]	160	135
Mittelwert (SD)	29,4 (22,3)	29,4 (25,4)
Median (Q1; Q3)	33,3 (11,1; 44,4)	33,3 (0,0; 33,3)
Min, Max	0,0; 100,0	0,0; 100,0
Woche 51		
N[d]	135	109
Mittelwert (SD)	29,5 (25,3)	30,7 (25,5)
Median (Q1; Q3)	33,3 (11,1; 44,4)	33,3 (11,1; 44,4)
Min, Max	0,0; 100,0	0,0; 100,0
Woche 63		
N[d]	45	43
Mittelwert (SD)	32,8 (27,7)	28,2 (20,3)
Median (Q1; Q3)	33,3 (22,2; 33,3)	33,3 (11,1; 33,3)
Min, Max	0,0; 100,0	0,0; 66,7
Woche 75		
N[d]	17	24
Mittelwert (SD)	43,8 (29,3)	43,1 (30,6)
Median (Q1; Q3)	33,3 (33,3; 66,7)	33,3 (22,2; 66,7)
Min, Max	0,0; 100,0	0,0; 100,0
Woche 87		
N[d]	7	8
Mittelwert (SD)	38,1 (34,5)	54,2 (36,3)
Median (Q1; Q3)	33,3 (11,1; 77,8)	50,0 (27,8; 88,9)
Min, Max	0,0; 88,9	0,0; 100,0
Woche 99		
N[d]	7	6
Mittelwert (SD)	41,3 (36,1)	16,7 (23,0)
Median (Q1; Q3)	33,3 (0,0; 66,7)	5,6 (0,0; 33,3)

EORTC QLQ-BIL21 Fatigue	Studie: KEYNOTE 966[a]	
	Pembrolizumab + Chemotherapie[b] N[c]= 520	Placebo + Chemotherapie[b] N[c]= 516
Min, Max	0,0; 100,0	0,0; 55,6
Woche 111		
N[d]	9	11
Mittelwert (SD)	28,4 (28,4)	27,3 (23,0)
Median (Q1; Q3)	22,2 (0,0; 33,3)	33,3 (0,0; 44,4)
Min, Max	0,0; 77,8	0,0; 66,7
Woche 123		
N[d]	3	1
Mittelwert (SD)	22,2 (19,2)	33,3 (-)
Median (Q1; Q3)	33,3 (0,0; 33,3)	33,3 (33,3; 33,3)
Min, Max	0,0; 33,3	33,3; 33,3
Woche 135		
N[d]	1	0
Mittelwert (SD)	0,0 (-)	- (-)
Median (Q1; Q3)	0,0 (0,0; 0,0)	- (-; -)
Min, Max	0,0; 0,0	-; -

a: Datenschnitt: 15. Dezember 2022
b: Chemotherapie: Gemcitabin + Cisplatin
c: Anzahl der Patient:innen: Full-Analysis-Set Population
d: Anzahl der Beobachtungen zu jedem Zeitpunkt
EORTC QLQ-BIL21: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Cholangiokarzinom und Gallenblasenkarzinom 21 Fragen; Max: Maximum; Min: Minimum; Q1: Erstes Quartil; Q3: Drittes Quartil; SD: Standardabweichung

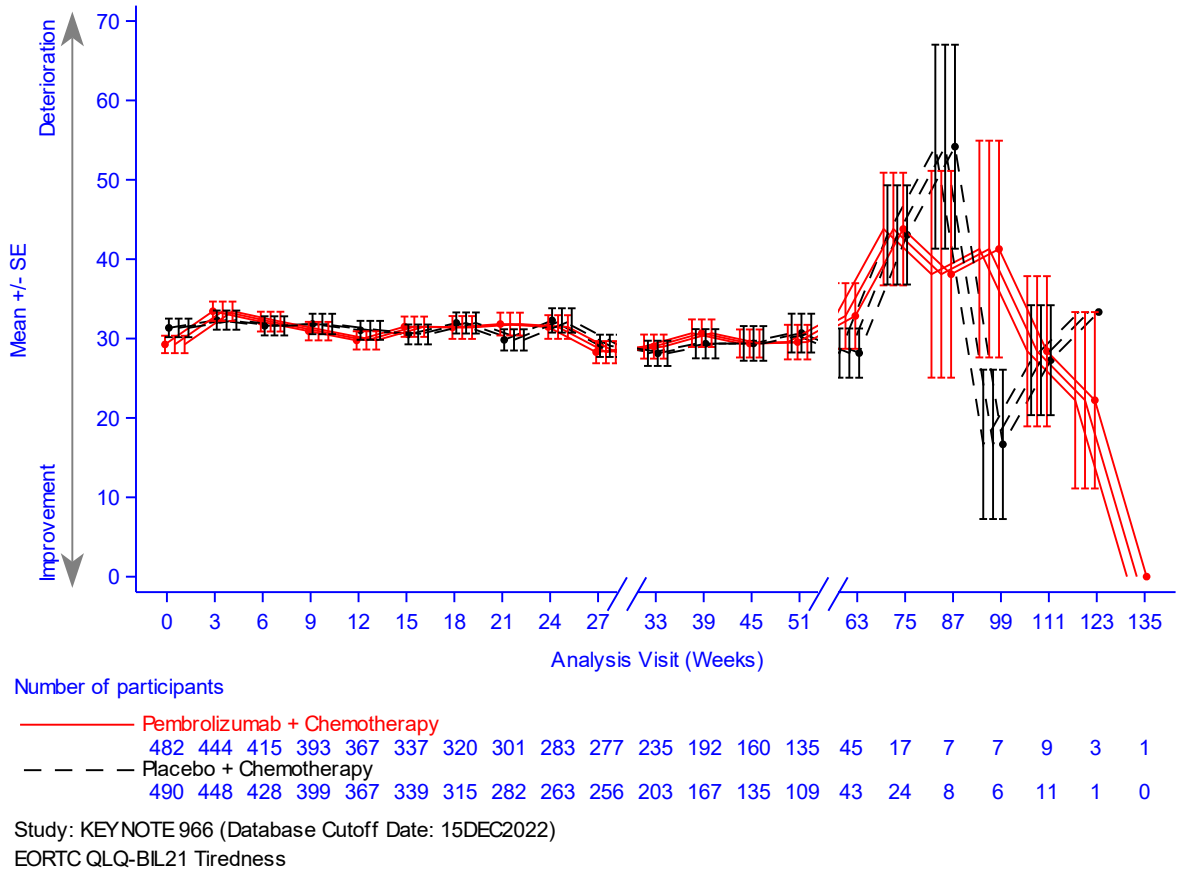


Abbildung 4G-11: EORTC QLQ-BIL21 Fatigue im Studienverlauf

Symptomskala Schmerzen

Tabelle 4G-15: EORTC QLQ-BIL21 Schmerzen im Studienverlauf

EORTC QLQ-BIL21 Schmerzen	Studie: KEYNOTE 966[a]	
	Pembrolizumab + Chemotherapie[b] N[c]= 520	Placebo + Chemotherapie[b] N[c]= 516
Baseline		
N[d]	482	490
Mittelwert (SD)	23,2 (21,2)	25,8 (22,6)
Median (Q1; Q3)	16,7 (8,3; 33,3)	25,0 (8,3; 41,7)
Min, Max	0,0; 100,0	0,0; 100,0
Woche 3		
N[d]	444	448
Mittelwert (SD)	20,6 (20,4)	20,1 (19,1)
Median (Q1; Q3)	16,7 (8,3; 33,3)	16,7 (8,3; 33,3)
Min, Max	0,0; 91,7	0,0; 100,0
Woche 6		
N[d]	415	428
Mittelwert (SD)	17,6 (18,1)	18,7 (19,0)
Median (Q1; Q3)	16,7 (0,0; 25,0)	16,7 (0,0; 25,0)
Min, Max	0,0; 100,0	0,0; 100,0
Woche 9		
N[d]	393	399
Mittelwert (SD)	15,4 (16,3)	17,7 (18,4)
Median (Q1; Q3)	8,3 (0,0; 25,0)	16,7 (0,0; 25,0)
Min, Max	0,0; 100,0	0,0; 91,7
Woche 12		
N[d]	367	367
Mittelwert (SD)	15,5 (16,4)	18,1 (18,4)
Median (Q1; Q3)	8,3 (0,0; 25,0)	16,7 (0,0; 25,0)
Min, Max	0,0; 100,0	0,0; 100,0
Woche 15		
N[d]	337	339
Mittelwert (SD)	15,4 (16,0)	16,3 (17,4)
Median (Q1; Q3)	8,3 (0,0; 25,0)	8,3 (0,0; 25,0)
Min, Max	0,0; 91,7	0,0; 83,3
Woche 18		
N[d]	320	315
Mittelwert (SD)	15,9 (17,0)	17,3 (17,2)
Median (Q1; Q3)	8,3 (0,0; 25,0)	16,7 (0,0; 25,0)
Min, Max	0,0; 83,3	0,0; 83,3
Woche 21		
N[d]	301	282
Mittelwert (SD)	17,8 (18,6)	17,0 (17,7)
Median (Q1; Q3)	16,7 (0,0; 25,0)	12,5 (0,0; 25,0)
Min, Max	0,0; 91,7	0,0; 100,0
Woche 24		
N[d]	283	263
Mittelwert (SD)	17,3 (18,6)	18,7 (19,7)

EORTC QLQ-BIL21 Schmerzen	Studie: KEYNOTE 966[a]	
	Pembrolizumab + Chemotherapie[b] N[c]= 520	Placebo + Chemotherapie[b] N[c]= 516
Median (Q1; Q3)	8,3 (0,0; 25,0)	16,7 (0,0; 25,0)
Min, Max	0,0; 91,7	0,0; 100,0
Woche 27		
N[d]	277	256
Mittelwert (SD)	14,8 (16,2)	17,2 (18,5)
Median (Q1; Q3)	8,3 (0,0; 25,0)	8,3 (0,0; 25,0)
Min, Max	0,0; 75,0	0,0; 91,7
Woche 33		
N[d]	235	203
Mittelwert (SD)	15,4 (17,2)	15,8 (16,0)
Median (Q1; Q3)	8,3 (0,0; 25,0)	8,3 (0,0; 25,0)
Min, Max	0,0; 75,0	0,0; 66,7
Woche 39		
N[d]	192	167
Mittelwert (SD)	15,8 (17,9)	18,0 (19,0)
Median (Q1; Q3)	8,3 (0,0; 25,0)	8,3 (0,0; 33,3)
Min, Max	0,0; 83,3	0,0; 83,3
Woche 45		
N[d]	160	135
Mittelwert (SD)	17,2 (18,9)	16,5 (18,3)
Median (Q1; Q3)	8,3 (0,0; 25,0)	8,3 (0,0; 25,0)
Min, Max	0,0; 83,3	0,0; 91,7
Woche 51		
N[d]	135	109
Mittelwert (SD)	15,1 (18,4)	19,3 (19,7)
Median (Q1; Q3)	8,3 (0,0; 16,7)	16,7 (0,0; 33,3)
Min, Max	0,0; 100,0	0,0; 91,7
Woche 63		
N[d]	45	43
Mittelwert (SD)	20,7 (26,1)	19,6 (18,5)
Median (Q1; Q3)	16,7 (0,0; 33,3)	16,7 (0,0; 33,3)
Min, Max	0,0; 100,0	0,0; 66,7
Woche 75		
N[d]	17	24
Mittelwert (SD)	34,3 (24,5)	31,3 (25,8)
Median (Q1; Q3)	25,0 (25,0; 33,3)	25,0 (12,5; 41,7)
Min, Max	0,0; 100,0	0,0; 100,0
Woche 87		
N[d]	7	8
Mittelwert (SD)	31,0 (40,5)	28,1 (20,4)
Median (Q1; Q3)	16,7 (0,0; 75,0)	33,3 (8,3; 45,8)
Min, Max	0,0; 100,0	0,0; 50,0
Woche 99		
N[d]	7	6
Mittelwert (SD)	27,4 (20,2)	9,7 (6,3)
Median (Q1; Q3)	25,0 (8,3; 50,0)	8,3 (8,3; 16,7)

EORTC QLQ-BIL21 Schmerzen	Studie: KEYNOTE 966[a]	
	Pembrolizumab + Chemotherapie[b] N[c]= 520	Placebo + Chemotherapie[b] N[c]= 516
Min, Max	0,0; 50,0	0,0; 16,7
Woche 111		
N[d]	9	11
Mittelwert (SD)	7,4 (10,6)	21,2 (17,2)
Median (Q1; Q3)	0,0 (0,0; 8,3)	16,7 (8,3; 41,7)
Min, Max	0,0; 25,0	0,0; 50,0
Woche 123		
N[d]	3	1
Mittelwert (SD)	0,0 (0,0)	8,3 (-)
Median (Q1; Q3)	0,0 (0,0; 0,0)	8,3 (8,3; 8,3)
Min, Max	0,0; 0,0	8,3; 8,3
Woche 135		
N[d]	1	0
Mittelwert (SD)	0,0 (-)	- (-)
Median (Q1; Q3)	0,0 (0,0; 0,0)	- (-; -)
Min, Max	0,0; 0,0	-; -

a: Datenschnitt: 15. Dezember 2022
b: Chemotherapie: Gemcitabin + Cisplatin
c: Anzahl der Patient:innen: Full-Analysis-Set Population
d: Anzahl der Beobachtungen zu jedem Zeitpunkt
EORTC QLQ-BIL21: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Cholangiokarzinom und Gallenblasenkarzinom 21 Fragen; Max: Maximum; Min: Minimum; Q1: Erstes Quartil; Q3: Drittes Quartil; SD: Standardabweichung

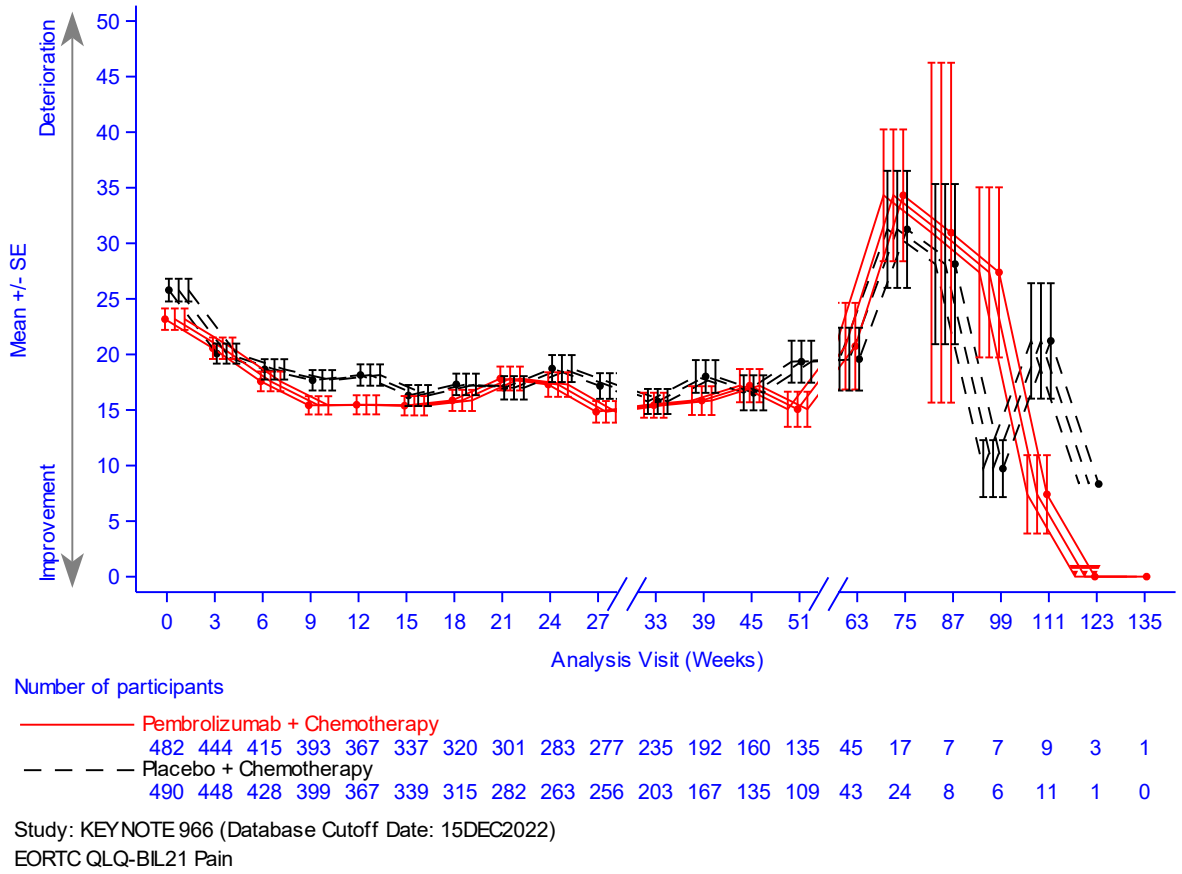


Abbildung 4G-12: EORTC QLQ-BIL21 Schmerzen im Studienverlauf

Symptomskala Angst

Tabelle 4G-16: EORTC QLQ-BIL21 Angst im Studienverlauf

EORTC QLQ-BIL21 Angst	Studie: KEYNOTE 966[a]	
	Pembrolizumab + Chemotherapie[b] N[c]= 520	Placebo + Chemotherapie[b] N[c]= 516
Baseline		
N[d]	482	490
Mittelwert (SD)	33,7 (24,0)	35,1 (24,9)
Median (Q1; Q3)	33,3 (16,7; 50,0)	33,3 (16,7; 50,0)
Min, Max	0,0; 100,0	0,0; 100,0
Woche 3		
N[d]	444	448
Mittelwert (SD)	31,9 (24,6)	30,6 (23,7)
Median (Q1; Q3)	25,0 (16,7; 50,0)	25,0 (16,7; 41,7)
Min, Max	0,0; 100,0	0,0; 100,0
Woche 6		
N[d]	415	428
Mittelwert (SD)	30,1 (24,2)	30,5 (23,3)
Median (Q1; Q3)	25,0 (8,3; 41,7)	25,0 (16,7; 41,7)
Min, Max	0,0; 100,0	0,0; 100,0
Woche 9		
N[d]	393	399
Mittelwert (SD)	29,3 (22,0)	28,0 (22,4)
Median (Q1; Q3)	33,3 (8,3; 41,7)	25,0 (8,3; 41,7)
Min, Max	0,0; 100,0	0,0; 100,0
Woche 12		
N[d]	367	367
Mittelwert (SD)	27,1 (22,2)	29,3 (23,2)
Median (Q1; Q3)	25,0 (8,3; 41,7)	25,0 (16,7; 41,7)
Min, Max	0,0; 100,0	0,0; 100,0
Woche 15		
N[d]	337	339
Mittelwert (SD)	27,9 (22,1)	28,8 (22,3)
Median (Q1; Q3)	25,0 (8,3; 41,7)	25,0 (16,7; 41,7)
Min, Max	0,0; 100,0	0,0; 100,0
Woche 18		
N[d]	320	315
Mittelwert (SD)	27,8 (23,7)	31,2 (23,2)
Median (Q1; Q3)	25,0 (8,3; 41,7)	33,3 (16,7; 41,7)
Min, Max	0,0; 100,0	0,0; 100,0
Woche 21		
N[d]	301	282
Mittelwert (SD)	28,8 (24,5)	28,3 (22,2)
Median (Q1; Q3)	25,0 (8,3; 41,7)	25,0 (8,3; 41,7)
Min, Max	0,0; 100,0	0,0; 91,7
Woche 24		
N[d]	283	263
Mittelwert (SD)	29,0 (24,2)	29,9 (24,1)

EORTC QLQ-BIL21 Angst	Studie: KEYNOTE 966[a]	
	Pembrolizumab + Chemotherapie[b] N[c]= 520	Placebo + Chemotherapie[b] N[c]= 516
Median (Q1; Q3)	25,0 (8,3; 41,7)	25,0 (16,7; 41,7)
Min, Max	0,0; 100,0	0,0; 100,0
Woche 27		
N[d]	277	256
Mittelwert (SD)	24,7 (21,0)	27,5 (21,8)
Median (Q1; Q3)	25,0 (8,3; 33,3)	25,0 (8,3; 41,7)
Min, Max	0,0; 100,0	0,0; 100,0
Woche 33		
N[d]	235	203
Mittelwert (SD)	27,3 (23,8)	26,8 (22,6)
Median (Q1; Q3)	25,0 (8,3; 41,7)	25,0 (8,3; 33,3)
Min, Max	0,0; 100,0	0,0; 100,0
Woche 39		
N[d]	192	167
Mittelwert (SD)	26,7 (23,3)	27,4 (21,5)
Median (Q1; Q3)	25,0 (4,2; 41,7)	25,0 (8,3; 41,7)
Min, Max	0,0; 100,0	0,0; 91,7
Woche 45		
N[d]	160	135
Mittelwert (SD)	26,2 (22,7)	28,3 (23,2)
Median (Q1; Q3)	25,0 (8,3; 41,7)	25,0 (8,3; 41,7)
Min, Max	0,0; 83,3	0,0; 91,7
Woche 51		
N[d]	135	109
Mittelwert (SD)	26,5 (24,3)	30,0 (26,7)
Median (Q1; Q3)	25,0 (0,0; 41,7)	25,0 (8,3; 41,7)
Min, Max	0,0; 100,0	0,0; 100,0
Woche 63		
N[d]	45	43
Mittelwert (SD)	31,9 (33,4)	29,7 (25,0)
Median (Q1; Q3)	25,0 (0,0; 50,0)	25,0 (8,3; 50,0)
Min, Max	0,0; 100,0	0,0; 83,3
Woche 75		
N[d]	17	24
Mittelwert (SD)	47,5 (26,5)	47,6 (32,4)
Median (Q1; Q3)	33,3 (25,0; 75,0)	45,8 (20,8; 75,0)
Min, Max	0,0; 83,3	0,0; 100,0
Woche 87		
N[d]	7	8
Mittelwert (SD)	31,0 (39,0)	50,0 (30,9)
Median (Q1; Q3)	8,3 (8,3; 83,3)	58,3 (25,0; 70,8)
Min, Max	0,0; 91,7	0,0; 91,7
Woche 99		
N[d]	7	6
Mittelwert (SD)	39,3 (34,9)	20,8 (18,8)
Median (Q1; Q3)	33,3 (0,0; 83,3)	20,8 (0,0; 41,7)

EORTC QLQ-BIL21 Angst	Studie: KEYNOTE 966[a]	
	Pembrolizumab + Chemotherapie[b] N[c]= 520	Placebo + Chemotherapie[b] N[c]= 516
Min, Max	0,0; 83,3	0,0; 41,7
Woche 111		
N[d]	9	11
Mittelwert (SD)	25,9 (30,5)	26,5 (21,3)
Median (Q1; Q3)	16,7 (0,0; 41,7)	25,0 (8,3; 33,3)
Min, Max	0,0; 91,7	0,0; 75,0
Woche 123		
N[d]	3	1
Mittelwert (SD)	13,9 (12,7)	25,0 (-)
Median (Q1; Q3)	16,7 (0,0; 25,0)	25,0 (25,0; 25,0)
Min, Max	0,0; 25,0	25,0; 25,0
Woche 135		
N[d]	1	0
Mittelwert (SD)	0,0 (-)	- (-)
Median (Q1; Q3)	0,0 (0,0; 0,0)	- (-; -)
Min, Max	0,0; 0,0	-; -

a: Datenschnitt: 15. Dezember 2022
b: Chemotherapie: Gemcitabin + Cisplatin
c: Anzahl der Patient:innen: Full-Analysis-Set Population
d: Anzahl der Beobachtungen zu jedem Zeitpunkt
EORTC QLQ-BIL21: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Cholangiokarzinom und Gallenblasenkarzinom 21 Fragen; Max: Maximum; Min: Minimum; Q1: Erstes Quartil; Q3: Drittes Quartil; SD: Standardabweichung

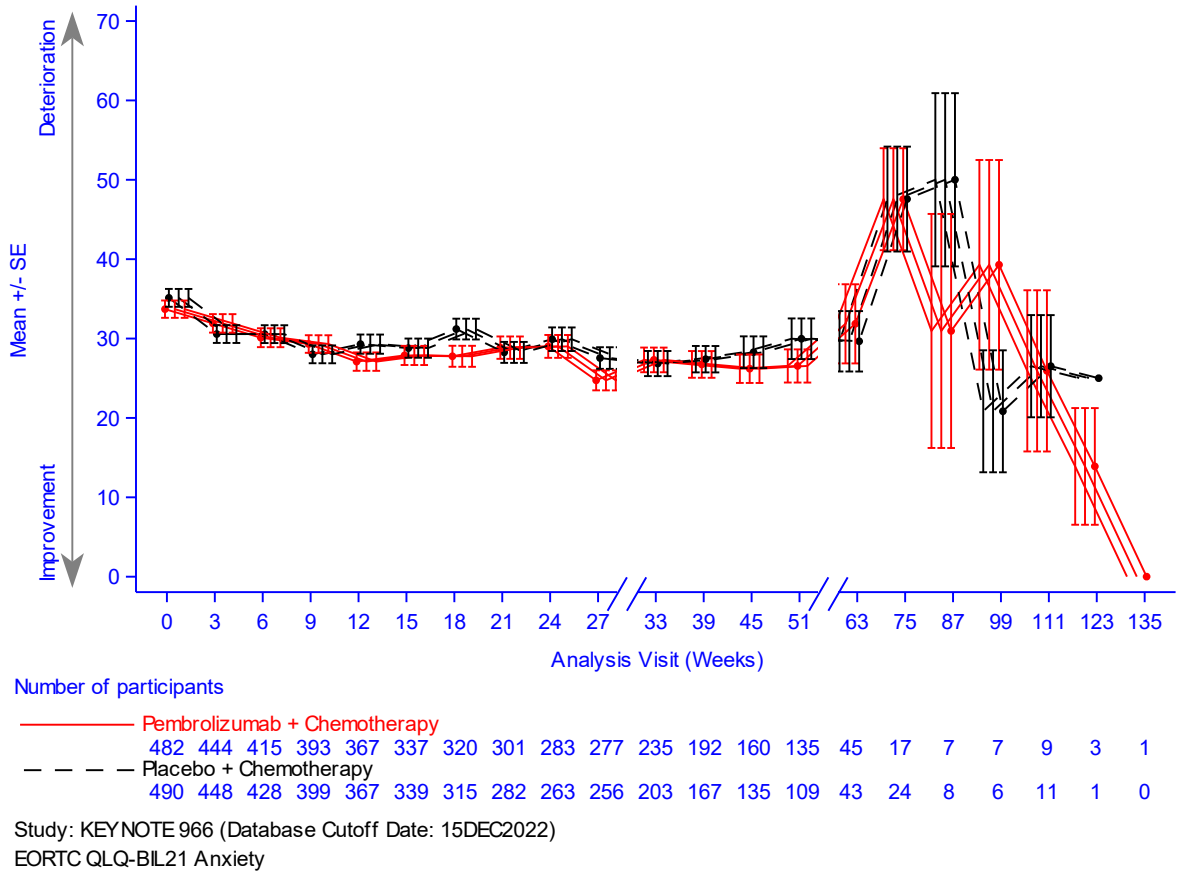


Abbildung 4G-13: EORTC QLQ-BIL21 Angst im Studienverlauf

Symptomskala Nebenwirkungen der Behandlung

Tabelle 4G-17: EORTC QLQ-BIL21 Nebenwirkungen der Behandlung im Studienverlauf

EORTC QLQ-BIL21 Nebenwirkungen der Behandlung	Studie: KEYNOTE 966[a]	
	Pembrolizumab + Chemotherapie[b] N[c]= 520	Placebo + Chemotherapie[b] N[c]= 516
Baseline		
N[d]	482	490
Mittelwert (SD)	13,6 (23,7)	15,6 (25,7)
Median (Q1; Q3)	0,0 (0,0; 33,3)	0,0 (0,0; 33,3)
Min, Max	0,0; 100,0	0,0; 100,0
Woche 3		
N[d]	444	448
Mittelwert (SD)	29,4 (27,1)	27,4 (25,6)
Median (Q1; Q3)	33,3 (0,0; 33,3)	33,3 (0,0; 33,3)
Min, Max	0,0; 100,0	0,0; 100,0
Woche 6		
N[d]	415	428
Mittelwert (SD)	25,5 (25,0)	28,0 (26,2)
Median (Q1; Q3)	33,3 (0,0; 33,3)	33,3 (0,0; 33,3)
Min, Max	0,0; 100,0	0,0; 100,0
Woche 9		
N[d]	393	399
Mittelwert (SD)	25,9 (23,9)	27,9 (25,5)
Median (Q1; Q3)	33,3 (0,0; 33,3)	33,3 (0,0; 33,3)
Min, Max	0,0; 100,0	0,0; 100,0
Woche 12		
N[d]	367	367
Mittelwert (SD)	27,6 (25,6)	27,3 (24,5)
Median (Q1; Q3)	33,3 (0,0; 33,3)	33,3 (0,0; 33,3)
Min, Max	0,0; 100,0	0,0; 100,0
Woche 15		
N[d]	337	339
Mittelwert (SD)	25,3 (23,8)	28,7 (24,8)
Median (Q1; Q3)	33,3 (0,0; 33,3)	33,3 (0,0; 33,3)
Min, Max	0,0; 100,0	0,0; 100,0
Woche 18		
N[d]	320	315
Mittelwert (SD)	25,8 (24,6)	29,4 (25,4)
Median (Q1; Q3)	33,3 (0,0; 33,3)	33,3 (0,0; 33,3)
Min, Max	0,0; 100,0	0,0; 100,0
Woche 21		
N[d]	301	282
Mittelwert (SD)	28,5 (24,9)	27,3 (25,1)
Median (Q1; Q3)	33,3 (0,0; 33,3)	33,3 (0,0; 33,3)
Min, Max	0,0; 100,0	0,0; 100,0
Woche 24		
N[d]	283	263

EORTC QLQ-BIL21 Nebenwirkungen der Behandlung	Studie: KEYNOTE 966[a]	
	Pembrolizumab + Chemotherapie[b]	Placebo + Chemotherapie[b]
	N[c]= 520	N[c]= 516
Mittelwert (SD)	28,4 (24,6)	28,1 (27,7)
Median (Q1; Q3)	33,3 (0,0; 33,3)	33,3 (0,0; 33,3)
Min, Max	0,0; 100,0	0,0; 100,0
Woche 27		
N[d]	277	256
Mittelwert (SD)	24,1 (23,9)	24,9 (24,6)
Median (Q1; Q3)	33,3 (0,0; 33,3)	33,3 (0,0; 33,3)
Min, Max	0,0; 100,0	0,0; 100,0
Woche 33		
N[d]	235	203
Mittelwert (SD)	22,4 (25,9)	23,6 (22,7)
Median (Q1; Q3)	33,3 (0,0; 33,3)	33,3 (0,0; 33,3)
Min, Max	0,0; 100,0	0,0; 100,0
Woche 39		
N[d]	192	167
Mittelwert (SD)	22,4 (24,2)	24,0 (24,8)
Median (Q1; Q3)	33,3 (0,0; 33,3)	33,3 (0,0; 33,3)
Min, Max	0,0; 100,0	0,0; 100,0
Woche 45		
N[d]	160	135
Mittelwert (SD)	22,9 (23,1)	24,0 (24,0)
Median (Q1; Q3)	33,3 (0,0; 33,3)	33,3 (0,0; 33,3)
Min, Max	0,0; 100,0	0,0; 100,0
Woche 51		
N[d]	135	109
Mittelwert (SD)	21,5 (23,2)	22,9 (25,9)
Median (Q1; Q3)	33,3 (0,0; 33,3)	33,3 (0,0; 33,3)
Min, Max	0,0; 100,0	0,0; 100,0
Woche 63		
N[d]	45	43
Mittelwert (SD)	28,9 (31,5)	24,8 (23,1)
Median (Q1; Q3)	33,3 (0,0; 33,3)	33,3 (0,0; 33,3)
Min, Max	0,0; 100,0	0,0; 66,7
Woche 75		
N[d]	17	24
Mittelwert (SD)	31,4 (30,0)	30,6 (31,0)
Median (Q1; Q3)	33,3 (0,0; 33,3)	33,3 (0,0; 66,7)
Min, Max	0,0; 100,0	0,0; 100,0
Woche 87		
N[d]	7	8
Mittelwert (SD)	14,3 (26,2)	54,2 (35,4)
Median (Q1; Q3)	0,0 (0,0; 33,3)	50,0 (33,3; 83,3)
Min, Max	0,0; 66,7	0,0; 100,0
Woche 99		
N[d]	7	6
Mittelwert (SD)	28,6 (35,6)	16,7 (27,9)

EORTC QLQ-BIL21 Nebenwirkungen der Behandlung	Studie: KEYNOTE 966[a]	
	Pembrolizumab + Chemotherapie[b]	Placebo + Chemotherapie[b]
	N[c]= 520	N[c]= 516
Median (Q1; Q3)	33,3 (0,0; 33,3)	0,0 (0,0; 33,3)
Min, Max	0,0; 100,0	0,0; 66,7
Woche 111		
N[d]	9	11
Mittelwert (SD)	11,1 (16,7)	24,2 (26,2)
Median (Q1; Q3)	0,0 (0,0; 33,3)	33,3 (0,0; 33,3)
Min, Max	0,0; 33,3	0,0; 66,7
Woche 123		
N[d]	3	1
Mittelwert (SD)	22,2 (19,2)	0,0 (-)
Median (Q1; Q3)	33,3 (0,0; 33,3)	0,0 (0,0; 0,0)
Min, Max	0,0; 33,3	0,0; 0,0
Woche 135		
N[d]	1	0
Mittelwert (SD)	0,0 (-)	- (-)
Median (Q1; Q3)	0,0 (0,0; 0,0)	- (-; -)
Min, Max	0,0; 0,0	-; -

a: Datenschnitt: 15. Dezember 2022
b: Chemotherapie: Gemcitabin + Cisplatin
c: Anzahl der Patient:innen: Full-Analysis-Set Population
d: Anzahl der Beobachtungen zu jedem Zeitpunkt
EORTC QLQ-BIL21: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Cholangiokarzinom und Gallenblasenkarzinom 21 Fragen; Max: Maximum; Min: Minimum; Q1: Erstes Quartil; Q3: Drittes Quartil; SD: Standardabweichung

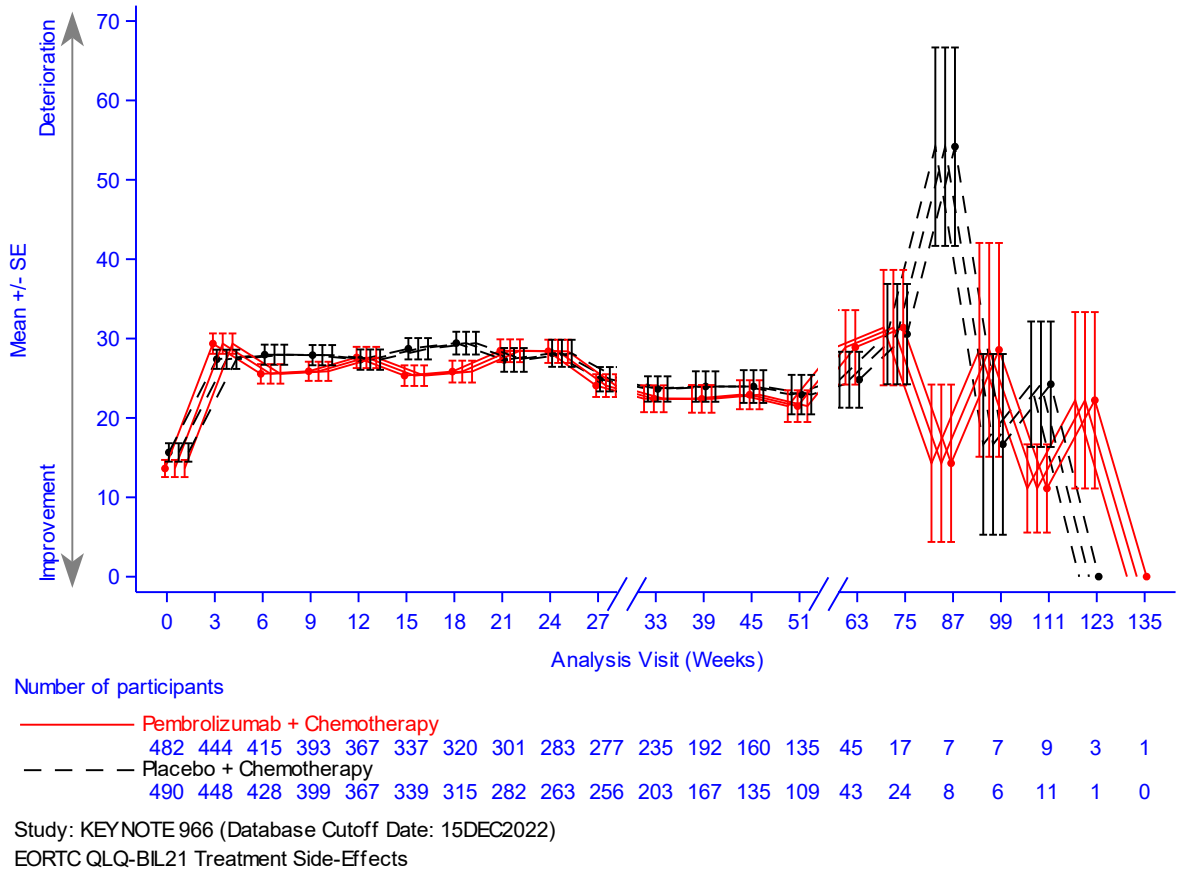


Abbildung 4G-14: EORTC QLQ-BIL21 Nebenwirkungen der Behandlung im Studienverlauf

Symptomskala Drainagebeutel/-schläuche

Tabelle 4G-18: EORTC QLQ-BIL21 Drainagebeutel/-schläuche im Studienverlauf

EORTC QLQ-BIL21 Schwierigkeiten mit der Drainage	Studie: KEYNOTE 966[a]	
	Pembrolizumab + Chemotherapie[b] N[c]= 520	Placebo + Chemotherapie[b] N[c]= 516
Baseline		
N[d]	482	490
Mittelwert (SD)	4,8 (15,4)	4,7 (15,5)
Median (Q1; Q3)	0,0 (0,0; 0,0)	0,0 (0,0; 0,0)
Min, Max	0,0; 100,0	0,0; 100,0
Woche 3		
N[d]	444	448
Mittelwert (SD)	4,6 (15,7)	4,8 (15,7)
Median (Q1; Q3)	0,0 (0,0; 0,0)	0,0 (0,0; 0,0)
Min, Max	0,0; 100,0	0,0; 100,0
Woche 6		
N[d]	414	427
Mittelwert (SD)	4,0 (14,1)	4,2 (14,6)
Median (Q1; Q3)	0,0 (0,0; 0,0)	0,0 (0,0; 0,0)
Min, Max	0,0; 100,0	0,0; 100,0
Woche 9		
N[d]	393	399
Mittelwert (SD)	3,9 (14,3)	3,9 (12,9)
Median (Q1; Q3)	0,0 (0,0; 0,0)	0,0 (0,0; 0,0)
Min, Max	0,0; 100,0	0,0; 66,7
Woche 12		
N[d]	367	367
Mittelwert (SD)	4,5 (15,3)	3,5 (12,1)
Median (Q1; Q3)	0,0 (0,0; 0,0)	0,0 (0,0; 0,0)
Min, Max	0,0; 100,0	0,0; 100,0
Woche 15		
N[d]	337	339
Mittelwert (SD)	3,7 (13,2)	3,3 (11,0)
Median (Q1; Q3)	0,0 (0,0; 0,0)	0,0 (0,0; 0,0)
Min, Max	0,0; 100,0	0,0; 66,7
Woche 18		
N[d]	320	315
Mittelwert (SD)	4,7 (16,3)	3,5 (12,1)
Median (Q1; Q3)	0,0 (0,0; 0,0)	0,0 (0,0; 0,0)
Min, Max	0,0; 100,0	0,0; 100,0
Woche 21		
N[d]	301	282
Mittelwert (SD)	4,4 (15,7)	2,8 (10,1)
Median (Q1; Q3)	0,0 (0,0; 0,0)	0,0 (0,0; 0,0)
Min, Max	0,0; 100,0	0,0; 66,7
Woche 24		
N[d]	283	263

EORTC QLQ-BIL21 Schwierigkeiten mit der Drainage	Studie: KEYNOTE 966[a]	
	Pembrolizumab + Chemotherapie[b]	Placebo + Chemotherapie[b]
	N[c]= 520	N[c]= 516
Mittelwert (SD)	4,0 (13,2)	3,2 (11,8)
Median (Q1; Q3)	0,0 (0,0; 0,0)	0,0 (0,0; 0,0)
Min, Max	0,0; 66,7	0,0; 100,0
Woche 27		
N[d]	277	256
Mittelwert (SD)	2,6 (11,4)	2,6 (9,4)
Median (Q1; Q3)	0,0 (0,0; 0,0)	0,0 (0,0; 0,0)
Min, Max	0,0; 100,0	0,0; 66,7
Woche 33		
N[d]	235	203
Mittelwert (SD)	3,4 (14,0)	2,0 (9,2)
Median (Q1; Q3)	0,0 (0,0; 0,0)	0,0 (0,0; 0,0)
Min, Max	0,0; 100,0	0,0; 66,7
Woche 39		
N[d]	192	167
Mittelwert (SD)	1,4 (6,7)	1,6 (8,0)
Median (Q1; Q3)	0,0 (0,0; 0,0)	0,0 (0,0; 0,0)
Min, Max	0,0; 33,3	0,0; 66,7
Woche 45		
N[d]	160	135
Mittelwert (SD)	2,9 (10,8)	2,0 (10,6)
Median (Q1; Q3)	0,0 (0,0; 0,0)	0,0 (0,0; 0,0)
Min, Max	0,0; 66,7	0,0; 100,0
Woche 51		
N[d]	135	109
Mittelwert (SD)	3,0 (11,8)	0,9 (7,1)
Median (Q1; Q3)	0,0 (0,0; 0,0)	0,0 (0,0; 0,0)
Min, Max	0,0; 100,0	0,0; 66,7
Woche 63		
N[d]	45	43
Mittelwert (SD)	3,0 (9,6)	4,7 (15,6)
Median (Q1; Q3)	0,0 (0,0; 0,0)	0,0 (0,0; 0,0)
Min, Max	0,0; 33,3	0,0; 66,7
Woche 75		
N[d]	17	24
Mittelwert (SD)	5,9 (13,1)	2,8 (13,6)
Median (Q1; Q3)	0,0 (0,0; 0,0)	0,0 (0,0; 0,0)
Min, Max	0,0; 33,3	0,0; 66,7
Woche 87		
N[d]	7	8
Mittelwert (SD)	19,0 (37,8)	4,2 (11,8)
Median (Q1; Q3)	0,0 (0,0; 33,3)	0,0 (0,0; 0,0)
Min, Max	0,0; 100,0	0,0; 33,3
Woche 99		
N[d]	7	6
Mittelwert (SD)	0,0 (0,0)	5,6 (13,6)

EORTC QLQ-BIL21 Schwierigkeiten mit der Drainage	Studie: KEYNOTE 966[a]	
	Pembrolizumab + Chemotherapie[b]	Placebo + Chemotherapie[b]
	N[c]= 520	N[c]= 516
Median (Q1; Q3)	0,0 (0,0; 0,0)	0,0 (0,0; 0,0)
Min, Max	0,0; 0,0	0,0; 33,3
Woche 111		
N[d]	9	11
Mittelwert (SD)	3,7 (11,1)	3,0 (10,1)
Median (Q1; Q3)	0,0 (0,0; 0,0)	0,0 (0,0; 0,0)
Min, Max	0,0; 33,3	0,0; 33,3
Woche 123		
N[d]	3	1
Mittelwert (SD)	0,0 (0,0)	0,0 (-)
Median (Q1; Q3)	0,0 (0,0; 0,0)	0,0 (0,0; 0,0)
Min, Max	0,0; 0,0	0,0; 0,0
Woche 135		
N[d]	1	0
Mittelwert (SD)	0,0 (-)	- (-)
Median (Q1; Q3)	0,0 (0,0; 0,0)	- (-; -)
Min, Max	0,0; 0,0	-; -

a: Datenschnitt: 15. Dezember 2022
b: Chemotherapie: Gemcitabin + Cisplatin
c: Anzahl der Patient:innen: Full-Analysis-Set Population
d: Anzahl der Beobachtungen zu jedem Zeitpunkt
EORTC QLQ-BIL21: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Cholangiokarzinom und Gallenblasenkarzinom 21 Fragen; Max: Maximum; Min: Minimum; Q1: Erstes Quartil; Q3: Drittes Quartil; SD: Standardabweichung

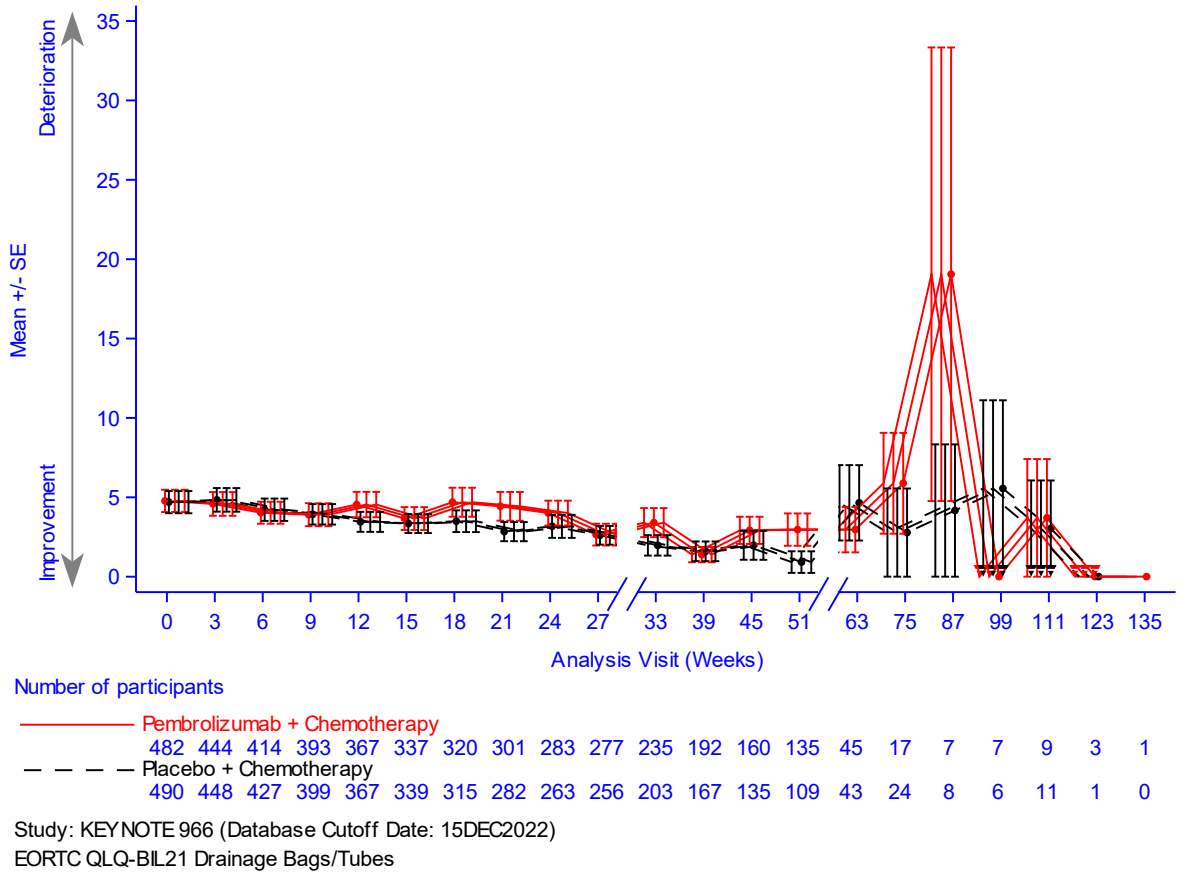


Abbildung 4G-15: EORTC QLQ-BIL21 Drainagebeutel/-schläuche im Studienverlauf

Symptomskala Sorge um Gewichtsverlust

Tabelle 4G-19: EORTC QLQ-BIL21 Gewichtsverlust im Studienverlauf

EORTC QLQ-BIL21 Sorge um Gewichtsverlust	Studie: KEYNOTE 966[a]	
	Pembrolizumab + Chemotherapie[b]	Placebo + Chemotherapie[b]
	N[c]= 520	N[c]= 516
Baseline		
N[d]	482	490
Mittelwert (SD)	23,2 (27,7)	22,8 (29,3)
Median (Q1; Q3)	0,0 (0,0; 33,3)	0,0 (0,0; 33,3)
Min, Max	0,0; 100,0	0,0; 100,0
Woche 3		
N[d]	444	448
Mittelwert (SD)	23,6 (28,2)	21,9 (28,1)
Median (Q1; Q3)	33,3 (0,0; 33,3)	0,0 (0,0; 33,3)
Min, Max	0,0; 100,0	0,0; 100,0
Woche 6		
N[d]	415	428
Mittelwert (SD)	21,0 (26,5)	19,4 (26,8)
Median (Q1; Q3)	0,0 (0,0; 33,3)	0,0 (0,0; 33,3)
Min, Max	0,0; 100,0	0,0; 100,0
Woche 9		
N[d]	393	399
Mittelwert (SD)	21,5 (27,0)	16,3 (24,4)
Median (Q1; Q3)	0,0 (0,0; 33,3)	0,0 (0,0; 33,3)
Min, Max	0,0; 100,0	0,0; 100,0
Woche 12		
N[d]	367	367
Mittelwert (SD)	18,1 (25,2)	15,3 (24,2)
Median (Q1; Q3)	0,0 (0,0; 33,3)	0,0 (0,0; 33,3)
Min, Max	0,0; 100,0	0,0; 100,0
Woche 15		
N[d]	337	339
Mittelwert (SD)	16,7 (24,0)	14,6 (23,3)
Median (Q1; Q3)	0,0 (0,0; 33,3)	0,0 (0,0; 33,3)
Min, Max	0,0; 100,0	0,0; 100,0
Woche 18		
N[d]	320	315
Mittelwert (SD)	17,1 (25,9)	14,7 (22,7)
Median (Q1; Q3)	0,0 (0,0; 33,3)	0,0 (0,0; 33,3)
Min, Max	0,0; 100,0	0,0; 100,0
Woche 21		
N[d]	301	282
Mittelwert (SD)	15,1 (24,1)	12,5 (21,1)
Median (Q1; Q3)	0,0 (0,0; 33,3)	0,0 (0,0; 33,3)
Min, Max	0,0; 100,0	0,0; 100,0
Woche 24		
N[d]	283	263

EORTC QLQ-BIL21 Sorge um Gewichtsverlust	Studie: KEYNOTE 966[a]	
	Pembrolizumab + Chemotherapie[b]	Placebo + Chemotherapie[b]
	N[c]= 520	N[c]= 516
Mittelwert (SD)	16,3 (24,7)	13,4 (20,7)
Median (Q1; Q3)	0,0 (0,0; 33,3)	0,0 (0,0; 33,3)
Min, Max	0,0; 100,0	0,0; 100,0
Woche 27		
N[d]	277	256
Mittelwert (SD)	14,0 (22,5)	12,0 (19,5)
Median (Q1; Q3)	0,0 (0,0; 33,3)	0,0 (0,0; 33,3)
Min, Max	0,0; 100,0	0,0; 100,0
Woche 33		
N[d]	235	203
Mittelwert (SD)	12,8 (22,4)	10,2 (18,3)
Median (Q1; Q3)	0,0 (0,0; 33,3)	0,0 (0,0; 33,3)
Min, Max	0,0; 100,0	0,0; 100,0
Woche 39		
N[d]	192	167
Mittelwert (SD)	13,7 (22,4)	11,0 (20,5)
Median (Q1; Q3)	0,0 (0,0; 33,3)	0,0 (0,0; 33,3)
Min, Max	0,0; 100,0	0,0; 100,0
Woche 45		
N[d]	160	135
Mittelwert (SD)	11,0 (19,0)	12,3 (20,7)
Median (Q1; Q3)	0,0 (0,0; 33,3)	0,0 (0,0; 33,3)
Min, Max	0,0; 100,0	0,0; 100,0
Woche 51		
N[d]	135	109
Mittelwert (SD)	11,9 (22,1)	12,2 (24,3)
Median (Q1; Q3)	0,0 (0,0; 33,3)	0,0 (0,0; 0,0)
Min, Max	0,0; 100,0	0,0; 100,0
Woche 63		
N[d]	45	43
Mittelwert (SD)	19,3 (33,7)	13,2 (23,2)
Median (Q1; Q3)	0,0 (0,0; 33,3)	0,0 (0,0; 33,3)
Min, Max	0,0; 100,0	0,0; 100,0
Woche 75		
N[d]	17	24
Mittelwert (SD)	25,5 (34,4)	30,6 (36,7)
Median (Q1; Q3)	0,0 (0,0; 33,3)	16,7 (0,0; 66,7)
Min, Max	0,0; 100,0	0,0; 100,0
Woche 87		
N[d]	7	8
Mittelwert (SD)	28,6 (40,5)	29,2 (37,5)
Median (Q1; Q3)	0,0 (0,0; 66,7)	16,7 (0,0; 50,0)
Min, Max	0,0; 100,0	0,0; 100,0
Woche 99		
N[d]	7	6
Mittelwert (SD)	14,3 (26,2)	16,7 (18,3)

EORTC QLQ-BIL21 Sorge um Gewichtsverlust	Studie: KEYNOTE 966[a]	
	Pembrolizumab + Chemotherapie[b]	Placebo + Chemotherapie[b]
	N[c]= 520	N[c]= 516
Median (Q1; Q3)	0,0 (0,0; 33,3)	16,7 (0,0; 33,3)
Min, Max	0,0; 66,7	0,0; 33,3
Woche 111		
N[d]	9	11
Mittelwert (SD)	7,4 (22,2)	6,1 (13,5)
Median (Q1; Q3)	0,0 (0,0; 0,0)	0,0 (0,0; 0,0)
Min, Max	0,0; 66,7	0,0; 33,3
Woche 123		
N[d]	3	1
Mittelwert (SD)	0,0 (0,0)	0,0 (-)
Median (Q1; Q3)	0,0 (0,0; 0,0)	0,0 (0,0; 0,0)
Min, Max	0,0; 0,0	0,0; 0,0
Woche 135		
N[d]	1	0
Mittelwert (SD)	0,0 (-)	- (-)
Median (Q1; Q3)	0,0 (0,0; 0,0)	- (-; -)
Min, Max	0,0; 0,0	-; -

a: Datenschnitt: 15. Dezember 2022
b: Chemotherapie: Gemcitabin + Cisplatin
c: Anzahl der Patient:innen: Full-Analysis-Set Population
d: Anzahl der Beobachtungen zu jedem Zeitpunkt
EORTC QLQ-BIL21: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Cholangiokarzinom und Gallenblasenkarzinom 21 Fragen; Max: Maximum; Min: Minimum; Q1: Erstes Quartil; Q3: Drittes Quartil; SD: Standardabweichung

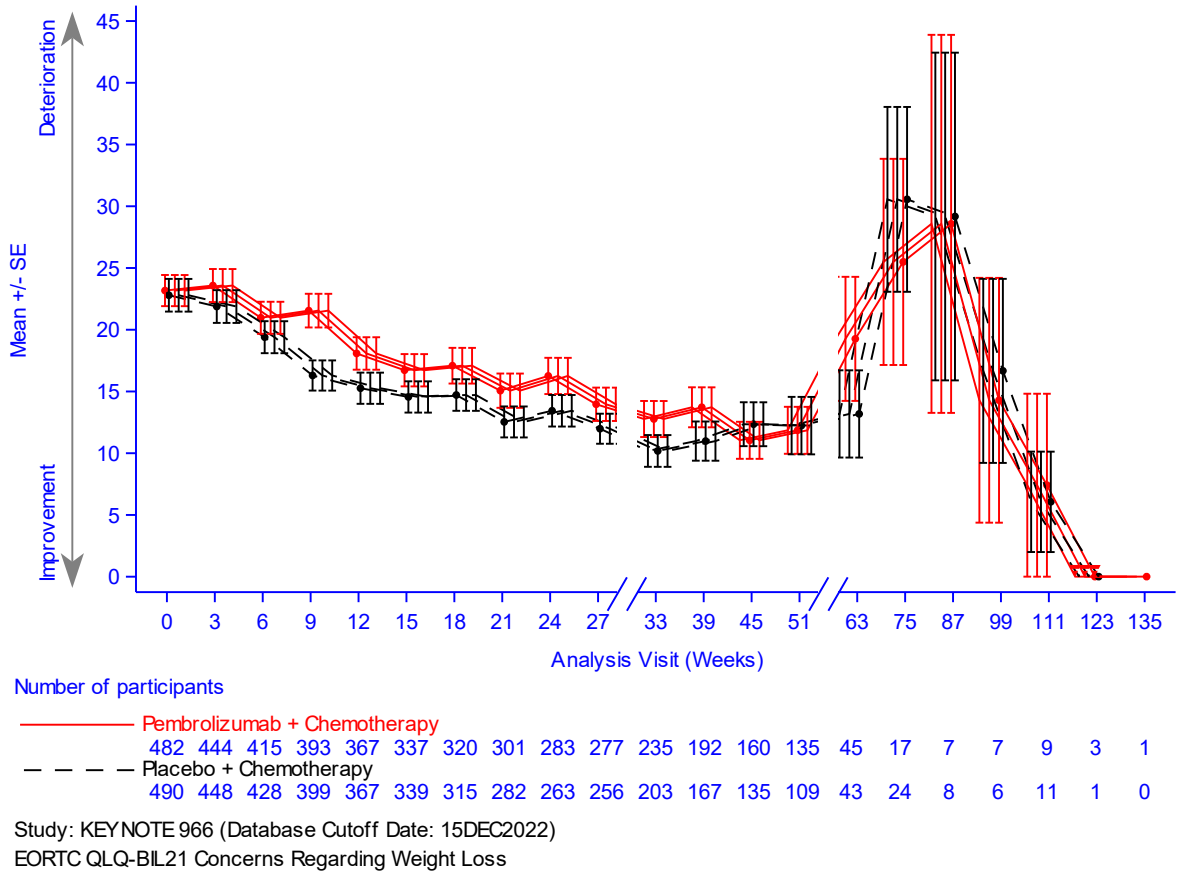


Abbildung 4G-16: EORTC QLQ-BIL21 Sorge um Gewichtsverlust im Studienverlauf

Anhang 4-G2.1: EQ-5D VAS im Studienverlauf

Tabelle 4G-20: EQ-5D VAS Gewichtsverlust im Studienverlauf

EQ-5D VAS	Studie: KEYNOTE 966[a]	
	Pembrolizumab + Chemotherapie[b] N[c]= 520	Placebo + Chemotherapie[b] N[c]= 517
Baseline		
N[d]	491	500
Mittelwert (SD)	74,4 (17,8)	74,7 (18,2)
Median (Q1; Q3)	79,0 (62,0; 89,0)	79,0 (65,0; 90,0)
Min, Max	0,0; 100,0	2,0; 100,0
Woche 3		
N[d]	449	456
Mittelwert (SD)	72,6 (18,6)	74,2 (18,2)
Median (Q1; Q3)	77,0 (60,0; 88,0)	79,0 (65,0; 89,5)
Min, Max	0,0; 100,0	3,0; 100,0
Woche 6		
N[d]	423	435
Mittelwert (SD)	74,7 (17,1)	75,1 (18,0)
Median (Q1; Q3)	80,0 (65,0; 89,0)	79,0 (69,0; 90,0)
Min, Max	9,0; 100,0	0,0; 100,0
Woche 9		
N[d]	395	405
Mittelwert (SD)	75,2 (16,3)	74,9 (17,7)
Median (Q1; Q3)	79,0 (65,0; 89,0)	80,0 (68,0; 89,0)
Min, Max	10,0; 100,0	9,0; 100,0
Woche 12		
N[d]	369	367
Mittelwert (SD)	75,3 (16,2)	75,7 (16,6)
Median (Q1; Q3)	79,0 (66,0; 89,0)	80,0 (65,0; 90,0)
Min, Max	5,0; 100,0	0,0; 100,0
Woche 15		
N[d]	340	344
Mittelwert (SD)	72,9 (17,9)	75,4 (16,6)
Median (Q1; Q3)	78,5 (60,0; 88,0)	79,0 (68,0; 90,0)
Min, Max	10,0; 100,0	5,0; 100,0
Woche 18		
N[d]	321	316
Mittelwert (SD)	74,3 (17,5)	75,6 (16,0)
Median (Q1; Q3)	78,0 (65,0; 89,0)	80,0 (67,0; 90,0)
Min, Max	5,0; 100,0	6,0; 100,0
Woche 21		
N[d]	306	284
Mittelwert (SD)	74,2 (18,3)	75,3 (16,6)
Median (Q1; Q3)	78,0 (63,0; 90,0)	79,5 (65,0; 90,0)
Min, Max	0,0; 100,0	10,0; 100,0
Woche 24		
N[d]	285	264
Mittelwert (SD)	73,8 (18,0)	74,1 (18,5)

EQ-5D VAS	Studie: KEYNOTE 966[a]	
	Pembrolizumab + Chemotherapie[b] N[c]= 520	Placebo + Chemotherapie[b] N[c]= 517
Median (Q1; Q3)	79,0 (62,0; 89,0)	80,0 (60,5; 90,0)
Min, Max	10,0; 100,0	0,0; 100,0
Woche 27		
N[d]	279	257
Mittelwert (SD)	75,1 (17,1)	75,1 (18,1)
Median (Q1; Q3)	78,0 (66,0; 89,0)	80,0 (69,0; 90,0)
Min, Max	19,0; 100,0	0,0; 100,0
Woche 33		
N[d]	235	205
Mittelwert (SD)	76,4 (16,4)	75,8 (15,8)
Median (Q1; Q3)	80,0 (69,0; 90,0)	80,0 (66,0; 90,0)
Min, Max	20,0; 100,0	30,0; 100,0
Woche 39		
N[d]	192	167
Mittelwert (SD)	75,3 (15,8)	74,4 (17,9)
Median (Q1; Q3)	79,0 (66,5; 89,0)	79,0 (61,0; 90,0)
Min, Max	30,0; 100,0	12,0; 100,0
Woche 45		
N[d]	161	137
Mittelwert (SD)	73,9 (16,1)	75,4 (16,4)
Median (Q1; Q3)	75,0 (68,0; 85,0)	80,0 (63,0; 90,0)
Min, Max	8,0; 100,0	30,0; 100,0
Woche 51		
N[d]	136	109
Mittelwert (SD)	73,0 (18,1)	74,8 (18,7)
Median (Q1; Q3)	78,0 (64,0; 88,0)	80,0 (65,0; 90,0)
Min, Max	3,0; 100,0	11,0; 100,0
Woche 63		
N[d]	45	43
Mittelwert (SD)	71,0 (21,7)	74,1 (16,9)
Median (Q1; Q3)	79,0 (60,0; 88,0)	71,0 (61,0; 90,0)
Min, Max	13,0; 98,0	30,0; 100,0
Woche 75		
N[d]	17	24
Mittelwert (SD)	57,6 (23,2)	67,7 (20,7)
Median (Q1; Q3)	60,0 (49,0; 70,0)	70,0 (53,5; 80,5)
Min, Max	0,0; 95,0	10,0; 98,0
Woche 87		
N[d]	7	8
Mittelwert (SD)	58,3 (25,4)	68,6 (21,9)
Median (Q1; Q3)	69,0 (30,0; 80,0)	75,0 (55,5; 84,0)
Min, Max	20,0; 80,0	30,0; 90,0
Woche 99		
N[d]	7	6
Mittelwert (SD)	70,6 (18,5)	81,7 (11,4)
Median (Q1; Q3)	78,0 (49,0; 84,0)	80,0 (70,0; 92,0)

EQ-5D VAS	Studie: KEYNOTE 966[a]	
	Pembrolizumab + Chemotherapie[b] N[c]= 520	Placebo + Chemotherapie[b] N[c]= 517
Min, Max	40,0; 88,0	70,0; 98,0
Woche 111		
N[d]	9	11
Mittelwert (SD)	80,3 (18,2)	80,5 (16,4)
Median (Q1; Q3)	89,0 (70,0; 90,0)	80,0 (64,0; 97,0)
Min, Max	45,0; 100,0	50,0; 100,0
Woche 123		
N[d]	3	1
Mittelwert (SD)	86,3 (8,1)	90,0 (-)
Median (Q1; Q3)	85,0 (79,0; 95,0)	90,0 (90,0; 90,0)
Min, Max	79,0; 95,0	90,0; 90,0
Woche 135		
N[d]	1	0
Mittelwert (SD)	71,0 (-)	- (-)
Median (Q1; Q3)	71,0 (71,0; 71,0)	- (-; -)
Min, Max	71,0; 71,0	-; -

a: Datenschnitt: 15. Dezember 2022

b: Chemotherapie: Gemcitabin + Cisplatin

c: Anzahl der Patient:innen: Full-Analysis-Set Population

d: Anzahl der Beobachtungen zu jedem Zeitpunkt

EQ-5D: European Quality of Life 5 Dimensions; Max: Maximum; Min: Minimum; Q1: Erstes Quartil; Q3: Drittes Quartil; SD: Standardabweichung; VAS: Visuelle Analogskala

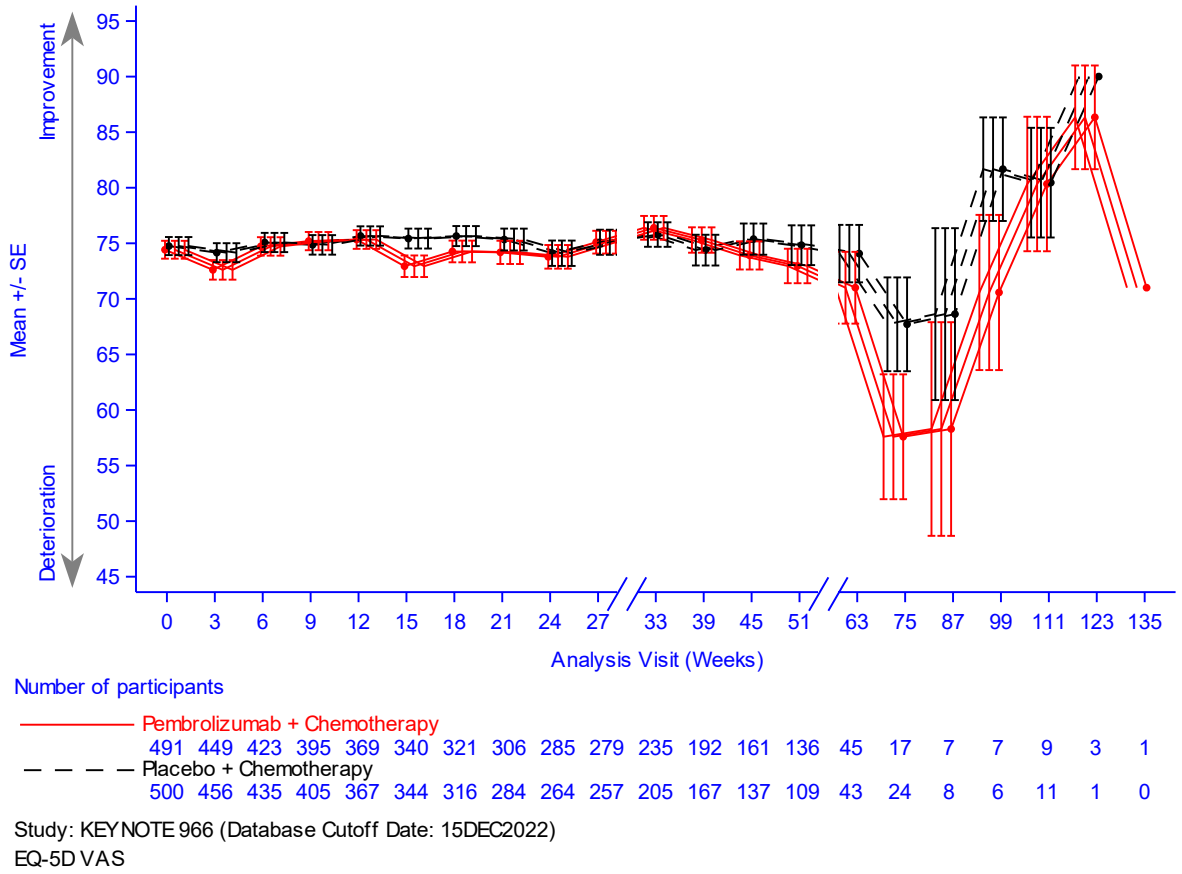


Abbildung 4G-17: EQ-5D VAS im Studienverlauf

Anhang 4-G3: Ergänzende Analysen

Anhang 4-G3.1: Beobachtungsdauer

Tabelle 4G-21: Behandlungs- und Beobachtungsdauer pro Endpunkt

Study: KEYNOTE 966[a]	Pembrolizumab + Chemotherapy[b]	Placebo + Chemotherapy[b]
Duration of Treatment (months)[c]		
N[d]	529	534
Mean (SD)	8.0 (6.9)	7.3 (6.3)
Median (Q1; Q3)	6.37 (2.79; 10.84)	5.54 (2.53; 9.69)
Min; Max	0.03; 36.40	0.03; 30.62
Observation Period		
Overall Survival (Months)[e]		
N[f]	533	536
Mean (SD)	14.0 (8.6)	12.7 (8.4)
Median (Q1; Q3)	12.71 (6.77; 20.27)	10.84 (5.70; 18.55)
Min; Max	0.20; 37.03	0.23; 36.21
Adverse Event (Months)[g]		
N[d]	529	534
Mean (SD)	9.0 (6.9)	8.2 (6.3)
Median (Q1; Q3)	7.36 (3.78; 11.83)	6.51 (3.38; 10.68)
Min; Max	0.16; 36.70	0.23; 30.65
Serious Adverse Event (Months) [g]		
N[d]	529	534
Mean (SD)	10.4 (6.9)	9.6 (6.4)
Median (Q1; Q3)	8.74 (5.29; 13.57)	8.25 (4.80; 12.42)
Min; Max	0.16; 36.70	0.23; 30.69
EORTC QLQ-C30 (Months)[h]		
N[i]	520	517
Mean (SD)	7.8 (5.8)	7.3 (5.6)
Median (Q1; Q3)	7.03 (3.25; 11.34)	6.05 (3.02; 10.15)
Min; Max	-0.07; 30.65	0.03; 28.32
EQ-5D VAS (Months)[h]		
N[i]	520	517
Mean (SD)	7.8 (5.8)	7.3 (5.6)
Median (Q1; Q3)	7.03 (3.25; 11.34)	6.05 (3.02; 10.15)
Min; Max	-0.07; 30.65	0.03; 28.32
EORTC QLQ-BIL21 (Months)[h]		
N[i]	520	516
Mean (SD)	7.8 (5.8)	7.4 (5.6)
Median (Q1; Q3)	7.03 (3.25; 11.34)	6.05 (3.02; 10.22)
Min; Max	-0.07; 30.65	0.03; 28.32

a: Database Cutoff Date: 15DEC2022
b: Chemotherapy: Gemcitabine + Cisplatin
c: Calculated from date of first dose until date of last dose
d: Number of participants: all-participants-as-treated population
e: Calculated from date of randomization until date of death, date of last contact, or the database cutoff date if the participant is still alive
f: Number of participants: intention-to-treat population
g: Adverse event follow-up duration is defined as the time from first dose to the earliest of the last dose + planned safety follow-up time, date of death, or the database cutoff date if the participant is still alive
h: Calculated from date of first dose until date of last questionnaire assessment
i: Number of participants: full-analysis-set population
EORTC QLQ-BIL21: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Cholangiocarcinoma and

Gallbladder Cancer 21 items; EORTC QLQ-C30: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Core 30 items; EQ-5D: European Quality of Life 5 Dimensions; Max: Maximum; Min: Minimum; Q1: First Quartile; Q3: Third Quartile; SD: Standard Deviation; VAS: Visual Analogue Scale

Anhang 4-G3.1: Ergänzende Analysen für die Endpunkte Progressionsfreies Überleben und Ansprechrate

Tabelle 4G-22: Progressionsfreie Überlebensrate zu spezifischen Zeitpunkten für die Studie KEYNOTE 966 basierend auf der BICR Analyse nach RECIST 1.1

Progressionsfreies Überleben (BICR Primäranalyse)	**Studie: KEYNOTE 966[a]**	
	Pembrolizumab + Chemotherapie[b] **N[c]= 533**	**Placebo + Chemotherapie[b]** **N[c]= 536**
Kaplan-Meier Rate zu einem spezifischen Zeitpunkt, % [95%-KI][d]		
Monat 6	52,3 [47,8; 56,5]	46,1 [41,7; 50,3]
Monat 9	34,8 [30,6; 39,1]	28,4 [24,5; 32,5]
Monat 12	24,4 [20,6; 28,5]	18,7 [15,3; 22,4]
Monat 15	19,0 [15,4; 22,8]	14,0 [10,9; 17,4]
Monat 18	12,4 [9,4; 15,8]	9,3 [6,8; 12,4]
Monat 21	9,8 [7,1; 13,1]	7,4 [5,0; 10,4]
Monat 24	9,1 [6,4; 12,3]	5,4 [3,2; 8,4]

a: Datenschnitt: 15. Dezember 2022
b: Chemotherapie: Gemcitabin + Cisplatin
c: Anzahl der Patient:innen: Intention-To-Treat Population
d: Produkt-Limit (Kaplan-Meier) Methode für zensierte Daten
BICR: Blinded Independent Central Review; KI: Konfidenzintervall

Tabelle 4G-23: Ergänzende Analysen für den Endpunkt Objektive Ansprechrate für die Studie KEYNOTE 966 basierend auf der BICR Analyse nach RECIST 1.1

Response Evaluation	Pembrolizumab + Chemotherapy			Placebo + Chemotherapy		
	n	(%)	(95% CI)[a]	n	(%)	(95% CI)[a]
Participants in population	533			536		
Complete Response (CR)	14	2.6	(1.4, 4.4)	9	1.7	(0.8, 3.2)
Partial Response (PR)	142	26.6	(22.9, 30.6)	143	26.7	(23.0, 30.6)
Objective Response Rate (CR+PR)	**156**	**29.3**	**(25.4, 33.3)**	**152**	**28.4**	**(24.6, 32.4)**
Stable Disease (SD)[b]	243	45.6	(41.3, 49.9)	253	47.2	(42.9, 51.5)
Disease Control (CR+PR+SD)	**399**	**74.9**	**(71.0, 78.5)**	**405**	**75.6**	**(71.7, 79.1)**
Progressive Disease (PD)	104	19.5	(16.2, 23.1)	97	18.1	(14.9, 21.6)
Non-evaluable (NE)	8	1.5	(0.7, 2.9)	11	2.1	(1.0, 3.6)
No Assessment	22	4.1	(2.6, 6.2)	23	4.3	(2.7, 6.4)

[a] Based on binomial exact confidence interval method.
[b] Stable disease includes SD, Non-CR/Non-PD and NED.
BICR = Blinded independent central review.
NE: post-baseline assessment(s) available however not being evaluable.
No Assessment: no post-baseline assessment(s) available for response evaluation.
Database Cutoff Date: 15DEC2022.

Tabelle 4G-24: Zeit bis zum Ansprechen und Dauer des Ansprechens für die Studie KEYNOTE 966 basierend auf der BICR Analyse nach RECIST 1.1

Studie: KEYNOTE 966[a]	**Pembrolizumab + Chemotherapie[b] N[c]= 533**	**Placebo + Chemotherapie[b] N[c]= 536**
Anzahl der Patient:innen mit Ansprechen[d]	156	152
Zeit bis zum Ansprechen (Monate)		
Mittelwert (SD)	3,4 (3,0)	3,2 (2,0)
Median (Q1; Q3)	2,79 (1,48; 4,16)	2,79 (1,48; 4,17)
Min, Max	1,08; 26,22	1,18; 12,52
Dauer des Ansprechens (Monate)		
Median[e] (Q1; Q3)	8,31 (5,03; 15,67)	6,83 (4,40; 12,68)
Min[f]; Max[f]	1,22+; 32,95+	1,15+; 30,03+
Anzahl (%[e]) der Patient:innen mit verlängerter Dauer des Ansprechens		
≥ 3 Monate	141 (93,5)	134 (90,0)
≥ 6 Monate	93 (64,6)	77 (54,7)
≥ 9 Monate	61 (45,8)	44 (35,5)
≥ 12 Monate	47 (38,0)	33 (27,3)
≥ 15 Monate	34 (27,5)	17 (18,1)
≥ 18 Monate	22 (24,2)	9 (14,4)
≥ 21 Monate	16 (20,5)	4 (7,7)
≥ 24 Monate	10 (17,6)	3 (5,7)

a: Datenschnitt: 15. Dezember 2022
b: Chemotherapie: Gemcitabin + Cisplatin
c: Anzahl der Patient:innen: Intention-To-Treat Population
d: Enthält Patient:innen mit komplettem Ansprechen oder partiellem Ansprechen
e: Produkt-Limit (Kaplan-Meier) Methode für zensierte Daten
f: '+' zeigt an, dass keine Krankheitsprogression zum Zeitpunkt der letzten Erhebung vorlag
Max: Maximum; Min: Minimum; Q1: Erstes Quartil; Q3: Drittes Quartil; SD: Standardabweichung

Anhang 4-G4: Kaplan-Meier-Kurven der Subgruppen mit statistisch signifikantem Interaktionstest (p < 0,05)

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

Anhang 4-G4.1: Mortalität

Für den Endpunkt Gesamtüberleben liegt kein statistisch signifikanter Interaktionstest vor.

Anhang 4-G4.2: Morbidität

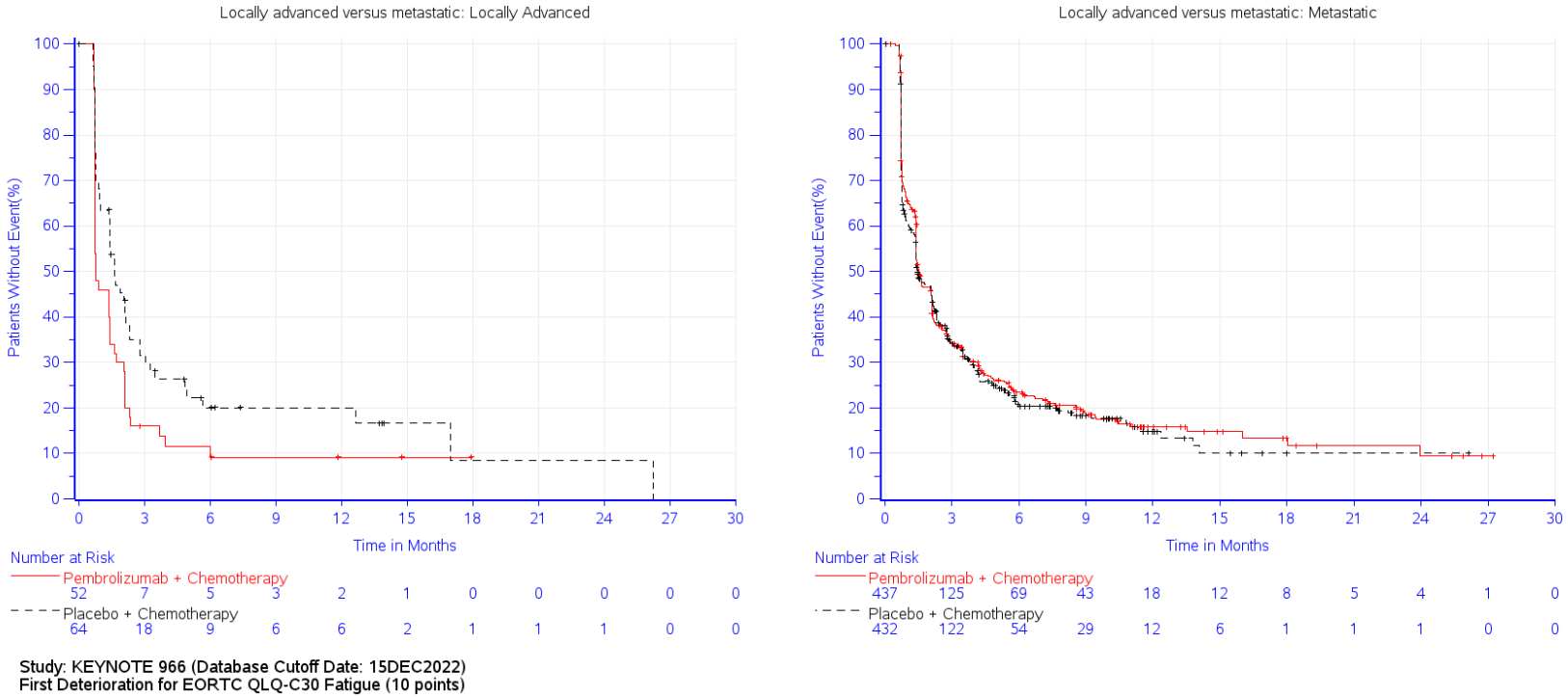


Abbildung 4G-18: Kaplan-Meier-Kurven für die Subgruppenanalyse nach Krankheitsstatus für den Endpunkt EORTC QLQ-C30 Erschöpfung der Studie KEYNOTE 966

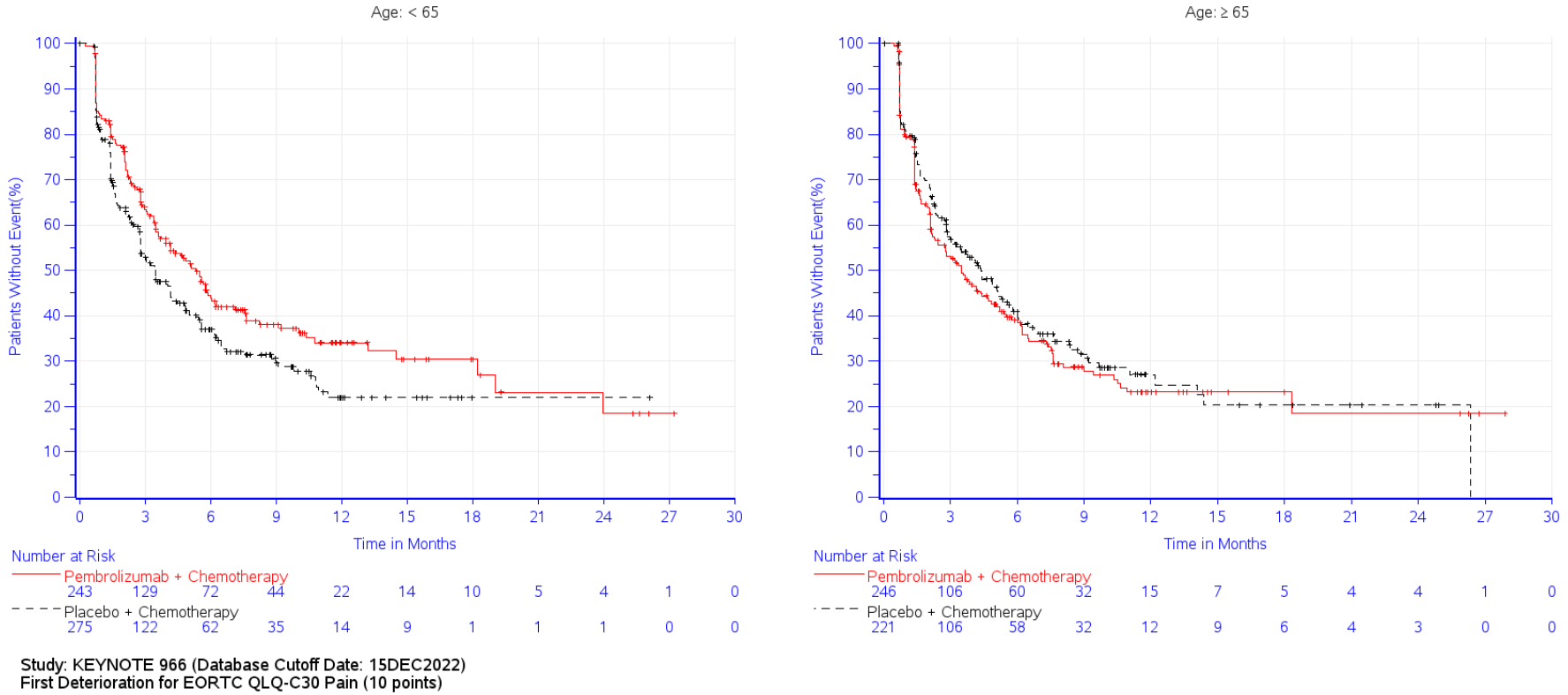


Abbildung 4G-19: Kaplan-Meier-Kurven für die Subgruppenanalyse nach Alter für den Endpunkt EORTC QLQ-C30 Schmerzen der Studie KEYNOTE 966

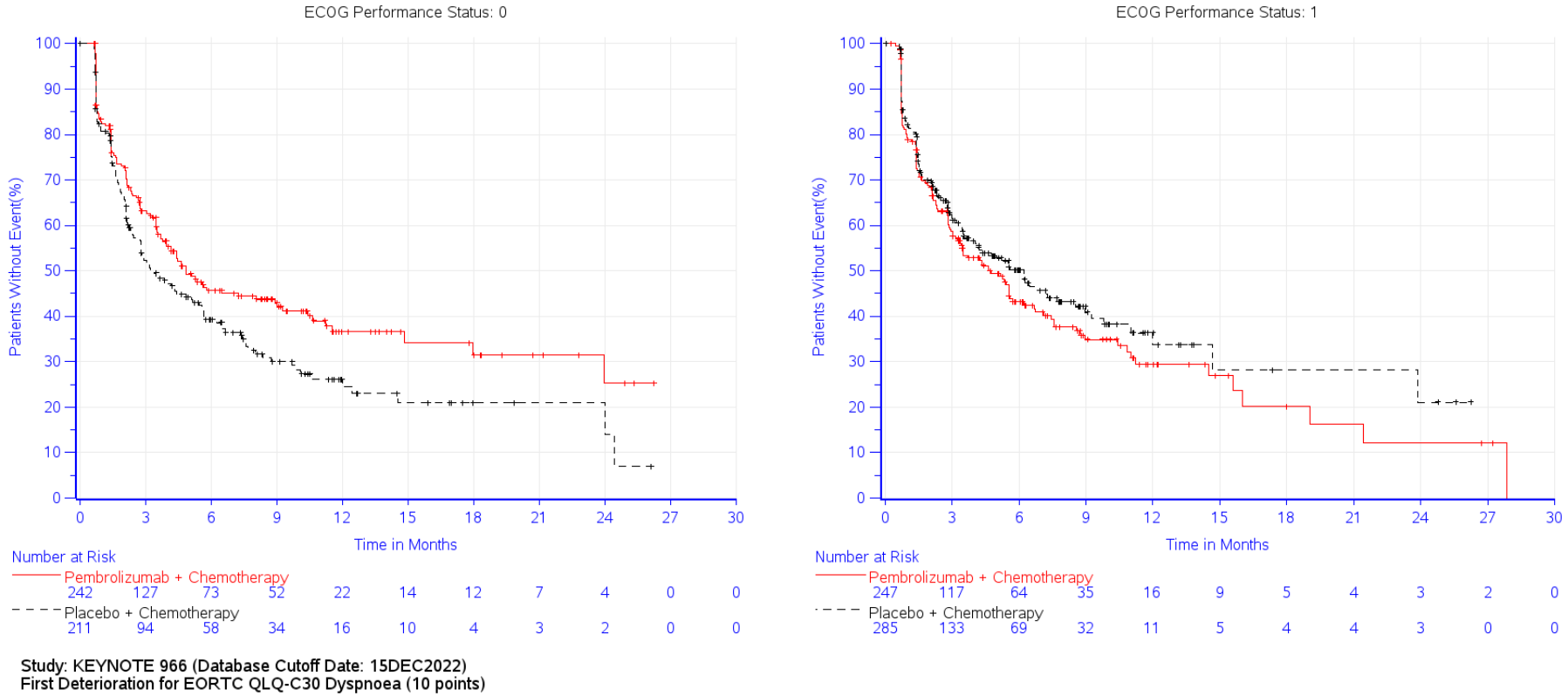


Abbildung 4G-20: Kaplan-Meier-Kurven für die Subgruppenanalyse nach ECOG-Leistungsstatus für den Endpunkt EORTC QLQ-C30 Dyspnoe der Studie KEYNOTE 966

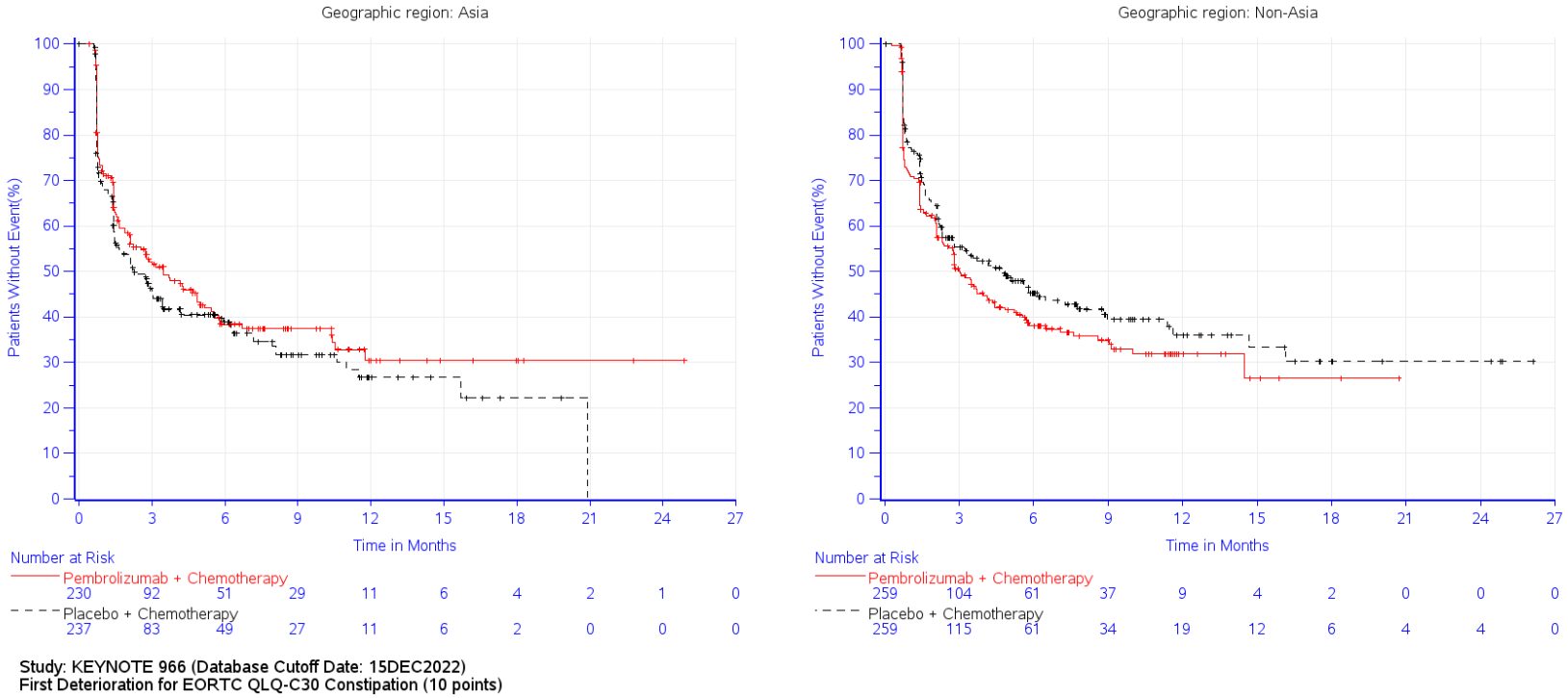
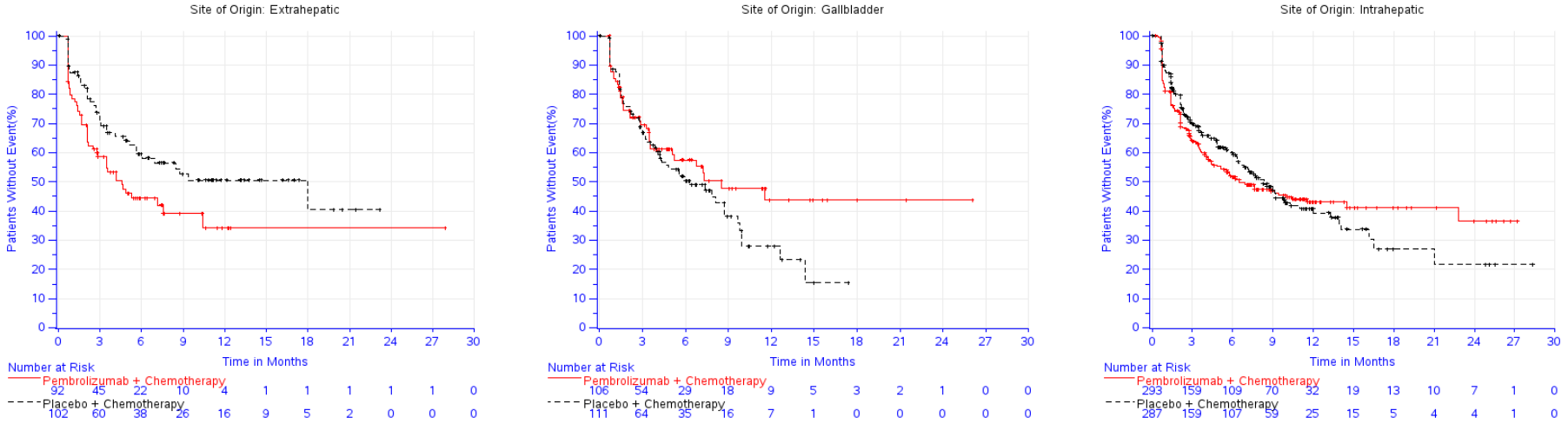


Abbildung 4G-21: Kaplan-Meier-Kurven für die Subgruppenanalyse nach Region für den Endpunkt EORTC QLQ-C30 Verstopfung der Studie KEYNOTE 966



Study: KEYNOTE 966 (Database Cutoff Date: 15DEC2022)
First Deterioration for EQ-5D VAS (15 points)

Abbildung 4G-22: Kaplan-Meier-Kurven für die Subgruppenanalyse nach Entstehungsort für den Endpunkt EQ-5D VAS der Studie KEYNOTE 966

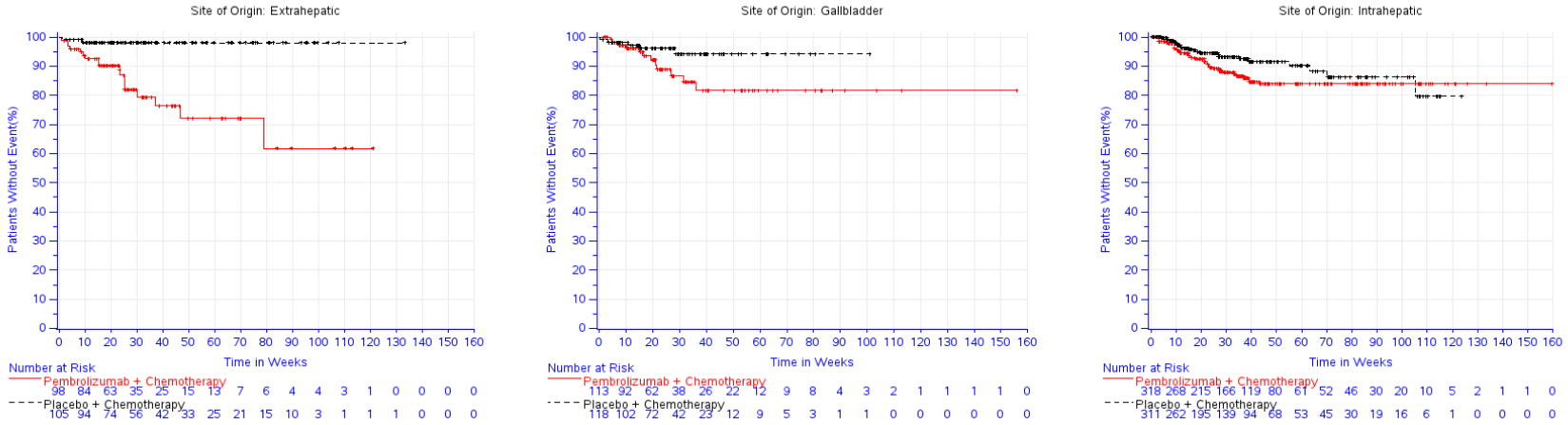
Anhang 4-G4.3: Gesundheitsbezogene Lebensqualität

Für die Endpunkte der Gesundheitsbezogenen Lebensqualität liegt jeweils kein statistisch signifikanter Interaktionstest vor.

Anhang 4-G4.3: Nebenwirkungen

Unerwünschte Ereignisse (gegliedert nach SOC und PT)

Unerwünschte Ereignisse gesamt (SOC und PT)



Study: KEYNOTE 966 (Database Cutoff Date: 15DEC2022)
Adverse Event - System Organ Class: Endocrine disorders

Abbildung 4G-23: Kaplan-Meier-Kurven für die Subgruppenanalyse nach Entstehungsort für den Endpunkt Unerwünschte Ereignisse gesamt (SOC und PT) für die SOC Endokrine Erkrankungen der Studie KEYNOTE 966

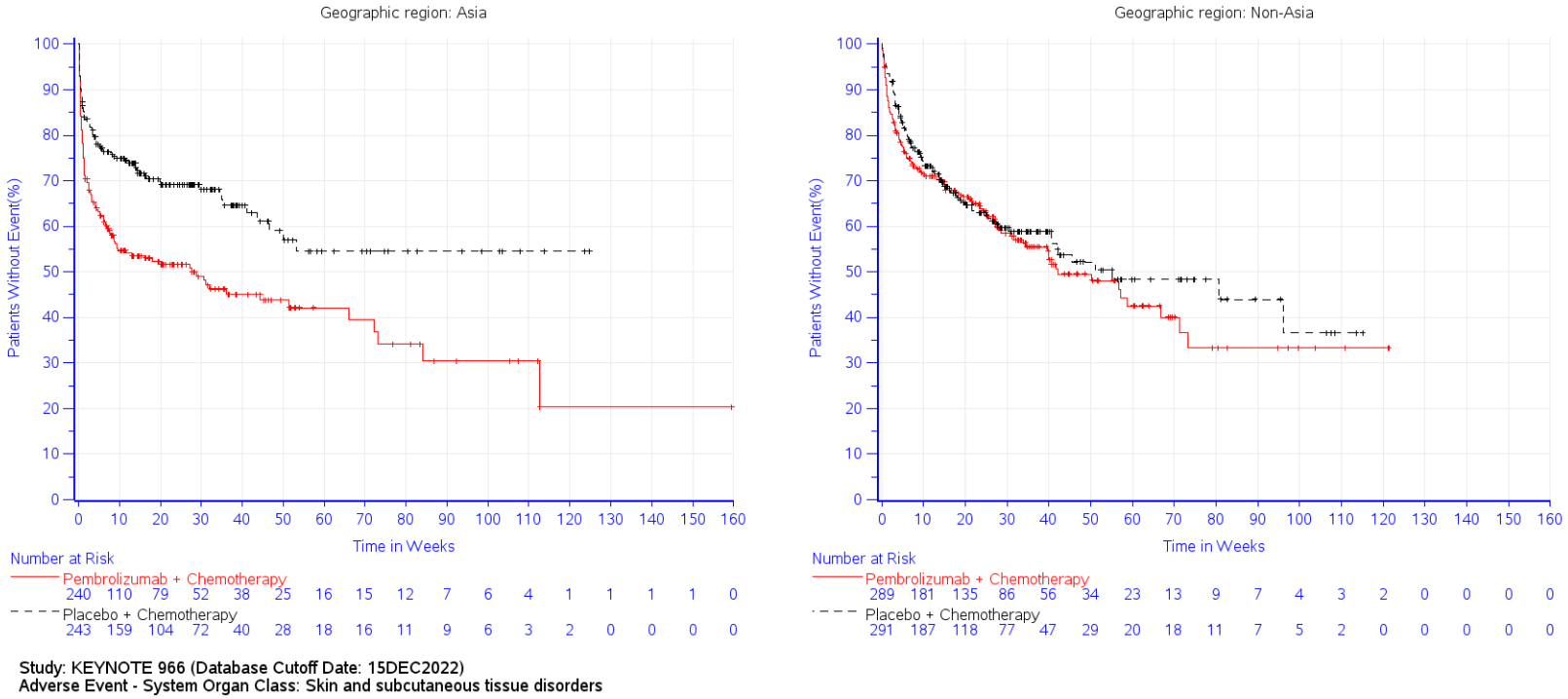
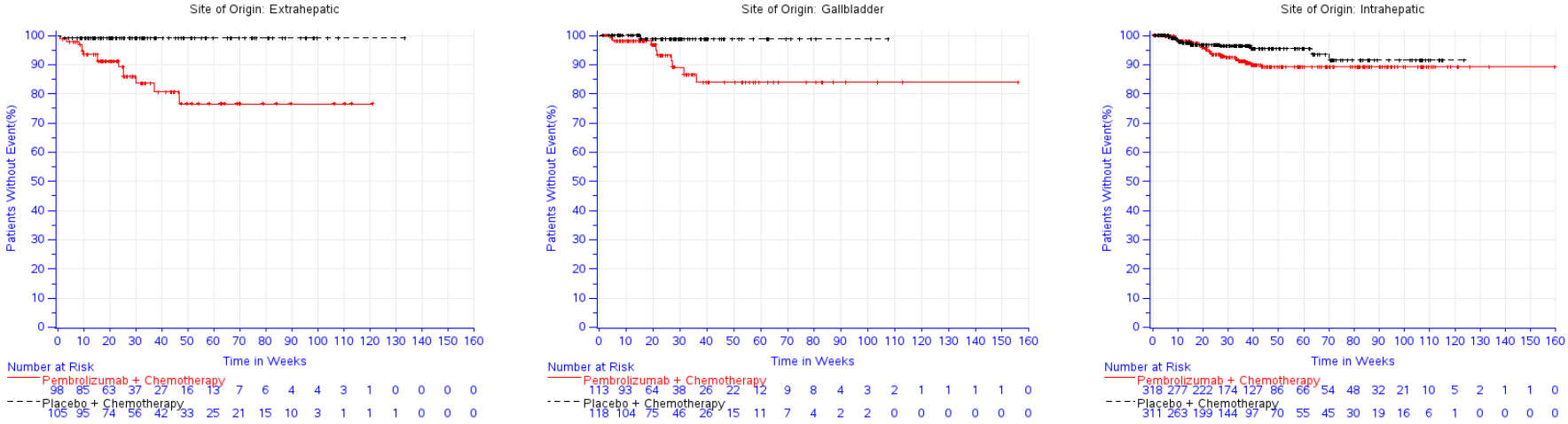


Abbildung 4G-24: Kaplan-Meier-Kurven für die Subgruppenanalyse nach Region für den Endpunkt Unerwünschte Ereignisse gesamt (SOC und PT) für die SOC Erkrankungen der Haut und des Unterhautzellgewebes der Studie KEYNOTE 966



Study: KEYNOTE 966 (Database Cutoff Date: 15DEC2022)
Adverse Event - Preferred Term: Hypothyroidism

Abbildung 4G-25: Kaplan-Meier-Kurven für die Subgruppenanalyse nach Entstehungsort für den Endpunkt Unerwünschte Ereignisse gesamt (SOC und PT) für den PT Hypothyreose der Studie KEYNOTE 966

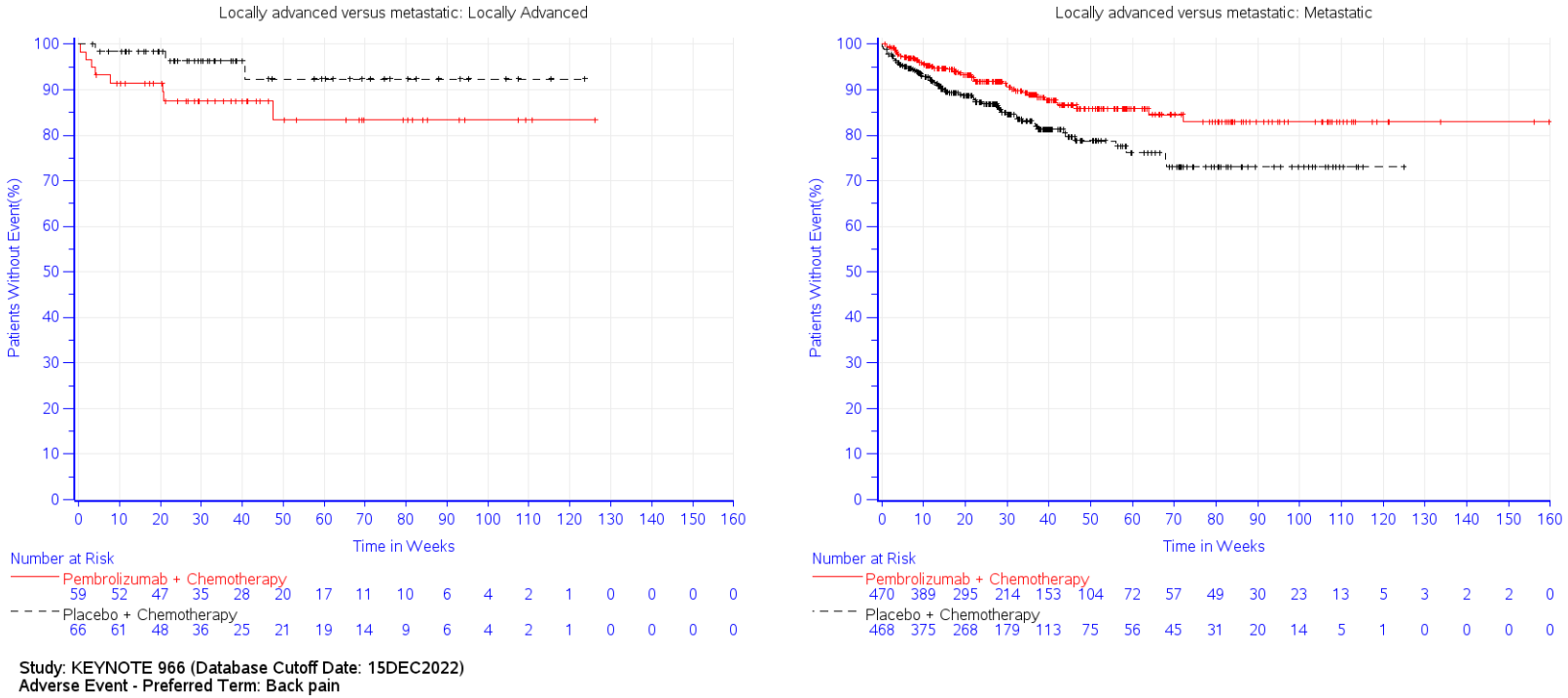


Abbildung 4G-26: Kaplan-Meier-Kurven für die Subgruppenanalyse nach Krankheitsstatus für den Endpunkt Unerwünschte Ereignisse gesamt (SOC und PT) für den PT Rückenschmerzen der Studie KEYNOTE 966

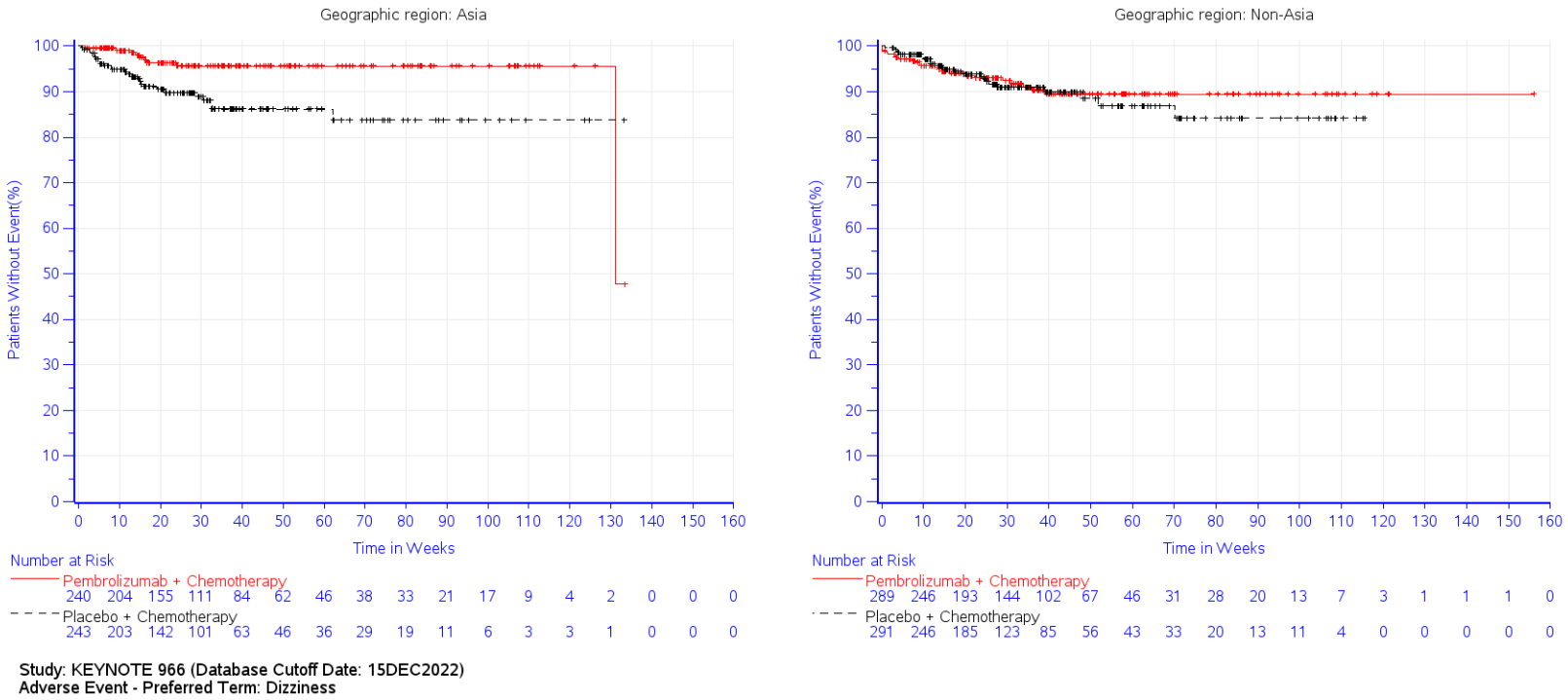


Abbildung 4G-27: Kaplan-Meier-Kurven für die Subgruppenanalyse nach Region für den Endpunkt Unerwünschte Ereignisse gesamt (SOC und PT) für den PT Schwindel erhöht der Studie KEYNOTE 966

Anhang 4-G5: Ergebnisse der Subgruppen mit nicht statistisch signifikantem Interaktionstest (p ≥ 0,05)

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

Anhang 4-G5.1: Mortalität

Tabelle 4G-25: Subgruppenanalysen mit nicht statistisch signifikantem Interaktionstest (p ≥ 0,05) für den Endpunkt Gesamtüberleben aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE 966[a]	Pembrolizumab + Chemotherapy[b]			Placebo + Chemotherapy[b]			Pembrolizumab + Chemotherapy[b] vs. Placebo + Chemotherapy[b]		
Overall Survival	N[c]	Participants with Event n (%)	Median Time[d] in Months [95 %-CI]	N[c]	Participants 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]
Sex									
Female	253	200 (79.1)	11.6 [10.5; 13.3]	264	220 (83.3)	10.0 [9.0; 11.5]	0.85 [0.70; 1.03]	0.092	0.891
Male	280	214 (76.4)	13.1 [11.9; 14.6]	272	223 (82.0)	11.4 [10.4; 13.5]	0.83 [0.69; 1.00]	0.052	
Age									
< 65	269	210 (78.1)	12.8 [11.6; 14.1]	298	242 (81.2)	10.9 [9.7; 12.0]	0.88 [0.73; 1.05]	0.159	0.463
≥ 65	264	204 (77.3)	12.0 [10.3; 14.1]	238	201 (84.5)	10.7 [9.5; 12.2]	0.79 [0.65; 0.97]	0.021	
ECOG Performance Status									
0	258	186 (72.1)	14.4 [12.6; 16.8]	228	177 (77.6)	14.2 [11.6; 15.7]	0.87 [0.71; 1.07]	0.186	0.737
1	274	227 (82.8)	10.9 [9.9; 12.7]	308	266 (86.4)	9.0 [8.3; 10.2]	0.84 [0.70; 1.00]	0.051	
Geographic region									
Asia	242	185 (76.4)	11.8 [10.3; 13.9]	244	201 (82.4)	11.5 [10.0; 13.5]	0.88 [0.72; 1.08]	0.217	0.484
Non-Asia	291	229 (78.7)	13.0 [11.6; 14.5]	292	242 (82.9)	10.5 [9.1; 11.4]	0.80 [0.67; 0.96]	0.018	
Locally advanced versus metastatic									
Locally Advanced	60	37 (61.7)	17.1 [13.9; 29.2]	66	52 (78.8)	17.4 [13.4; 19.7]	0.69 [0.45; 1.06]	0.092	0.522
Metastatic	473	377 (79.7)	11.9 [10.8; 13.1]	470	391 (83.2)	10.2 [9.4; 11.1]	0.85 [0.74; 0.98]	0.022	
Site of Origin									
Extrahepatic	98	78 (79.6)	12.9 [10.2; 15.4]	105	83 (79.0)	13.0 [9.6; 16.3]	0.99 [0.73; 1.35]	0.962	0.198
Gallbladder	115	102 (88.7)	9.2 [7.5; 10.5]	118	104 (88.1)	9.3 [8.0; 10.6]	0.96 [0.73; 1.26]	0.782	
Intrahepatic	320	234 (73.1)	14.0 [12.4; 15.2]	313	256 (81.8)	11.5 [10.2; 13.1]	0.76 [0.64; 0.91]	0.003	
Biliary stent and or a biliary drain									
Yes	33	26 (78.8)	12.9 [6.6; 16.9]	41	37 (90.2)	9.4 [6.3; 13.5]	0.72 [0.43; 1.19]	0.196	0.501
No	500	388 (77.6)	12.7 [11.5; 13.6]	495	406 (82.0)	10.9 [9.9; 11.7]	0.85 [0.74; 0.98]	0.023	

Antibiotics within 1 month of study start									
Yes	291	224 (77.0)	11.9 [10.5; 14.1]	273	230 (84.2)	11.0 [9.5; 12.3]	0.81 [0.68; 0.98]	0.028	0.617
No	242	190 (78.5)	12.9 [11.8; 14.0]	263	213 (81.0)	10.7 [9.7; 11.8]	0.86 [0.71; 1.05]	0.144	
Prior Chemotherapy									
Yes	50	32 (64.0)	22.0 [13.3; 28.9]	48	35 (72.9)	15.9 [8.6; 19.7]	0.66 [0.41; 1.08]	0.098	0.442
No	483	382 (79.1)	12.0 [11.0; 13.1]	488	408 (83.6)	10.7 [9.8; 11.5]	0.86 [0.75; 0.99]	0.031	
Smoking Status									
Current Smoker	56	42 (75.0)	13.5 [10.4; 17.9]	49	38 (77.6)	13.9 [10.4; 17.4]	0.90 [0.58; 1.40]	0.655	0.833
Former Smoker	205	160 (78.0)	12.7 [10.8; 14.4]	191	160 (83.8)	11.1 [9.8; 13.5]	0.87 [0.70; 1.09]	0.231	
Never Smoker	272	212 (77.9)	12.2 [10.7; 13.6]	295	244 (82.7)	10.3 [9.1; 11.4]	0.82 [0.68; 0.98]	0.030	
PD-L1 expression (CPS ≥1 versus <1)									
CPS≥1	363	287 (79.1)	11.6 [10.6; 13.1]	365	309 (84.7)	10.7 [9.7; 11.6]	0.85 [0.72; 1.00]	0.044	0.937
CPS<1	113	86 (76.1)	14.2 [12.1; 16.6]	110	87 (79.1)	13.0 [10.0; 15.5]	0.84 [0.62; 1.14]	0.259	
Indeterminate	57	41 (71.9)	14.1 [11.1; 16.9]	61	47 (77.0)	9.4 [6.6; 13.0]	0.77 [0.51; 1.18]	0.232	

a: Database Cutoff Date: 15DEC2022

b: Chemotherapy: Gemcitabine + Cisplatin

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

d: From product-limit (Kaplan-Meier) method for censored data

e: Based on Cox regression model with treatment as a covariate

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

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

CI: Confidence Interval; CPS: Combined Positive Score; ECOG: Eastern Cooperative Oncology Group; PD-L1: Programmed Cell Death - Ligand 1

Anhang 4-G5.2: Morbidität

Zeit bis zur ersten Folgetherapie oder Tod

Tabelle 4G-26: Subgruppenanalysen mit nicht statistisch 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 966[a]	Pembrolizumab + Chemotherapy[b]			Placebo + Chemotherapy[b]			Pembrolizumab + Chemotherapy[b] vs. Placebo + Chemotherapy[b]		p-Value for Interaction Test[g]
	N[c]	Participants with Event n (%)	Median Time[d] in Months [95 %-CI]	N[c]	Participants with Event n (%)	Median Time[d] in Months [95 %-CI]	Hazard Ratio [95 %-CI][e]	p-Value[e,f]	
Sex									
Female	253	233 (92.1)	9.1 [8.0; 10.2]	264	245 (92.8)	7.2 [6.4; 8.2]	0.85 [0.71; 1.02]	0.074	0.971
Male	280	246 (87.9)	8.2 [7.4; 9.2]	272	249 (91.5)	8.2 [7.2; 8.8]	0.86 [0.72; 1.02]	0.085	
Age									
< 65	269	245 (91.1)	8.8 [7.4; 9.9]	298	277 (93.0)	7.8 [6.7; 8.6]	0.89 [0.75; 1.06]	0.192	0.484
≥ 65	264	234 (88.6)	8.5 [7.7; 10.1]	238	217 (91.2)	7.6 [6.4; 8.3]	0.82 [0.68; 0.98]	0.034	
ECOG Performance Status									
0	258	228 (88.4)	9.1 [8.1; 10.5]	228	206 (90.4)	8.9 [7.7; 10.0]	0.90 [0.75; 1.09]	0.299	0.402
1	274	250 (91.2)	8.0 [7.2; 9.2]	308	288 (93.5)	6.7 [6.0; 7.7]	0.82 [0.69; 0.97]	0.021	
Geographic region									
Asia	242	212 (87.6)	8.3 [7.2; 9.2]	244	223 (91.4)	7.8 [6.6; 8.5]	0.88 [0.73; 1.06]	0.168	0.742
Non-Asia	291	267 (91.8)	9.0 [7.9; 10.3]	292	271 (92.8)	7.6 [6.7; 8.3]	0.83 [0.70; 0.99]	0.034	
Locally advanced versus metastatic									
Locally Advanced	60	50 (83.3)	12.2 [9.2; 15.8]	66	60 (90.9)	8.7 [7.4; 13.4]	0.73 [0.50; 1.07]	0.104	0.505
Metastatic	473	429 (90.7)	8.3 [7.5; 9.0]	470	434 (92.3)	7.4 [6.6; 8.2]	0.87 [0.76; 0.99]	0.039	
Site of Origin									
Extrahepatic	98	87 (88.8)	8.5 [7.3; 10.7]	105	92 (87.6)	8.7 [6.9; 11.3]	1.01 [0.75; 1.35]	0.970	0.279
Gallbladder	115	106 (92.2)	6.1 [5.2; 7.4]	118	112 (94.9)	7.1 [5.9; 8.0]	0.94 [0.72; 1.22]	0.627	
Intrahepatic	320	286 (89.4)	9.5 [8.6; 10.5]	313	290 (92.7)	7.7 [6.7; 8.4]	0.78 [0.67; 0.92]	0.004	

a: Database Cutoff Date: 15DEC2022
b: Chemotherapy: Gemcitabine + Cisplatin
c: Number of participants: intention-to-treat population
d: From product-limit (Kaplan-Meier) method for censored data
e: Based on Cox regression model with treatment as a covariate
f: Two-sided p-value using Wald test (Score test in case of zero event in one treatment group)
g: Based on Cox 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

EORTC QLQ-C30

Symptomskala Erschöpfung

Tabelle 4G-27: Subgruppenanalysen mit nicht statistisch signifikantem Interaktionstest ($p \geq 0,05$) für den Endpunkt EORTC QLQ-C30 Erschöpfung aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE 966[a]	**Pembrolizumab + Chemotherapy[b]**			**Placebo + Chemotherapy[b]**			**Pembrolizumab + Chemotherapy[b] vs. Placebo + Chemotherapy[b]**		**p-Value for Interaction Test[g]**
EORTC QLQ-C30 Fatigue (10 points)	**N[c]**	**Participants with Event n (%)**	**Median Time[d] in months [95 %-CI]**	**N[c]**	**Participants with Event n (%)**	**Median Time[d] in months [95 %-CI]**	**Hazard Ratio [95 %-CI][e]**	**p-Value[e,f]**	
Sex									
Female	224	179 (79.9)	1.4 [1.0; 1.4]	241	178 (73.9)	1.4 [1.4; 2.1]	1.16 [0.94; 1.43]	0.154	0.059
Male	265	185 (69.8)	2.0 [1.4; 2.1]	255	193 (75.7)	1.6 [1.4; 2.1]	0.88 [0.72; 1.08]	0.236	
Age									
< 65	243	173 (71.2)	1.7 [1.4; 2.1]	275	195 (70.9)	2.1 [1.4; 2.3]	0.97 [0.79; 1.20]	0.804	0.862
≥ 65	246	191 (77.6)	1.4 [1.3; 1.6]	221	176 (79.6)	1.4 [1.1; 1.5]	1.01 [0.82; 1.24]	0.943	
ECOG Performance Status									
0	242	188 (77.7)	1.4 [1.1; 1.5]	211	170 (80.6)	1.4 [1.4; 1.8]	1.02 [0.83; 1.25]	0.876	0.768
1	247	176 (71.3)	1.6 [1.4; 2.1]	285	201 (70.5)	1.9 [1.4; 2.3]	0.97 [0.79; 1.19]	0.763	
Geographic region									
Asia	230	166 (72.2)	1.5 [1.4; 2.1]	237	181 (76.4)	1.4 [1.4; 2.2]	0.92 [0.75; 1.14]	0.451	0.334
Non-Asia	259	198 (76.4)	1.4 [1.4; 2.1]	259	190 (73.4)	1.5 [1.4; 2.1]	1.07 [0.88; 1.30]	0.514	
Site of Origin									
Extrahepatic	91	74 (81.3)	1.4 [1.3; 2.1]	101	79 (78.2)	1.6 [1.0; 2.5]	1.08 [0.79; 1.48]	0.633	0.931
Gallbladder	106	73 (68.9)	1.4 [1.1; 2.6]	110	84 (76.4)	1.7 [1.4; 2.3]	0.95 [0.69; 1.30]	0.729	
Intrahepatic	292	217 (74.3)	1.5 [1.4; 2.1]	285	208 (73.0)	1.4 [1.4; 2.1]	1.00 [0.83; 1.21]	0.971	

a: Database Cutoff Date: 15DEC2022

b: Chemotherapy: Gemcitabine + Cisplatin

c: Number of participants: full-analysis-set population, participants with baseline

d: From product-limit (Kaplan-Meier) method for censored data

e: Based on Cox regression model with treatment as a covariate

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

g: Based on Cox 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; EORTC QLQ-C30: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Core 30 items

Symptomskala Übelkeit und Erbrechen

Tabelle 4G-28: Subgruppenanalysen mit nicht statistisch signifikantem Interaktionstest ($p \geq 0,05$) für den Endpunkt EORTC QLQ-C30 Übelkeit und Erbrechen aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE 966[a]	**Pembrolizumab + Chemotherapy[b]**			**Placebo + Chemotherapy[b]**			**Pembrolizumab + Chemotherapy[b] vs. Placebo + Chemotherapy[b]**		**p-Value for Interaction Test[g]**
EORTC QLQ-C30 Nausea and Vomiting (10 points)	**N[c]**	**Participants with Event n (%)**	**Median Time[d] in months [95 %-CI]**	**N[c]**	**Participants with Event n (%)**	**Median Time[d] in months [95 %-CI]**	**Hazard Ratio [95 %-CI][e]**	**p-Value[e,f]**	
Sex									
Female	224	157 (70.1)	2.1 [1.4; 2.1]	241	162 (67.2)	2.5 [2.1; 3.0]	1.10 [0.88; 1.37]	0.391	0.108
Male	265	144 (54.3)	3.5 [2.8; 5.6]	255	153 (60.0)	2.8 [2.1; 4.1]	0.86 [0.68; 1.07]	0.179	
Age									
< 65	243	159 (65.4)	2.2 [2.0; 3.4]	275	180 (65.5)	2.3 [2.0; 2.9]	0.98 [0.79; 1.22]	0.876	0.816
≥ 65	246	142 (57.7)	2.8 [2.1; 4.2]	221	135 (61.1)	2.8 [2.2; 4.4]	0.95 [0.75; 1.20]	0.663	
ECOG Performance Status									
0	242	152 (62.8)	2.8 [2.1; 3.5]	211	135 (64.0)	2.8 [2.1; 4.2]	1.02 [0.81; 1.29]	0.853	0.482
1	247	149 (60.3)	2.6 [2.1; 3.5]	285	180 (63.2)	2.5 [2.1; 3.0]	0.91 [0.73; 1.13]	0.390	
Geographic region									
Asia	230	146 (63.5)	2.1 [2.0; 3.4]	237	151 (63.7)	2.3 [1.7; 2.8]	0.96 [0.76; 1.21]	0.723	0.944
Non-Asia	259	155 (59.8)	2.8 [2.1; 3.5]	259	164 (63.3)	2.9 [2.1; 4.2]	0.95 [0.76; 1.18]	0.631	
Locally advanced versus metastatic									
Locally Advanced	52	34 (65.4)	2.1 [1.4; 4.9]	64	39 (60.9)	2.1 [1.4; 3.5]	1.10 [0.69; 1.74]	0.694	0.559
Metastatic	437	267 (61.1)	2.8 [2.1; 3.3]	432	276 (63.9)	2.8 [2.1; 3.4]	0.94 [0.79; 1.11]	0.455	
Site of Origin									
Extrahepatic	91	53 (58.2)	2.8 [2.1; 4.9]	101	65 (64.4)	2.3 [1.7; 3.8]	0.89 [0.62; 1.28]	0.517	0.863
Gallbladder	106	64 (60.4)	2.1 [1.7; 3.3]	110	72 (65.5)	2.5 [1.6; 4.2]	1.00 [0.71; 1.40]	0.993	
Intrahepatic	292	184 (63.0)	2.8 [2.1; 3.5]	285	178 (62.5)	2.8 [2.1; 3.5]	0.98 [0.80; 1.21]	0.864	

a: Database Cutoff Date: 15DEC2022
b: Chemotherapy: Gemcitabine + Cisplatin
c: Number of participants: full-analysis-set population, participants with baseline
d: From product-limit (Kaplan-Meier) method for censored data
e: Based on Cox regression model with treatment as a covariate
f: Two-sided p-value using Wald test (Score test in case of zero event in one treatment group)
g: Based on Cox 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; EORTC QLQ-C30: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Core 30 items

Symptomskala Schmerzen

Tabelle 4G-29: Subgruppenanalysen mit nicht statistisch signifikantem Interaktionstest ($p \geq 0,05$) für den Endpunkt EORTC QLQ-C30 Schmerzen aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE 966[a]	**Pembrolizumab + Chemotherapy[b]**			**Placebo + Chemotherapy[b]**			**Pembrolizumab + Chemotherapy[b] vs. Placebo + Chemotherapy[b]**		
EORTC QLQ-C30 Pain (10 points)	**N[c]**	**Participants with Event n (%)**	**Median Time[d] in months [95 %-CI]**	**N[c]**	**Participants 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]**
Sex									
Female	224	129 (57.6)	4.6 [3.4; 5.8]	241	149 (61.8)	3.8 [3.0; 4.9]	0.91 [0.72; 1.16]	0.460	0.904
Male	265	156 (58.9)	4.2 [3.0; 5.6]	255	155 (60.8)	4.0 [2.8; 5.0]	0.91 [0.73; 1.14]	0.405	
ECOG Performance Status									
0	242	152 (62.8)	3.6 [2.8; 4.9]	211	132 (62.6)	3.5 [2.8; 5.0]	1.04 [0.82; 1.31]	0.739	0.110
1	247	133 (53.8)	5.5 [3.6; 6.5]	285	172 (60.4)	4.0 [3.0; 4.9]	0.79 [0.63; 0.99]	0.041	
Geographic region									
Asia	230	123 (53.5)	4.4 [3.5; 7.6]	237	139 (58.6)	4.8 [3.1; 5.8]	0.91 [0.71; 1.16]	0.441	0.989
Non-Asia	259	162 (62.5)	4.2 [2.8; 5.5]	259	165 (63.7)	3.3 [2.4; 4.2]	0.91 [0.73; 1.13]	0.370	
Locally advanced versus metastatic									
Locally Advanced	52	36 (69.2)	3.2 [1.6; 5.5]	64	42 (65.6)	3.5 [2.1; 6.5]	1.08 [0.69; 1.69]	0.722	0.429
Metastatic	437	249 (57.0)	4.4 [3.5; 5.6]	432	262 (60.6)	3.8 [3.0; 4.8]	0.89 [0.75; 1.06]	0.189	
Site of Origin									
Extrahepatic	91	59 (64.8)	3.4 [2.1; 5.1]	101	59 (58.4)	3.0 [2.3; 6.2]	1.11 [0.77; 1.59]	0.577	0.485
Gallbladder	106	54 (50.9)	5.5 [3.5; 7.3]	110	71 (64.5)	4.8 [3.5; 6.0]	0.83 [0.58; 1.18]	0.300	
Intrahepatic	292	172 (58.9)	4.2 [3.4; 5.8]	285	174 (61.1)	3.5 [2.8; 4.4]	0.88 [0.71; 1.08]	0.222	

a: Database Cutoff Date: 15DEC2022
b: Chemotherapy: Gemcitabine + Cisplatin
c: Number of participants: full-analysis-set population, participants with baseline
d: From product-limit (Kaplan-Meier) method for censored data
e: Based on Cox regression model with treatment as a covariate
f: Two-sided p-value using Wald test (Score test in case of zero event in one treatment group)
g: Based on Cox 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; EORTC QLQ-C30: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Core 30 items

Symptomskala Dyspnoe

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

Study: KEYNOTE 966[a]	**Pembrolizumab + Chemotherapy[b]**			**Placebo + Chemotherapy[b]**			**Pembrolizumab + Chemotherapy[b] vs. Placebo + Chemotherapy[b]**		
EORTC QLQ-C30 Dyspnoea (10 points)	**N[c]**	**Participants with Event n (%)**	**Median Time[d] in months [95 %-CI]**	**N[c]**	**Participants 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]**
Sex									
Female	224	123 (54.9)	4.4 [3.0; 7.1]	241	127 (52.7)	5.0 [3.2; 7.2]	1.01 [0.79; 1.29]	0.945	0.441
Male	265	141 (53.2)	5.2 [3.9; 6.5]	255	146 (57.3)	4.2 [3.0; 6.2]	0.88 [0.70; 1.11]	0.275	
Age									
< 65	243	127 (52.3)	5.3 [4.3; 10.4]	275	154 (56.0)	4.2 [2.9; 6.3]	0.86 [0.68; 1.09]	0.210	0.290
≥ 65	246	137 (55.7)	4.2 [3.5; 5.6]	221	119 (53.8)	5.1 [3.2; 6.5]	1.04 [0.81; 1.33]	0.763	
Geographic region									
Asia	230	120 (52.2)	5.2 [3.7; 8.0]	237	136 (57.4)	3.5 [2.9; 6.3]	0.84 [0.66; 1.08]	0.170	0.259
Non-Asia	259	144 (55.6)	4.6 [3.5; 5.7]	259	137 (52.9)	5.3 [3.5; 7.3]	1.03 [0.82; 1.30]	0.803	
Locally advanced versus metastatic									
Locally Advanced	52	35 (67.3)	3.4 [2.1; 5.6]	64	38 (59.4)	3.7 [2.3; 6.7]	1.12 [0.71; 1.78]	0.626	0.404
Metastatic	437	229 (52.4)	5.3 [4.2; 6.7]	432	235 (54.4)	4.8 [3.4; 6.2]	0.91 [0.76; 1.10]	0.327	

a: Database Cutoff Date: 15DEC2022

b: Chemotherapy: Gemcitabine + Cisplatin

c: Number of participants: full-analysis-set population, participants with baseline

d: From product-limit (Kaplan-Meier) method for censored data

e: Based on Cox regression model with treatment as a covariate

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

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

CI: Confidence Interval; EORTC QLQ-C30: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Core 30 items

Symptomskala Schlaflosigkeit

Tabelle 4G-31: Subgruppenanalysen mit nicht statistisch signifikantem Interaktionstest ($p \geq 0,05$) für den Endpunkt EORTC QLQ-C30 Schlaflosigkeit aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE 966[a]	**Pembrolizumab + Chemotherapy[b]**			**Placebo + Chemotherapy[b]**			**Pembrolizumab + Chemotherapy[b] vs. Placebo + Chemotherapy[b]**		
EORTC QLQ-C30 Insomnia (10 points)	**N[c]**	**Participants with Event n (%)**	**Median Time[d] in months [95 %-CI]**	**N[c]**	**Participants 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]**
Sex									
Female	224	113 (50.4)	5.3 [3.6; 9.1]	241	125 (51.9)	4.9 [3.5; 6.2]	0.93 [0.72; 1.21]	0.604	0.132
Male	265	138 (52.1)	5.1 [3.5; 7.3]	255	117 (45.9)	8.7 [5.1; 13.9]	1.22 [0.96; 1.57]	0.108	
Age									
< 65	243	122 (50.2)	5.3 [3.9; 7.2]	275	128 (46.5)	6.2 [4.8; 9.9]	1.10 [0.86; 1.41]	0.455	0.775
≥ 65	246	129 (52.4)	4.9 [3.5; 9.0]	221	114 (51.6)	5.6 [3.7; 9.2]	1.04 [0.81; 1.34]	0.755	
ECOG Performance Status									
0	242	128 (52.9)	4.9 [3.6; 8.9]	211	106 (50.2)	5.9 [4.4; 11.3]	1.18 [0.91; 1.53]	0.214	0.366
1	247	123 (49.8)	5.5 [3.6; 8.4]	285	136 (47.7)	5.6 [4.2; 8.7]	1.00 [0.78; 1.27]	0.987	
Geographic region									
Asia	230	110 (47.8)	6.7 [4.2; 10.4]	237	115 (48.5)	6.2 [4.3; 9.5]	0.97 [0.75; 1.26]	0.837	0.312
Non-Asia	259	141 (54.4)	4.4 [3.2; 6.1]	259	127 (49.0)	5.7 [4.2; 8.9]	1.18 [0.93; 1.50]	0.174	
Locally advanced versus metastatic									
Locally Advanced	52	28 (53.8)	6.0 [3.2; 9.0]	64	30 (46.9)	5.7 [2.8; -]	1.15 [0.69; 1.93]	0.594	0.700
Metastatic	437	223 (51.0)	4.9 [3.7; 7.3]	432	212 (49.1)	5.8 [4.4; 8.9]	1.06 [0.88; 1.28]	0.537	
Site of Origin									
Extrahepatic	91	49 (53.8)	4.2 [2.6; 10.4]	101	52 (51.5)	5.8 [3.8; 11.0]	1.06 [0.72; 1.56]	0.779	0.753
Gallbladder	106	54 (50.9)	3.9 [2.3; 9.0]	110	53 (48.2)	5.7 [3.8; 9.9]	1.20 [0.82; 1.76]	0.340	
Intrahepatic	292	148 (50.7)	5.8 [4.2; 9.0]	285	137 (48.1)	5.9 [4.4; 9.3]	1.04 [0.83; 1.32]	0.726	

a: Database Cutoff Date: 15DEC2022
b: Chemotherapy: Gemcitabine + Cisplatin
c: Number of participants: full-analysis-set population, participants with baseline
d: From product-limit (Kaplan-Meier) method for censored data
e: Based on Cox regression model with treatment as a covariate
f: Two-sided p-value using Wald test (Score test in case of zero event in one treatment group)
g: Based on Cox 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; EORTC QLQ-C30: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Core 30 items

Symptomskala Appetitverlust

Tabelle 4G-32: Subgruppenanalysen mit nicht statistisch signifikantem Interaktionstest ($p \geq 0,05$) für den Endpunkt EORTC QLQ-C30 Appetitverlust aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE 966[a]	**Pembrolizumab + Chemotherapy[b]**			**Placebo + Chemotherapy[b]**			**Pembrolizumab + Chemotherapy[b] vs. Placebo + Chemotherapy[b]**		
EORTC QLQ-C30 Appetite Loss (10 points)	**N[c]**	**Participants with Event n (%)**	**Median Time[d] in months [95 %-CI]**	**N[c]**	**Participants 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]**
Sex									
Female	224	135 (60.3)	3.4 [2.1; 4.4]	241	122 (50.6)	5.1 [3.9; 6.8]	1.35 [1.06; 1.73]	0.016	0.155
Male	265	151 (57.0)	4.0 [2.9; 5.8]	255	142 (55.7)	4.2 [3.0; 5.6]	1.06 [0.85; 1.34]	0.602	
Age									
< 65	243	143 (58.8)	3.7 [2.8; 4.4]	275	141 (51.3)	4.9 [4.1; 7.2]	1.29 [1.03; 1.63]	0.030	0.287
≥ 65	246	143 (58.1)	3.7 [2.3; 5.6]	221	123 (55.7)	4.2 [3.2; 5.6]	1.08 [0.85; 1.37]	0.547	
ECOG Performance Status									
0	242	159 (65.7)	2.9 [2.1; 4.4]	211	119 (56.4)	4.8 [3.3; 6.4]	1.39 [1.10; 1.76]	0.007	0.073
1	247	127 (51.4)	4.2 [3.4; 7.6]	285	145 (50.9)	4.2 [3.7; 6.1]	1.02 [0.80; 1.30]	0.862	
Geographic region									
Asia	230	139 (60.4)	2.8 [2.1; 3.8]	237	140 (59.1)	3.8 [2.8; 4.4]	1.10 [0.87; 1.39]	0.438	0.330
Non-Asia	259	147 (56.8)	4.4 [3.4; 5.7]	259	124 (47.9)	5.7 [4.2; 11.2]	1.30 [1.02; 1.65]	0.032	
Locally advanced versus metastatic									
Locally Advanced	52	37 (71.2)	1.9 [1.4; 4.0]	64	37 (57.8)	3.3 [2.1; 13.9]	1.44 [0.91; 2.27]	0.118	0.354
Metastatic	437	249 (57.0)	3.8 [2.9; 5.2]	432	227 (52.5)	4.4 [3.9; 5.8]	1.16 [0.97; 1.39]	0.098	
Site of Origin									
Extrahepatic	91	51 (56.0)	3.8 [2.2; 8.2]	101	55 (54.5)	4.2 [2.8; 6.1]	1.03 [0.71; 1.52]	0.860	0.703
Gallbladder	106	58 (54.7)	3.5 [2.1; 5.6]	110	63 (57.3)	4.2 [3.3; 6.8]	1.21 [0.84; 1.73]	0.304	
Intrahepatic	292	177 (60.6)	3.7 [2.8; 5.3]	285	146 (51.2)	4.9 [3.5; 7.6]	1.25 [1.01; 1.56]	0.042	

a: Database Cutoff Date: 15DEC2022
b: Chemotherapy: Gemcitabine + Cisplatin
c: Number of participants: full-analysis-set population, participants with baseline
d: From product-limit (Kaplan-Meier) method for censored data
e: Based on Cox regression model with treatment as a covariate
f: Two-sided p-value using Wald test (Score test in case of zero event in one treatment group)
g: Based on Cox 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; EORTC QLQ-C30: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Core 30 items

Symptomskala Verstopfung

Tabelle 4G-33: Subgruppenanalysen mit nicht statistisch signifikantem Interaktionstest ($p \geq 0,05$) für den Endpunkt EORTC QLQ-C30 Verstopfung aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE 966[a]	**Pembrolizumab + Chemotherapy[b]**			**Placebo + Chemotherapy[b]**			**Pembrolizumab + Chemotherapy[b] vs. Placebo + Chemotherapy[b]**		
EORTC QLQ-C30 Constipation (10 points)	**N[c]**	**Participants with Event n (%)**	**Median Time[d] in months [95 %-CI]**	**N[c]**	**Participants 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]**
Sex									
Female	224	131 (58.5)	2.8 [2.1; 3.7]	241	126 (52.3)	4.2 [2.3; 7.1]	1.17 [0.92; 1.49]	0.211	0.156
Male	265	142 (53.6)	4.2 [2.8; 5.6]	255	150 (58.8)	2.8 [2.1; 4.2]	0.92 [0.73; 1.15]	0.457	
Age									
< 65	243	144 (59.3)	2.8 [2.1; 4.4]	275	155 (56.4)	2.9 [2.1; 5.1]	1.05 [0.84; 1.32]	0.664	0.767
≥ 65	246	129 (52.4)	3.7 [2.8; 5.4]	221	121 (54.8)	3.3 [2.3; 6.1]	1.00 [0.78; 1.28]	> 0.999	
ECOG Performance Status									
0	242	137 (56.6)	3.0 [2.3; 4.4]	211	123 (58.3)	2.3 [1.6; 4.8]	0.99 [0.78; 1.26]	0.944	0.770
1	247	136 (55.1)	3.5 [2.1; 5.2]	285	153 (53.7)	3.4 [2.8; 6.1]	1.04 [0.83; 1.31]	0.721	
Locally advanced versus metastatic									
Locally Advanced	52	28 (53.8)	3.5 [0.9; -]	64	33 (51.6)	5.0 [2.1; 15.7]	1.15 [0.70; 1.91]	0.581	0.611
Metastatic	437	245 (56.1)	3.1 [2.7; 4.3]	432	243 (56.3)	3.0 [2.2; 4.8]	1.01 [0.84; 1.20]	0.944	
Site of Origin									
Extrahepatic	91	50 (54.9)	3.7 [2.2; 5.8]	101	50 (49.5)	7.3 [2.7; 10.6]	1.17 [0.79; 1.74]	0.437	0.325
Gallbladder	106	51 (48.1)	4.2 [1.6; -]	110	67 (60.9)	2.3 [1.5; 4.2]	0.81 [0.56; 1.16]	0.248	
Intrahepatic	292	172 (58.9)	2.8 [2.1; 4.1]	285	159 (55.8)	3.3 [2.1; 5.0]	1.08 [0.87; 1.34]	0.496	

a: Database Cutoff Date: 15DEC2022
b: Chemotherapy: Gemcitabine + Cisplatin
c: Number of participants: full-analysis-set population, participants with baseline
d: From product-limit (Kaplan-Meier) method for censored data
e: Based on Cox regression model with treatment as a covariate
f: Two-sided p-value using Wald test (Score test in case of zero event in one treatment group)
g: Based on Cox 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; EORTC QLQ-C30: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Core 30 items

Symptomskala Diarhö

Tabelle 4G-34: Subgruppenanalysen mit nicht statistisch signifikantem Interaktionstest ($p \geq 0,05$) für den Endpunkt EORTC QLQ-C30 Diarrhö aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE 966[a]	**Pembrolizumab + Chemotherapy[b]**			**Placebo + Chemotherapy[b]**			**Pembrolizumab + Chemotherapy[b] vs. Placebo + Chemotherapy[b]**		
EORTC QLQ-C30 Diarrhea (10 points)	**N[c]**	**Participants with Event n (%)**	**Median Time[d] in months [95 %-CI]**	**N[c]**	**Participants 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]**
Sex									
Female	224	92 (41.1)	10.4 [5.7; -]	241	103 (42.7)	8.8 [4.9; 16.1]	0.94 [0.71; 1.25]	0.688	0.441
Male	265	103 (38.9)	10.6 [7.5; -]	255	88 (34.5)	13.4 [9.9; -]	1.11 [0.83; 1.47]	0.476	
Age									
< 65	243	96 (39.5)	11.9 [7.2; -]	275	114 (41.5)	9.8 [5.1; 18.2]	0.88 [0.67; 1.16]	0.368	0.112
≥ 65	246	99 (40.2)	9.2 [6.9; -]	221	77 (34.8)	13.4 [10.4; -]	1.22 [0.90; 1.64]	0.197	
ECOG Performance Status									
0	242	94 (38.8)	11.5 [7.6; -]	211	82 (38.9)	13.3 [8.8; 24.0]	1.07 [0.80; 1.44]	0.643	0.659
1	247	101 (40.9)	10.4 [6.2; 14.5]	285	109 (38.2)	9.9 [5.6; -]	0.98 [0.74; 1.28]	0.859	
Geographic region									
Asia	230	91 (39.6)	10.4 [6.9; 24.9]	237	87 (36.7)	14.5 [8.8; -]	1.07 [0.79; 1.43]	0.668	0.655
Non-Asia	259	104 (40.2)	11.5 [7.1; -]	259	104 (40.2)	9.8 [6.0; 16.1]	0.98 [0.74; 1.28]	0.859	
Locally advanced versus metastatic									
Locally Advanced	52	21 (40.4)	11.9 [6.9; -]	64	28 (43.8)	10.4 [5.1; 16.1]	0.81 [0.46; 1.42]	0.456	0.492
Metastatic	437	174 (39.8)	10.6 [7.2; 14.8]	432	163 (37.7)	12.4 [8.8; 23.9]	1.04 [0.84; 1.29]	0.688	
Site of Origin									
Extrahepatic	91	35 (38.5)	10.7 [5.9; -]	101	43 (42.6)	11.9 [4.8; 18.2]	0.90 [0.57; 1.40]	0.628	0.326
Gallbladder	106	44 (41.5)	6.0 [3.5; -]	110	40 (36.4)	Not reached [5.6; -]	1.37 [0.89; 2.11]	0.149	
Intrahepatic	292	116 (39.7)	11.2 [8.0; 24.9]	285	108 (37.9)	13.3 [7.6; -]	0.97 [0.74; 1.26]	0.804	

a: Database Cutoff Date: 15DEC2022

b: Chemotherapy: Gemcitabine + Cisplatin

c: Number of participants: full-analysis-set population, participants with baseline

d: From product-limit (Kaplan-Meier) method for censored data

e: Based on Cox regression model with treatment as a covariate

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

g: Based on Cox 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; EORTC QLQ-C30: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Core 30 items

EORTC QLQ-BIL21

Symptomskala Essen

Tabelle 4G-35: Subgruppenanalysen mit nicht statistisch signifikantem Interaktionstest ($p \geq 0,05$) für den Endpunkt EORTC QLQ-BIL21 Essen aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE 966[a]	**Pembrolizumab + Chemotherapy[b]**			**Placebo + Chemotherapy[b]**			**Pembrolizumab + Chemotherapy[b] vs. Placebo + Chemotherapy[b]**		**p-Value for Interaction Test[g]**
EORTC QLQ-BIL21 Eating (10 points)	**N[c]**	**Participants with Event n (%)**	**Median Time[d] in months [95 %-CI]**	**N[c]**	**Participants with Event n (%)**	**Median Time[d] in months [95 %-CI]**	**Hazard Ratio [95 %-CI][e]**	**p-Value[e,f]**	
Sex									
Female	220	137 (62.3)	3.5 [2.7; 4.6]	240	130 (54.2)	4.8 [3.4; 6.4]	1.21 [0.95; 1.54]	0.120	0.271
Male	262	145 (55.3)	4.9 [3.5; 6.0]	250	139 (55.6)	4.2 [2.9; 5.6]	1.00 [0.80; 1.27]	0.971	
Age									
< 65	240	141 (58.8)	3.5 [2.8; 4.9]	271	140 (51.7)	4.8 [3.5; 6.2]	1.21 [0.95; 1.52]	0.117	0.227
≥ 65	242	141 (58.3)	4.4 [3.4; 6.0]	219	129 (58.9)	3.8 [2.8; 5.6]	0.97 [0.76; 1.23]	0.806	
ECOG Performance Status									
0	239	144 (60.3)	3.9 [2.8; 5.1]	209	119 (56.9)	4.4 [3.0; 5.6]	1.11 [0.87; 1.42]	0.398	0.913
1	243	138 (56.8)	3.7 [3.4; 5.8]	281	150 (53.4)	4.2 [3.0; 6.2]	1.08 [0.86; 1.37]	0.492	
Geographic region									
Asia	229	136 (59.4)	3.5 [2.8; 4.9]	235	129 (54.9)	4.2 [3.0; 5.2]	1.12 [0.88; 1.43]	0.358	0.827
Non-Asia	253	146 (57.7)	4.8 [3.5; 5.8]	255	140 (54.9)	4.8 [3.3; 6.5]	1.07 [0.85; 1.35]	0.548	
Locally advanced versus metastatic									
Locally Advanced	51	30 (58.8)	3.9 [1.4; 6.4]	63	37 (58.7)	3.5 [2.1; 13.9]	1.00 [0.61; 1.61]	0.988	0.710
Metastatic	431	252 (58.5)	3.7 [3.4; 5.0]	427	232 (54.3)	4.4 [3.5; 5.6]	1.11 [0.93; 1.32]	0.269	
Site of Origin									
Extrahepatic	89	54 (60.7)	3.8 [2.8; 5.6]	101	59 (58.4)	3.4 [2.8; 5.3]	0.98 [0.67; 1.41]	0.902	0.802
Gallbladder	105	58 (55.2)	3.5 [2.1; 7.6]	110	60 (54.5)	4.2 [3.0; 7.8]	1.13 [0.79; 1.63]	0.499	
Intrahepatic	288	170 (59.0)	3.9 [3.2; 5.3]	279	150 (53.8)	4.4 [3.3; 6.4]	1.13 [0.90; 1.40]	0.293	

a: Database Cutoff Date: 15DEC2022
b: Chemotherapy: Gemcitabine + Cisplatin
c: Number of participants: full-analysis-set population, participants with baseline
d: From product-limit (Kaplan-Meier) method for censored data
e: Based on Cox regression model with treatment as a covariate
f: Two-sided p-value using Wald test (Score test in case of zero event in one treatment group)
g: Based on Cox 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; EORTC QLQ-BIL21: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Cholangiocarcinoma and Gallbladder Cancer 21 items

Symptomskala Ikterus

Tabelle 4G-36: Subgruppenanalysen mit nicht statistisch signifikantem Interaktionstest ($p \geq 0,05$) für den Endpunkt EORTC QLQ-BIL21 Ikterus aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE 966[a]	**Pembrolizumab + Chemotherapy[b]**			**Placebo + Chemotherapy[b]**			**Pembrolizumab + Chemotherapy[b] vs. Placebo + Chemotherapy[b]**		
EORTC QLQ-BIL21 Jaundice (10 points)	**N[c]**	**Participants with Event n (%)**	**Median Time[d] in months [95 %-CI]**	**N[c]**	**Participants 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]**
Sex									
Female	220	124 (56.4)	4.9 [3.5; 6.2]	240	121 (50.4)	4.8 [3.4; 7.6]	1.11 [0.87; 1.43]	0.396	0.305
Male	262	151 (57.6)	3.4 [2.5; 5.3]	250	125 (50.0)	5.6 [3.5; 7.6]	1.33 [1.05; 1.68]	0.020	
Age									
< 65	240	145 (60.4)	3.5 [2.8; 4.9]	271	152 (56.1)	3.9 [3.0; 5.3]	1.17 [0.93; 1.47]	0.178	0.456
≥ 65	242	130 (53.7)	5.6 [3.4; 7.6]	219	94 (42.9)	11.6 [5.4; 18.0]	1.34 [1.03; 1.74]	0.032	
ECOG Performance Status									
0	239	140 (58.6)	3.5 [2.8; 5.0]	209	107 (51.2)	5.1 [3.6; 11.6]	1.35 [1.05; 1.74]	0.020	0.285
1	243	135 (55.6)	5.1 [3.2; 6.5]	281	139 (49.5)	5.7 [3.0; 7.6]	1.11 [0.88; 1.41]	0.370	
Geographic region									
Asia	229	135 (59.0)	3.5 [2.5; 5.1]	235	127 (54.0)	3.7 [2.9; 5.8]	1.18 [0.92; 1.50]	0.189	0.620
Non-Asia	253	140 (55.3)	4.9 [3.5; 6.5]	255	119 (46.7)	6.2 [4.2; 11.6]	1.28 [1.00; 1.63]	0.049	
Locally advanced versus metastatic									
Locally Advanced	51	34 (66.7)	2.8 [1.4; 6.0]	63	32 (50.8)	5.0 [2.1; -]	1.46 [0.90; 2.38]	0.124	0.349
Metastatic	431	241 (55.9)	4.2 [3.4; 5.5]	427	214 (50.1)	5.1 [3.6; 6.7]	1.19 [0.99; 1.43]	0.065	
Site of Origin									
Extrahepatic	89	41 (46.1)	9.9 [2.8; -]	101	47 (46.5)	5.7 [3.5; -]	1.04 [0.68; 1.58]	0.863	0.722
Gallbladder	105	57 (54.3)	3.5 [2.8; 6.2]	110	55 (50.0)	5.9 [3.0; 10.8]	1.28 [0.89; 1.86]	0.188	
Intrahepatic	288	177 (61.5)	4.1 [3.0; 5.3]	279	144 (51.6)	4.4 [3.3; 6.2]	1.24 [1.00; 1.55]	0.052	

a: Database Cutoff Date: 15DEC2022
b: Chemotherapy: Gemcitabine + Cisplatin
c: Number of participants: full-analysis-set population, participants with baseline
d: From product-limit (Kaplan-Meier) method for censored data
e: Based on Cox regression model with treatment as a covariate
f: Two-sided p-value using Wald test (Score test in case of zero event in one treatment group)
g: Based on Cox 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; EORTC QLQ-BIL21: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Cholangiocarcinoma and Gallbladder Cancer 21 items

Symptomskala Fatigue

Tabelle 4G-37: Subgruppenanalysen mit nicht statistisch signifikantem Interaktionstest ($p \geq 0,05$) für den Endpunkt EORTC QLQ-BIL21 Fatigue aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE 966[a]	**Pembrolizumab + Chemotherapy[b]**			**Placebo + Chemotherapy[b]**			**Pembrolizumab + Chemotherapy[b] vs. Placebo + Chemotherapy[b]**		
EORTC QLQ-BIL21 Tiredness (10 points)	**N[c]**	**Participants with Event n (%)**	**Median Time[d] in months [95 %-CI]**	**N[c]**	**Participants 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]**
Sex									
Female	220	168 (76.4)	1.4 [1.1; 1.7]	240	166 (69.2)	2.0 [1.4; 2.8]	1.28 [1.03; 1.58]	0.025	0.389
Male	262	182 (69.5)	2.0 [1.4; 2.1]	250	172 (68.8)	2.2 [1.6; 2.9]	1.12 [0.91; 1.38]	0.272	
Age									
< 65	240	169 (70.4)	2.0 [1.4; 2.3]	271	176 (64.9)	2.3 [1.6; 2.9]	1.19 [0.96; 1.46]	0.114	0.899
≥ 65	242	181 (74.8)	1.4 [1.3; 1.7]	219	162 (74.0)	2.1 [1.6; 2.4]	1.17 [0.95; 1.45]	0.147	
ECOG Performance Status									
0	239	178 (74.5)	1.5 [1.4; 2.1]	209	155 (74.2)	1.8 [1.4; 2.7]	1.12 [0.90; 1.39]	0.295	0.537
1	243	172 (70.8)	1.6 [1.4; 2.1]	281	183 (65.1)	2.3 [1.9; 3.0]	1.23 [1.00; 1.52]	0.049	
Geographic region									
Asia	229	159 (69.4)	1.4 [1.2; 2.1]	235	166 (70.6)	2.0 [1.5; 2.7]	1.10 [0.88; 1.36]	0.407	0.312
Non-Asia	253	191 (75.5)	1.6 [1.4; 2.1]	255	172 (67.5)	2.2 [1.7; 2.9]	1.28 [1.04; 1.58]	0.018	
Locally advanced versus metastatic									
Locally Advanced	51	41 (80.4)	2.1 [1.4; 2.8]	63	47 (74.6)	2.2 [1.6; 4.2]	1.28 [0.84; 1.95]	0.248	0.696
Metastatic	431	309 (71.7)	1.5 [1.4; 2.0]	427	291 (68.1)	2.1 [1.6; 2.7]	1.17 [1.00; 1.37]	0.053	
Site of Origin									
Extrahepatic	89	69 (77.5)	1.4 [1.0; 2.1]	101	71 (70.3)	2.2 [1.4; 3.5]	1.33 [0.96; 1.86]	0.091	0.713
Gallbladder	105	75 (71.4)	1.6 [1.1; 2.1]	110	77 (70.0)	2.7 [1.5; 3.7]	1.22 [0.88; 1.67]	0.231	
Intrahepatic	288	206 (71.5)	1.6 [1.4; 2.1]	279	190 (68.1)	2.1 [1.5; 2.4]	1.13 [0.93; 1.38]	0.217	

a: Database Cutoff Date: 15DEC2022

b: Chemotherapy: Gemcitabine + Cisplatin

c: Number of participants: full-analysis-set population, participants with baseline

d: From product-limit (Kaplan-Meier) method for censored data

e: Based on Cox regression model with treatment as a covariate

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

g: Based on Cox 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; EORTC QLQ-BIL21: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Cholangiocarcinoma and Gallbladder Cancer 21 items

Symptomskala Schmerzen

Tabelle 4G-38: Subgruppenanalysen mit nicht statistisch signifikantem Interaktionstest ($p \geq 0,05$) für den Endpunkt EORTC QLQ-BIL21 Schmerzen aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE 966[a]	**Pembrolizumab + Chemotherapy[b]**			**Placebo + Chemotherapy[b]**			**Pembrolizumab + Chemotherapy[b] vs. Placebo + Chemotherapy[b]**		
EORTC QLQ-BIL21 Pain (10 points)	**N[c]**	**Participants with Event n (%)**	**Median Time[d] in months [95 %-CI]**	**N[c]**	**Participants 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]**
Sex									
Female	220	102 (46.4)	7.9 [5.6; 11.5]	240	113 (47.1)	7.0 [5.2; 10.6]	0.97 [0.74; 1.27]	0.844	0.681
Male	262	110 (42.0)	10.4 [6.2; 18.6]	250	99 (39.6)	11.9 [8.3; 14.4]	1.06 [0.81; 1.40]	0.655	
Age									
< 65	240	113 (47.1)	7.6 [5.6; 10.4]	271	124 (45.8)	7.8 [5.3; 10.9]	1.01 [0.79; 1.31]	0.917	0.985
≥ 65	242	99 (40.9)	10.5 [6.5; 21.4]	219	88 (40.2)	11.0 [7.0; 14.1]	1.02 [0.77; 1.37]	0.867	
ECOG Performance Status									
0	239	109 (45.6)	9.2 [6.4; 14.8]	209	93 (44.5)	10.7 [5.3; 13.8]	1.06 [0.81; 1.40]	0.658	0.696
1	243	103 (42.4)	8.2 [5.6; 10.8]	281	119 (42.3)	8.7 [6.3; 10.9]	0.97 [0.75; 1.27]	0.841	
Geographic region									
Asia	229	95 (41.5)	10.4 [5.6; 22.8]	235	93 (39.6)	10.9 [7.6; 14.1]	1.09 [0.82; 1.45]	0.559	0.475
Non-Asia	253	117 (46.2)	7.9 [5.8; 10.7]	255	119 (46.7)	7.8 [5.3; 10.7]	0.95 [0.73; 1.23]	0.688	
Locally advanced versus metastatic									
Locally Advanced	51	27 (52.9)	4.7 [2.8; -]	63	27 (42.9)	13.3 [3.7; -]	1.31 [0.77; 2.23]	0.325	0.256
Metastatic	431	185 (42.9)	9.2 [7.3; 11.5]	427	185 (43.3)	9.0 [6.7; 11.0]	0.97 [0.79; 1.19]	0.757	
Site of Origin									
Extrahepatic	89	40 (44.9)	8.2 [5.3; -]	101	44 (43.6)	10.7 [4.2; 12.1]	1.11 [0.72; 1.70]	0.644	0.918
Gallbladder	105	43 (41.0)	7.6 [5.6; 11.7]	110	48 (43.6)	9.2 [5.3; 14.4]	1.04 [0.69; 1.57]	0.843	
Intrahepatic	288	129 (44.8)	10.4 [6.2; 18.3]	279	120 (43.0)	9.2 [6.3; 13.8]	1.00 [0.78; 1.28]	0.991	

a: Database Cutoff Date: 15DEC2022

b: Chemotherapy: Gemcitabine + Cisplatin

c: Number of participants: full-analysis-set population, participants with baseline

d: From product-limit (Kaplan-Meier) method for censored data

e: Based on Cox regression model with treatment as a covariate

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

g: Based on Cox 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; EORTC QLQ-BIL21: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Cholangiocarcinoma and Gallbladder Cancer 21 items

Symptomskala Angst

Tabelle 4G-39: Subgruppenanalysen mit nicht statistisch signifikantem Interaktionstest ($p \geq 0,05$) für den Endpunkt EORTC QLQ-BIL21 Angst aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE 966[a]	**Pembrolizumab + Chemotherapy[b]**			**Placebo + Chemotherapy[b]**			**Pembrolizumab + Chemotherapy[b] vs. Placebo + Chemotherapy[b]**		
EORTC QLQ-BIL21 Anxiety (10 points)	**N[c]**	**Participants with Event n (%)**	**Median Time[d] in months [95 %-CI]**	**N[c]**	**Participants 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]**
Sex									
Female	220	118 (53.6)	7.6 [4.2; 9.1]	240	112 (46.7)	8.3 [4.4; 12.0]	1.19 [0.92; 1.54]	0.197	0.937
Male	262	135 (51.5)	5.6 [4.4; 7.1]	250	115 (46.0)	7.4 [5.1; 9.8]	1.20 [0.93; 1.54]	0.152	
Age									
< 65	240	128 (53.3)	5.1 [4.3; 7.6]	271	118 (43.5)	8.8 [5.6; 24.4]	1.29 [1.00; 1.66]	0.047	0.326
≥ 65	242	125 (51.7)	6.5 [4.2; 9.2]	219	109 (49.8)	6.0 [4.6; 9.2]	1.08 [0.83; 1.39]	0.576	
ECOG Performance Status									
0	239	121 (50.6)	7.3 [4.9; 10.4]	209	105 (50.2)	6.5 [5.1; 9.2]	1.06 [0.81; 1.38]	0.668	0.205
1	243	132 (54.3)	5.4 [3.5; 6.9]	281	122 (43.4)	8.3 [4.8; 11.3]	1.33 [1.04; 1.70]	0.023	
Geographic region									
Asia	229	120 (52.4)	5.1 [3.7; 7.6]	235	112 (47.7)	6.2 [4.2; 11.0]	1.15 [0.89; 1.49]	0.299	0.698
Non-Asia	253	133 (52.6)	6.5 [4.7; 8.6]	255	115 (45.1)	8.3 [5.3; 13.4]	1.22 [0.95; 1.57]	0.113	
Locally advanced versus metastatic									
Locally Advanced	51	28 (54.9)	5.0 [1.7; -]	63	31 (49.2)	6.5 [4.2; -]	1.21 [0.72; 2.02]	0.469	0.944
Metastatic	431	225 (52.2)	5.6 [4.7; 7.6]	427	196 (45.9)	8.2 [5.1; 10.6]	1.18 [0.98; 1.43]	0.088	
Site of Origin									
Extrahepatic	89	45 (50.6)	5.6 [4.2; 11.2]	101	52 (51.5)	5.1 [4.2; 9.8]	1.02 [0.68; 1.51]	0.940	0.679
Gallbladder	105	51 (48.6)	4.4 [2.4; 9.5]	110	49 (44.5)	8.5 [4.4; -]	1.32 [0.89; 1.95]	0.171	
Intrahepatic	288	157 (54.5)	6.0 [4.8; 8.6]	279	126 (45.2)	8.5 [5.6; 13.4]	1.21 [0.96; 1.54]	0.105	

a: Database Cutoff Date: 15DEC2022

b: Chemotherapy: Gemcitabine + Cisplatin

c: Number of participants: full-analysis-set population, participants with baseline

d: From product-limit (Kaplan-Meier) method for censored data

e: Based on Cox regression model with treatment as a covariate

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

g: Based on Cox 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; EORTC QLQ-BIL21: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Cholangiocarcinoma and Gallbladder Cancer 21 items

Symptomskala Nebenwirkungen der Behandlung

Tabelle 4G-40: Subgruppenanalysen mit nicht statistisch signifikantem Interaktionstest ($p \geq 0,05$) für den Endpunkt EORTC QLQ-BIL21 Nebenwirkungen der Behandlung aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE 966[a]	Pembrolizumab + Chemotherapy[b]			Placebo + Chemotherapy[b]			Pembrolizumab + Chemotherapy[b] vs. Placebo + Chemotherapy[b]		p-Value for Interaction Test[g]
EORTC QLQ-BIL21 Treatment Side-Effects (10 points)	N[c]	Participants with Event n (%)	Median Time[d] in months [95 %-CI]	N[c]	Participants with Event n (%)	Median Time[d] in months [95 %-CI]	Hazard Ratio [95 %-CI][e]	p-Value[e,f]	
Sex									
Female	220	155 (70.5)	1.4 [1.0; 1.9]	240	167 (69.6)	1.6 [1.4; 2.1]	1.09 [0.87; 1.35]	0.453	0.338
Male	262	187 (71.4)	1.4 [1.0; 2.1]	250	162 (64.8)	2.2 [1.5; 2.8]	1.26 [1.02; 1.55]	0.034	
Age									
< 65	240	170 (70.8)	1.5 [1.4; 2.1]	271	178 (65.7)	2.1 [1.4; 2.7]	1.17 [0.95; 1.44]	0.152	0.987
≥ 65	242	172 (71.1)	1.4 [0.8; 1.6]	219	151 (68.9)	1.6 [1.4; 2.4]	1.17 [0.94; 1.45]	0.165	
ECOG Performance Status									
0	239	168 (70.3)	1.4 [1.0; 2.1]	209	150 (71.8)	1.4 [1.1; 1.6]	1.02 [0.82; 1.27]	0.870	0.095
1	243	174 (71.6)	1.4 [1.0; 1.9]	281	179 (63.7)	2.4 [1.9; 3.0]	1.31 [1.06; 1.62]	0.011	
Geographic region									
Asia	229	157 (68.6)	1.4 [1.0; 2.1]	235	153 (65.1)	2.1 [1.5; 3.0]	1.20 [0.96; 1.50]	0.110	0.776
Non-Asia	253	185 (73.1)	1.4 [1.0; 1.9]	255	176 (69.0)	1.6 [1.4; 2.2]	1.14 [0.93; 1.40]	0.213	
Locally advanced versus metastatic									
Locally Advanced	51	40 (78.4)	0.7 [0.7; 1.4]	63	46 (73.0)	1.6 [1.3; 3.1]	1.42 [0.93; 2.18]	0.104	0.343
Metastatic	431	302 (70.1)	1.4 [1.4; 2.1]	427	283 (66.3)	1.9 [1.4; 2.3]	1.15 [0.97; 1.35]	0.099	
Site of Origin									
Extrahepatic	89	70 (78.7)	1.4 [0.7; 2.1]	101	68 (67.3)	2.1 [1.4; 3.0]	1.41 [1.01; 1.98]	0.046	0.599
Gallbladder	105	66 (62.9)	1.6 [1.1; 2.4]	110	70 (63.6)	2.2 [1.4; 3.5]	1.15 [0.82; 1.61]	0.415	
Intrahepatic	288	206 (71.5)	1.4 [0.9; 2.0]	279	191 (68.5)	1.6 [1.4; 2.2]	1.12 [0.92; 1.37]	0.248	

a: Database Cutoff Date: 15DEC2022
b: Chemotherapy: Gemcitabine + Cisplatin
c: Number of participants: full-analysis-set population, participants with baseline
d: From product-limit (Kaplan-Meier) method for censored data
e: Based on Cox regression model with treatment as a covariate
f: Two-sided p-value using Wald test (Score test in case of zero event in one treatment group)
g: Based on Cox 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; EORTC QLQ-BIL21: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Cholangiocarcinoma and Gallbladder Cancer 21 items

Symptomskala Drainagebeutel/-schläuche

Tabelle 4G-41: Subgruppenanalysen mit nicht statistisch signifikantem Interaktionstest ($p \geq 0,05$) für den Endpunkt EORTC QLQ-BIL21 Drainagebeutel/-schläuche aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE 966[a]	**Pembrolizumab + Chemotherapy[b]**			**Placebo + Chemotherapy[b]**			**Pembrolizumab + Chemotherapy[b] vs. Placebo + Chemotherapy[b]**		
EORTC QLQ-BIL21 Drainage Bags/Tubes (10 points)	**N[c]**	**Participants with Event n (%)**	**Median Time[d] in months [95 %-CI]**	**N[c]**	**Participants 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]**
Sex									
Female	220	47 (21.4)	Not reached [16.0; -]	240	50 (20.8)	Not reached [-; -]	1.01 [0.68; 1.50]	0.978	0.851
Male	262	58 (22.1)	Not reached [-; -]	250	59 (23.6)	Not reached [20.5; -]	0.97 [0.67; 1.39]	0.867	
Age									
< 65	240	49 (20.4)	Not reached [-; -]	271	56 (20.7)	Not reached [24.4; -]	0.97 [0.66; 1.43]	0.896	0.915
≥ 65	242	56 (23.1)	Not reached [18.3; -]	219	53 (24.2)	Not reached [20.5; -]	0.99 [0.68; 1.44]	0.943	
ECOG Performance Status									
0	239	39 (16.3)	Not reached [-; -]	209	36 (17.2)	Not reached [20.5; -]	0.99 [0.63; 1.56]	0.972	0.866
1	243	66 (27.2)	18.3 [16.0; -]	281	73 (26.0)	Not reached [-; -]	1.04 [0.74; 1.45]	0.836	
Geographic region									
Asia	229	50 (21.8)	Not reached [18.3; -]	235	63 (26.8)	Not reached [20.5; -]	0.79 [0.54; 1.14]	0.204	0.086
Non-Asia	253	55 (21.7)	Not reached [-; -]	255	46 (18.0)	Not reached [24.4; -]	1.26 [0.85; 1.86]	0.251	
Locally advanced versus metastatic									
Locally Advanced	51	15 (29.4)	Not reached [6.3; -]	63	14 (22.2)	24.4 [14.7; -]	1.41 [0.68; 2.93]	0.351	0.295
Metastatic	431	90 (20.9)	Not reached [-; -]	427	95 (22.2)	Not reached [20.5; -]	0.93 [0.70; 1.25]	0.639	
Site of Origin									
Extrahepatic	89	20 (22.5)	Not reached [-; -]	101	30 (29.7)	20.5 [8.2; -]	0.81 [0.46; 1.42]	0.460	0.677
Gallbladder	105	18 (17.1)	18.3 [18.3; -]	110	21 (19.1)	Not reached [-; -]	0.98 [0.52; 1.85]	0.956	
Intrahepatic	288	67 (23.3)	Not reached [-; -]	279	58 (20.8)	Not reached [24.4; -]	1.08 [0.76; 1.54]	0.658	

a: Database Cutoff Date: 15DEC2022
b: Chemotherapy: Gemcitabine + Cisplatin
c: Number of participants: full-analysis-set population, participants with baseline
d: From product-limit (Kaplan-Meier) method for censored data
e: Based on Cox regression model with treatment as a covariate
f: Two-sided p-value using Wald test (Score test in case of zero event in one treatment group)
g: Based on Cox 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; EORTC QLQ-BIL21: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Cholangiocarcinoma and Gallbladder Cancer 21 items

Symptomskala Sorge um Gewichtsverlust

Tabelle 4G-42: Subgruppenanalysen mit nicht statistisch signifikantem Interaktionstest ($p \geq 0,05$) für den Endpunkt EORTC QLQ-BIL21 Sorge um Gewichtsverlust aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE 966[a]	**Pembrolizumab + Chemotherapy[b]**			**Placebo + Chemotherapy[b]**			**Pembrolizumab + Chemotherapy[b] vs. Placebo + Chemotherapy[b]**		
EORTC QLQ-BIL21 Concerns Regarding Weight Loss (10 points)	**N[c]**	**Participants with Event n (%)**	**Median Time[d] in months [95 %-CI]**	**N[c]**	**Participants 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]**
Sex									
Female	220	87 (39.5)	15.6 [5.6; -]	240	97 (40.4)	11.7 [7.6; -]	1.03 [0.77; 1.37]	0.850	0.977
Male	262	112 (42.7)	10.4 [6.9; -]	250	108 (43.2)	9.0 [5.6; 15.7]	1.01 [0.78; 1.32]	0.923	
Age									
< 65	240	97 (40.4)	10.7 [7.6; -]	271	113 (41.7)	11.7 [6.3; 16.1]	0.97 [0.74; 1.28]	0.844	0.619
≥ 65	242	102 (42.1)	11.2 [5.3; -]	219	92 (42.0)	10.6 [6.2; 20.5]	1.07 [0.81; 1.42]	0.621	
ECOG Performance Status									
0	239	89 (37.2)	22.8 [10.4; -]	209	83 (39.7)	15.7 [9.5; 20.5]	0.98 [0.73; 1.33]	0.910	0.620
1	243	110 (45.3)	6.7 [3.7; -]	281	122 (43.4)	6.3 [4.8; 11.6]	1.09 [0.84; 1.41]	0.504	
Geographic region									
Asia	229	99 (43.2)	10.4 [6.7; -]	235	99 (42.1)	12.0 [6.3; 16.1]	1.11 [0.84; 1.47]	0.447	0.401
Non-Asia	253	100 (39.5)	15.6 [5.8; -]	255	106 (41.6)	9.5 [6.0; -]	0.94 [0.72; 1.24]	0.676	
Locally advanced versus metastatic									
Locally Advanced	51	25 (49.0)	8.2 [2.8; -]	63	25 (39.7)	15.7 [5.7; -]	1.36 [0.78; 2.38]	0.273	0.304
Metastatic	431	174 (40.4)	12.2 [7.6; -]	427	180 (42.2)	9.8 [6.6; 13.8]	0.98 [0.80; 1.21]	0.856	
Site of Origin									
Extrahepatic	89	39 (43.8)	10.4 [3.3; -]	101	48 (47.5)	7.7 [3.0; 20.5]	0.99 [0.64; 1.52]	0.963	0.138
Gallbladder	105	45 (42.9)	5.6 [2.6; -]	110	38 (34.5)	Not reached [9.7; -]	1.52 [0.99; 2.35]	0.057	
Intrahepatic	288	115 (39.9)	22.8 [7.9; -]	279	119 (42.7)	9.8 [6.3; 14.5]	0.92 [0.71; 1.19]	0.531	

a: Database Cutoff Date: 15DEC2022
b: Chemotherapy: Gemcitabine + Cisplatin
c: Number of participants: full-analysis-set population, participants with baseline
d: From product-limit (Kaplan-Meier) method for censored data
e: Based on Cox regression model with treatment as a covariate
f: Two-sided p-value using Wald test (Score test in case of zero event in one treatment group)
g: Based on Cox 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; EORTC QLQ-BIL21: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Cholangiocarcinoma and Gallbladder Cancer 21 items

EQ-5D VAS

Tabelle 4G-43: Subgruppenanalysen mit nicht statistisch signifikantem Interaktionstest ($p \geq 0,05$) für den Endpunkt EQ-5D VAS aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE 966[a]	**Pembrolizumab + Chemotherapy[b]**			**Placebo + Chemotherapy[b]**			**Pembrolizumab + Chemotherapy[b] vs. Placebo + Chemotherapy[b]**		**p-Value for Interaction Test[g]**
EQ-5D VAS (15 points)	**N[c]**	**Participants with Event n (%)**	**Median Time[d] in months [95 %-CI]**	**N[c]**	**Participants with Event n (%)**	**Median Time[d] in months [95 %-CI]**	**Hazard Ratio [95 %-CI][e]**	**p-Value[e,f]**	
Sex									
Female	226	112 (49.6)	5.2 [3.5; 9.1]	244	116 (47.5)	7.6 [5.9; 9.2]	1.10 [0.85; 1.43]	0.454	0.827
Male	265	119 (44.9)	6.9 [5.3; 22.8]	256	118 (46.1)	8.5 [6.4; 11.0]	1.05 [0.82; 1.36]	0.687	
Age									
< 65	243	110 (45.3)	7.6 [5.6; 11.5]	277	135 (48.7)	7.2 [5.6; 9.0]	0.95 [0.74; 1.22]	0.683	0.166
≥ 65	248	121 (48.8)	5.2 [3.5; 9.4]	223	99 (44.4)	9.2 [7.2; 13.9]	1.22 [0.94; 1.60]	0.139	
ECOG Performance Status									
0	243	110 (45.3)	9.1 [5.3; -]	214	100 (46.7)	8.8 [6.4; 13.3]	1.06 [0.81; 1.39]	0.682	0.809
1	248	121 (48.8)	5.1 [3.5; 7.2]	286	134 (46.9)	7.6 [5.6; 9.2]	1.11 [0.87; 1.42]	0.402	
Geographic region									
Asia	230	110 (47.8)	6.2 [3.5; 10.4]	237	120 (50.6)	6.4 [4.6; 8.7]	0.99 [0.76; 1.28]	0.913	0.384
Non-Asia	261	121 (46.4)	7.2 [4.8; 11.6]	263	114 (43.3)	9.0 [7.4; 12.0]	1.16 [0.90; 1.50]	0.250	
Locally advanced versus metastatic									
Locally Advanced	52	24 (46.2)	7.6 [3.0; -]	65	31 (47.7)	9.1 [5.3; 16.1]	1.09 [0.64; 1.85]	0.762	0.985
Metastatic	439	207 (47.2)	6.5 [4.6; 9.4]	435	203 (46.7)	8.1 [6.3; 9.4]	1.07 [0.88; 1.29]	0.521	

a: Database Cutoff Date: 15DEC2022

b: Chemotherapy: Gemcitabine + Cisplatin

c: Number of participants: full-analysis-set population, participants with baseline

d: From product-limit (Kaplan-Meier) method for censored data

e: Based on Cox regression model with treatment as a covariate

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

g: Based on Cox 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; EQ-5D: European Quality of Life 5 Dimensions; VAS: Visual Analogue Scale

Anhang 4-G5.3: Gesundheitsbezogene Lebensqualität

EORTC QLQ-C30

Globaler Gesundheitsstatus

Tabelle 4G-44: Subgruppenanalysen mit nicht statistisch signifikantem Interaktionstest ($p \geq 0,05$) für den globalen Gesundheitsstatus des EORTC QLQ-C30 aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE 966[a]	**Pembrolizumab + Chemotherapy[b]**			**Placebo + Chemotherapy[b]**			**Pembrolizumab + Chemotherapy[b] vs. Placebo + Chemotherapy[b]**		**p-Value for Interaction Test[g]**
EORTC QLQ-C30 Global Health Status/QoL (10 points)	**N[c]**	**Participants with Event n (%)**	**Median Time[d] in months [95 %-CI]**	**N[c]**	**Participants with Event n (%)**	**Median Time[d] in months [95 %-CI]**	**Hazard Ratio [95 %-CI][e]**	**p-Value[e,f]**	
Sex									
Female	224	141 (62.9)	3.4 [2.2; 4.8]	241	152 (63.1)	2.7 [2.1; 3.4]	0.93 [0.74; 1.17]	0.516	0.815
Male	265	156 (58.9)	3.6 [3.0; 5.1]	255	158 (62.0)	3.5 [2.8; 4.6]	0.88 [0.70; 1.09]	0.241	
Age									
< 65	243	145 (59.7)	3.8 [2.8; 5.5]	275	172 (62.5)	2.8 [2.2; 4.1]	0.86 [0.69; 1.07]	0.171	0.503
≥ 65	246	152 (61.8)	3.4 [2.4; 4.4]	221	138 (62.4)	3.2 [2.6; 4.3]	0.95 [0.75; 1.19]	0.637	
ECOG Performance Status									
0	242	147 (60.7)	3.5 [2.6; 5.1]	211	152 (72.0)	2.7 [2.1; 3.4]	0.77 [0.62; 0.97]	0.028	0.077
1	247	150 (60.7)	3.5 [3.0; 4.9]	285	158 (55.4)	3.5 [2.8; 4.4]	1.03 [0.82; 1.29]	0.812	
Geographic region									
Asia	230	144 (62.6)	3.2 [2.1; 4.1]	237	158 (66.7)	2.8 [2.1; 3.5]	0.88 [0.70; 1.11]	0.276	0.749
Non-Asia	259	153 (59.1)	4.0 [3.2; 5.3]	259	152 (58.7)	3.5 [2.8; 4.3]	0.92 [0.73; 1.15]	0.459	
Locally advanced versus metastatic									
Locally Advanced	52	31 (59.6)	3.5 [2.7; 7.6]	64	48 (75.0)	2.8 [2.1; 3.4]	0.63 [0.40; 1.00]	0.049	0.096
Metastatic	437	266 (60.9)	3.5 [2.8; 4.4]	432	262 (60.6)	3.3 [2.6; 4.2]	0.95 [0.80; 1.12]	0.525	
Site of Origin									
Extrahepatic	91	59 (64.8)	3.1 [2.1; 4.9]	101	60 (59.4)	3.5 [2.1; 4.8]	1.03 [0.72; 1.47]	0.888	0.684
Gallbladder	106	55 (51.9)	3.5 [2.2; 8.1]	110	69 (62.7)	3.5 [2.3; 4.4]	0.90 [0.63; 1.28]	0.548	
Intrahepatic	292	183 (62.7)	3.6 [2.8; 5.1]	285	181 (63.5)	2.8 [2.2; 3.5]	0.86 [0.70; 1.06]	0.155	

a: Database Cutoff Date: 15DEC2022
b: Chemotherapy: Gemcitabine + Cisplatin
c: Number of participants: full-analysis-set population, participants with baseline
d: From product-limit (Kaplan-Meier) method for censored data
e: Based on Cox regression model with treatment as a covariate
f: Two-sided p-value using Wald test (Score test in case of zero event in one treatment group)

g: Based on Cox 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; EORTC QLQ-C30: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Core 30 items; QoL: Quality of Life

Funktionsskala Körperliche Funktion

Tabelle 4G-45: Subgruppenanalysen mit nicht statistisch signifikantem Interaktionstest ($p \geq 0,05$) für die Funktionsskala Körperliche Funktion des EORTC QLQ-C30 aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE 966[a]	**Pembrolizumab + Chemotherapy[b]**			**Placebo + Chemotherapy[b]**			**Pembrolizumab + Chemotherapy[b] vs. Placebo + Chemotherapy[b]**		**p-Value for Interaction Test[g]**
EORTC QLQ-C30 Physical Functioning (10 points)	**N[c]**	**Participants with Event n (%)**	**Median Time[d] in months [95 %-CI]**	**N[c]**	**Participants with Event n (%)**	**Median Time[d] in months [95 %-CI]**	**Hazard Ratio [95 %-CI][e]**	**p-Value[e,f]**	
Sex									
Female	224	153 (68.3)	3.4 [2.3; 3.7]	241	162 (67.2)	2.4 [2.1; 3.4]	0.98 [0.79; 1.23]	0.893	0.931
Male	265	167 (63.0)	3.5 [2.8; 4.9]	255	163 (63.9)	3.4 [2.8; 4.3]	0.97 [0.78; 1.21]	0.809	
Age									
< 65	243	161 (66.3)	3.5 [2.8; 4.2]	275	168 (61.1)	3.2 [2.4; 4.2]	1.06 [0.86; 1.32]	0.568	0.201
≥ 65	246	159 (64.6)	3.4 [2.7; 4.2]	221	157 (71.0)	2.9 [2.2; 3.5]	0.87 [0.70; 1.09]	0.231	
ECOG Performance Status									
0	242	157 (64.9)	3.5 [2.8; 4.2]	211	143 (67.8)	3.0 [2.2; 4.2]	0.98 [0.78; 1.23]	0.863	0.979
1	247	163 (66.0)	3.4 [2.3; 4.1]	285	182 (63.9)	2.9 [2.3; 3.5]	0.98 [0.79; 1.21]	0.830	
Geographic region									
Asia	230	141 (61.3)	3.4 [2.7; 4.6]	237	150 (63.3)	3.2 [2.7; 4.1]	0.92 [0.73; 1.16]	0.499	0.515
Non-Asia	259	179 (69.1)	3.5 [2.8; 4.1]	259	175 (67.6)	2.8 [2.2; 3.7]	1.02 [0.83; 1.26]	0.838	
Locally advanced versus metastatic									
Locally Advanced	52	33 (63.5)	3.0 [2.1; 6.5]	64	39 (60.9)	4.9 [2.8; 10.6]	1.17 [0.74; 1.87]	0.497	0.353
Metastatic	437	287 (65.7)	3.5 [2.8; 4.0]	432	286 (66.2)	2.8 [2.3; 3.4]	0.94 [0.80; 1.11]	0.452	
Site of Origin									
Extrahepatic	91	59 (64.8)	3.5 [2.1; 4.6]	101	68 (67.3)	3.0 [2.3; 4.1]	0.90 [0.64; 1.28]	0.567	0.675
Gallbladder	106	68 (64.2)	3.0 [2.1; 4.9]	110	74 (67.3)	3.1 [2.1; 3.9]	1.10 [0.79; 1.53]	0.575	
Intrahepatic	292	193 (66.1)	3.5 [2.8; 4.2]	285	183 (64.2)	2.8 [2.3; 3.9]	0.96 [0.79; 1.18]	0.726	

a: Database Cutoff Date: 15DEC2022
b: Chemotherapy: Gemcitabine + Cisplatin
c: Number of participants: full-analysis-set population, participants with baseline
d: From product-limit (Kaplan-Meier) method for censored data
e: Based on Cox regression model with treatment as a covariate
f: Two-sided p-value using Wald test (Score test in case of zero event in one treatment group)
g: Based on Cox 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; EORTC QLQ-C30: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Core 30 items

Funktionsskala Rollenfunktion

Tabelle 4G-46: Subgruppenanalysen mit nicht statistisch signifikantem Interaktionstest ($p \geq 0,05$) für die Funktionsskala Rollenfunktion des EORTC QLQ-C30 aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE 966[a]	**Pembrolizumab + Chemotherapy[b]**			**Placebo + Chemotherapy[b]**			**Pembrolizumab + Chemotherapy[b] vs. Placebo + Chemotherapy[b]**		**p-Value for Interaction Test[g]**
EORTC QLQ-C30 Role Functioning (10 points)	**N[c]**	**Participants with Event n (%)**	**Median Time[d] in months [95 %-CI]**	**N[c]**	**Participants with Event n (%)**	**Median Time[d] in months [95 %-CI]**	**Hazard Ratio [95 %-CI][e]**	**p-Value[e,f]**	
Sex									
Female	224	155 (69.2)	2.1 [1.4; 2.8]	241	168 (69.7)	2.1 [1.5; 2.7]	0.97 [0.78; 1.21]	0.789	0.654
Male	265	173 (65.3)	2.6 [2.1; 3.5]	255	178 (69.8)	2.3 [1.9; 3.0]	0.90 [0.73; 1.11]	0.323	
Age									
< 65	243	161 (66.3)	2.7 [2.1; 3.4]	275	187 (68.0)	2.1 [1.6; 2.8]	0.92 [0.75; 1.14]	0.458	0.940
≥ 65	246	167 (67.9)	2.1 [1.6; 2.8]	221	159 (71.9)	2.3 [1.6; 2.9]	0.93 [0.75; 1.16]	0.537	
ECOG Performance Status									
0	242	166 (68.6)	2.1 [1.5; 2.8]	211	157 (74.4)	2.1 [1.6; 2.3]	0.90 [0.72; 1.12]	0.339	0.684
1	247	162 (65.6)	2.7 [2.1; 3.5]	285	189 (66.3)	2.6 [1.9; 3.5]	0.95 [0.77; 1.18]	0.665	
Geographic region									
Asia	230	152 (66.1)	2.3 [1.6; 3.4]	237	173 (73.0)	1.6 [1.4; 2.3]	0.83 [0.67; 1.03]	0.089	0.134
Non-Asia	259	176 (68.0)	2.3 [1.6; 3.2]	259	173 (66.8)	2.7 [2.1; 3.5]	1.03 [0.84; 1.27]	0.764	
Locally advanced versus metastatic									
Locally Advanced	52	37 (71.2)	2.2 [1.4; 5.1]	64	51 (79.7)	2.1 [1.4; 2.9]	0.82 [0.53; 1.25]	0.352	0.505
Metastatic	437	291 (66.6)	2.3 [2.1; 2.9]	432	295 (68.3)	2.3 [1.8; 2.8]	0.95 [0.81; 1.12]	0.554	
Site of Origin									
Extrahepatic	91	63 (69.2)	2.1 [1.4; 3.5]	101	74 (73.3)	2.7 [1.5; 3.5]	0.87 [0.62; 1.22]	0.408	0.808
Gallbladder	106	68 (64.2)	3.3 [1.6; 3.5]	110	75 (68.2)	3.0 [2.1; 3.9]	1.01 [0.73; 1.40]	0.949	
Intrahepatic	292	197 (67.5)	2.1 [1.5; 2.8]	285	197 (69.1)	2.1 [1.4; 2.3]	0.94 [0.77; 1.14]	0.532	

a: Database Cutoff Date: 15DEC2022

b: Chemotherapy: Gemcitabine + Cisplatin

c: Number of participants: full-analysis-set population, participants with baseline

d: From product-limit (Kaplan-Meier) method for censored data

e: Based on Cox regression model with treatment as a covariate

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

g: Based on Cox 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; EORTC QLQ-C30: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Core 30 items

Funktionsskala Emotionale Funktion

Tabelle 4G-47: Subgruppenanalysen mit nicht statistisch signifikantem Interaktionstest ($p \geq 0,05$) für die Funktionsskala Emotionale Funktion des EORTC QLQ-C30 aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE 966[a]	**Pembrolizumab + Chemotherapy[b]**			**Placebo + Chemotherapy[b]**			**Pembrolizumab + Chemotherapy[b] vs. Placebo + Chemotherapy[b]**		**p-Value for Interaction Test[g]**
EORTC QLQ-C30 Emotional Functioning (10 points)	**N[c]**	**Participants with Event n (%)**	**Median Time[d] in months [95 %-CI]**	**N[c]**	**Participants with Event n (%)**	**Median Time[d] in months [95 %-CI]**	**Hazard Ratio [95 %-CI][e]**	**p-Value[e,f]**	
Sex									
Female	224	116 (51.8)	5.3 [3.9; 8.5]	241	116 (48.1)	5.1 [4.1; 16.5]	1.09 [0.84; 1.41]	0.502	0.357
Male	265	129 (48.7)	5.8 [4.2; 10.6]	255	109 (42.7)	7.8 [6.2; 12.0]	1.29 [1.00; 1.67]	0.051	
Age									
< 65	243	121 (49.8)	5.8 [4.3; 9.1]	275	126 (45.8)	6.5 [4.9; 12.0]	1.14 [0.89; 1.46]	0.310	0.668
≥ 65	246	124 (50.4)	4.9 [3.7; 9.0]	221	99 (44.8)	6.2 [4.8; 10.4]	1.23 [0.95; 1.61]	0.120	
ECOG Performance Status									
0	242	114 (47.1)	8.9 [4.9; 10.9]	211	100 (47.4)	7.6 [5.1; 18.0]	1.07 [0.82; 1.40]	0.614	0.264
1	247	131 (53.0)	4.3 [3.3; 5.8]	285	125 (43.9)	6.2 [4.6; 10.4]	1.32 [1.04; 1.69]	0.025	
Geographic region									
Asia	230	115 (50.0)	4.9 [3.5; 10.4]	237	114 (48.1)	5.8 [4.2; 9.2]	1.10 [0.84; 1.42]	0.493	0.417
Non-Asia	259	130 (50.2)	5.6 [4.4; 8.9]	259	111 (42.9)	7.8 [5.5; 17.5]	1.27 [0.99; 1.64]	0.062	
Locally advanced versus metastatic									
Locally Advanced	52	22 (42.3)	12.3 [4.4; -]	64	31 (48.4)	6.5 [3.7; 24.4]	0.95 [0.55; 1.64]	0.841	0.391
Metastatic	437	223 (51.0)	4.9 [4.1; 8.0]	432	194 (44.9)	6.2 [5.1; 9.7]	1.21 [1.00; 1.47]	0.049	
Site of Origin									
Extrahepatic	91	46 (50.5)	4.2 [2.8; -]	101	45 (44.6)	7.7 [4.2; -]	1.28 [0.85; 1.95]	0.237	0.269
Gallbladder	106	57 (53.8)	4.2 [2.1; 8.1]	110	49 (44.5)	6.1 [4.2; -]	1.54 [1.05; 2.26]	0.026	
Intrahepatic	292	142 (48.6)	7.1 [4.8; 10.4]	285	131 (46.0)	6.2 [5.1; 10.4]	1.06 [0.84; 1.35]	0.629	

a: Database Cutoff Date: 15DEC2022
b: Chemotherapy: Gemcitabine + Cisplatin
c: Number of participants: full-analysis-set population, participants with baseline
d: From product-limit (Kaplan-Meier) method for censored data
e: Based on Cox regression model with treatment as a covariate
f: Two-sided p-value using Wald test (Score test in case of zero event in one treatment group)
g: Based on Cox 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; EORTC QLQ-C30: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Core 30 items

Funktionsskala Kognitive Funktion

Tabelle 4G-48: Subgruppenanalysen mit nicht statistisch signifikantem Interaktionstest ($p \geq 0,05$) für die Funktionsskala Kognitive Funktion des EORTC QLQ-C30 aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE 966[a]	**Pembrolizumab + Chemotherapy[b]**			**Placebo + Chemotherapy[b]**			**Pembrolizumab + Chemotherapy[b] vs. Placebo + Chemotherapy[b]**		**p-Value for Interaction Test[g]**
EORTC QLQ-C30 Cognitive Functioning (10 points)	**N[c]**	**Participants with Event n (%)**	**Median Time[d] in months [95 %-CI]**	**N[c]**	**Participants with Event n (%)**	**Median Time[d] in months [95 %-CI]**	**Hazard Ratio [95 %-CI][e]**	**p-Value[e,f]**	
Sex									
Female	224	145 (64.7)	2.9 [2.1; 3.5]	241	147 (61.0)	3.3 [2.6; 3.8]	1.05 [0.83; 1.32]	0.678	0.152
Male	265	149 (56.2)	3.5 [2.7; 5.2]	255	169 (66.3)	3.0 [2.3; 4.1]	0.83 [0.66; 1.03]	0.096	
Age									
< 65	243	139 (57.2)	3.7 [3.0; 5.6]	275	168 (61.1)	3.3 [2.4; 4.1]	0.86 [0.69; 1.08]	0.197	0.338
≥ 65	246	155 (63.0)	2.7 [2.0; 3.5]	221	148 (67.0)	3.0 [2.4; 3.8]	0.99 [0.79; 1.24]	0.950	
ECOG Performance Status									
0	242	150 (62.0)	2.8 [2.1; 4.1]	211	136 (64.5)	3.5 [2.8; 4.4]	1.02 [0.81; 1.29]	0.859	0.225
1	247	144 (58.3)	3.5 [2.3; 4.7]	285	180 (63.2)	2.8 [2.3; 3.5]	0.84 [0.68; 1.05]	0.131	
Geographic region									
Asia	230	137 (59.6)	3.0 [2.2; 3.7]	237	159 (67.1)	2.8 [2.2; 3.5]	0.82 [0.66; 1.04]	0.101	0.187
Non-Asia	259	157 (60.6)	3.5 [2.3; 4.4]	259	157 (60.6)	3.5 [2.8; 4.5]	1.02 [0.82; 1.27]	0.880	
Locally advanced versus metastatic									
Locally Advanced	52	36 (69.2)	2.1 [1.4; 4.6]	64	43 (67.2)	3.5 [2.3; 5.1]	1.28 [0.82; 2.00]	0.278	0.146
Metastatic	437	258 (59.0)	3.5 [2.8; 4.1]	432	273 (63.2)	2.8 [2.6; 3.5]	0.88 [0.74; 1.05]	0.150	
Site of Origin									
Extrahepatic	91	55 (60.4)	3.0 [2.2; 5.0]	101	64 (63.4)	3.5 [2.3; 5.8]	0.97 [0.67; 1.39]	0.860	0.762
Gallbladder	106	63 (59.4)	3.4 [1.4; 7.1]	110	71 (64.5)	3.5 [2.6; 4.4]	0.99 [0.71; 1.39]	0.963	
Intrahepatic	292	176 (60.3)	3.2 [2.3; 4.2]	285	181 (63.5)	2.8 [2.3; 3.5]	0.89 [0.72; 1.10]	0.271	

a: Database Cutoff Date: 15DEC2022
b: Chemotherapy: Gemcitabine + Cisplatin
c: Number of participants: full-analysis-set population, participants with baseline
d: From product-limit (Kaplan-Meier) method for censored data
e: Based on Cox regression model with treatment as a covariate
f: Two-sided p-value using Wald test (Score test in case of zero event in one treatment group)
g: Based on Cox 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; EORTC QLQ-C30: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Core 30 items

Funktionsskala Soziale Funktion

Tabelle 4G-49: Subgruppenanalysen mit nicht statistisch signifikantem Interaktionstest ($p \geq 0,05$) für die Funktionsskala Soziale Funktion des EORTC QLQ-C30 aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE 966[a]	**Pembrolizumab + Chemotherapy[b]**			**Placebo + Chemotherapy[b]**			**Pembrolizumab + Chemotherapy[b] vs. Placebo + Chemotherapy[b]**		**p-Value for Interaction Test[g]**
EORTC QLQ-C30 Social Functioning (10 points)	**N[c]**	**Participants with Event n (%)**	**Median Time[d] in months [95 %-CI]**	**N[c]**	**Participants with Event n (%)**	**Median Time[d] in months [95 %-CI]**	**Hazard Ratio [95 %-CI][e]**	**p-Value[e,f]**	
Sex									
Female	224	157 (70.1)	2.1 [1.5; 2.6]	241	162 (67.2)	2.2 [2.0; 2.8]	1.10 [0.88; 1.37]	0.411	0.328
Male	265	170 (64.2)	2.8 [2.1; 3.4]	255	166 (65.1)	2.6 [2.0; 3.2]	0.94 [0.76; 1.17]	0.587	
Age									
< 65	243	159 (65.4)	2.7 [2.1; 3.3]	275	181 (65.8)	2.4 [2.0; 3.0]	0.96 [0.78; 1.19]	0.737	0.527
≥ 65	246	168 (68.3)	2.1 [1.6; 2.8]	221	147 (66.5)	2.3 [2.0; 3.0]	1.06 [0.85; 1.32]	0.603	
ECOG Performance Status									
0	242	165 (68.2)	2.1 [1.7; 2.8]	211	141 (66.8)	2.2 [2.0; 3.4]	1.11 [0.89; 1.39]	0.363	0.234
1	247	162 (65.6)	2.7 [2.1; 3.2]	285	187 (65.6)	2.3 [1.8; 2.9]	0.92 [0.75; 1.14]	0.454	
Geographic region									
Asia	230	149 (64.8)	2.2 [1.6; 3.4]	237	154 (65.0)	2.4 [2.0; 3.2]	0.98 [0.78; 1.23]	0.863	0.805
Non-Asia	259	178 (68.7)	2.2 [2.1; 2.8]	259	174 (67.2)	2.1 [1.9; 2.9]	1.02 [0.83; 1.26]	0.835	
Locally advanced versus metastatic									
Locally Advanced	52	37 (71.2)	2.5 [1.4; 3.8]	64	43 (67.2)	2.7 [2.0; 4.2]	1.14 [0.74; 1.78]	0.547	0.531
Metastatic	437	290 (66.4)	2.2 [2.0; 2.8]	432	285 (66.0)	2.3 [2.1; 2.8]	0.99 [0.84; 1.16]	0.874	
Site of Origin									
Extrahepatic	91	63 (69.2)	2.8 [1.6; 3.6]	101	65 (64.4)	3.0 [1.7; 3.8]	1.08 [0.76; 1.54]	0.652	0.218
Gallbladder	106	73 (68.9)	2.1 [1.5; 2.8]	110	69 (62.7)	2.3 [1.4; 3.5]	1.24 [0.89; 1.73]	0.201	
Intrahepatic	292	191 (65.4)	2.2 [2.0; 2.8]	285	194 (68.1)	2.2 [2.0; 2.8]	0.91 [0.75; 1.11]	0.356	

a: Database Cutoff Date: 15DEC2022
b: Chemotherapy: Gemcitabine + Cisplatin
c: Number of participants: full-analysis-set population, participants with baseline
d: From product-limit (Kaplan-Meier) method for censored data
e: Based on Cox regression model with treatment as a covariate
f: Two-sided p-value using Wald test (Score test in case of zero event in one treatment group)
g: Based on Cox 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; EORTC QLQ-C30: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Core 30 items

Anhang 4-G5.4: Nebenwirkungen

Unerwünschte Ereignisse Gesamtraten

Unerwünschte Ereignisse gesamt

Tabelle 4G-50: Subgruppenanalysen mit nicht statistisch signifikantem Interaktionstest ($p \geq 0,05$) für den Endpunkt Unerwünschte Ereignisse gesamt aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE 966[a]	Pembrolizumab + Chemotherapy[b]			Placebo + Chemotherapy[b]			Pembrolizumab + Chemotherapy[b] vs. Placebo + Chemotherapy[b]		p-Value for Interaction Test[g]
	N[c]	Participants with Event n (%)	Median Time[d] in Weeks [95 %-CI]	N[c]	Participants with Event n (%)	Median Time[d] in Weeks [95 %-CI]	Hazard Ratio [95 %-CI][e]	p-Value[e,f]	
Adverse Events									
Sex									
Female	250	247 (98.8)	0.6 [0.4; 0.7]	264	263 (99.6)	0.4 [0.4; 0.6]	0.92 [0.77; 1.09]	0.334	0.464
Male	279	277 (99.3)	0.6 [0.4; 0.9]	270	269 (99.6)	0.7 [0.6; 0.9]	1.00 [0.85; 1.18]	0.989	
Age									
< 65	266	261 (98.1)	0.6 [0.4; 0.7]	296	296 (100.0)	0.6 [0.4; 0.7]	1.03 [0.87; 1.22]	0.720	0.189
≥ 65	263	263 (100.0)	0.7 [0.6; 0.9]	238	236 (99.2)	0.6 [0.4; 0.7]	0.86 [0.72; 1.03]	0.103	
ECOG Performance Status									
0	257	254 (98.8)	0.7 [0.6; 0.9]	226	226 (100.0)	0.6 [0.4; 0.9]	0.97 [0.81; 1.16]	0.746	0.843
1	271	269 (99.3)	0.6 [0.4; 0.7]	308	306 (99.4)	0.6 [0.4; 0.7]	0.95 [0.80; 1.11]	0.507	
Geographic region									
Asia	240	238 (99.2)	0.6 [0.6; 0.9]	243	242 (99.6)	0.6 [0.4; 0.9]	1.07 [0.89; 1.28]	0.460	0.085
Non-Asia	289	286 (99.0)	0.6 [0.4; 0.7]	291	290 (99.7)	0.6 [0.4; 0.7]	0.87 [0.74; 1.02]	0.095	
Locally advanced versus metastatic									
Locally Advanced	59	59 (100.0)	0.6 [0.3; 1.0]	66	66 (100.0)	0.6 [0.3; 1.1]	1.17 [0.82; 1.67]	0.396	0.241
Metastatic	470	465 (98.9)	0.6 [0.6; 0.7]	468	466 (99.6)	0.6 [0.4; 0.7]	0.93 [0.82; 1.06]	0.266	
Site of Origin									
Extrahepatic	98	98 (100.0)	0.7 [0.4; 1.0]	105	104 (99.0)	0.7 [0.4; 1.0]	0.97 [0.74; 1.29]	0.853	0.956
Gallbladder	113	111 (98.2)	0.6 [0.4; 0.7]	118	118 (100.0)	0.6 [0.3; 0.9]	0.98 [0.76; 1.27]	0.892	
Intrahepatic	318	315 (99.1)	0.6 [0.6; 0.9]	311	310 (99.7)	0.6 [0.4; 0.7]	0.94 [0.80; 1.10]	0.454	

a: Database Cutoff Date: 15DEC2022
b: Chemotherapy: Gemcitabine + Cisplatin
c: Number of participants: all-participants-as-treated population
d: From product-limit (Kaplan-Meier) method for censored data
e: Based on Cox regression model with treatment as a covariate 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 Cox 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

Schwerwiegende unerwünschte Ereignisse

Tabelle 4G-51: Subgruppenanalysen mit nicht statistisch signifikantem Interaktionstest ($p \geq 0,05$) für den Endpunkt Schwerwiegende unerwünschte Ereignisse aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE 966[a]	**Pembrolizumab + Chemotherapy[b]**			**Placebo + Chemotherapy[b]**			**Pembrolizumab + Chemotherapy[b] vs. Placebo + Chemotherapy[b]**		
	N[c]	**Participants with Event n (%)**	**Median Time[d] in Weeks [95 %-CI]**	**N[c]**	**Participants with Event n (%)**	**Median Time[d] in Weeks [95 %-CI]**	**Hazard Ratio [95 %-CI][e]**	**p-Value[e,f]**	**p-Value for Interaction Test[g]**
Serious Adverse Events									
Sex									
Female	250	128 (51.2)	45.9 [32.1; 58.9]	264	132 (50.0)	36.3 [29.0; 56.6]	1.01 [0.79; 1.29]	0.940	0.630
Male	279	148 (53.0)	34.0 [26.6; 59.1]	270	131 (48.5)	39.9 [27.6; 82.7]	1.10 [0.87; 1.39]	0.436	
Age									
< 65	266	128 (48.1)	50.1 [33.9; 65.1]	296	133 (44.9)	48.1 [32.3; 82.7]	1.10 [0.86; 1.40]	0.461	0.540
≥ 65	263	148 (56.3)	33.0 [25.6; 42.6]	238	130 (54.6)	29.3 [22.3; 42.3]	0.99 [0.78; 1.25]	0.919	
ECOG Performance Status									
0	257	123 (47.9)	45.0 [35.0; -]	226	102 (45.1)	73.7 [39.4; -]	1.10 [0.85; 1.44]	0.460	0.703
1	271	152 (56.1)	31.4 [24.7; 48.1]	308	161 (52.3)	30.1 [26.1; 42.3]	1.04 [0.83; 1.30]	0.743	
Geographic region									
Asia	240	110 (45.8)	59.1 [31.4; -]	243	104 (42.8)	75.4 [39.0; -]	1.10 [0.84; 1.44]	0.488	0.692
Non-Asia	289	166 (57.4)	34.1 [26.6; 40.1]	291	159 (54.6)	30.0 [24.9; 39.4]	1.02 [0.82; 1.26]	0.882	
Locally advanced versus metastatic									
Locally Advanced	59	32 (54.2)	42.6 [25.1; -]	66	29 (43.9)	80.0 [27.3; -]	1.28 [0.77; 2.12]	0.336	0.422
Metastatic	470	244 (51.9)	35.4 [29.6; 52.1]	468	234 (50.0)	35.1 [29.0; 43.7]	1.03 [0.86; 1.23]	0.750	
Site of Origin									
Extrahepatic	98	56 (57.1)	31.3 [21.7; 45.0]	105	58 (55.2)	33.0 [21.1; 73.7]	1.09 [0.75; 1.57]	0.652	0.578
Gallbladder	113	66 (58.4)	28.9 [13.9; 54.9]	118	59 (50.0)	31.7 [26.7; 56.6]	1.21 [0.85; 1.72]	0.293	
Intrahepatic	318	154 (48.4)	48.1 [35.1; 87.3]	311	146 (46.9)	42.6 [30.1; -]	1.00 [0.80; 1.25]	0.996	

a: Database Cutoff Date: 15DEC2022

b: Chemotherapy: Gemcitabine + Cisplatin

c: Number of participants: all-participants-as-treated population

d: From product-limit (Kaplan-Meier) method for censored data

e: Based on Cox regression model with treatment as a covariate 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 Cox 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

Schwere unerwünschte Ereignisse (CTCAE-Grad 3-5)

Tabelle 4G-52: Subgruppenanalysen mit nicht statistisch 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 966[a]	**Pembrolizumab + Chemotherapy[b]**			**Placebo + Chemotherapy[b]**			**Pembrolizumab + Chemotherapy[b] vs. Placebo + Chemotherapy[b]**		
	N[c]	**Participants with Event n (%)**	**Median Time[d] in Weeks [95 %-CI]**	**N[c]**	**Participants with Event n (%)**	**Median Time[d] in Weeks [95 %-CI]**	**Hazard Ratio [95 %-CI][e]**	**p-Value[e,f]**	**p-Value for Interaction Test[g]**
Severe Adverse Events (CTCAE-Grade 3-5)									
Sex									
Female	250	210 (84.0)	8.6 [6.9; 10.1]	264	228 (86.4)	7.1 [5.9; 9.6]	0.94 [0.78; 1.13]	0.523	0.444
Male	279	241 (86.4)	8.1 [6.1; 10.1]	270	221 (81.9)	8.1 [6.1; 10.0]	1.04 [0.86; 1.24]	0.703	
Age									
< 65	266	224 (84.2)	10.1 [7.3; 11.3]	296	241 (81.4)	9.9 [7.1; 10.1]	1.04 [0.87; 1.25]	0.640	0.357
≥ 65	263	227 (86.3)	7.0 [5.4; 9.1]	238	208 (87.4)	6.9 [4.6; 7.4]	0.92 [0.76; 1.11]	0.362	
ECOG Performance Status									
0	257	217 (84.4)	10.1 [7.9; 10.9]	226	192 (85.0)	9.0 [5.4; 10.1]	0.97 [0.80; 1.18]	0.751	0.639
1	271	233 (86.0)	7.0 [5.7; 9.1]	308	257 (83.4)	7.1 [6.0; 9.4]	1.03 [0.86; 1.23]	0.747	
Geographic region									
Asia	240	196 (81.7)	9.1 [7.0; 10.3]	243	203 (83.5)	7.4 [6.3; 10.0]	1.00 [0.82; 1.21]	0.971	0.949
Non-Asia	289	255 (88.2)	7.4 [6.1; 10.1]	291	246 (84.5)	7.1 [6.0; 9.4]	0.99 [0.83; 1.18]	0.903	
Site of Origin									
Extrahepatic	98	83 (84.7)	6.1 [4.0; 10.1]	105	91 (86.7)	7.0 [4.0; 9.4]	0.94 [0.69; 1.26]	0.664	0.749
Gallbladder	113	94 (83.2)	5.4 [4.1; 9.1]	118	99 (83.9)	9.1 [5.4; 10.1]	1.08 [0.82; 1.44]	0.581	
Intrahepatic	318	274 (86.2)	10.0 [7.3; 10.6]	311	259 (83.3)	7.3 [6.1; 10.0]	0.99 [0.83; 1.17]	0.878	

a: Database Cutoff Date: 15DEC2022
b: Chemotherapy: Gemcitabine + Cisplatin
c: Number of participants: all-participants-as-treated population
d: From product-limit (Kaplan-Meier) method for censored data
e: Based on Cox regression model with treatment as a covariate 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 Cox model with treatment and subgroup as covariates, and treatment-by-subgroup interaction (p-value of likelihood ratio test for interaction term)
CI: Confidence Interval; CTCAE: Common Terminology Criteria for Adverse Events; ECOG: Eastern Cooperative Oncology Group

Therapieabbruch wegen unerwünschter Ereignisse

Tabelle 4G-53: Subgruppenanalysen mit nicht statistisch signifikantem Interaktionstest ($p \geq 0,05$) für den Endpunkt Therapieabbruch wegen unerwünschter Ereignisse aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE 966[a]	**Pembrolizumab + Chemotherapy[b]**			**Placebo + Chemotherapy[b]**			**Pembrolizumab + Chemotherapy[b] vs. Placebo + Chemotherapy[b]**		**p-Value for Interaction Test[g]**
	N[c]	**Participants with Event n (%)**	**Median Time[d] in Weeks [95 %-CI]**	**N[c]**	**Participants with Event n (%)**	**Median Time[d] in Weeks [95 %-CI]**	**Hazard Ratio [95 %-CI][e]**	**p-Value[e,f]**	
Adverse Events Leading to Treatment Discontinuation									
Sex									
Female	250	65 (26.0)	101.6 [62.3; -]	264	51 (19.3)	Not reached [86.7; -]	1.31 [0.90; 1.88]	0.154	0.223
Male	279	73 (26.2)	Not reached [70.1; -]	270	71 (26.3)	97.1 [78.3; -]	0.97 [0.70; 1.35]	0.875	
Age									
< 65	266	62 (23.3)	Not reached [67.1; -]	296	52 (17.6)	Not reached [-; -]	1.31 [0.90; 1.89]	0.153	0.191
≥ 65	263	76 (28.9)	96.1 [64.1; -]	238	70 (29.4)	85.0 [74.3; -]	0.94 [0.68; 1.30]	0.718	
ECOG Performance Status									
0	257	59 (23.0)	Not reached [96.1; -]	226	52 (23.0)	Not reached [85.0; -]	1.02 [0.71; 1.49]	0.898	0.508
1	271	79 (29.2)	73.7 [62.3; -]	308	70 (22.7)	Not reached [74.3; -]	1.23 [0.89; 1.69]	0.215	
Geographic region									
Asia	240	54 (22.5)	Not reached [96.1; -]	243	46 (18.9)	Not reached [97.1; -]	1.24 [0.84; 1.84]	0.283	0.463
Non-Asia	289	84 (29.1)	80.1 [64.1; -]	291	76 (26.1)	Not reached [69.7; -]	1.04 [0.76; 1.41]	0.825	
Locally advanced versus metastatic									
Locally Advanced	59	21 (35.6)	73.7 [56.3; -]	66	16 (24.2)	Not reached [74.3; -]	1.47 [0.77; 2.81]	0.248	0.380
Metastatic	470	117 (24.9)	Not reached [76.9; -]	468	106 (22.6)	Not reached [86.7; -]	1.07 [0.82; 1.39]	0.616	
Site of Origin									
Extrahepatic	98	24 (24.5)	64.1 [61.6; -]	105	26 (24.8)	97.1 [78.3; -]	1.24 [0.70; 2.19]	0.466	0.543
Gallbladder	113	29 (25.7)	76.9 [54.1; -]	118	22 (18.6)	Not reached [-; -]	1.44 [0.82; 2.50]	0.201	
Intrahepatic	318	85 (26.7)	Not reached [96.1; -]	311	74 (23.8)	Not reached [82.0; -]	1.02 [0.75; 1.40]	0.893	

a: Database Cutoff Date: 15DEC2022
b: Chemotherapy: Gemcitabine + Cisplatin
c: Number of participants: all-participants-as-treated population
d: From product-limit (Kaplan-Meier) method for censored data
e: Based on Cox regression model with treatment as a covariate 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 Cox 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-54: Subgruppenanalysen mit nicht statistisch signifikantem Interaktionstest ($p \geq 0,05$) für den Endpunkt Unerwünschte Ereignisse gesamt (SOC und PT) für SOC aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE 966[a]	**Pembrolizumab + Chemotherapy[b]**			**Placebo + Chemotherapy[b]**			**Pembrolizumab + Chemotherapy[b] vs. Placebo + Chemotherapy[b]**		
Adverse Events	**N[c]**	**Participants with Event n (%)**	**Median Time[d] in Weeks [95 %-CI]**	**N[c]**	**Participants with Event n (%)**	**Median Time[d] in Weeks [95 %-CI]**	**Hazard Ratio [95 %-CI][e]**	**p-Value[e,f]**	**p-Value for Interaction Test[g]**
SOC[h]: Endocrine disorders									
Sex									
Female	250	39 (15.6)	Not reached [-; -]	264	17 (6.4)	Not reached [-; -]	2.39 [1.35; 4.23]	0.003	0.872
Male	279	28 (10.0)	Not reached [-; -]	270	12 (4.4)	Not reached [105.1; -]	2.20 [1.12; 4.33]	0.023	
Age									
< 65	266	31 (11.7)	Not reached [-; -]	296	14 (4.7)	Not reached [-; -]	2.45 [1.30; 4.61]	0.005	0.777
≥ 65	263	36 (13.7)	Not reached [-; -]	238	15 (6.3)	Not reached [-; -]	2.17 [1.19; 3.95]	0.012	
ECOG Performance Status									
0	257	29 (11.3)	Not reached [-; -]	226	9 (4.0)	Not reached [105.1; -]	2.94 [1.39; 6.21]	0.005	0.435
1	271	38 (14.0)	Not reached [-; -]	308	20 (6.5)	Not reached [-; -]	2.07 [1.20; 3.55]	0.009	
Geographic region									
Asia	240	29 (12.1)	Not reached [-; -]	243	12 (4.9)	Not reached [-; -]	2.59 [1.32; 5.07]	0.006	0.688
Non-Asia	289	38 (13.1)	Not reached [-; -]	291	17 (5.8)	Not reached [-; -]	2.12 [1.19; 3.75]	0.010	
Locally advanced versus metastatic									
Locally Advanced	59	10 (16.9)	Not reached [-; -]	66	1 (1.5)	Not reached [-; -]	10.78 [1.38; 84.23]	0.023	0.052
Metastatic	470	57 (12.1)	Not reached [-; -]	468	28 (6.0)	Not reached [-; -]	2.00 [1.27; 3.15]	0.003	
SOC[h]: Gastrointestinal disorders									
Sex									
Female	250	203 (81.2)	2.9 [1.7; 3.4]	264	226 (85.6)	1.3 [1.1; 2.1]	0.83 [0.69; 1.00]	0.054	0.532
Male	279	216 (77.4)	3.1 [1.9; 4.1]	270	217 (80.4)	2.7 [1.4; 3.9]	0.89 [0.74; 1.08]	0.229	

Age									
< 65	266	215 (80.8)	3.0 [1.7; 3.9]	296	244 (82.4)	1.6 [1.1; 3.0]	0.91 [0.75; 1.09]	0.296	0.375
≥ 65	263	204 (77.6)	3.0 [1.7; 4.1]	238	199 (83.6)	2.6 [1.3; 3.6]	0.80 [0.66; 0.97]	0.026	
ECOG Performance Status									
0	257	206 (80.2)	3.3 [2.1; 4.1]	226	197 (87.2)	1.5 [1.1; 3.0]	0.77 [0.63; 0.93]	0.008	0.178
1	271	212 (78.2)	2.6 [1.3; 3.1]	308	246 (79.9)	2.1 [1.3; 3.3]	0.94 [0.78; 1.13]	0.485	
Geographic region									
Asia	240	190 (79.2)	3.0 [1.4; 4.1]	243	198 (81.5)	3.0 [1.3; 4.3]	0.93 [0.76; 1.14]	0.495	0.240
Non-Asia	289	229 (79.2)	3.0 [2.1; 4.0]	291	245 (84.2)	1.6 [1.1; 2.6]	0.80 [0.67; 0.96]	0.015	
Locally advanced versus metastatic									
Locally Advanced	59	45 (76.3)	3.0 [0.9; 6.9]	66	57 (86.4)	1.8 [1.1; 5.0]	0.71 [0.47; 1.06]	0.096	0.307
Metastatic	470	374 (79.6)	3.0 [2.1; 3.4]	468	386 (82.5)	1.7 [1.3; 3.0]	0.88 [0.76; 1.01]	0.075	
Site of Origin									
Extrahepatic	98	78 (79.6)	2.9 [1.1; 6.0]	105	89 (84.8)	1.9 [1.0; 3.3]	0.82 [0.61; 1.12]	0.215	0.950
Gallbladder	113	90 (79.6)	2.9 [1.3; 4.1]	118	99 (83.9)	1.1 [0.9; 3.3]	0.89 [0.67; 1.18]	0.411	
Intrahepatic	318	251 (78.9)	3.1 [1.9; 4.0]	311	255 (82.0)	2.1 [1.3; 3.3]	0.86 [0.72; 1.02]	0.082	
SOC[h]: Skin and subcutaneous tissue disorders									
Sex									
Female	250	119 (47.6)	30.9 [21.9; 66.1]	264	99 (37.5)	55.1 [41.1; -]	1.37 [1.05; 1.79]	0.020	0.721
Male	279	129 (46.2)	40.6 [31.0; 58.7]	270	91 (33.7)	80.7 [45.6; -]	1.46 [1.12; 1.91]	0.006	
Age									
< 65	266	120 (45.1)	40.6 [27.1; 71.3]	296	106 (35.8)	96.1 [43.6; -]	1.32 [1.01; 1.71]	0.038	0.483
≥ 65	263	128 (48.7)	39.7 [26.7; 66.1]	238	84 (35.3)	55.1 [42.0; -]	1.52 [1.15; 2.00]	0.003	
ECOG Performance Status									
0	257	142 (55.3)	25.1 [9.7; 34.0]	226	96 (42.5)	46.7 [35.0; 96.1]	1.55 [1.20; 2.01]	< 0.001	0.292
1	271	106 (39.1)	58.7 [39.7; -]	308	94 (30.5)	Not reached [80.7; -]	1.27 [0.96; 1.68]	0.091	
Locally advanced versus metastatic									
Locally Advanced	59	33 (55.9)	39.7 [6.7; 72.1]	66	28 (42.4)	50.1 [19.9; -]	1.32 [0.80; 2.19]	0.276	0.798
Metastatic	470	215 (45.7)	39.9 [27.7; 57.3]	468	162 (34.6)	80.7 [46.7; -]	1.43 [1.17; 1.76]	< 0.001	
Site of Origin									
Extrahepatic	98	39	112.6	105	39	50.1	1.17	0.498	0.680

		(39.8)	[27.3; -]		(37.1)	[35.3; -]	[0.75; 1.83]		
Gallbladder	113	51 (45.1)	28.0 [16.4; 66.7]	118	40 (33.9)	Not reached [43.6; -]	1.43 [0.94; 2.16]	0.092	
Intrahepatic	318	158 (49.7)	40.6 [25.1; 57.3]	311	111 (35.7)	80.7 [46.7; -]	1.49 [1.17; 1.90]	0.001	

a: Database Cutoff Date: 15DEC2022

b: Chemotherapy: Gemcitabine + Cisplatin

c: Number of participants: all-participants-as-treated population

d: From product-limit (Kaplan-Meier) method for censored data

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

h: A system organ class appears on this report only if its incidence ≥10% or (incidence ≥1% and in at least 10 participants) in One or More Treatment Groups and p-value of main treatment effect is greater or equal than 0.05 or rule of 10 is not met

CI: Confidence Interval; ECOG: Eastern Cooperative Oncology Group; SOC: System Organ Class

Tabelle 4G-55: Subgruppenanalysen mit nicht statistisch signifikantem Interaktionstest ($p \geq 0,05$) für den Endpunkt Unerwünschte Ereignisse gesamt (SOC und PT) für PT aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE 966[a]	Pembrolizumab + Chemotherapy[b]			Placebo + Chemotherapy[b]			Pembrolizumab + Chemotherapy[b] vs. Placebo + Chemotherapy[b]		p-Value for Interaction Test[g]
Adverse Events	N[c]	Participants with Event n (%)	Median Time[d] in Weeks [95 %-CI]	N[c]	Participants with Event n (%)	Median Time[d] in Weeks [95 %-CI]	Hazard Ratio [95 %-CI][e]	p-Value[e,f]	
SOC: Endocrine disorders - PT[h]: Hypothyroidism									
Sex									
Female	250	28 (11.2)	Not reached [-; -]	264	8 (3.0)	Not reached [-; -]	3.65 [1.66; 8.00]	0.001	0.703
Male	279	18 (6.5)	Not reached [-; -]	270	6 (2.2)	Not reached [-; -]	2.83 [1.12; 7.13]	0.027	
Age									
< 65	266	20 (7.5)	Not reached [-; -]	296	6 (2.0)	Not reached [-; -]	3.61 [1.45; 9.00]	0.006	0.746
≥ 65	263	26 (9.9)	Not reached [-; -]	238	8 (3.4)	Not reached [-; -]	2.94 [1.33; 6.49]	0.008	
ECOG Performance Status									
0	257	21 (8.2)	Not reached [-; -]	226	3 (1.3)	Not reached [-; -]	6.55 [1.95; 21.96]	0.002	0.142
1	271	25 (9.2)	Not reached [-; -]	308	11 (3.6)	Not reached [-; -]	2.42 [1.19; 4.92]	0.015	
Geographic region									
Asia	240	18 (7.5)	Not reached [-; -]	243	7 (2.9)	Not reached [-; -]	2.68 [1.12; 6.41]	0.027	0.564
Non-Asia	289	28 (9.7)	Not reached [-; -]	291	7 (2.4)	Not reached [-; -]	3.80 [1.66; 8.70]	0.002	
Locally advanced versus metastatic									
Locally Advanced	59	7 (11.9)	Not reached [-; -]	66	1 (1.5)	Not reached [-; -]	7.25 [0.89; 58.98]	0.064	0.364
Metastatic	470	39 (8.3)	Not reached [-; -]	468	13 (2.8)	Not reached [-; -]	2.96 [1.58; 5.54]	< 0.001	
SOC: Gastrointestinal disorders - PT[h]: Abdominal pain									
Sex									
Female	250	55 (22.0)	Not reached [-; -]	264	72 (27.3)	94.7 [64.7; -]	0.75 [0.53; 1.07]	0.115	0.618
Male	279	37 (13.3)	Not reached [-; -]	270	50 (18.5)	Not reached [-; -]	0.67 [0.43; 1.02]	0.061	
Age									
< 65	266	52 (19.5)	Not reached [-; -]	296	68 (23.0)	Not reached [71.9; -]	0.80 [0.56; 1.15]	0.238	0.306
≥ 65	263	40 (15.2)	Not reached [-; -]	238	54 (22.7)	Not reached [94.7; -]	0.61 [0.40; 0.92]	0.018	
ECOG Performance Status									
0	257	42 (16.3)	Not reached [-; -]	226	48 (21.2)	Not reached [97.1; -]	0.72 [0.48; 1.09]	0.124	0.958
1	271	50 (18.5)	Not reached [-; -]	308	74 (24.0)	94.7 [58.3; -]	0.71 [0.50; 1.02]	0.064	
Geographic region									
Asia	240	29	Not reached	243	37	Not reached	0.78	0.311	0.563

		(12.1)	[-; -]		(15.2)	[-; -]	[0.48; 1.26]		
Non-Asia	289	63 (21.8)	Not reached [-; -]	291	85 (29.2)	94.7 [64.7; -]	0.65 [0.47; 0.91]	0.011	
Locally advanced versus metastatic									
Locally Advanced	59	5 (8.5)	Not reached [-; -]	66	16 (24.2)	Not reached [65.7; -]	0.29 [0.11; 0.79]	0.016	0.057
Metastatic	470	87 (18.5)	Not reached [-; -]	468	106 (22.6)	Not reached [94.7; -]	0.77 [0.58; 1.02]	0.067	
Site of Origin									
Extrahepatic	98	17 (17.3)	Not reached [62.6; -]	105	31 (29.5)	71.9 [55.1; -]	0.63 [0.35; 1.15]	0.132	0.472
Gallbladder	113	23 (20.4)	Not reached [-; -]	118	25 (21.2)	Not reached [51.9; -]	0.98 [0.56; 1.73]	0.949	
Intrahepatic	318	52 (16.4)	Not reached [-; -]	311	66 (21.2)	Not reached [97.1; -]	0.68 [0.48; 0.99]	0.041	
SOC: Gastrointestinal disorders - PT[h]: Abdominal pain upper									
Sex									
Female	250	27 (10.8)	Not reached [-; -]	264	32 (12.1)	Not reached [-; -]	0.84 [0.50; 1.41]	0.512	0.168
Male	279	13 (4.7)	Not reached [-; -]	270	25 (9.3)	Not reached [-; -]	0.48 [0.24; 0.93]	0.030	
Age									
< 65	266	23 (8.6)	Not reached [-; -]	296	34 (11.5)	Not reached [-; -]	0.71 [0.42; 1.20]	0.201	0.778
≥ 65	263	17 (6.5)	Not reached [-; -]	238	23 (9.7)	Not reached [-; -]	0.61 [0.33; 1.15]	0.127	
ECOG Performance Status									
0	257	18 (7.0)	Not reached [-; -]	226	25 (11.1)	Not reached [-; -]	0.63 [0.34; 1.15]	0.134	0.773
1	271	22 (8.1)	Not reached [-; -]	308	32 (10.4)	Not reached [-; -]	0.70 [0.40; 1.20]	0.192	
Geographic region									
Asia	240	10 (4.2)	Not reached [-; -]	243	15 (6.2)	Not reached [-; -]	0.65 [0.29; 1.44]	0.285	0.955
Non-Asia	289	30 (10.4)	Not reached [-; -]	291	42 (14.4)	Not reached [-; -]	0.66 [0.41; 1.05]	0.082	
Locally advanced versus metastatic									
Locally Advanced	59	4 (6.8)	Not reached [-; -]	66	7 (10.6)	Not reached [-; -]	0.58 [0.17; 1.99]	0.388	0.772
Metastatic	470	36 (7.7)	Not reached [-; -]	468	50 (10.7)	Not reached [-; -]	0.67 [0.44; 1.03]	0.070	
Site of Origin									
Extrahepatic	98	6 (6.1)	Not reached [-; -]	105	14 (13.3)	Not reached [-; -]	0.45 [0.17; 1.18]	0.106	0.101
Gallbladder	113	14 (12.4)	Not reached [-; -]	118	11 (9.3)	Not reached [-; -]	1.43 [0.65; 3.15]	0.377	
Intrahepatic	318	20 (6.3)	Not reached [-; -]	311	32 (10.3)	Not reached [-; -]	0.52 [0.30; 0.92]	0.024	
SOC: Gastrointestinal disorders - PT[h]: Dyspepsia									
Sex									
Female	250	13 (5.2)	Not reached [-; -]	264	30 (11.4)	Not reached [-; -]	0.41 [0.22; 0.79]	0.008	0.205
Male	279	20 (7.2)	Not reached [-; -]	270	25 (9.3)	Not reached [-; -]	0.74 [0.41; 1.33]	0.313	
Age									
< 65	266	17	Not reached	296	31	Not reached	0.58	0.068	0.903

		(6.4)	[-; -]		(10.5)	[-; -]	[0.32; 1.04]		
≥ 65	263	16 (6.1)	Not reached [-; -]	238	24 (10.1)	Not reached [-; -]	0.55 [0.29; 1.04]	0.064	
ECOG Performance Status									
0	257	15 (5.8)	Not reached [-; -]	226	20 (8.8)	Not reached [-; -]	0.64 [0.33; 1.25]	0.191	0.646
1	271	18 (6.6)	Not reached [-; -]	308	35 (11.4)	Not reached [-; -]	0.52 [0.29; 0.91]	0.023	
Geographic region									
Asia	240	19 (7.9)	Not reached [-; -]	243	29 (11.9)	Not reached [-; -]	0.63 [0.35; 1.11]	0.111	0.594
Non-Asia	289	14 (4.8)	Not reached [-; -]	291	26 (8.9)	Not reached [-; -]	0.50 [0.26; 0.96]	0.037	
Locally advanced versus metastatic									
Locally Advanced	59	3 (5.1)	Not reached [-; -]	66	3 (4.5)	Not reached [-; -]	1.03 [0.21; 5.11]	0.971	0.444
Metastatic	470	30 (6.4)	Not reached [-; -]	468	52 (11.1)	Not reached [-; -]	0.53 [0.34; 0.83]	0.006	
Site of Origin									
Extrahepatic	98	6 (6.1)	Not reached [94.3; -]	105	13 (12.4)	Not reached [-; -]	0.50 [0.19; 1.32]	0.160	0.732
Gallbladder	113	4 (3.5)	Not reached [-; -]	118	10 (8.5)	Not reached [-; -]	0.38 [0.12; 1.22]	0.104	
Intrahepatic	318	23 (7.2)	Not reached [-; -]	311	32 (10.3)	Not reached [-; -]	0.64 [0.37; 1.09]	0.098	
SOC: General disorders and administration site conditions - PT[h]: Pyrexia									
Sex									
Female	250	59 (23.6)	Not reached [-; -]	264	44 (16.7)	Not reached [-; -]	1.41 [0.95; 2.08]	0.087	0.864
Male	279	80 (28.7)	108.3 [84.4; -]	270	60 (22.2)	Not reached [98.3; -]	1.35 [0.96; 1.89]	0.081	
Age									
< 65	266	64 (24.1)	Not reached [-; -]	296	64 (21.6)	Not reached [78.6; -]	1.12 [0.80; 1.59]	0.507	0.087
≥ 65	263	75 (28.5)	108.3 [84.4; -]	238	40 (16.8)	Not reached [-; -]	1.75 [1.19; 2.57]	0.004	
ECOG Performance Status									
0	257	71 (27.6)	108.3 [84.4; -]	226	42 (18.6)	Not reached [-; -]	1.62 [1.10; 2.37]	0.014	0.274
1	271	68 (25.1)	Not reached [-; -]	308	62 (20.1)	Not reached [98.3; -]	1.24 [0.88; 1.74]	0.227	
Geographic region									
Asia	240	58 (24.2)	Not reached [84.4; -]	243	51 (21.0)	Not reached [78.6; -]	1.22 [0.84; 1.77]	0.307	0.405
Non-Asia	289	81 (28.0)	Not reached [108.3; -]	291	53 (18.2)	Not reached [-; -]	1.53 [1.08; 2.16]	0.016	
Locally advanced versus metastatic									
Locally Advanced	59	18 (30.5)	Not reached [57.1; -]	66	13 (19.7)	Not reached [68.1; -]	1.49 [0.73; 3.05]	0.271	0.820
Metastatic	470	121 (25.7)	Not reached [108.3; -]	468	91 (19.4)	Not reached [98.3; -]	1.36 [1.04; 1.79]	0.026	
Site of Origin									
Extrahepatic	98	35 (35.7)	Not reached [49.3; -]	105	36 (34.3)	68.1 [34.9; -]	1.17 [0.73; 1.87]	0.511	0.610
Gallbladder	113	24 (21.2)	108.3 [-; -]	118	19 (16.1)	Not reached [78.6; -]	1.40 [0.76; 2.59]	0.275	

Intrahepatic	318	80 (25.2)	Not reached [-; -]	311	49 (15.8)	Not reached [-; -]	1.55 [1.09; 2.22]	0.015	
SOC: Infections and infestations - PT[h]: Liver abscess									
Sex									
Female	250	2 (0.8)	n.c.	264	7 (2.7)	n.c.	n.c.	n.c.	n.c.
Male	279	2 (0.7)	n.c.	270	6 (2.2)	n.c.	n.c.	n.c.	
Age									
< 65	266	3 (1.1)	n.c.	296	6 (2.0)	n.c.	n.c.	n.c.	n.c.
≥ 65	263	1 (0.4)	n.c.	238	7 (2.9)	n.c.	n.c.	n.c.	
ECOG Performance Status									
0	257	1 (0.4)	Not reached [-; -]	226	4 (1.8)	Not reached [-; -]	0.21 [0.02; 1.91]	0.167	0.741
1	271	3 (1.1)	Not reached [-; -]	308	9 (2.9)	Not reached [-; -]	0.33 [0.09; 1.22]	0.096	
Geographic region									
Asia	240	1 (0.4)	n.c.	243	8 (3.3)	n.c.	n.c.	n.c.	n.c.
Non-Asia	289	3 (1.0)	n.c.	291	5 (1.7)	n.c.	n.c.	n.c.	
Locally advanced versus metastatic									
Locally Advanced	59	2 (3.4)	Not reached [-; -]	66	2 (3.0)	Not reached [-; -]	1.09 [0.15; 7.73]	0.932	0.145
Metastatic	470	2 (0.4)	Not reached [-; -]	468	11 (2.4)	Not reached [-; -]	0.16 [0.04; 0.72]	0.017	
Site of Origin									
Extrahepatic	98	1 (1.0)	n.c.	105	7 (6.7)	n.c.	n.c.	n.c.	n.c.
Gallbladder	113	2 (1.8)	n.c.	118	2 (1.7)	n.c.	n.c.	n.c.	
Intrahepatic	318	1 (0.3)	n.c.	311	4 (1.3)	n.c.	n.c.	n.c.	
SOC: Injury, poisoning and procedural complications - PT[h]: Contusion									
Sex									
Female	250	1 (0.4)	n.c.	264	7 (2.7)	n.c.	n.c.	n.c.	n.c.
Male	279	2 (0.7)	n.c.	270	4 (1.5)	n.c.	n.c.	n.c.	
Age									
< 65	266	0 (0.0)	Not reached [-; -]	296	3 (1.0)	Not reached [-; -]	n.a. [n.a.; n.a.]	0.094	0.235
≥ 65	263	3 (1.1)	Not reached [-; -]	238	8 (3.4)	Not reached [-; -]	0.32 [0.08; 1.20]	0.090	
ECOG Performance Status									
0	257	1 (0.4)	n.c.	226	5 (2.2)	n.c.	n.c.	n.c.	n.c.
1	271	2 (0.7)	n.c.	308	6 (1.9)	n.c.	n.c.	n.c.	
Geographic region									
Asia	240	1 (0.4)	n.c.	243	5 (2.1)	n.c.	n.c.	n.c.	n.c.
Non-Asia	289	2	n.c.	291	6	n.c.	n.c.	n.c.	

		(0.7)			(2.1)				
Locally advanced versus metastatic									
Locally Advanced	59	0 (0.0)	Not reached [-; -]	66	0 (0.0)	Not reached [-; -]	n.a. [n.a.; n.a.]	n.a.	0.998
Metastatic	470	3 (0.6)	Not reached [-; -]	468	11 (2.4)	Not reached [-; -]	0.26 [0.07; 0.92]	0.037	
Site of Origin									
Extrahepatic	98	0 (0.0)	n.c.	105	3 (2.9)	n.c.	n.c.	n.c.	n.c.
Gallbladder	113	0 (0.0)	n.c.	118	2 (1.7)	n.c.	n.c.	n.c.	
Intrahepatic	318	3 (0.9)	n.c.	311	6 (1.9)	n.c.	n.c.	n.c.	
SOC: Investigations - PT[h]: Alanine aminotransferase increased									
Sex									
Female	250	53 (21.2)	Not reached [-; -]	264	62 (23.5)	Not reached [86.7; -]	0.87 [0.60; 1.26]	0.460	0.172
Male	279	34 (12.2)	Not reached [-; -]	270	51 (18.9)	Not reached [-; -]	0.59 [0.38; 0.91]	0.017	
Age									
< 65	266	51 (19.2)	Not reached [-; -]	296	71 (24.0)	Not reached [-; -]	0.75 [0.52; 1.08]	0.118	0.937
≥ 65	263	36 (13.7)	Not reached [-; -]	238	42 (17.6)	Not reached [86.7; -]	0.73 [0.46; 1.13]	0.159	
ECOG Performance Status									
0	257	44 (17.1)	Not reached [-; -]	226	42 (18.6)	Not reached [-; -]	0.92 [0.60; 1.41]	0.708	0.174
1	271	43 (15.9)	Not reached [-; -]	308	71 (23.1)	Not reached [84.7; -]	0.62 [0.42; 0.91]	0.014	
Geographic region									
Asia	240	36 (15.0)	Not reached [-; -]	243	48 (19.8)	Not reached [-; -]	0.75 [0.48; 1.15]	0.184	0.904
Non-Asia	289	51 (17.6)	Not reached [-; -]	291	65 (22.3)	Not reached [-; -]	0.72 [0.50; 1.03]	0.075	
Locally advanced versus metastatic									
Locally Advanced	59	12 (20.3)	Not reached [-; -]	66	16 (24.2)	Not reached [64.4; -]	0.80 [0.38; 1.69]	0.554	0.870
Metastatic	470	75 (16.0)	Not reached [-; -]	468	97 (20.7)	Not reached [-; -]	0.72 [0.53; 0.98]	0.034	
Site of Origin									
Extrahepatic	98	13 (13.3)	Not reached [-; -]	105	21 (20.0)	Not reached [-; -]	0.64 [0.32; 1.29]	0.213	0.717
Gallbladder	113	24 (21.2)	83.1 [55.9; -]	118	29 (24.6)	84.7 [50.6; -]	0.90 [0.53; 1.55]	0.713	
Intrahepatic	318	50 (15.7)	Not reached [-; -]	311	63 (20.3)	Not reached [-; -]	0.71 [0.49; 1.03]	0.070	
SOC: Metabolism and nutrition disorders - PT[h]: Hypochloraemia									
Sex									
Female	250	1 (0.4)	n.c.	264	5 (1.9)	n.c.	n.c.	n.c.	n.c.
Male	279	1 (0.4)	n.c.	270	6 (2.2)	n.c.	n.c.	n.c.	
Age									
< 65	266	0 (0.0)	n.c.	296	9 (3.0)	n.c.	n.c.	n.c.	n.c.

≥ 65	263	2 (0.8)	n.c.	238	2 (0.8)	n.c.	n.c.	n.c.	
ECOG Performance Status									
0	257	0 (0.0)	n.c.	226	4 (1.8)	n.c.	n.c.	n.c.	n.c.
1	271	2 (0.7)	n.c.	308	7 (2.3)	n.c.	n.c.	n.c.	
Geographic region									
Asia	240	2 (0.8)	Not reached [-; -]	243	9 (3.7)	Not reached [-; -]	0.22 [0.05; 1.02]	0.054	0.388
Non-Asia	289	0 (0.0)	Not reached [-; -]	291	2 (0.7)	Not reached [-; -]	n.a. [n.a.; n.a.]	0.131	
Locally advanced versus metastatic									
Locally Advanced	59	0 (0.0)	Not reached [-; -]	66	2 (3.0)	Not reached [-; -]	n.a. [n.a.; n.a.]	0.180	0.413
Metastatic	470	2 (0.4)	Not reached [-; -]	468	9 (1.9)	Not reached [-; -]	0.21 [0.05; 0.98]	0.047	
Site of Origin									
Extrahepatic	98	0 (0.0)	n.c.	105	3 (2.9)	n.c.	n.c.	n.c.	n.c.
Gallbladder	113	0 (0.0)	n.c.	118	1 (0.8)	n.c.	n.c.	n.c.	
Intrahepatic	318	2 (0.6)	n.c.	311	7 (2.3)	n.c.	n.c.	n.c.	
SOC: Musculoskeletal and connective tissue disorders - PT[h]: Back pain									
Sex									
Female	250	32 (12.8)	Not reached [-; -]	264	35 (13.3)	Not reached [-; -]	0.90 [0.56; 1.45]	0.666	0.118
Male	279	22 (7.9)	Not reached [-; -]	270	38 (14.1)	Not reached [-; -]	0.52 [0.31; 0.87]	0.014	
Age									
< 65	266	27 (10.2)	Not reached [-; -]	296	37 (12.5)	Not reached [-; -]	0.76 [0.46; 1.24]	0.270	0.621
≥ 65	263	27 (10.3)	Not reached [-; -]	238	36 (15.1)	Not reached [-; -]	0.62 [0.38; 1.02]	0.061	
ECOG Performance Status									
0	257	26 (10.1)	Not reached [-; -]	226	30 (13.3)	Not reached [-; -]	0.75 [0.44; 1.26]	0.275	0.704
1	271	28 (10.3)	Not reached [-; -]	308	43 (14.0)	Not reached [-; -]	0.64 [0.40; 1.04]	0.072	
Geographic region									
Asia	240	13 (5.4)	Not reached [-; -]	243	18 (7.4)	Not reached [-; -]	0.69 [0.34; 1.40]	0.302	0.959
Non-Asia	289	41 (14.2)	Not reached [-; -]	291	55 (18.9)	Not reached [-; -]	0.68 [0.45; 1.02]	0.061	
Site of Origin									
Extrahepatic	98	13 (13.3)	Not reached [-; -]	105	15 (14.3)	Not reached [-; -]	0.96 [0.46; 2.02]	0.916	0.588
Gallbladder	113	9 (8.0)	Not reached [-; -]	118	13 (11.0)	Not reached [-; -]	0.66 [0.28; 1.55]	0.338	
Intrahepatic	318	32 (10.1)	Not reached [-; -]	311	45 (14.5)	Not reached [-; -]	0.62 [0.39; 0.97]	0.038	
SOC: Nervous system disorders - PT[h]: Dizziness									
Sex									
Female	250	16 (6.4)	131.1 [131.1; -]	264	20 (7.6)	Not reached [-; -]	0.74 [0.38; 1.45]	0.378	0.304

Male	279	16 (5.7)	Not reached [-; -]	270	30 (11.1)	Not reached [-; -]	0.49 [0.27; 0.91]	0.023	
Age									
< 65	266	12 (4.5)	Not reached [-; -]	296	23 (7.8)	Not reached [-; -]	0.55 [0.27; 1.10]	0.092	0.775
≥ 65	263	20 (7.6)	Not reached [131.1; -]	238	27 (11.3)	Not reached [-; -]	0.62 [0.35; 1.11]	0.107	
ECOG Performance Status									
0	257	18 (7.0)	Not reached [-; -]	226	23 (10.2)	Not reached [-; -]	0.68 [0.37; 1.26]	0.222	0.628
1	271	14 (5.2)	131.1 [-; -]	308	27 (8.8)	Not reached [-; -]	0.54 [0.28; 1.03]	0.062	
Locally advanced versus metastatic									
Locally Advanced	59	4 (6.8)	Not reached [-; -]	66	6 (9.1)	Not reached [-; -]	0.65 [0.18; 2.29]	0.498	0.860
Metastatic	470	28 (6.0)	Not reached [131.1; -]	468	44 (9.4)	Not reached [-; -]	0.59 [0.37; 0.95]	0.031	
Site of Origin									
Extrahepatic	98	6 (6.1)	Not reached [-; -]	105	12 (11.4)	Not reached [-; -]	0.58 [0.22; 1.56]	0.284	0.877
Gallbladder	113	6 (5.3)	Not reached [-; -]	118	8 (6.8)	Not reached [-; -]	0.79 [0.27; 2.29]	0.668	
Intrahepatic	318	20 (6.3)	131.1 [131.1; -]	311	30 (9.6)	Not reached [-; -]	0.56 [0.32; 1.00]	0.052	
SOC: Respiratory, thoracic and mediastinal disorders - PT[h]: Pneumonitis									
Sex									
Female	250	11 (4.4)	Not reached [-; -]	264	4 (1.5)	Not reached [-; -]	2.60 [0.83; 8.16]	0.103	0.936
Male	279	12 (4.3)	Not reached [-; -]	270	4 (1.5)	Not reached [-; -]	2.82 [0.91; 8.75]	0.072	
Age									
< 65	266	6 (2.3)	Not reached [-; -]	296	4 (1.4)	Not reached [-; -]	1.55 [0.44; 5.48]	0.500	0.302
≥ 65	263	17 (6.5)	Not reached [-; -]	238	4 (1.7)	Not reached [-; -]	3.64 [1.22; 10.82]	0.020	
ECOG Performance Status									
0	257	13 (5.1)	Not reached [-; -]	226	6 (2.7)	Not reached [-; -]	1.94 [0.74; 5.11]	0.179	0.282
1	271	10 (3.7)	Not reached [-; -]	308	2 (0.6)	Not reached [-; -]	5.13 [1.12; 23.44]	0.035	
Geographic region									
Asia	240	9 (3.8)	Not reached [-; -]	243	5 (2.1)	Not reached [-; -]	1.79 [0.60; 5.33]	0.299	0.297
Non-Asia	289	14 (4.8)	Not reached [-; -]	291	3 (1.0)	Not reached [-; -]	4.16 [1.20; 14.49]	0.025	
Locally advanced versus metastatic									
Locally Advanced	59	3 (5.1)	Not reached [-; -]	66	0 (0.0)	Not reached [-; -]	n.a. [n.a.; n.a.]	0.095	0.160
Metastatic	470	20 (4.3)	Not reached [-; -]	468	8 (1.7)	Not reached [-; -]	2.35 [1.03; 5.33]	0.041	
Site of Origin									
Extrahepatic	98	4 (4.1)	Not reached [-; -]	105	1 (1.0)	Not reached [-; -]	5.35 [0.59; 48.21]	0.135	0.770
Gallbladder	113	6 (5.3)	Not reached [-; -]	118	3 (2.5)	Not reached [-; -]	2.07 [0.52; 8.32]	0.305	
Intrahepatic	318	13	Not reached	311	4	Not reached	2.64	0.089	

		(4.1)	[-; -]		(1.3)	[-; -]	[0.86; 8.12]		
SOC: Skin and subcutaneous tissue disorders - PT[h]: Pruritus									
Sex									
Female	250	42 (16.8)	Not reached [-; -]	264	22 (8.3)	Not reached [-; -]	2.09 [1.25; 3.51]	0.005	0.102
Male	279	35 (12.5)	Not reached [-; -]	270	29 (10.7)	Not reached [-; -]	1.15 [0.71; 1.89]	0.570	
Age									
< 65	266	32 (12.0)	Not reached [-; -]	296	23 (7.8)	Not reached [-; -]	1.55 [0.91; 2.65]	0.110	0.840
≥ 65	263	45 (17.1)	Not reached [-; -]	238	28 (11.8)	Not reached [-; -]	1.45 [0.91; 2.33]	0.121	
ECOG Performance Status									
0	257	42 (16.3)	Not reached [-; -]	226	28 (12.4)	Not reached [-; -]	1.40 [0.87; 2.26]	0.166	0.643
1	271	35 (12.9)	Not reached [-; -]	308	23 (7.5)	Not reached [-; -]	1.67 [0.99; 2.83]	0.057	
Geographic region									
Asia	240	37 (15.4)	Not reached [-; -]	243	28 (11.5)	Not reached [-; -]	1.37 [0.84; 2.24]	0.209	0.540
Non-Asia	289	40 (13.8)	Not reached [-; -]	291	23 (7.9)	Not reached [-; -]	1.69 [1.01; 2.83]	0.045	
Locally advanced versus metastatic									
Locally Advanced	59	10 (16.9)	Not reached [-; -]	66	6 (9.1)	Not reached [-; -]	1.73 [0.63; 4.77]	0.290	0.756
Metastatic	470	67 (14.3)	Not reached [-; -]	468	45 (9.6)	Not reached [-; -]	1.49 [1.02; 2.18]	0.038	
Site of Origin									
Extrahepatic	98	15 (15.3)	Not reached [-; -]	105	11 (10.5)	Not reached [-; -]	1.52 [0.70; 3.32]	0.289	0.932
Gallbladder	113	13 (11.5)	Not reached [-; -]	118	10 (8.5)	Not reached [-; -]	1.35 [0.59; 3.08]	0.475	
Intrahepatic	318	49 (15.4)	Not reached [-; -]	311	30 (9.6)	Not reached [-; -]	1.55 [0.98; 2.44]	0.060	
SOC: Skin and subcutaneous tissue disorders - PT[h]: Rash									
Sex									
Female	250	39 (15.6)	Not reached [-; -]	264	29 (11.0)	Not reached [-; -]	1.45 [0.90; 2.34]	0.131	0.117
Male	279	51 (18.3)	Not reached [112.6; -]	270	20 (7.4)	Not reached [-; -]	2.52 [1.50; 4.23]	< 0.001	
Age									
< 65	266	46 (17.3)	Not reached [-; -]	296	35 (11.8)	Not reached [-; -]	1.46 [0.94; 2.27]	0.090	0.057
≥ 65	263	44 (16.7)	Not reached [112.6; -]	238	14 (5.9)	Not reached [-; -]	2.99 [1.64; 5.45]	< 0.001	
ECOG Performance Status									
0	257	54 (21.0)	Not reached [-; -]	226	24 (10.6)	Not reached [-; -]	2.15 [1.33; 3.47]	0.002	0.409
1	271	36 (13.3)	Not reached [112.6; -]	308	25 (8.1)	Not reached [-; -]	1.60 [0.96; 2.67]	0.071	
Geographic region									
Asia	240	58 (24.2)	Not reached [112.6; -]	243	27 (11.1)	Not reached [-; -]	2.30 [1.45; 3.63]	< 0.001	0.190
Non-Asia	289	32 (11.1)	Not reached [-; -]	291	22 (7.6)	Not reached [-; -]	1.45 [0.84; 2.49]	0.181	

Locally advanced versus metastatic									
Locally Advanced	59	10 (16.9)	Not reached [-; -]	66	11 (16.7)	Not reached [-; -]	1.01 [0.43; 2.38]	0.984	0.111
Metastatic	470	80 (17.0)	Not reached [112.6; -]	468	38 (8.1)	Not reached [-; -]	2.15 [1.46; 3.16]	< 0.001	
Site of Origin									
Extrahepatic	98	17 (17.3)	112.6 [112.6; -]	105	8 (7.6)	Not reached [-; -]	2.48 [1.06; 5.77]	0.035	0.484
Gallbladder	113	18 (15.9)	Not reached [-; -]	118	8 (6.8)	Not reached [-; -]	2.68 [1.16; 6.17]	0.021	
Intrahepatic	318	55 (17.3)	Not reached [-; -]	311	33 (10.6)	Not reached [-; -]	1.61 [1.05; 2.48]	0.030	

a: Database Cutoff Date: 15DEC2022

b: Chemotherapy: Gemcitabine + Cisplatin

c: Number of participants: all-participants-as-treated population

d: From product-limit (Kaplan-Meier) method for censored data

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

h: A specific adverse event appears on this report only if its incidence ≥10% or (incidence ≥1% and in at least 10 participants) in One or More Treatment Groups and p-value of main treatment effect is greater or equal than 0.05 or rule of 10 is not met

CI: Confidence Interval; ECOG: Eastern Cooperative Oncology Group; n.a.: not applicable (when estimation not possible); n.c.: not calculated (at least 10 participants per subgroup category and at least 10 participants with events in one of the subgroup categories necessary); PT:Preferred Term; SOC: System Organ Class

Schwerwiegende unerwünschte Ereignisse (SOC und PT)

Tabelle 4G-56: Subgruppenanalysen mit nicht statistisch signifikantem Interaktionstest ($p \geq 0,05$) für den Endpunkt Schwerwiegende unerwünschte Ereignisse (SOC und PT) für SOC aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE 966[a]	**Pembrolizumab + Chemotherapy[b]**			**Placebo + Chemotherapy[b]**			**Pembrolizumab + Chemotherapy[b] vs. Placebo + Chemotherapy[b]**		**p-Value for Interaction Test[g]**
Serious Adverse Events	**N[c]**	**Participants with Event n (%)**	**Median Time[d] in Weeks [95 %-CI]**	**N[c]**	**Participants with Event n (%)**	**Median Time[d] in Weeks [95 %-CI]**	**Hazard Ratio [95 %-CI][e]**	**p-Value[e,f]**	
SOC[h]: Cardiac disorders									
Sex									
Female	250	8 (3.2)	Not reached [-; -]	264	3 (1.1)	Not reached [-; -]	2.75 [0.73; 10.38]	0.135	0.932
Male	279	11 (3.9)	Not reached [-; -]	270	4 (1.5)	Not reached [-; -]	2.52 [0.80; 7.91]	0.114	
Age									
< 65	266	7 (2.6)	Not reached [-; -]	296	2 (0.7)	Not reached [-; -]	3.86 [0.80; 18.62]	0.092	0.502
≥ 65	263	12 (4.6)	Not reached [-; -]	238	5 (2.1)	Not reached [-; -]	2.02 [0.71; 5.76]	0.186	
ECOG Performance Status									
0	257	9 (3.5)	Not reached [-; -]	226	3 (1.3)	Not reached [-; -]	2.60 [0.70; 9.59]	0.152	0.997
1	271	10 (3.7)	Not reached [-; -]	308	4 (1.3)	Not reached [-; -]	2.61 [0.82; 8.33]	0.105	
Geographic region									
Asia	240	7 (2.9)	Not reached [-; -]	243	3 (1.2)	Not reached [-; -]	2.34 [0.60; 9.03]	0.219	0.822
Non-Asia	289	12 (4.2)	Not reached [-; -]	291	4 (1.4)	Not reached [-; -]	2.86 [0.92; 8.86]	0.069	
Locally advanced versus metastatic									
Locally Advanced	59	5 (8.5)	Not reached [-; -]	66	1 (1.5)	Not reached [-; -]	5.37 [0.63; 45.99]	0.125	0.419
Metastatic	470	14 (3.0)	Not reached [-; -]	468	6 (1.3)	Not reached [-; -]	2.20 [0.85; 5.74]	0.106	
Site of Origin									
Extrahepatic	98	1 (1.0)	Not reached [-; -]	105	0 (0.0)	Not reached [-; -]	n.a. [n.a.; n.a.]	0.309	0.613
Gallbladder	113	3 (2.7)	Not reached [-; -]	118	2 (1.7)	Not reached [-; -]	1.48 [0.25; 8.90]	0.669	
Intrahepatic	318	15 (4.7)	Not reached [-; -]	311	5 (1.6)	Not reached [-; -]	2.70 [0.98; 7.43]	0.055	
a: Database Cutoff Date: 15DEC2022									

b: Chemotherapy: Gemcitabine + Cisplatin
c: Number of participants: all-participants-as-treated population
d: From product-limit (Kaplan-Meier) method for censored data
e: Based on Cox regression model with treatment as a covariate 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 Cox model with treatment and subgroup as covariates, and treatment-by-subgroup interaction (p-value of likelihood ratio test for interaction term)
h: A system organ class appears on this report only if its incidence ≥5% or (incidence ≥1% and in at least 10 participants) in One or More Treatment Groups and p-value of main treatment effect is greater or equal than 0.05 or rule of 10 is not met
CI: Confidence Interval; ECOG: Eastern Cooperative Oncology Group; n.a.: not applicable (when estimation not possible); SOC: System Organ Class

Tabelle 4G-57: Subgruppenanalysen mit nicht statistisch signifikantem Interaktionstest ($p \geq 0,05$) für den Endpunkt Schwerwiegende unerwünschte Ereignisse (SOC und PT) für PT aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE 966[a]	**Pembrolizumab + Chemotherapy[b]**			**Placebo + Chemotherapy[b]**			**Pembrolizumab + Chemotherapy[b] vs. Placebo + Chemotherapy[b]**		
Serious Adverse Event	**N[c]**	**Participants with Event n (%)**	**Median Time[d] in Weeks [95 %-CI]**	**N[c]**	**Participants with Event n (%)**	**Median Time[d] in Weeks [95 %-CI]**	**Hazard Ratio [95 %-CI][e]**	**p-Value[e,f]**	**p-Value for Interaction Test[g]**
SOC: General disorders and administration site conditions - PT[h]: Pyrexia									
Sex									
Female	250	14 (5.6)	Not reached [-; -]	264	8 (3.0)	Not reached [-; -]	1.80 [0.76; 4.30]	0.183	0.284
Male	279	16 (5.7)	Not reached [-; -]	270	4 (1.5)	Not reached [-; -]	3.84 [1.28; 11.48]	0.016	
Age									
< 65	266	14 (5.3)	Not reached [-; -]	296	4 (1.4)	Not reached [-; -]	3.86 [1.27; 11.74]	0.017	0.261
≥ 65	263	16 (6.1)	Not reached [-; -]	238	8 (3.4)	Not reached [-; -]	1.75 [0.75; 4.10]	0.194	
ECOG Performance Status									
0	257	16 (6.2)	Not reached [-; -]	226	3 (1.3)	Not reached [-; -]	4.75 [1.38; 16.31]	0.013	0.152
1	271	14 (5.2)	Not reached [-; -]	308	9 (2.9)	Not reached [-; -]	1.68 [0.73; 3.89]	0.224	
Geographic region									
Asia	240	12 (5.0)	Not reached [-; -]	243	6 (2.5)	Not reached [-; -]	2.03 [0.76; 5.41]	0.157	0.597
Non-Asia	289	18 (6.2)	Not reached [-; -]	291	6 (2.1)	Not reached [-; -]	2.89 [1.15; 7.28]	0.025	
Locally advanced versus metastatic									
Locally Advanced	59	2 (3.4)	Not reached [-; -]	66	0 (0.0)	Not reached [-; -]	n.a. [n.a.; n.a.]	0.150	0.220
Metastatic	470	28 (6.0)	Not reached [-; -]	468	12 (2.6)	Not reached [-; -]	2.29 [1.16; 4.49]	0.017	
Site of Origin									
Extrahepatic	98	9 (9.2)	Not reached [-; -]	105	3 (2.9)	Not reached [-; -]	3.27 [0.89; 12.09]	0.075	0.835
Gallbladder	113	5 (4.4)	Not reached [-; -]	118	2 (1.7)	Not reached [-; -]	2.75 [0.53; 14.18]	0.227	
Intrahepatic	318	16 (5.0)	Not reached [-; -]	311	7 (2.3)	Not reached [-; -]	2.08 [0.85; 5.05]	0.108	
SOC: Investigations - PT[h]: Neutrophil count decreased									
Sex									
Female	250	7 (2.8)	n.c.	264	1 (0.4)	n.c.	n.c.	n.c.	n.c.
Male	279	4 (1.4)	n.c.	270	0 (0.0)	n.c.	n.c.	n.c.	
Age									
< 65	266	5 (1.9)	n.c.	296	1 (0.3)	n.c.	n.c.	n.c.	n.c.
≥ 65	263	6 (2.3)	n.c.	238	0 (0.0)	n.c.	n.c.	n.c.	

ECOG Performance Status									
0	257	7 (2.7)	n.c.	226	0 (0.0)	n.c.	n.c.	n.c.	n.c.
1	271	4 (1.5)	n.c.	308	1 (0.3)	n.c.	n.c.	n.c.	
Geographic region									
Asia	240	7 (2.9)	n.c.	243	1 (0.4)	n.c.	n.c.	n.c.	n.c.
Non-Asia	289	4 (1.4)	n.c.	291	0 (0.0)	n.c.	n.c.	n.c.	
Locally advanced versus metastatic									
Locally Advanced	59	2 (3.4)	Not reached [-; -]	66	0 (0.0)	Not reached [-; -]	n.a. [n.a.; n.a.]	0.147	0.515
Metastatic	470	9 (1.9)	Not reached [-; -]	468	1 (0.2)	Not reached [-; -]	8.81 [1.12; 69.50]	0.039	
Site of Origin									
Extrahepatic	98	3 (3.1)	n.c.	105	1 (1.0)	n.c.	n.c.	n.c.	n.c.
Gallbladder	113	3 (2.7)	n.c.	118	0 (0.0)	n.c.	n.c.	n.c.	
Intrahepatic	318	5 (1.6)	n.c.	311	0 (0.0)	n.c.	n.c.	n.c.	

a: Database Cutoff Date: 15DEC2022

b: Chemotherapy: Gemcitabine + Cisplatin

c: Number of participants: all-participants-as-treated population

d: From product-limit (Kaplan-Meier) method for censored data

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

h: A specific adverse event appears on this report only if its incidence ≥5% or (incidence ≥1% and in at least 10 participants) in One or More Treatment Groups and p-value of main treatment effect is greater or equal than 0.05 or rule of 10 is not met

CI: Confidence Interval; ECOG: Eastern Cooperative Oncology Group; n.a.: not applicable (when estimation not possible); n.c.: not calculated (at least 10 participants per subgroup category and at least 10 participants with events in one of the subgroup categories necessary); PT:Preferred Term; SOC: System Organ Class

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

Tabelle 4G-58: Subgruppenanalysen mit nicht statistisch signifikantem Interaktionstest (p ≥ 0,05) für den Endpunkt Schwere unerwünschte Ereignisse (CTCAE-Grad 3-5) (SOC und PT) für PT aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE 966[a]	Pembrolizumab + Chemotherapy[b]			Placebo + Chemotherapy[b]			Pembrolizumab + Chemotherapy[b] vs. Placebo + Chemotherapy[b]		
Severe Adverse Event (CTCAE-Grade 3-5)	N[c]	Participants with Event n (%)	Median Time[d] in Weeks [95 %-CI]	N[c]	Participants with Event n (%)	Median Time[d] in Weeks [95 %-CI]	Hazard Ratio [95 %-CI][e]	p-Value[e,f]	p-Value for Interaction Test[g]
SOC: Infections and infestations - PT[h]: Liver abscess									
Sex									
Female	250	2 (0.8)	n.c.	264	7 (2.7)	n.c.	n.c.	n.c.	n.c.
Male	279	2 (0.7)	n.c.	270	5 (1.9)	n.c.	n.c.	n.c.	
Age									
< 65	266	3 (1.1)	n.c.	296	6 (2.0)	n.c.	n.c.	n.c.	n.c.
≥ 65	263	1 (0.4)	n.c.	238	6 (2.5)	n.c.	n.c.	n.c.	
ECOG Performance Status									
0	257	1 (0.4)	Not reached [-; -]	226	3 (1.3)	Not reached [-; -]	0.28 [0.03; 2.73]	0.274	0.929
1	271	3 (1.1)	Not reached [-; -]	308	9 (2.9)	Not reached [-; -]	0.33 [0.09; 1.21]	0.094	
Geographic region									
Asia	240	1 (0.4)	n.c.	243	7 (2.9)	n.c.	n.c.	n.c.	n.c.
Non-Asia	289	3 (1.0)	n.c.	291	5 (1.7)	n.c.	n.c.	n.c.	
Locally advanced versus metastatic									
Locally Advanced	59	2 (3.4)	Not reached [-; -]	66	2 (3.0)	Not reached [-; -]	1.09 [0.15; 7.73]	0.932	0.168
Metastatic	470	2 (0.4)	Not reached [-; -]	468	10 (2.1)	Not reached [-; -]	0.17 [0.04; 0.79]	0.024	
Site of Origin									
Extrahepatic	98	1 (1.0)	n.c.	105	6 (5.7)	n.c.	n.c.	n.c.	n.c.
Gallbladder	113	2 (1.8)	n.c.	118	2 (1.7)	n.c.	n.c.	n.c.	
Intrahepatic	318	1 (0.3)	n.c.	311	4 (1.3)	n.c.	n.c.	n.c.	

a: Database Cutoff Date: 15DEC2022

b: Chemotherapy: Gemcitabine + Cisplatin

c: Number of participants: all-participants-as-treated population

d: From product-limit (Kaplan-Meier) method for censored data

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

h: A specific adverse event appears on this report only if its incidence ≥5% or (incidence ≥1% and in at least 10 participants) in One or More Treatment Groups and p-value of main treatment effect is greater or equal than 0.05 or rule of 10 is not met

CI: Confidence Interval; CTCAE: Common Terminology Criteria for Adverse Events; ECOG: Eastern Cooperative Oncology Group; n.c.: not

calculated (at least 10 participants per subgroup category and at least 10 participants with events in one of the subgroup categories necessary); PT:Preferred Term; SOC: System Organ Class

Anhang 4-G6: Definition der Immunvermittelten unerwünschten Ereignisse (AEOSI)

Im Folgenden wird ergänzend zu Abschnitt 4.3.1.3.1.4.3 die Definition der Immunvermittelten unerwünschten Ereignisse (AEOSI) anhand der zugeordneten PT dargestellt.

Tabelle 4G-59: Definition der Immunvermittelten unerwünschten Ereignisse (AEOSI) anhand der zugeordneten PT in der Studie KEYNOTE 966 (Version 23.1 vom 07.11.2022 basierend auf MedDRA Version 25.1)

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 lung disease	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	Yes

	nephritis, Nephrotic syndrome, Immune-mediated nephritis	
Adrenal Insufficiency	Adrenal insufficiency, Adrenocortical insufficiency acute, Secondary adrenocortical insufficiency, Primary adrenal insufficiency, Addison's disease, Immune-mediated adrenal insufficiency	Yes
Hypophysitis	Hypophysitis, Hypopituitarism, Lymphocytic hypophysitis, Immune-mediated hypophysitis	Yes
Hyperthyroidism	Hyperthyroidism, Basedow's disease, Thyrotoxic crisis, Immune-mediated hyperthyroidism	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 (SJS) and Toxic Epidermal Necrolysis (TEN): or	Dermatitis bullous, Dermatitis exfoliative, Dermatitis exfoliative generalised, Epidermal necrosis, Erythema multiforme, Exfoliative rash, Pemphigoid, Mucous membrane pemphigoid, Pemphigus, Skin necrosis, Stevens-Johnson syndrome, Toxic epidermal necrolysis, Toxic skin eruption, SJS-TEN overlap, Lichen planus pemphigoides	Yes
Severe Skin (continued): **If grade 3 or higher**:	Rash, Rash erythematous, Rash maculo-papular, Rash pruritic, Rash pustular, Pruritus, Pruritus genital, Lichen planus, Oral lichen planus, Cutaneous vasculitis, Vasculitic rash	Yes
Uveitis	Iritis, Uveitis, Cyclitis, Autoimmune uveitis, Iridocyclitis, Vogt-Koyanagi-Harada disease, Chorioretinitis, Choroiditis, Immune-mediated uveitis, Choroidal effusion, Choroidal detachment, Serous retinal detachment	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, Sarcoidosis of lymph node	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, Immune-mediated myasthenia gravis	Yes
Myelitis	Myelitis, Myelitis transverse, Acute necrotising myelitis	Yes

Vasculitis	Anti-neutrophil cytoplasmic antibody positive vasculitis, Aortitis, Arteritis, Arteritis coronary, Behcet's syndrome, Central nervous system vasculitis, Cerebral arteritis, Diffuse vasculitis, Eosinophilic granulomatosis with polyangiitis, Granulomatosis with polyangiitis, Haemorrhagic vasculitis, Hypersensitivity vasculitis, Microscopic polyangiitis, Ocular vasculitis, Polyarteritis nodosa, Pulmonary vasculitis, Renal arteritis, Renal vasculitis, Retinal vasculitis, Takayasu's arteritis, Giant cell arteritis, Vasculitis, Vasculitis gastrointestinal, Vasculitis necrotising	Yes
Cholangitis Sclerosing	Cholangitis sclerosing, Autoimmune cholangitis, Immune-mediated cholangitis	Yes
Hypoparathyroidism	Hypoparathyroidism, Primary hypoparathyroidism	Yes
Arthritis	Autoimmune arthritis, Immune-mediated arthritis	Yes
HLH	Haemophagocytic lymphohistiocytosis	Yes
Optic Neuritis	Optic neuritis	Yes