Dossier zur Nutzenbewertung gemäß § 35a SGB V

Pembrolizumab (KEYTRUDA®)

MSD Sharp & Dohme GmbH

Modul 4 A

Anhang 4-G: Weitere Ergebnisse

Erstlinienbehandlung des fortgeschrittenen Nierenzellkarzinoms bei erwachsenen Patienten in Kombination mit Lenvatinib

Stand: 10.12.2021

Inhaltsverzeichnis

Seite

Tabellenverzeichnis

Seite

Abbildungsverzeichnis

Seite

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

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

Alle Ergebnisse beziehen sich auf den Datenschnitt vom 28. August 2020 der Studie KEYNOTE 581/CLEAR.

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

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

Study: KEYNOTE 581[a]		Pembrolizumab + Lenvatinib N[b]=351		Sunitinib N[b]=340	
Treatment Visit	Questionnaire Completion Status (EORTC QLQ-C30)[c]	n	(%)	n	(%)
Week 0	**Expected to Complete Questionnaires**	**351**	**(100.0)**	**340**	**(100.0)**
	Completed	335	(95.4)	326	(95.9)
	Compliance (% in those expected to complete questionnaires)[d]	335	(95.4)	326	(95.9)
	Not completed	16	(4.6)	14	(4.1)
	Other	16	(4.6)	14	(4.1)
	Missing by Design	**0**	**(0.0)**	**0**	**(0.0)**
Week 3	**Expected to Complete Questionnaires**	**345**	**(98.3)**	**333**	**(97.9)**
	Completed	321	(91.5)	290	(85.3)
	Compliance (% in those expected to complete questionnaires)[d]	321	(93.0)	290	(87.1)
	Not completed	24	(6.8)	43	(12.6)
	Other	24	(6.8)	43	(12.6)
	Missing by Design	**6**	**(1.7)**	**7**	**(2.1)**
	Discontinued due to adverse event	5	(1.4)	2	(0.6)
	Discontinued due to clinical disease progression	1	(0.3)	1	(0.3)
	Discontinued due to radiological disease progression	0	(0.0)	1	(0.3)
	Discontinued due to subject choice	0	(0.0)	1	(0.3)
	Discontinued due to withdrawal of consent	0	(0.0)	2	(0.6)
Week 6	**Expected to Complete Questionnaires**	**341**	**(97.2)**	**323**	**(95.0)**
	Completed	298	(84.9)	292	(85.9)
	Compliance (% in those expected to complete questionnaires)[d]	298	(87.4)	292	(90.4)
	Not completed	43	(12.3)	31	(9.1)
	Other	43	(12.3)	31	(9.1)
	Missing by Design	**10**	**(2.8)**	**17**	**(5.0)**
	Discontinued due to adverse event	8	(2.3)	3	(0.9)

Study: KEYNOTE 581[a]		Pembrolizumab + Lenvatinib N[b]=351		Sunitinib N[b]=340	
Treatment Visit	Questionnaire Completion Status (EORTC QLQ-C30)[c]	n	(%)	n	(%)
	Discontinued due to clinical disease progression	1	(0.3)	4	(1.2)
	Discontinued due to radiological disease progression	1	(0.3)	2	(0.6)
	Discontinued due to subject choice	0	(0.0)	5	(1.5)
	Discontinued due to withdrawal of consent	0	(0.0)	3	(0.9)
Week 9	**Expected to Complete Questionnaires**	**338**	**(96.3)**	**310**	**(91.2)**
Week 9	Completed	301	(85.8)	271	(79.7)
	Compliance (% in those expected to complete questionnaires)[d]	301	(89.1)	271	(87.4)
	Not completed	37	(10.5)	39	(11.5)
	Other	37	(10.5)	39	(11.5)
	Missing by Design	**13**	**(3.7)**	**30**	**(8.8)**
	Discontinued due to adverse event	10	(2.8)	7	(2.1)
	Discontinued due to clinical disease progression	1	(0.3)	5	(1.5)
	Discontinued due to radiological disease progression	2	(0.6)	9	(2.6)
	Discontinued due to subject choice	0	(0.0)	5	(1.5)
	Discontinued due to withdrawal of consent	0	(0.0)	4	(1.2)
Week 12	**Expected to Complete Questionnaires**	**332**	**(94.6)**	**285**	**(83.8)**
	Completed	299	(85.2)	260	(76.5)
	Compliance (% in those expected to complete questionnaires)[d]	299	(90.1)	260	(91.2)
	Not completed	33	(9.4)	25	(7.4)
	Other	33	(9.4)	25	(7.4)
	Missing by Design	**19**	**(5.4)**	**55**	**(16.2)**
	Discontinued due to adverse event	12	(3.4)	9	(2.6)
	Discontinued due to clinical disease progression	3	(0.9)	6	(1.8)
	Discontinued due to radiological disease progression	4	(1.1)	26	(7.6)
	Discontinued due to subject choice	0	(0.0)	10	(2.9)
	Discontinued due to withdrawal of consent	0	(0.0)	4	(1.2)
Week 15	**Expected to Complete Questionnaires**	**328**	**(93.4)**	**277**	**(81.5)**
	Completed	296	(84.3)	247	(72.6)
	Compliance (% in those expected to complete questionnaires)[d]	296	(90.2)	247	(89.2)
	Not completed	32	(9.1)	30	(8.8)
	Other	32	(9.1)	30	(8.8)
	Missing by Design	**23**	**(6.6)**	**63**	**(18.5)**
	Discontinued due to adverse event	13	(3.7)	11	(3.2)
	Discontinued due to clinical disease progression	3	(0.9)	6	(1.8)

Study: KEYNOTE 581[a]		Pembrolizumab + Lenvatinib N[b]=351		Sunitinib N[b]=340	
Treatment Visit	Questionnaire Completion Status (EORTC QLQ-C30)[c]	n	(%)	n	(%)
Week 15	Discontinued due to radiological disease progression	6	(1.7)	31	(9.1)
	Discontinued due to subject choice	1	(0.3)	11	(3.2)
	Discontinued due to withdrawal of consent	0	(0.0)	4	(1.2)
Week 18	**Expected to Complete Questionnaires**	**323**	**(92.0)**	**267**	**(78.5)**
	Completed	297	(84.6)	245	(72.1)
	Compliance (% in those expected to complete questionnaires)[d]	297	(92.0)	245	(91.8)
	Not completed	26	(7.4)	22	(6.5)
	Other	26	(7.4)	22	(6.5)
	Missing by Design	**28**	**(8.0)**	**73**	**(21.5)**
	Discontinued due to adverse event	17	(4.8)	13	(3.8)
	Discontinued due to clinical disease progression	3	(0.9)	9	(2.6)
	Discontinued due to radiological disease progression	7	(2.0)	34	(10.0)
	Discontinued due to subject choice	1	(0.3)	12	(3.5)
	Discontinued due to withdrawal of consent	0	(0.0)	5	(1.5)
Week 21	**Expected to Complete Questionnaires**	**319**	**(90.9)**	**252**	**(74.1)**
	Completed	291	(82.9)	218	(64.1)
	Compliance (% in those expected to complete questionnaires)[d]	291	(91.2)	218	(86.5)
	Not completed	28	(8.0)	34	(10.0)
	Other	28	(8.0)	34	(10.0)
	Missing by Design	**32**	**(9.1)**	**88**	**(25.9)**
	Discontinued due to adverse event	19	(5.4)	16	(4.7)
	Discontinued due to clinical disease progression	3	(0.9)	9	(2.6)
	Discontinued due to other	0	(0.0)	1	(0.3)
	Discontinued due to radiological disease progression	8	(2.3)	44	(12.9)
	Discontinued due to subject choice	2	(0.6)	13	(3.8)
	Discontinued due to withdrawal of consent	0	(0.0)	5	(1.5)
Week 24	**Expected to Complete Questionnaires**	**315**	**(89.7)**	**240**	**(70.6)**
	Completed	287	(81.8)	217	(63.8)
	Compliance (% in those expected to complete questionnaires)[d]	287	(91.1)	217	(90.4)
Week 24	Not completed	28	(8.0)	23	(6.8)
	Other	28	(8.0)	23	(6.8)
	Missing by Design	**36**	**(10.3)**	**100**	**(29.4)**
	Discontinued due to adverse event	20	(5.7)	19	(5.6)
	Discontinued due to clinical disease progression	4	(1.1)	12	(3.5)

Study: KEYNOTE 581[a]		Pembrolizumab + Lenvatinib N[b]=351		Sunitinib N[b]=340	
Treatment Visit	Questionnaire Completion Status (EORTC QLQ-C30)[c]	n	(%)	n	(%)
	Discontinued due to other	1	(0.3)	1	(0.3)
	Discontinued due to radiological disease progression	9	(2.6)	50	(14.7)
	Discontinued due to subject choice	2	(0.6)	13	(3.8)
	Discontinued due to withdrawal of consent	0	(0.0)	5	(1.5)
Week 27	**Expected to Complete Questionnaires**	**304**	**(86.6)**	**214**	**(62.9)**
	Completed	275	(78.3)	194	(57.1)
	Compliance (% in those expected to complete questionnaires)[d]	275	(90.5)	194	(90.7)
	Not completed	29	(8.3)	20	(5.9)
	Other	29	(8.3)	20	(5.9)
	Missing by Design	**47**	**(13.4)**	**126**	**(37.1)**
	Discontinued due to adverse event	23	(6.6)	22	(6.5)
	Discontinued due to clinical disease progression	4	(1.1)	14	(4.1)
	Discontinued due to other	1	(0.3)	1	(0.3)
	Discontinued due to radiological disease progression	14	(4.0)	70	(20.6)
	Discontinued due to subject choice	5	(1.4)	14	(4.1)
	Discontinued due to withdrawal of consent	0	(0.0)	5	(1.5)
Week 30	**Expected to Complete Questionnaires**	**298**	**(84.9)**	**202**	**(59.4)**
	Completed	276	(78.6)	182	(53.5)
	Compliance (% in those expected to complete questionnaires)[d]	276	(92.6)	182	(90.1)
	Not completed	22	(6.3)	20	(5.9)
	Other	22	(6.3)	20	(5.9)
	Missing by Design	**53**	**(15.1)**	**138**	**(40.6)**
	Discontinued due to adverse event	24	(6.8)	23	(6.8)
	Discontinued due to clinical disease progression	5	(1.4)	15	(4.4)
Week 30	Discontinued due to other	1	(0.3)	1	(0.3)
	Discontinued due to radiological disease progression	18	(5.1)	77	(22.6)
	Discontinued due to subject choice	5	(1.4)	16	(4.7)
	Discontinued due to withdrawal of consent	0	(0.0)	6	(1.8)
Week 33	**Expected to Complete Questionnaires**	**291**	**(82.9)**	**191**	**(56.2)**
	Completed	262	(74.6)	170	(50.0)
	Compliance (% in those expected to complete questionnaires)[d]	262	(90.0)	170	(89.0)
	Not completed	29	(8.3)	21	(6.2)
	Other	29	(8.3)	21	(6.2)
	Missing by Design	**60**	**(17.1)**	**149**	**(43.8)**

Study: KEYNOTE 581[a]		Pembrolizumab + Lenvatinib N[b]=351		Sunitinib N[b]=340	
Treatment Visit	Questionnaire Completion Status (EORTC QLQ-C30)[c]	n	(%)	n	(%)
	Discontinued due to adverse event	27	(7.7)	25	(7.4)
	Discontinued due to clinical disease progression	5	(1.4)	15	(4.4)
	Discontinued due to other	1	(0.3)	1	(0.3)
	Discontinued due to radiological disease progression	21	(6.0)	85	(25.0)
	Discontinued due to subject choice	6	(1.7)	17	(5.0)
	Discontinued due to withdrawal of consent	0	(0.0)	6	(1.8)
Week 36	**Expected to Complete Questionnaires**	**284**	**(80.9)**	**182**	**(53.5)**
	Completed	257	(73.2)	159	(46.8)
	Compliance (% in those expected to complete questionnaires)[d]	257	(90.5)	159	(87.4)
	Not completed	27	(7.7)	23	(6.8)
	Other	27	(7.7)	23	(6.8)
	Missing by Design	**67**	**(19.1)**	**158**	**(46.5)**
	Discontinued due to adverse event	29	(8.3)	26	(7.6)
	Discontinued due to clinical disease progression	5	(1.4)	15	(4.4)
	Discontinued due to other	1	(0.3)	1	(0.3)
	Discontinued due to radiological disease progression	26	(7.4)	91	(26.8)
	Discontinued due to subject choice	6	(1.7)	18	(5.3)
	Discontinued due to withdrawal of consent	0	(0.0)	7	(2.1)
Week 39	**Expected to Complete Questionnaires**	**280**	**(79.8)**	**177**	**(52.1)**
Week 39	Completed	253	(72.1)	153	(45.0)
	Compliance (% in those expected to complete questionnaires)[d]	253	(90.4)	153	(86.4)
	Not completed	27	(7.7)	24	(7.1)
	Other	27	(7.7)	24	(7.1)
	Missing by Design	**71**	**(20.2)**	**163**	**(47.9)**
	Discontinued due to adverse event	30	(8.5)	27	(7.9)
	Discontinued due to clinical disease progression	6	(1.7)	15	(4.4)
	Discontinued due to lost to follow-up	0	(0.0)	1	(0.3)
	Discontinued due to other	1	(0.3)	1	(0.3)
	Discontinued due to radiological disease progression	28	(8.0)	94	(27.6)
	Discontinued due to subject choice	6	(1.7)	18	(5.3)
	Discontinued due to withdrawal of consent	0	(0.0)	7	(2.1)
Week 42	**Expected to Complete Questionnaires**	**274**	**(78.1)**	**171**	**(50.3)**
	Completed	246	(70.1)	148	(43.5)
	Compliance (% in those expected to complete questionnaires)[d]	246	(89.8)	148	(86.5)

Study: KEYNOTE 581[a]		Pembrolizumab + Lenvatinib N[b]=351		Sunitinib N[b]=340	
Treatment Visit	Questionnaire Completion Status (EORTC QLQ-C30)[c]	n	(%)	n	(%)
	Not completed	28	(8.0)	23	(6.8)
	Other	28	(8.0)	23	(6.8)
	Missing by Design	**77**	**(21.9)**	**169**	**(49.7)**
	Discontinued due to adverse event	30	(8.5)	27	(7.9)
	Discontinued due to clinical disease progression	10	(2.8)	15	(4.4)
	Discontinued due to lost to follow-up	0	(0.0)	1	(0.3)
	Discontinued due to other	1	(0.3)	2	(0.6)
	Discontinued due to radiological disease progression	30	(8.5)	98	(28.8)
	Discontinued due to subject choice	6	(1.7)	18	(5.3)
	Discontinued due to withdrawal of consent	0	(0.0)	8	(2.4)
Week 45	**Expected to Complete Questionnaires**	**266**	**(75.8)**	**160**	**(47.1)**
	Completed	233	(66.4)	140	(41.2)
	Compliance (% in those expected to complete questionnaires)[d]	233	(87.6)	140	(87.5)
	Not completed	33	(9.4)	20	(5.9)
Week 45	Other	33	(9.4)	20	(5.9)
	Missing by Design	**85**	**(24.2)**	**180**	**(52.9)**
	Discontinued due to adverse event	32	(9.1)	27	(7.9)
	Discontinued due to clinical disease progression	10	(2.8)	15	(4.4)
	Discontinued due to lost to follow-up	0	(0.0)	1	(0.3)
	Discontinued due to other	1	(0.3)	2	(0.6)
	Discontinued due to radiological disease progression	36	(10.3)	109	(32.1)
	Discontinued due to subject choice	6	(1.7)	18	(5.3)
	Discontinued due to withdrawal of consent	0	(0.0)	8	(2.4)
Week 48	**Expected to Complete Questionnaires**	**259**	**(73.8)**	**153**	**(45.0)**
	Completed	232	(66.1)	136	(40.0)
	Compliance (% in those expected to complete questionnaires)[d]	232	(89.6)	136	(88.9)
	Not completed	27	(7.7)	17	(5.0)
	Other	27	(7.7)	17	(5.0)
	Missing by Design	**92**	**(26.2)**	**187**	**(55.0)**
	Discontinued due to adverse event	32	(9.1)	28	(8.2)
	Discontinued due to clinical disease progression	10	(2.8)	16	(4.7)
	Discontinued due to lost to follow-up	0	(0.0)	1	(0.3)
	Discontinued due to other	1	(0.3)	2	(0.6)
	Discontinued due to radiological disease progression	41	(11.7)	114	(33.5)
	Discontinued due to subject choice	7	(2.0)	18	(5.3)

Study: KEYNOTE 581[a]		Pembrolizumab + Lenvatinib N[b]=351		Sunitinib N[b]=340	
Treatment Visit	Questionnaire Completion Status (EORTC QLQ-C30)[c]	n	(%)	n	(%)
	Discontinued due to withdrawal of consent	1	(0.3)	8	(2.4)
Week 51	**Expected to Complete Questionnaires**	**254**	**(72.4)**	**149**	**(43.8)**
	Completed	229	(65.2)	123	(36.2)
	Compliance (% in those expected to complete questionnaires)[d]	229	(90.2)	123	(82.6)
	Not completed	25	(7.1)	26	(7.6)
	Other	25	(7.1)	26	(7.6)
	Missing by Design	**97**	**(27.6)**	**191**	**(56.2)**
	Discontinued due to adverse event	35	(10.0)	29	(8.5)
Week 51	Discontinued due to clinical disease progression	10	(2.8)	16	(4.7)
	Discontinued due to lost to follow-up	0	(0.0)	1	(0.3)
	Discontinued due to other	1	(0.3)	2	(0.6)
	Discontinued due to radiological disease progression	43	(12.3)	117	(34.4)
	Discontinued due to subject choice	7	(2.0)	18	(5.3)
	Discontinued due to withdrawal of consent	1	(0.3)	8	(2.4)
Week 54	**Expected to Complete Questionnaires**	**251**	**(71.5)**	**139**	**(40.9)**
	Completed	216	(61.5)	116	(34.1)
	Compliance (% in those expected to complete questionnaires)[d]	216	(86.1)	116	(83.5)
	Not completed	35	(10.0)	23	(6.8)
	Other	35	(10.0)	23	(6.8)
	Missing by Design	**100**	**(28.5)**	**201**	**(59.1)**
	Discontinued due to adverse event	35	(10.0)	31	(9.1)
	Discontinued due to clinical disease progression	10	(2.8)	16	(4.7)
	Discontinued due to lost to follow-up	0	(0.0)	1	(0.3)
	Discontinued due to other	2	(0.6)	2	(0.6)
	Discontinued due to radiological disease progression	45	(12.8)	125	(36.8)
	Discontinued due to subject choice	7	(2.0)	18	(5.3)
	Discontinued due to withdrawal of consent	1	(0.3)	8	(2.4)
Week 57	**Expected to Complete Questionnaires**	**244**	**(69.5)**	**137**	**(40.3)**
	Completed	212	(60.4)	115	(33.8)
	Compliance (% in those expected to complete questionnaires)[d]	212	(86.9)	115	(83.9)
	Not completed	32	(9.1)	22	(6.5)
	Other	32	(9.1)	22	(6.5)
	Missing by Design	**107**	**(30.5)**	**203**	**(59.7)**
	Discontinued due to adverse event	37	(10.5)	31	(9.1)

Study: KEYNOTE 581[a]		Pembrolizumab + Lenvatinib N[b]=351		Sunitinib N[b]=340	
Treatment Visit	Questionnaire Completion Status (EORTC QLQ-C30)[c]	n	(%)	n	(%)
	Discontinued due to clinical disease progression	12	(3.4)	16	(4.7)
	Discontinued due to lost to follow-up	0	(0.0)	1	(0.3)
	Discontinued due to other	2	(0.6)	2	(0.6)
Week 57	Discontinued due to radiological disease progression	47	(13.4)	127	(37.4)
	Discontinued due to subject choice	8	(2.3)	18	(5.3)
	Discontinued due to withdrawal of consent	1	(0.3)	8	(2.4)
Week 60	**Expected to Complete Questionnaires**	**241**	**(68.7)**	**130**	**(38.2)**
	Completed	213	(60.7)	110	(32.4)
	Compliance (% in those expected to complete questionnaires)[d]	213	(88.4)	110	(84.6)
	Not completed	28	(8.0)	20	(5.9)
	Other	28	(8.0)	20	(5.9)
	Missing by Design	**110**	**(31.3)**	**210**	**(61.8)**
	Discontinued due to adverse event	37	(10.5)	31	(9.1)
	Discontinued due to clinical disease progression	14	(4.0)	17	(5.0)
	Discontinued due to lost to follow-up	0	(0.0)	1	(0.3)
	Discontinued due to other	3	(0.9)	2	(0.6)
	Discontinued due to radiological disease progression	47	(13.4)	132	(38.8)
	Discontinued due to subject choice	8	(2.3)	18	(5.3)
	Discontinued due to withdrawal of consent	1	(0.3)	8	(2.4)
	No visit scheduled	0	(0.0)	1	(0.3)
Week 63	**Expected to Complete Questionnaires**	**230**	**(65.5)**	**124**	**(36.5)**
	Completed	201	(57.3)	101	(29.7)
	Compliance (% in those expected to complete questionnaires)[d]	201	(87.4)	101	(81.5)
	Not completed	29	(8.3)	23	(6.8)
	Other	29	(8.3)	23	(6.8)
	Missing by Design	**121**	**(34.5)**	**216**	**(63.5)**
	Discontinued due to adverse event	37	(10.5)	32	(9.4)
	Discontinued due to clinical disease progression	14	(4.0)	17	(5.0)
	Discontinued due to lost to follow-up	0	(0.0)	1	(0.3)
	Discontinued due to other	3	(0.9)	2	(0.6)
	Discontinued due to radiological disease progression	49	(14.0)	132	(38.8)
	Discontinued due to subject choice	9	(2.6)	19	(5.6)
Week 63	Discontinued due to withdrawal of consent	1	(0.3)	8	(2.4)
	No visit scheduled	8	(2.3)	5	(1.5)
Week 66	**Expected to Complete Questionnaires**	**217**	**(61.8)**	**119**	**(35.0)**

Study: KEYNOTE 581[a]		Pembrolizumab + Lenvatinib N[b]=351		Sunitinib N[b]=340	
Treatment Visit	Questionnaire Completion Status (EORTC QLQ-C30)[c]	n	(%)	n	(%)
	Completed	189	(53.8)	100	(29.4)
	Compliance (% in those expected to complete questionnaires)[d]	189	(87.1)	100	(84.0)
	Not completed	28	(8.0)	19	(5.6)
	Other	28	(8.0)	19	(5.6)
	Missing by Design	**134**	**(38.2)**	**221**	**(65.0)**
	Discontinued due to adverse event	40	(11.4)	32	(9.4)
	Discontinued due to clinical disease progression	14	(4.0)	17	(5.0)
	Discontinued due to lost to follow-up	0	(0.0)	1	(0.3)
	Discontinued due to other	3	(0.9)	2	(0.6)
	Discontinued due to radiological disease progression	52	(14.8)	135	(39.7)
	Discontinued due to subject choice	10	(2.8)	19	(5.6)
	Discontinued due to withdrawal of consent	1	(0.3)	8	(2.4)
	No visit scheduled	14	(4.0)	7	(2.1)
Week 69	**Expected to Complete Questionnaires**	**208**	**(59.3)**	**114**	**(33.5)**
	Completed	183	(52.1)	93	(27.4)
	Compliance (% in those expected to complete questionnaires)[d]	183	(88.0)	93	(81.6)
	Not completed	25	(7.1)	21	(6.2)
	Other	25	(7.1)	21	(6.2)
	Missing by Design	**143**	**(40.7)**	**226**	**(66.5)**
	Discontinued due to adverse event	40	(11.4)	33	(9.7)
	Discontinued due to clinical disease progression	15	(4.3)	18	(5.3)
	Discontinued due to lost to follow-up	0	(0.0)	1	(0.3)
	Discontinued due to other	3	(0.9)	2	(0.6)
	Discontinued due to radiological disease progression	55	(15.7)	136	(40.0)
	Discontinued due to subject choice	10	(2.8)	19	(5.6)
	Discontinued due to withdrawal of consent	1	(0.3)	8	(2.4)
Week 69	No visit scheduled	19	(5.4)	9	(2.6)
Week 72	**Expected to Complete Questionnaires**	**202**	**(57.5)**	**108**	**(31.8)**
	Completed	176	(50.1)	90	(26.5)
	Compliance (% in those expected to complete questionnaires)[d]	176	(87.1)	90	(83.3)
	Not completed	26	(7.4)	18	(5.3)
	Other	26	(7.4)	18	(5.3)
	Missing by Design	**149**	**(42.5)**	**232**	**(68.2)**
	Discontinued due to adverse event	41	(11.7)	34	(10.0)

Study: KEYNOTE 581[a]		Pembrolizumab + Lenvatinib N[b]=351		Sunitinib N[b]=340	
Treatment Visit	Questionnaire Completion Status (EORTC QLQ-C30)[c]	n	(%)	n	(%)
	Discontinued due to clinical disease progression	15	(4.3)	18	(5.3)
	Discontinued due to lost to follow-up	0	(0.0)	1	(0.3)
	Discontinued due to other	3	(0.9)	2	(0.6)
	Discontinued due to radiological disease progression	57	(16.2)	139	(40.9)
	Discontinued due to subject choice	10	(2.8)	19	(5.6)
	Discontinued due to withdrawal of consent	1	(0.3)	8	(2.4)
	No visit scheduled	22	(6.3)	11	(3.2)
Week 75	**Expected to Complete Questionnaires**	**189**	**(53.8)**	**104**	**(30.6)**
	Completed	164	(46.7)	81	(23.8)
	Compliance (% in those expected to complete questionnaires)[d]	164	(86.8)	81	(77.9)
	Not completed	25	(7.1)	23	(6.8)
	Other	25	(7.1)	23	(6.8)
	Missing by Design	**162**	**(46.2)**	**236**	**(69.4)**
	Discontinued due to adverse event	41	(11.7)	34	(10.0)
	Discontinued due to clinical disease progression	15	(4.3)	18	(5.3)
	Discontinued due to lost to follow-up	0	(0.0)	1	(0.3)
	Discontinued due to other	3	(0.9)	2	(0.6)
	Discontinued due to radiological disease progression	61	(17.4)	141	(41.5)
	Discontinued due to subject choice	10	(2.8)	19	(5.6)
	Discontinued due to withdrawal of consent	1	(0.3)	8	(2.4)
	No visit scheduled	31	(8.8)	13	(3.8)
Week 78	**Expected to Complete Questionnaires**	**181**	**(51.6)**	**100**	**(29.4)**
	Completed	158	(45.0)	84	(24.7)
	Compliance (% in those expected to complete questionnaires)[d]	158	(87.3)	84	(84.0)
	Not completed	23	(6.6)	16	(4.7)
	Other	23	(6.6)	16	(4.7)
	Missing by Design	**170**	**(48.4)**	**240**	**(70.6)**
	Discontinued due to adverse event	43	(12.3)	34	(10.0)
	Discontinued due to clinical disease progression	16	(4.6)	18	(5.3)
	Discontinued due to lost to follow-up	0	(0.0)	1	(0.3)
	Discontinued due to other	3	(0.9)	2	(0.6)
	Discontinued due to radiological disease progression	65	(18.5)	145	(42.6)
	Discontinued due to subject choice	10	(2.8)	19	(5.6)
	Discontinued due to withdrawal of consent	1	(0.3)	8	(2.4)
	No visit scheduled	32	(9.1)	13	(3.8)

Study: KEYNOTE 581[a]		Pembrolizumab + Lenvatinib N[b]=351		Sunitinib N[b]=340	
Treatment Visit	Questionnaire Completion Status (EORTC QLQ-C30)[c]	n	(%)	n	(%)
Week 81	**Expected to Complete Questionnaires**	**176**	**(50.1)**	**97**	**(28.5)**
	Completed	157	(44.7)	78	(22.9)
	Compliance (% in those expected to complete questionnaires)[d]	157	(89.2)	78	(80.4)
	Not completed	19	(5.4)	19	(5.6)
	Other	19	(5.4)	19	(5.6)
	Missing by Design	**175**	**(49.9)**	**243**	**(71.5)**
	Discontinued due to adverse event	44	(12.5)	34	(10.0)
	Discontinued due to clinical disease progression	16	(4.6)	18	(5.3)
	Discontinued due to lost to follow-up	0	(0.0)	1	(0.3)
	Discontinued due to other	3	(0.9)	2	(0.6)
	Discontinued due to radiological disease progression	65	(18.5)	146	(42.9)
	Discontinued due to subject choice	10	(2.8)	19	(5.6)
	Discontinued due to withdrawal of consent	1	(0.3)	9	(2.6)
	No visit scheduled	36	(10.3)	14	(4.1)
Week 84	**Expected to Complete Questionnaires**	**170**	**(48.4)**	**89**	**(26.2)**
Week 84	Completed	150	(42.7)	73	(21.5)
	Compliance (% in those expected to complete questionnaires)[d]	150	(88.2)	73	(82.0)
	Not completed	20	(5.7)	16	(4.7)
	Other	20	(5.7)	16	(4.7)
	Missing by Design	**181**	**(51.6)**	**251**	**(73.8)**
	Discontinued due to adverse event	45	(12.8)	35	(10.3)
	Discontinued due to clinical disease progression	17	(4.8)	18	(5.3)
	Discontinued due to lost to follow-up	0	(0.0)	1	(0.3)
	Discontinued due to other	3	(0.9)	2	(0.6)
	Discontinued due to radiological disease progression	67	(19.1)	150	(44.1)
	Discontinued due to subject choice	11	(3.1)	20	(5.9)
	Discontinued due to withdrawal of consent	1	(0.3)	9	(2.6)
	No visit scheduled	37	(10.5)	16	(4.7)
Week 87	**Expected to Complete Questionnaires**	**167**	**(47.6)**	**84**	**(24.7)**
	Completed	144	(41.0)	65	(19.1)
	Compliance (% in those expected to complete questionnaires)[d]	144	(86.2)	65	(77.4)
	Not completed	23	(6.6)	19	(5.6)
	Other	23	(6.6)	19	(5.6)
	Missing by Design	**184**	**(52.4)**	**256**	**(75.3)**

Study: KEYNOTE 581[a]		Pembrolizumab + Lenvatinib N[b]=351		Sunitinib N[b]=340	
Treatment Visit	Questionnaire Completion Status (EORTC QLQ-C30)[c]	n	(%)	n	(%)
	Discontinued due to adverse event	46	(13.1)	36	(10.6)
	Discontinued due to clinical disease progression	17	(4.8)	18	(5.3)
	Discontinued due to lost to follow-up	0	(0.0)	1	(0.3)
	Discontinued due to other	3	(0.9)	2	(0.6)
	Discontinued due to radiological disease progression	67	(19.1)	151	(44.4)
	Discontinued due to subject choice	11	(3.1)	20	(5.9)
	Discontinued due to withdrawal of consent	1	(0.3)	9	(2.6)
	No visit scheduled	39	(11.1)	19	(5.6)
Week 90	**Expected to Complete Questionnaires**	**162**	**(46.2)**	**79**	**(23.2)**
	Completed	137	(39.0)	62	(18.2)
Week 90	Compliance (% in those expected to complete questionnaires)[d]	137	(84.6)	62	(78.5)
	Not completed	25	(7.1)	17	(5.0)
	Other	25	(7.1)	17	(5.0)
	Missing by Design	**189**	**(53.8)**	**261**	**(76.8)**
	Discontinued due to adverse event	46	(13.1)	37	(10.9)
	Discontinued due to clinical disease progression	17	(4.8)	18	(5.3)
	Discontinued due to lost to follow-up	0	(0.0)	1	(0.3)
	Discontinued due to other	3	(0.9)	2	(0.6)
	Discontinued due to radiological disease progression	68	(19.4)	153	(45.0)
	Discontinued due to subject choice	11	(3.1)	21	(6.2)
	Discontinued due to withdrawal of consent	1	(0.3)	9	(2.6)
	No visit scheduled	43	(12.3)	20	(5.9)
Week 93	**Expected to Complete Questionnaires**	**153**	**(43.6)**	**73**	**(21.5)**
	Completed	123	(35.0)	55	(16.2)
	Compliance (% in those expected to complete questionnaires)[d]	123	(80.4)	55	(75.3)
	Not completed	30	(8.5)	18	(5.3)
	Other	30	(8.5)	18	(5.3)
	Missing by Design	**198**	**(56.4)**	**267**	**(78.5)**
	Discontinued due to adverse event	46	(13.1)	37	(10.9)
	Discontinued due to clinical disease progression	17	(4.8)	18	(5.3)
	Discontinued due to lost to follow-up	0	(0.0)	1	(0.3)
	Discontinued due to other	3	(0.9)	2	(0.6)
	Discontinued due to radiological disease progression	74	(21.1)	156	(45.9)
	Discontinued due to subject choice	11	(3.1)	21	(6.2)
	Discontinued due to withdrawal of consent	1	(0.3)	9	(2.6)

Study: KEYNOTE 581[a]		Pembrolizumab + Lenvatinib N[b]=351		Sunitinib N[b]=340	
Treatment Visit	Questionnaire Completion Status (EORTC QLQ-C30)[c]	n	(%)	n	(%)
	No visit scheduled	46	(13.1)	23	(6.8)
Week 96	**Expected to Complete Questionnaires**	**146**	**(41.6)**	**73**	**(21.5)**
	Completed	120	(34.2)	58	(17.1)
	Compliance (% in those expected to complete questionnaires)[d]	120	(82.2)	58	(79.5)
Week 96	Not completed	26	(7.4)	15	(4.4)
	Other	26	(7.4)	15	(4.4)
	Missing by Design	**205**	**(58.4)**	**267**	**(78.5)**
	Discontinued due to adverse event	46	(13.1)	37	(10.9)
	Discontinued due to clinical disease progression	17	(4.8)	18	(5.3)
	Discontinued due to lost to follow-up	0	(0.0)	1	(0.3)
	Discontinued due to other	3	(0.9)	2	(0.6)
	Discontinued due to radiological disease progression	75	(21.4)	156	(45.9)
	Discontinued due to subject choice	12	(3.4)	21	(6.2)
	Discontinued due to withdrawal of consent	1	(0.3)	9	(2.6)
	No visit scheduled	51	(14.5)	23	(6.8)
Week 99	**Expected to Complete Questionnaires**	**137**	**(39.0)**	**72**	**(21.2)**
	Completed	110	(31.3)	52	(15.3)
	Compliance (% in those expected to complete questionnaires)[d]	110	(80.3)	52	(72.2)
	Not completed	27	(7.7)	20	(5.9)
	Other	27	(7.7)	20	(5.9)
	Missing by Design	**214**	**(61.0)**	**268**	**(78.8)**
	Discontinued due to adverse event	46	(13.1)	37	(10.9)
	Discontinued due to clinical disease progression	17	(4.8)	18	(5.3)
	Discontinued due to lost to follow-up	0	(0.0)	1	(0.3)
	Discontinued due to other	3	(0.9)	2	(0.6)
	Discontinued due to radiological disease progression	78	(22.2)	156	(45.9)
	Discontinued due to subject choice	12	(3.4)	21	(6.2)
	Discontinued due to withdrawal of consent	1	(0.3)	9	(2.6)
	No visit scheduled	57	(16.2)	24	(7.1)
Week 102	**Expected to Complete Questionnaires**	**130**	**(37.0)**	**69**	**(20.3)**
	Completed	103	(29.3)	49	(14.4)
	Compliance (% in those expected to complete questionnaires)[d]	103	(79.2)	49	(71.0)
	Not completed	27	(7.7)	20	(5.9)
Week 102	Other	27	(7.7)	20	(5.9)

Study: KEYNOTE 581[a]		Pembrolizumab + Lenvatinib N[b]=351		Sunitinib N[b]=340	
Treatment Visit	Questionnaire Completion Status (EORTC QLQ-C30)[c]	n	(%)	n	(%)
	Missing by Design	**221**	**(63.0)**	**271**	**(79.7)**
	Discontinued due to adverse event	46	(13.1)	38	(11.2)
	Discontinued due to clinical disease progression	18	(5.1)	18	(5.3)
	Discontinued due to lost to follow-up	0	(0.0)	1	(0.3)
	Discontinued due to other	3	(0.9)	2	(0.6)
	Discontinued due to radiological disease progression	82	(23.4)	158	(46.5)
	Discontinued due to subject choice	13	(3.7)	21	(6.2)
	Discontinued due to withdrawal of consent	1	(0.3)	9	(2.6)
	No visit scheduled	58	(16.5)	24	(7.1)
Week 105	**Expected to Complete Questionnaires**	**126**	**(35.9)**	**66**	**(19.4)**
	Completed	99	(28.2)	46	(13.5)
	Compliance (% in those expected to complete questionnaires)[d]	99	(78.6)	46	(69.7)
	Not completed	27	(7.7)	20	(5.9)
	Other	27	(7.7)	20	(5.9)
	Missing by Design	**225**	**(64.1)**	**274**	**(80.6)**
	Discontinued due to adverse event	47	(13.4)	38	(11.2)
	Discontinued due to clinical disease progression	18	(5.1)	18	(5.3)
	Discontinued due to lost to follow-up	0	(0.0)	1	(0.3)
	Discontinued due to other	3	(0.9)	3	(0.9)
	Discontinued due to radiological disease progression	83	(23.6)	159	(46.8)
	Discontinued due to subject choice	13	(3.7)	21	(6.2)
	Discontinued due to withdrawal of consent	1	(0.3)	9	(2.6)
	No visit scheduled	60	(17.1)	25	(7.4)
Week 108	**Expected to Complete Questionnaires**	**114**	**(32.5)**	**64**	**(18.8)**
	Completed	87	(24.8)	43	(12.6)
	Compliance (% in those expected to complete questionnaires)[d]	87	(76.3)	43	(67.2)
	Not completed	27	(7.7)	21	(6.2)
	Other	27	(7.7)	21	(6.2)
Week 108	**Missing by Design**	**237**	**(67.5)**	**276**	**(81.2)**
	Discontinued due to adverse event	48	(13.7)	38	(11.2)
	Discontinued due to clinical disease progression	18	(5.1)	18	(5.3)
	Discontinued due to lost to follow-up	0	(0.0)	1	(0.3)
	Discontinued due to other	8	(2.3)	3	(0.9)
	Discontinued due to radiological disease progression	86	(24.5)	160	(47.1)
	Discontinued due to subject choice	13	(3.7)	21	(6.2)

Study: KEYNOTE 581[a]		Pembrolizumab + Lenvatinib N[b]=351		Sunitinib N[b]=340	
Treatment Visit	Questionnaire Completion Status (EORTC QLQ-C30)[c]	n	(%)	n	(%)
	Discontinued due to withdrawal of consent	1	(0.3)	9	(2.6)
	No visit scheduled	63	(17.9)	26	(7.6)
Week 111	**Expected to Complete Questionnaires**	**102**	**(29.1)**	**58**	**(17.1)**
	Completed	78	(22.2)	42	(12.4)
	Compliance (% in those expected to complete questionnaires)[d]	78	(76.5)	42	(72.4)
	Not completed	24	(6.8)	16	(4.7)
	Other	24	(6.8)	16	(4.7)
	Missing by Design	**249**	**(70.9)**	**282**	**(82.9)**
	Discontinued due to adverse event	50	(14.2)	38	(11.2)
	Discontinued due to clinical disease progression	18	(5.1)	19	(5.6)
	Discontinued due to lost to follow-up	0	(0.0)	1	(0.3)
	Discontinued due to other	9	(2.6)	3	(0.9)
	Discontinued due to radiological disease progression	87	(24.8)	161	(47.4)
	Discontinued due to subject choice	15	(4.3)	21	(6.2)
	Discontinued due to withdrawal of consent	1	(0.3)	9	(2.6)
	No visit scheduled	69	(19.7)	30	(8.8)
Week 114	**Expected to Complete Questionnaires**	**91**	**(25.9)**	**55**	**(16.2)**
	Completed	64	(18.2)	38	(11.2)
	Compliance (% in those expected to complete questionnaires)[d]	64	(70.3)	38	(69.1)
	Not completed	27	(7.7)	17	(5.0)
	Other	27	(7.7)	17	(5.0)
	Missing by Design	**260**	**(74.1)**	**285**	**(83.8)**
Week 114	Discontinued due to adverse event	52	(14.8)	38	(11.2)
	Discontinued due to clinical disease progression	18	(5.1)	19	(5.6)
	Discontinued due to lost to follow-up	0	(0.0)	1	(0.3)
	Discontinued due to other	10	(2.8)	3	(0.9)
	Discontinued due to radiological disease progression	87	(24.8)	161	(47.4)
	Discontinued due to subject choice	16	(4.6)	21	(6.2)
	Discontinued due to withdrawal of consent	1	(0.3)	9	(2.6)
	No visit scheduled	76	(21.7)	33	(9.7)
Week 117	**Expected to Complete Questionnaires**	**78**	**(22.2)**	**49**	**(14.4)**
	Completed	55	(15.7)	29	(8.5)
	Compliance (% in those expected to complete questionnaires)[d]	55	(70.5)	29	(59.2)
	Not completed	23	(6.6)	20	(5.9)

Study: KEYNOTE 581[a]		Pembrolizumab + Lenvatinib N[b]=351		Sunitinib N[b]=340	
Treatment Visit	Questionnaire Completion Status (EORTC QLQ-C30)[c]	n	(%)	n	(%)
	Other	23	(6.6)	20	(5.9)
	Missing by Design	**273**	**(77.8)**	**291**	**(85.6)**
	Discontinued due to adverse event	54	(15.4)	38	(11.2)
	Discontinued due to clinical disease progression	18	(5.1)	19	(5.6)
	Discontinued due to lost to follow-up	0	(0.0)	1	(0.3)
	Discontinued due to other	10	(2.8)	3	(0.9)
	Discontinued due to radiological disease progression	87	(24.8)	163	(47.9)
	Discontinued due to subject choice	16	(4.6)	21	(6.2)
	Discontinued due to withdrawal of consent	1	(0.3)	9	(2.6)
	No visit scheduled	87	(24.8)	37	(10.9)
Week 120	**Expected to Complete Questionnaires**	**67**	**(19.1)**	**46**	**(13.5)**
	Completed	47	(13.4)	30	(8.8)
	Compliance (% in those expected to complete questionnaires)[d]	47	(70.1)	30	(65.2)
	Not completed	20	(5.7)	16	(4.7)
	Other	20	(5.7)	16	(4.7)
	Missing by Design	**284**	**(80.9)**	**294**	**(86.5)**
	Discontinued due to adverse event	55	(15.7)	38	(11.2)
Week 120	Discontinued due to clinical disease progression	18	(5.1)	20	(5.9)
	Discontinued due to lost to follow-up	0	(0.0)	1	(0.3)
	Discontinued due to other	10	(2.8)	3	(0.9)
	Discontinued due to radiological disease progression	89	(25.4)	163	(47.9)
	Discontinued due to subject choice	17	(4.8)	21	(6.2)
	Discontinued due to withdrawal of consent	1	(0.3)	9	(2.6)
	No visit scheduled	94	(26.8)	39	(11.5)
Week 123	**Expected to Complete Questionnaires**	**57**	**(16.2)**	**42**	**(12.4)**
	Completed	40	(11.4)	24	(7.1)
	Compliance (% in those expected to complete questionnaires)[d]	40	(70.2)	24	(57.1)
	Not completed	17	(4.8)	18	(5.3)
	Other	17	(4.8)	18	(5.3)
	Missing by Design	**294**	**(83.8)**	**298**	**(87.6)**
	Discontinued due to adverse event	55	(15.7)	38	(11.2)
	Discontinued due to clinical disease progression	18	(5.1)	20	(5.9)
	Discontinued due to lost to follow-up	0	(0.0)	1	(0.3)
	Discontinued due to other	12	(3.4)	3	(0.9)
	Discontinued due to radiological disease progression	90	(25.6)	165	(48.5)

Study: KEYNOTE 581[a]		Pembrolizumab + Lenvatinib N[b]=351		Sunitinib N[b]=340	
Treatment Visit	Questionnaire Completion Status (EORTC QLQ-C30)[c]	n	(%)	n	(%)
	Discontinued due to subject choice	17	(4.8)	21	(6.2)
	Discontinued due to withdrawal of consent	2	(0.6)	9	(2.6)
	No visit scheduled	100	(28.5)	41	(12.1)
Week 126	**Expected to Complete Questionnaires**	**53**	**(15.1)**	**37**	**(10.9)**
	Completed	35	(10.0)	21	(6.2)
	Compliance (% in those expected to complete questionnaires)[d]	35	(66.0)	21	(56.8)
	Not completed	18	(5.1)	16	(4.7)
	Other	18	(5.1)	16	(4.7)
	Missing by Design	**298**	**(84.9)**	**303**	**(89.1)**
	Discontinued due to adverse event	56	(16.0)	38	(11.2)
	Discontinued due to clinical disease progression	18	(5.1)	20	(5.9)
Week 126	Discontinued due to lost to follow-up	0	(0.0)	1	(0.3)
	Discontinued due to other	12	(3.4)	3	(0.9)
	Discontinued due to radiological disease progression	90	(25.6)	166	(48.8)
	Discontinued due to subject choice	17	(4.8)	21	(6.2)
	Discontinued due to withdrawal of consent	2	(0.6)	9	(2.6)
	No visit scheduled	103	(29.3)	45	(13.2)
Week 129	**Expected to Complete Questionnaires**	**46**	**(13.1)**	**33**	**(9.7)**
	Completed	28	(8.0)	18	(5.3)
	Compliance (% in those expected to complete questionnaires)[d]	28	(60.9)	18	(54.5)
	Not completed	18	(5.1)	15	(4.4)
	Other	18	(5.1)	15	(4.4)
	Missing by Design	**305**	**(86.9)**	**307**	**(90.3)**
	Discontinued due to adverse event	56	(16.0)	38	(11.2)
	Discontinued due to clinical disease progression	18	(5.1)	20	(5.9)
	Discontinued due to lost to follow-up	0	(0.0)	1	(0.3)
	Discontinued due to other	12	(3.4)	3	(0.9)
	Discontinued due to radiological disease progression	90	(25.6)	166	(48.8)
	Discontinued due to subject choice	17	(4.8)	21	(6.2)
	Discontinued due to withdrawal of consent	2	(0.6)	9	(2.6)
	No visit scheduled	110	(31.3)	49	(14.4)
Week 132	**Expected to Complete Questionnaires**	**41**	**(11.7)**	**26**	**(7.6)**
	Completed	23	(6.6)	9	(2.6)
	Compliance (% in those expected to complete questionnaires)[d]	23	(56.1)	9	(34.6)

Study: KEYNOTE 581[a]		Pembrolizumab + Lenvatinib N[b]=351		Sunitinib N[b]=340	
Treatment Visit	Questionnaire Completion Status (EORTC QLQ-C30)[c]	n	(%)	n	(%)
	Not completed	18	(5.1)	17	(5.0)
	Other	18	(5.1)	17	(5.0)
	Missing by Design	**310**	**(88.3)**	**314**	**(92.4)**
	Discontinued due to adverse event	56	(16.0)	38	(11.2)
	Discontinued due to clinical disease progression	18	(5.1)	20	(5.9)
	Discontinued due to lost to follow-up	0	(0.0)	1	(0.3)
Week 132	Discontinued due to other	12	(3.4)	3	(0.9)
	Discontinued due to radiological disease progression	90	(25.6)	168	(49.4)
	Discontinued due to subject choice	17	(4.8)	21	(6.2)
	Discontinued due to withdrawal of consent	2	(0.6)	9	(2.6)
	No visit scheduled	115	(32.8)	54	(15.9)
Week 135	**Expected to Complete Questionnaires**	**38**	**(10.8)**	**24**	**(7.1)**
	Completed	20	(5.7)	10	(2.9)
	Compliance (% in those expected to complete questionnaires)[d]	20	(52.6)	10	(41.7)
	Not completed	18	(5.1)	14	(4.1)
	Other	18	(5.1)	14	(4.1)
	Missing by Design	**313**	**(89.2)**	**316**	**(92.9)**
	Discontinued due to adverse event	56	(16.0)	38	(11.2)
	Discontinued due to clinical disease progression	18	(5.1)	20	(5.9)
	Discontinued due to lost to follow-up	0	(0.0)	1	(0.3)
	Discontinued due to other	12	(3.4)	3	(0.9)
	Discontinued due to radiological disease progression	91	(25.9)	168	(49.4)
	Discontinued due to subject choice	17	(4.8)	21	(6.2)
	Discontinued due to withdrawal of consent	2	(0.6)	9	(2.6)
	No visit scheduled	117	(33.3)	56	(16.5)
Week 138	**Expected to Complete Questionnaires**	**33**	**(9.4)**	**23**	**(6.8)**
	Completed	16	(4.6)	8	(2.4)
	Compliance (% in those expected to complete questionnaires)[d]	16	(48.5)	8	(34.8)
	Not completed	17	(4.8)	15	(4.4)
	Other	17	(4.8)	15	(4.4)
	Missing by Design	**318**	**(90.6)**	**317**	**(93.2)**
	Discontinued due to adverse event	56	(16.0)	38	(11.2)
	Discontinued due to clinical disease progression	18	(5.1)	20	(5.9)
	Discontinued due to lost to follow-up	0	(0.0)	1	(0.3)
	Discontinued due to other	12	(3.4)	3	(0.9)

Study: KEYNOTE 581[a]		Pembrolizumab + Lenvatinib N[b]=351		Sunitinib N[b]=340	
Treatment Visit	Questionnaire Completion Status (EORTC QLQ-C30)[c]	n	(%)	n	(%)
Week 138	Discontinued due to radiological disease progression	92	(26.2)	168	(49.4)
	Discontinued due to subject choice	17	(4.8)	21	(6.2)
	Discontinued due to withdrawal of consent	2	(0.6)	9	(2.6)
	No visit scheduled	121	(34.5)	57	(16.8)
Week 141	**Expected to Complete Questionnaires**	**27**	**(7.7)**	**20**	**(5.9)**
	Completed	8	(2.3)	6	(1.8)
	Compliance (% in those expected to complete questionnaires)[d]	8	(29.6)	6	(30.0)
	Not completed	19	(5.4)	14	(4.1)
	Other	19	(5.4)	14	(4.1)
	Missing by Design	**324**	**(92.3)**	**320**	**(94.1)**
	Discontinued due to adverse event	56	(16.0)	38	(11.2)
	Discontinued due to clinical disease progression	18	(5.1)	20	(5.9)
	Discontinued due to lost to follow-up	0	(0.0)	1	(0.3)
	Discontinued due to other	12	(3.4)	3	(0.9)
	Discontinued due to radiological disease progression	92	(26.2)	169	(49.7)
	Discontinued due to subject choice	17	(4.8)	21	(6.2)
	Discontinued due to withdrawal of consent	2	(0.6)	9	(2.6)
	No visit scheduled	127	(36.2)	59	(17.4)
Week 144	**Expected to Complete Questionnaires**	**24**	**(6.8)**	**19**	**(5.6)**
	Completed	8	(2.3)	5	(1.5)
	Compliance (% in those expected to complete questionnaires)[d]	8	(33.3)	5	(26.3)
	Not completed	16	(4.6)	14	(4.1)
	Other	16	(4.6)	14	(4.1)
	Missing by Design	**327**	**(93.2)**	**321**	**(94.4)**
	Discontinued due to adverse event	56	(16.0)	38	(11.2)
	Discontinued due to clinical disease progression	18	(5.1)	20	(5.9)
	Discontinued due to lost to follow-up	0	(0.0)	1	(0.3)
	Discontinued due to other	12	(3.4)	3	(0.9)
	Discontinued due to radiological disease progression	92	(26.2)	169	(49.7)
Week 144	Discontinued due to subject choice	17	(4.8)	21	(6.2)
	Discontinued due to withdrawal of consent	2	(0.6)	9	(2.6)
	No visit scheduled	130	(37.0)	60	(17.6)
Week 147	**Expected to Complete Questionnaires**	**24**	**(6.8)**	**18**	**(5.3)**
	Completed	8	(2.3)	3	(0.9)
	Compliance (% in those expected to complete	8	(33.3)	3	(16.7)

Study: KEYNOTE 581[a]		Pembrolizumab + Lenvatinib N[b]=351		Sunitinib N[b]=340	
Treatment Visit	Questionnaire Completion Status (EORTC QLQ-C30)[c]	n	(%)	n	(%)
	questionnaires)[d]				
	Not completed	16	(4.6)	15	(4.4)
	Other	16	(4.6)	15	(4.4)
	Missing by Design	**327**	**(93.2)**	**322**	**(94.7)**
	Discontinued due to adverse event	56	(16.0)	38	(11.2)
	Discontinued due to clinical disease progression	18	(5.1)	20	(5.9)
	Discontinued due to lost to follow-up	0	(0.0)	1	(0.3)
	Discontinued due to other	12	(3.4)	3	(0.9)
	Discontinued due to radiological disease progression	92	(26.2)	169	(49.7)
	Discontinued due to subject choice	17	(4.8)	21	(6.2)
	Discontinued due to withdrawal of consent	2	(0.6)	9	(2.6)
	No visit scheduled	130	(37.0)	61	(17.9)
Week 150	**Expected to Complete Questionnaires**	**23**	**(6.6)**	**17**	**(5.0)**
	Completed	7	(2.0)	3	(0.9)
	Compliance (% in those expected to complete questionnaires)[d]	7	(30.4)	3	(17.6)
	Not completed	16	(4.6)	14	(4.1)
	Other	16	(4.6)	14	(4.1)
	Missing by Design	**328**	**(93.4)**	**323**	**(95.0)**
	Discontinued due to adverse event	56	(16.0)	38	(11.2)
	Discontinued due to clinical disease progression	18	(5.1)	20	(5.9)
	Discontinued due to lost to follow-up	0	(0.0)	1	(0.3)
	Discontinued due to other	12	(3.4)	3	(0.9)
	Discontinued due to radiological disease progression	93	(26.5)	169	(49.7)
	Discontinued due to subject choice	17	(4.8)	21	(6.2)
Week 150	Discontinued due to withdrawal of consent	2	(0.6)	9	(2.6)
	No visit scheduled	130	(37.0)	62	(18.2)
Week 153	**Expected to Complete Questionnaires**	**22**	**(6.3)**	**16**	**(4.7)**
	Completed	6	(1.7)	2	(0.6)
	Compliance (% in those expected to complete questionnaires)[d]	6	(27.3)	2	(12.5)
	Not completed	16	(4.6)	14	(4.1)
	Other	16	(4.6)	14	(4.1)
	Missing by Design	**329**	**(93.7)**	**324**	**(95.3)**
	Discontinued due to adverse event	56	(16.0)	38	(11.2)
	Discontinued due to clinical disease progression	18	(5.1)	20	(5.9)
	Discontinued due to lost to follow-up	0	(0.0)	1	(0.3)

Study: KEYNOTE 581[a]		Pembrolizumab + Lenvatinib N[b]=351		Sunitinib N[b]=340	
Treatment Visit	Questionnaire Completion Status (EORTC QLQ-C30)[c]	n	(%)	n	(%)
	Discontinued due to other	12	(3.4)	3	(0.9)
	Discontinued due to radiological disease progression	93	(26.5)	169	(49.7)
	Discontinued due to subject choice	17	(4.8)	21	(6.2)
	Discontinued due to withdrawal of consent	2	(0.6)	9	(2.6)
	No visit scheduled	131	(37.3)	63	(18.5)
Week 156	**Expected to Complete Questionnaires**	**20**	**(5.7)**	**16**	**(4.7)**
	Completed	4	(1.1)	1	(0.3)
	Compliance (% in those expected to complete questionnaires)[d]	4	(20.0)	1	(6.3)
	Not completed	16	(4.6)	15	(4.4)
	Other	16	(4.6)	15	(4.4)
	Missing by Design	**331**	**(94.3)**	**324**	**(95.3)**
	Discontinued due to adverse event	56	(16.0)	38	(11.2)
	Discontinued due to clinical disease progression	18	(5.1)	20	(5.9)
	Discontinued due to lost to follow-up	0	(0.0)	1	(0.3)
	Discontinued due to other	12	(3.4)	3	(0.9)
	Discontinued due to radiological disease progression	93	(26.5)	169	(49.7)
	Discontinued due to subject choice	17	(4.8)	21	(6.2)
	Discontinued due to withdrawal of consent	2	(0.6)	9	(2.6)
Week 156	No visit scheduled	133	(37.9)	63	(18.5)
Week 159	**Expected to Complete Questionnaires**	**18**	**(5.1)**	**15**	**(4.4)**
	Completed	2	(0.6)	1	(0.3)
	Compliance (% in those expected to complete questionnaires)[d]	2	(11.1)	1	(6.7)
	Not completed	16	(4.6)	14	(4.1)
	Other	16	(4.6)	14	(4.1)
	Missing by Design	**333**	**(94.9)**	**325**	**(95.6)**
	Discontinued due to adverse event	57	(16.2)	38	(11.2)
	Discontinued due to clinical disease progression	18	(5.1)	20	(5.9)
	Discontinued due to lost to follow-up	0	(0.0)	1	(0.3)
	Discontinued due to other	12	(3.4)	3	(0.9)
	Discontinued due to radiological disease progression	93	(26.5)	169	(49.7)
	Discontinued due to subject choice	17	(4.8)	21	(6.2)
	Discontinued due to withdrawal of consent	2	(0.6)	9	(2.6)
	No visit scheduled	134	(38.2)	64	(18.8)
Week 162	**Expected to Complete Questionnaires**	**18**	**(5.1)**	**14**	**(4.1)**
	Completed	2	(0.6)	0	(0.0)

Study: KEYNOTE 581[a]		Pembrolizumab + Lenvatinib N[b]=351		Sunitinib N[b]=340	
Treatment Visit	Questionnaire Completion Status (EORTC QLQ-C30)[c]	n	(%)	n	(%)
	Compliance (% in those expected to complete questionnaires)[d]	2	(11.1)	0	(0.0)
	Not completed	16	(4.6)	14	(4.1)
	Other	16	(4.6)	14	(4.1)
	Missing by Design	**333**	**(94.9)**	**326**	**(95.9)**
	Discontinued due to adverse event	57	(16.2)	38	(11.2)
	Discontinued due to clinical disease progression	18	(5.1)	20	(5.9)
	Discontinued due to lost to follow-up	0	(0.0)	1	(0.3)
	Discontinued due to other	12	(3.4)	3	(0.9)
	Discontinued due to radiological disease progression	93	(26.5)	169	(49.7)
	Discontinued due to subject choice	17	(4.8)	21	(6.2)
	Discontinued due to withdrawal of consent	2	(0.6)	9	(2.6)
	No visit scheduled	134	(38.2)	65	(19.1)
Week 165	**Expected to Complete Questionnaires**	**18**	**(5.1)**	**14**	**(4.1)**
	Completed	2	(0.6)	0	(0.0)
	Compliance (% in those expected to complete questionnaires)[d]	2	(11.1)	0	(0.0)
	Not completed	16	(4.6)	14	(4.1)
	Other	16	(4.6)	14	(4.1)
	Missing by Design	**333**	**(94.9)**	**326**	**(95.9)**
	Discontinued due to adverse event	57	(16.2)	38	(11.2)
	Discontinued due to clinical disease progression	18	(5.1)	20	(5.9)
	Discontinued due to lost to follow-up	0	(0.0)	1	(0.3)
	Discontinued due to other	12	(3.4)	3	(0.9)
	Discontinued due to radiological disease progression	93	(26.5)	169	(49.7)
	Discontinued due to subject choice	17	(4.8)	21	(6.2)
	Discontinued due to withdrawal of consent	2	(0.6)	9	(2.6)
	No visit scheduled	134	(38.2)	65	(19.1)
Week 168	**Expected to Complete Questionnaires**	**18**	**(5.1)**	**14**	**(4.1)**
	Completed	2	(0.6)	0	(0.0)
	Compliance (% in those expected to complete questionnaires)[d]	2	(11.1)	0	(0.0)
	Not completed	16	(4.6)	14	(4.1)
	Other	16	(4.6)	14	(4.1)
	Missing by Design	**333**	**(94.9)**	**326**	**(95.9)**
	Discontinued due to adverse event	57	(16.2)	38	(11.2)
	Discontinued due to clinical disease progression	18	(5.1)	20	(5.9)

Study: KEYNOTE 581[a]		Pembrolizumab + Lenvatinib N[b]=351		Sunitinib N[b]=340	
Treatment Visit	Questionnaire Completion Status (EORTC QLQ-C30)[c]	n	(%)	n	(%)
	Discontinued due to lost to follow-up	0	(0.0)	1	(0.3)
	Discontinued due to other	12	(3.4)	3	(0.9)
	Discontinued due to radiological disease progression	93	(26.5)	169	(49.7)
	Discontinued due to subject choice	17	(4.8)	21	(6.2)
	Discontinued due to withdrawal of consent	2	(0.6)	9	(2.6)
	No visit scheduled	134	(38.2)	65	(19.1)
Week 171	**Expected to Complete Questionnaires**	**16**	**(4.6)**	**14**	**(4.1)**
Week 171	Not completed	16	(4.6)	14	(4.1)
	Other	16	(4.6)	14	(4.1)
	Missing by Design	**335**	**(95.4)**	**326**	**(95.9)**
	Discontinued due to adverse event	57	(16.2)	38	(11.2)
	Discontinued due to clinical disease progression	18	(5.1)	20	(5.9)
	Discontinued due to lost to follow-up	0	(0.0)	1	(0.3)
	Discontinued due to other	12	(3.4)	3	(0.9)
	Discontinued due to radiological disease progression	93	(26.5)	169	(49.7)
	Discontinued due to subject choice	17	(4.8)	21	(6.2)
	Discontinued due to withdrawal of consent	2	(0.6)	9	(2.6)
	No visit scheduled	136	(38.7)	65	(19.1)
Week 174	**Expected to Complete Questionnaires**	**16**	**(4.6)**	**14**	**(4.1)**
	Not completed	16	(4.6)	14	(4.1)
	Other	16	(4.6)	14	(4.1)
	Missing by Design	**335**	**(95.4)**	**326**	**(95.9)**
	Discontinued due to adverse event	57	(16.2)	38	(11.2)
	Discontinued due to clinical disease progression	18	(5.1)	20	(5.9)
	Discontinued due to lost to follow-up	0	(0.0)	1	(0.3)
	Discontinued due to other	12	(3.4)	3	(0.9)
	Discontinued due to radiological disease progression	93	(26.5)	169	(49.7)
	Discontinued due to subject choice	17	(4.8)	21	(6.2)
	Discontinued due to withdrawal of consent	2	(0.6)	9	(2.6)
Week 174	No visit scheduled	136	(38.7)	65	(19.1)

Study: KEYNOTE 581[a]		Pembrolizumab + Lenvatinib		Sunitinib	
		N[b]=351		N[b]=340	
Treatment Visit	Questionnaire Completion Status (EORTC QLQ-C30)[c]	n	(%)	n	(%)
a: Database Cutoff Date: 28AUG2020					
b: Number of participants: full-analysis-set population					
c: Questionnaire completion status is missing by design in case of discontinuation, death, and no visit scheduled else is expected to complete questionnaires					
d: Compliance Rate is defined as the number of subjects completed the questionnaire over the number of subjects expected to complete the questionnaire, excluding those missing by design					
EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire - Cancer 30 questions					

Anhang 4-G1.2: Rücklaufquoten des FKSI-DRS

Tabelle 4G-2: Gründe für das Fehlen von Werten im FKSI-DRS

Study: KEYNOTE 581[a]		Pembrolizumab + Lenvatinib		Sunitinib	
		N[b]=351		N[b]=340	
Treatment Visit	Questionnaire Completion Status (FKSI-DRS)[c]	n	(%)	n	(%)
Week 0	**Expected to Complete Questionnaires**	**351**	**(100.0)**	**340**	**(100.0)**
	Completed	336	(95.7)	323	(95.0)
	Compliance (% in those expected to complete questionnaires)[d]	336	(95.7)	323	(95.0)
	Not completed	15	(4.3)	17	(5.0)
	Other	15	(4.3)	17	(5.0)
	Missing by Design	**0**	**(0.0)**	**0**	**(0.0)**
Week 3	**Expected to Complete Questionnaires**	**345**	**(98.3)**	**334**	**(98.2)**
	Completed	320	(91.2)	288	(84.7)
	Compliance (% in those expected to complete questionnaires)[d]	320	(92.8)	288	(86.2)
	Not completed	25	(7.1)	46	(13.5)
	Other	25	(7.1)	46	(13.5)
	Missing by Design	**6**	**(1.7)**	**6**	**(1.8)**
	Discontinued due to adverse event	5	(1.4)	2	(0.6)
	Discontinued due to clinical disease progression	1	(0.3)	1	(0.3)
	Discontinued due to subject choice	0	(0.0)	1	(0.3)
	Discontinued due to withdrawal of consent	0	(0.0)	2	(0.6)
Week 6	**Expected to Complete Questionnaires**	**342**	**(97.4)**	**325**	**(95.6)**

Study: KEYNOTE 581[a]		Pembrolizumab + Lenvatinib N[b]=351		Sunitinib N[b]=340	
Treatment Visit	Questionnaire Completion Status (FKSI-DRS)[c]	n	(%)	n	(%)
	Completed	298	(84.9)	289	(85.0)
	Compliance (% in those expected to complete questionnaires)[d]	298	(87.1)	289	(88.9)
	Not completed	44	(12.5)	36	(10.6)
	Other	44	(12.5)	36	(10.6)
	Missing by Design	**9**	**(2.6)**	**15**	**(4.4)**
	Discontinued due to adverse event	8	(2.3)	3	(0.9)
	Discontinued due to clinical disease progression	1	(0.3)	4	(1.2)
	Discontinued due to radiological disease progression	0	(0.0)	1	(0.3)
	Discontinued due to subject choice	0	(0.0)	5	(1.5)
	Discontinued due to withdrawal of consent	0	(0.0)	2	(0.6)
Week 9	**Expected to Complete Questionnaires**	**339**	**(96.6)**	**308**	**(90.6)**
	Completed	304	(86.6)	266	(78.2)
	Compliance (% in those expected to complete questionnaires)[d]	304	(89.7)	266	(86.4)
Week 9	Not completed	35	(10.0)	42	(12.4)
	Other	35	(10.0)	42	(12.4)
	Missing by Design	**12**	**(3.4)**	**32**	**(9.4)**
	Discontinued due to adverse event	10	(2.8)	7	(2.1)
	Discontinued due to clinical disease progression	1	(0.3)	5	(1.5)
	Discontinued due to radiological disease progression	1	(0.3)	10	(2.9)
	Discontinued due to subject choice	0	(0.0)	7	(2.1)
	Discontinued due to withdrawal of consent	0	(0.0)	3	(0.9)
Week 12	**Expected to Complete Questionnaires**	**331**	**(94.3)**	**285**	**(83.8)**
	Completed	295	(84.0)	257	(75.6)
	Compliance (% in those expected to complete questionnaires)[d]	295	(89.1)	257	(90.2)
	Not completed	36	(10.3)	28	(8.2)
	Other	36	(10.3)	28	(8.2)
	Missing by Design	**20**	**(5.7)**	**55**	**(16.2)**
	Discontinued due to adverse event	12	(3.4)	9	(2.6)
	Discontinued due to clinical disease progression	3	(0.9)	6	(1.8)
	Discontinued due to radiological disease progression	5	(1.4)	26	(7.6)
	Discontinued due to subject choice	0	(0.0)	11	(3.2)
	Discontinued due to withdrawal of consent	0	(0.0)	3	(0.9)
Week 15	**Expected to Complete Questionnaires**	**327**	**(93.2)**	**279**	**(82.1)**
	Completed	299	(85.2)	249	(73.2)

Study: KEYNOTE 581[a]		Pembrolizumab + Lenvatinib N[b]=351		Sunitinib N[b]=340	
Treatment Visit	Questionnaire Completion Status (FKSI-DRS)[c]	n	(%)	n	(%)
	Compliance (% in those expected to complete questionnaires)[d]	299	(91.4)	249	(89.2)
	Not completed	28	(8.0)	30	(8.8)
	Other	28	(8.0)	30	(8.8)
	Missing by Design	**24**	**(6.8)**	**61**	**(17.9)**
	Discontinued due to adverse event	13	(3.7)	11	(3.2)
	Discontinued due to clinical disease progression	3	(0.9)	6	(1.8)
	Discontinued due to radiological disease progression	7	(2.0)	30	(8.8)
	Discontinued due to subject choice	1	(0.3)	11	(3.2)
	Discontinued due to withdrawal of consent	0	(0.0)	3	(0.9)
Week 18	**Expected to Complete Questionnaires**	**322**	**(91.7)**	**269**	**(79.1)**
	Completed	295	(84.0)	242	(71.2)
	Compliance (% in those expected to complete questionnaires)[d]	295	(91.6)	242	(90.0)
	Not completed	27	(7.7)	27	(7.9)
	Other	27	(7.7)	27	(7.9)
	Missing by Design	**29**	**(8.3)**	**71**	**(20.9)**
	Discontinued due to adverse event	17	(4.8)	13	(3.8)
	Discontinued due to clinical disease progression	3	(0.9)	9	(2.6)
	Discontinued due to radiological disease progression	8	(2.3)	33	(9.7)
	Discontinued due to subject choice	1	(0.3)	12	(3.5)
	Discontinued due to withdrawal of consent	0	(0.0)	4	(1.2)
Week 21	**Expected to Complete Questionnaires**	**318**	**(90.6)**	**254**	**(74.7)**
	Completed	290	(82.6)	220	(64.7)
	Compliance (% in those expected to complete questionnaires)[d]	290	(91.2)	220	(86.6)
	Not completed	28	(8.0)	34	(10.0)
	Other	28	(8.0)	34	(10.0)
	Missing by Design	**33**	**(9.4)**	**86**	**(25.3)**
	Discontinued due to adverse event	19	(5.4)	16	(4.7)
	Discontinued due to clinical disease progression	3	(0.9)	9	(2.6)
	Discontinued due to other	0	(0.0)	1	(0.3)
	Discontinued due to radiological disease progression	9	(2.6)	43	(12.6)
	Discontinued due to subject choice	2	(0.6)	13	(3.8)
	Discontinued due to withdrawal of consent	0	(0.0)	4	(1.2)
Week 24	**Expected to Complete Questionnaires**	**314**	**(89.5)**	**243**	**(71.5)**
	Completed	285	(81.2)	217	(63.8)

Study: KEYNOTE 581[a]		Pembrolizumab + Lenvatinib N[b]=351		Sunitinib N[b]=340	
Treatment Visit	Questionnaire Completion Status (FKSI-DRS)[c]	n	(%)	n	(%)
	Compliance (% in those expected to complete questionnaires)[d]	285	(90.8)	217	(89.3)
	Not completed	29	(8.3)	26	(7.6)
	Other	29	(8.3)	26	(7.6)
	Missing by Design	**37**	**(10.5)**	**97**	**(28.5)**
	Discontinued due to adverse event	20	(5.7)	18	(5.3)
Week 24	Discontinued due to clinical disease progression	4	(1.1)	12	(3.5)
	Discontinued due to other	1	(0.3)	1	(0.3)
	Discontinued due to radiological disease progression	10	(2.8)	49	(14.4)
	Discontinued due to subject choice	2	(0.6)	13	(3.8)
	Discontinued due to withdrawal of consent	0	(0.0)	4	(1.2)
Week 27	**Expected to Complete Questionnaires**	**303**	**(86.3)**	**218**	**(64.1)**
	Completed	275	(78.3)	194	(57.1)
	Compliance (% in those expected to complete questionnaires)[d]	275	(90.8)	194	(89.0)
	Not completed	28	(8.0)	24	(7.1)
	Other	28	(8.0)	24	(7.1)
	Missing by Design	**48**	**(13.7)**	**122**	**(35.9)**
	Discontinued due to adverse event	23	(6.6)	21	(6.2)
	Discontinued due to clinical disease progression	4	(1.1)	14	(4.1)
	Discontinued due to other	1	(0.3)	1	(0.3)
	Discontinued due to radiological disease progression	15	(4.3)	68	(20.0)
	Discontinued due to subject choice	5	(1.4)	14	(4.1)
	Discontinued due to withdrawal of consent	0	(0.0)	4	(1.2)
Week 30	**Expected to Complete Questionnaires**	**297**	**(84.6)**	**206**	**(60.6)**
	Completed	275	(78.3)	183	(53.8)
	Compliance (% in those expected to complete questionnaires)[d]	275	(92.6)	183	(88.8)
	Not completed	22	(6.3)	23	(6.8)
	Other	22	(6.3)	23	(6.8)
	Missing by Design	**54**	**(15.4)**	**134**	**(39.4)**
	Discontinued due to adverse event	24	(6.8)	22	(6.5)
	Discontinued due to clinical disease progression	5	(1.4)	15	(4.4)
	Discontinued due to other	1	(0.3)	1	(0.3)
	Discontinued due to radiological disease progression	19	(5.4)	75	(22.1)
	Discontinued due to subject choice	5	(1.4)	16	(4.7)
	Discontinued due to withdrawal of consent	0	(0.0)	5	(1.5)

Study: KEYNOTE 581[a]		Pembrolizumab + Lenvatinib N[b]=351		Sunitinib N[b]=340	
Treatment Visit	Questionnaire Completion Status (FKSI-DRS)[c]	n	(%)	n	(%)
Week 33	**Expected to Complete Questionnaires**	**289**	**(82.3)**	**195**	**(57.4)**
Week 33	Completed	265	(75.5)	171	(50.3)
	Compliance (% in those expected to complete questionnaires)[d]	265	(91.7)	171	(87.7)
	Not completed	24	(6.8)	24	(7.1)
	Other	24	(6.8)	24	(7.1)
	Missing by Design	**62**	**(17.7)**	**145**	**(42.6)**
	Discontinued due to adverse event	28	(8.0)	24	(7.1)
	Discontinued due to clinical disease progression	5	(1.4)	15	(4.4)
	Discontinued due to other	1	(0.3)	1	(0.3)
	Discontinued due to radiological disease progression	22	(6.3)	83	(24.4)
	Discontinued due to subject choice	6	(1.7)	17	(5.0)
	Discontinued due to withdrawal of consent	0	(0.0)	5	(1.5)
Week 36	**Expected to Complete Questionnaires**	**282**	**(80.3)**	**186**	**(54.7)**
	Completed	257	(73.2)	160	(47.1)
	Compliance (% in those expected to complete questionnaires)[d]	257	(91.1)	160	(86.0)
	Not completed	25	(7.1)	26	(7.6)
	Other	25	(7.1)	26	(7.6)
	Missing by Design	**69**	**(19.7)**	**154**	**(45.3)**
	Discontinued due to adverse event	30	(8.5)	25	(7.4)
	Discontinued due to clinical disease progression	5	(1.4)	15	(4.4)
	Discontinued due to other	1	(0.3)	1	(0.3)
	Discontinued due to radiological disease progression	27	(7.7)	89	(26.2)
	Discontinued due to subject choice	6	(1.7)	18	(5.3)
	Discontinued due to withdrawal of consent	0	(0.0)	6	(1.8)
Week 39	**Expected to Complete Questionnaires**	**279**	**(79.5)**	**180**	**(52.9)**
	Completed	252	(71.8)	153	(45.0)
	Compliance (% in those expected to complete questionnaires)[d]	252	(90.3)	153	(85.0)
	Not completed	27	(7.7)	27	(7.9)
	Other	27	(7.7)	27	(7.9)
	Missing by Design	**72**	**(20.5)**	**160**	**(47.1)**
	Discontinued due to adverse event	30	(8.5)	26	(7.6)
Week 39	Discontinued due to clinical disease progression	6	(1.7)	16	(4.7)
	Discontinued due to lost to follow-up	0	(0.0)	1	(0.3)
	Discontinued due to other	1	(0.3)	1	(0.3)

Study: KEYNOTE 581[a]		Pembrolizumab + Lenvatinib N[b]=351		Sunitinib N[b]=340	
Treatment Visit	Questionnaire Completion Status (FKSI-DRS)[c]	n	(%)	n	(%)
	Discontinued due to radiological disease progression	29	(8.3)	92	(27.1)
	Discontinued due to subject choice	6	(1.7)	18	(5.3)
	Discontinued due to withdrawal of consent	0	(0.0)	6	(1.8)
Week 42	**Expected to Complete Questionnaires**	**273**	**(77.8)**	**174**	**(51.2)**
	Completed	244	(69.5)	148	(43.5)
	Compliance (% in those expected to complete questionnaires)[d]	244	(89.4)	148	(85.1)
	Not completed	29	(8.3)	26	(7.6)
	Other	29	(8.3)	26	(7.6)
	Missing by Design	**78**	**(22.2)**	**166**	**(48.8)**
	Discontinued due to adverse event	30	(8.5)	26	(7.6)
	Discontinued due to clinical disease progression	10	(2.8)	16	(4.7)
	Discontinued due to lost to follow-up	0	(0.0)	1	(0.3)
	Discontinued due to other	1	(0.3)	2	(0.6)
	Discontinued due to radiological disease progression	31	(8.8)	96	(28.2)
	Discontinued due to subject choice	6	(1.7)	18	(5.3)
	Discontinued due to withdrawal of consent	0	(0.0)	7	(2.1)
Week 45	**Expected to Complete Questionnaires**	**265**	**(75.5)**	**163**	**(47.9)**
	Completed	233	(66.4)	140	(41.2)
	Compliance (% in those expected to complete questionnaires)[d]	233	(87.9)	140	(85.9)
	Not completed	32	(9.1)	23	(6.8)
	Other	32	(9.1)	23	(6.8)
	Missing by Design	**86**	**(24.5)**	**177**	**(52.1)**
	Discontinued due to adverse event	32	(9.1)	26	(7.6)
	Discontinued due to clinical disease progression	10	(2.8)	16	(4.7)
	Discontinued due to lost to follow-up	0	(0.0)	1	(0.3)
	Discontinued due to other	1	(0.3)	2	(0.6)
	Discontinued due to radiological disease progression	37	(10.5)	107	(31.5)
Week 45	Discontinued due to subject choice	6	(1.7)	18	(5.3)
	Discontinued due to withdrawal of consent	0	(0.0)	7	(2.1)
Week 48	**Expected to Complete Questionnaires**	**258**	**(73.5)**	**156**	**(45.9)**
	Completed	233	(66.4)	137	(40.3)
	Compliance (% in those expected to complete questionnaires)[d]	233	(90.3)	137	(87.8)
	Not completed	25	(7.1)	19	(5.6)
	Other	25	(7.1)	19	(5.6)

Study: KEYNOTE 581[a]		Pembrolizumab + Lenvatinib N[b]=351		Sunitinib N[b]=340	
Treatment Visit	Questionnaire Completion Status (FKSI-DRS)[c]	n	(%)	n	(%)
	Missing by Design	**93**	**(26.5)**	**184**	**(54.1)**
	Discontinued due to adverse event	32	(9.1)	27	(7.9)
	Discontinued due to clinical disease progression	10	(2.8)	17	(5.0)
	Discontinued due to lost to follow-up	0	(0.0)	1	(0.3)
	Discontinued due to other	1	(0.3)	2	(0.6)
	Discontinued due to radiological disease progression	42	(12.0)	112	(32.9)
	Discontinued due to subject choice	7	(2.0)	18	(5.3)
	Discontinued due to withdrawal of consent	1	(0.3)	7	(2.1)
Week 51	**Expected to Complete Questionnaires**	**253**	**(72.1)**	**152**	**(44.7)**
	Completed	229	(65.2)	123	(36.2)
	Compliance (% in those expected to complete questionnaires)[d]	229	(90.5)	123	(80.9)
	Not completed	24	(6.8)	29	(8.5)
	Other	24	(6.8)	29	(8.5)
	Missing by Design	**98**	**(27.9)**	**188**	**(55.3)**
	Discontinued due to adverse event	35	(10.0)	28	(8.2)
	Discontinued due to clinical disease progression	10	(2.8)	17	(5.0)
	Discontinued due to lost to follow-up	0	(0.0)	1	(0.3)
	Discontinued due to other	1	(0.3)	2	(0.6)
	Discontinued due to radiological disease progression	44	(12.5)	115	(33.8)
	Discontinued due to subject choice	7	(2.0)	18	(5.3)
	Discontinued due to withdrawal of consent	1	(0.3)	7	(2.1)
Week 54	**Expected to Complete Questionnaires**	**250**	**(71.2)**	**142**	**(41.8)**
	Completed	218	(62.1)	117	(34.4)
Week 54	Compliance (% in those expected to complete questionnaires)[d]	218	(87.2)	117	(82.4)
	Not completed	32	(9.1)	25	(7.4)
	Other	32	(9.1)	25	(7.4)
	Missing by Design	**101**	**(28.8)**	**198**	**(58.2)**
	Discontinued due to adverse event	35	(10.0)	30	(8.8)
	Discontinued due to clinical disease progression	10	(2.8)	17	(5.0)
	Discontinued due to lost to follow-up	0	(0.0)	1	(0.3)
	Discontinued due to other	2	(0.6)	2	(0.6)
	Discontinued due to radiological disease progression	46	(13.1)	123	(36.2)
	Discontinued due to subject choice	7	(2.0)	18	(5.3)
	Discontinued due to withdrawal of consent	1	(0.3)	7	(2.1)
Week 57	**Expected to Complete Questionnaires**	**243**	**(69.2)**	**140**	**(41.2)**

Study: KEYNOTE 581[a]		Pembrolizumab + Lenvatinib N[b]=351		Sunitinib N[b]=340	
Treatment Visit	Questionnaire Completion Status (FKSI-DRS)[c]	n	(%)	n	(%)
	Completed	211	(60.1)	117	(34.4)
	Compliance (% in those expected to complete questionnaires)[d]	211	(86.8)	117	(83.6)
	Not completed	32	(9.1)	23	(6.8)
	Other	32	(9.1)	23	(6.8)
	Missing by Design	**108**	**(30.8)**	**200**	**(58.8)**
	Discontinued due to adverse event	37	(10.5)	30	(8.8)
	Discontinued due to clinical disease progression	12	(3.4)	17	(5.0)
	Discontinued due to lost to follow-up	0	(0.0)	1	(0.3)
	Discontinued due to other	2	(0.6)	2	(0.6)
	Discontinued due to radiological disease progression	48	(13.7)	125	(36.8)
	Discontinued due to subject choice	8	(2.3)	18	(5.3)
	Discontinued due to withdrawal of consent	1	(0.3)	7	(2.1)
Week 60	**Expected to Complete Questionnaires**	**240**	**(68.4)**	**133**	**(39.1)**
	Completed	210	(59.8)	110	(32.4)
	Compliance (% in those expected to complete questionnaires)[d]	210	(87.5)	110	(82.7)
	Not completed	30	(8.5)	23	(6.8)
	Other	30	(8.5)	23	(6.8)
	Missing by Design	**111**	**(31.6)**	**207**	**(60.9)**
Week 60	Discontinued due to adverse event	37	(10.5)	30	(8.8)
	Discontinued due to clinical disease progression	14	(4.0)	18	(5.3)
	Discontinued due to lost to follow-up	0	(0.0)	1	(0.3)
	Discontinued due to other	3	(0.9)	2	(0.6)
	Discontinued due to radiological disease progression	48	(13.7)	130	(38.2)
	Discontinued due to subject choice	8	(2.3)	18	(5.3)
	Discontinued due to withdrawal of consent	1	(0.3)	7	(2.1)
	No visit scheduled	0	(0.0)	1	(0.3)
Week 63	**Expected to Complete Questionnaires**	**229**	**(65.2)**	**127**	**(37.4)**
	Completed	202	(57.5)	102	(30.0)
	Compliance (% in those expected to complete questionnaires)[d]	202	(88.2)	102	(80.3)
	Not completed	27	(7.7)	25	(7.4)
	Other	27	(7.7)	25	(7.4)
	Missing by Design	**122**	**(34.8)**	**213**	**(62.6)**
	Discontinued due to adverse event	37	(10.5)	31	(9.1)
	Discontinued due to clinical disease progression	14	(4.0)	18	(5.3)

Study: KEYNOTE 581[a]		Pembrolizumab + Lenvatinib N[b]=351		Sunitinib N[b]=340	
Treatment Visit	Questionnaire Completion Status (FKSI-DRS)[c]	n	(%)	n	(%)
	Discontinued due to lost to follow-up	0	(0.0)	1	(0.3)
	Discontinued due to other	3	(0.9)	2	(0.6)
	Discontinued due to radiological disease progression	50	(14.2)	130	(38.2)
	Discontinued due to subject choice	9	(2.6)	19	(5.6)
	Discontinued due to withdrawal of consent	1	(0.3)	7	(2.1)
	No visit scheduled	8	(2.3)	5	(1.5)
Week 66	**Expected to Complete Questionnaires**	**216**	**(61.5)**	**122**	**(35.9)**
	Completed	189	(53.8)	99	(29.1)
	Compliance (% in those expected to complete questionnaires)[d]	189	(87.5)	99	(81.1)
	Not completed	27	(7.7)	23	(6.8)
	Other	27	(7.7)	23	(6.8)
	Missing by Design	**135**	**(38.5)**	**218**	**(64.1)**
	Discontinued due to adverse event	40	(11.4)	31	(9.1)
	Discontinued due to clinical disease progression	14	(4.0)	18	(5.3)
Week 66	Discontinued due to lost to follow-up	0	(0.0)	1	(0.3)
	Discontinued due to other	3	(0.9)	2	(0.6)
	Discontinued due to radiological disease progression	53	(15.1)	133	(39.1)
	Discontinued due to subject choice	10	(2.8)	19	(5.6)
	Discontinued due to withdrawal of consent	1	(0.3)	7	(2.1)
	No visit scheduled	14	(4.0)	7	(2.1)
Week 69	**Expected to Complete Questionnaires**	**207**	**(59.0)**	**117**	**(34.4)**
	Completed	185	(52.7)	93	(27.4)
	Compliance (% in those expected to complete questionnaires)[d]	185	(89.4)	93	(79.5)
	Not completed	22	(6.3)	24	(7.1)
	Other	22	(6.3)	24	(7.1)
	Missing by Design	**144**	**(41.0)**	**223**	**(65.6)**
	Discontinued due to adverse event	40	(11.4)	32	(9.4)
	Discontinued due to clinical disease progression	15	(4.3)	19	(5.6)
	Discontinued due to lost to follow-up	0	(0.0)	1	(0.3)
	Discontinued due to other	3	(0.9)	2	(0.6)
	Discontinued due to radiological disease progression	56	(16.0)	134	(39.4)
	Discontinued due to subject choice	10	(2.8)	19	(5.6)
	Discontinued due to withdrawal of consent	1	(0.3)	7	(2.1)
	No visit scheduled	19	(5.4)	9	(2.6)
Week 72	**Expected to Complete Questionnaires**	**201**	**(57.3)**	**111**	**(32.6)**

Study: KEYNOTE 581[a]		Pembrolizumab + Lenvatinib N[b]=351		Sunitinib N[b]=340	
Treatment Visit	Questionnaire Completion Status (FKSI-DRS)[c]	n	(%)	n	(%)
	Completed	175	(49.9)	90	(26.5)
	Compliance (% in those expected to complete questionnaires)[d]	175	(87.1)	90	(81.1)
	Not completed	26	(7.4)	21	(6.2)
	Other	26	(7.4)	21	(6.2)
	Missing by Design	**150**	**(42.7)**	**229**	**(67.4)**
	Discontinued due to adverse event	41	(11.7)	33	(9.7)
	Discontinued due to clinical disease progression	15	(4.3)	19	(5.6)
	Discontinued due to lost to follow-up	0	(0.0)	1	(0.3)
	Discontinued due to other	3	(0.9)	2	(0.6)
Week 72	Discontinued due to radiological disease progression	58	(16.5)	137	(40.3)
	Discontinued due to subject choice	10	(2.8)	19	(5.6)
	Discontinued due to withdrawal of consent	1	(0.3)	7	(2.1)
	No visit scheduled	22	(6.3)	11	(3.2)
Week 75	**Expected to Complete Questionnaires**	**188**	**(53.6)**	**107**	**(31.5)**
	Completed	164	(46.7)	81	(23.8)
	Compliance (% in those expected to complete questionnaires)[d]	164	(87.2)	81	(75.7)
	Not completed	24	(6.8)	26	(7.6)
	Other	24	(6.8)	26	(7.6)
	Missing by Design	**163**	**(46.4)**	**233**	**(68.5)**
	Discontinued due to adverse event	41	(11.7)	33	(9.7)
	Discontinued due to clinical disease progression	15	(4.3)	19	(5.6)
	Discontinued due to lost to follow-up	0	(0.0)	1	(0.3)
	Discontinued due to other	3	(0.9)	2	(0.6)
	Discontinued due to radiological disease progression	62	(17.7)	139	(40.9)
	Discontinued due to subject choice	10	(2.8)	19	(5.6)
	Discontinued due to withdrawal of consent	1	(0.3)	7	(2.1)
	No visit scheduled	31	(8.8)	13	(3.8)
Week 78	**Expected to Complete Questionnaires**	**180**	**(51.3)**	**103**	**(30.3)**
	Completed	158	(45.0)	84	(24.7)
	Compliance (% in those expected to complete questionnaires)[d]	158	(87.8)	84	(81.6)
	Not completed	22	(6.3)	19	(5.6)
	Other	22	(6.3)	19	(5.6)
	Missing by Design	**171**	**(48.7)**	**237**	**(69.7)**
	Discontinued due to adverse event	43	(12.3)	33	(9.7)

Study: KEYNOTE 581[a]		Pembrolizumab + Lenvatinib N[b]=351		Sunitinib N[b]=340	
Treatment Visit	Questionnaire Completion Status (FKSI-DRS)[c]	n	(%)	n	(%)
	Discontinued due to clinical disease progression	16	(4.6)	19	(5.6)
	Discontinued due to lost to follow-up	0	(0.0)	1	(0.3)
	Discontinued due to other	3	(0.9)	2	(0.6)
	Discontinued due to radiological disease progression	66	(18.8)	143	(42.1)
	Discontinued due to subject choice	10	(2.8)	19	(5.6)
Week 78	Discontinued due to withdrawal of consent	1	(0.3)	7	(2.1)
	No visit scheduled	32	(9.1)	13	(3.8)
Week 81	**Expected to Complete Questionnaires**	**175**	**(49.9)**	**100**	**(29.4)**
	Completed	157	(44.7)	77	(22.6)
	Compliance (% in those expected to complete questionnaires)[d]	157	(89.7)	77	(77.0)
	Not completed	18	(5.1)	23	(6.8)
	Other	18	(5.1)	23	(6.8)
	Missing by Design	**176**	**(50.1)**	**240**	**(70.6)**
	Discontinued due to adverse event	44	(12.5)	33	(9.7)
	Discontinued due to clinical disease progression	16	(4.6)	19	(5.6)
	Discontinued due to lost to follow-up	0	(0.0)	1	(0.3)
	Discontinued due to other	3	(0.9)	2	(0.6)
	Discontinued due to radiological disease progression	66	(18.8)	144	(42.4)
	Discontinued due to subject choice	10	(2.8)	19	(5.6)
	Discontinued due to withdrawal of consent	1	(0.3)	8	(2.4)
	No visit scheduled	36	(10.3)	14	(4.1)
Week 84	**Expected to Complete Questionnaires**	**169**	**(48.1)**	**92**	**(27.1)**
	Completed	149	(42.5)	74	(21.8)
	Compliance (% in those expected to complete questionnaires)[d]	149	(88.2)	74	(80.4)
	Not completed	20	(5.7)	18	(5.3)
	Other	20	(5.7)	18	(5.3)
	Missing by Design	**182**	**(51.9)**	**248**	**(72.9)**
	Discontinued due to adverse event	45	(12.8)	34	(10.0)
	Discontinued due to clinical disease progression	17	(4.8)	19	(5.6)
	Discontinued due to lost to follow-up	0	(0.0)	1	(0.3)
	Discontinued due to other	3	(0.9)	2	(0.6)
	Discontinued due to radiological disease progression	68	(19.4)	148	(43.5)
	Discontinued due to subject choice	11	(3.1)	20	(5.9)
	Discontinued due to withdrawal of consent	1	(0.3)	8	(2.4)
	No visit scheduled	37	(10.5)	16	(4.7)

Study: KEYNOTE 581[a]		Pembrolizumab + Lenvatinib N[b]=351		Sunitinib N[b]=340	
Treatment Visit	Questionnaire Completion Status (FKSI-DRS)[c]	n	(%)	n	(%)
Week 87	**Expected to Complete Questionnaires**	**166**	**(47.3)**	**87**	**(25.6)**
	Completed	143	(40.7)	65	(19.1)
	Compliance (% in those expected to complete questionnaires)[d]	143	(86.1)	65	(74.7)
	Not completed	23	(6.6)	22	(6.5)
	Other	23	(6.6)	22	(6.5)
	Missing by Design	**185**	**(52.7)**	**253**	**(74.4)**
	Discontinued due to adverse event	46	(13.1)	35	(10.3)
	Discontinued due to clinical disease progression	17	(4.8)	19	(5.6)
	Discontinued due to lost to follow-up	0	(0.0)	1	(0.3)
	Discontinued due to other	3	(0.9)	2	(0.6)
	Discontinued due to radiological disease progression	68	(19.4)	149	(43.8)
	Discontinued due to subject choice	11	(3.1)	20	(5.9)
	Discontinued due to withdrawal of consent	1	(0.3)	8	(2.4)
	No visit scheduled	39	(11.1)	19	(5.6)
Week 90	**Expected to Complete Questionnaires**	**161**	**(45.9)**	**82**	**(24.1)**
	Completed	136	(38.7)	63	(18.5)
	Compliance (% in those expected to complete questionnaires)[d]	136	(84.5)	63	(76.8)
	Not completed	25	(7.1)	19	(5.6)
	Other	25	(7.1)	19	(5.6)
	Missing by Design	**190**	**(54.1)**	**258**	**(75.9)**
	Discontinued due to adverse event	46	(13.1)	36	(10.6)
	Discontinued due to clinical disease progression	17	(4.8)	19	(5.6)
	Discontinued due to lost to follow-up	0	(0.0)	1	(0.3)
	Discontinued due to other	3	(0.9)	2	(0.6)
	Discontinued due to radiological disease progression	69	(19.7)	151	(44.4)
	Discontinued due to subject choice	11	(3.1)	21	(6.2)
	Discontinued due to withdrawal of consent	1	(0.3)	8	(2.4)
	No visit scheduled	43	(12.3)	20	(5.9)
Week 93	**Expected to Complete Questionnaires**	**151**	**(43.0)**	**76**	**(22.4)**
	Completed	121	(34.5)	54	(15.9)
Week 93	Compliance (% in those expected to complete questionnaires)[d]	121	(80.1)	54	(71.1)
	Not completed	30	(8.5)	22	(6.5)
	Other	30	(8.5)	22	(6.5)
	Missing by Design	**200**	**(57.0)**	**264**	**(77.6)**

Study: KEYNOTE 581[a]		Pembrolizumab + Lenvatinib N[b]=351		Sunitinib N[b]=340	
Treatment Visit	Questionnaire Completion Status (FKSI-DRS)[c]	n	(%)	n	(%)
	Discontinued due to adverse event	46	(13.1)	36	(10.6)
	Discontinued due to clinical disease progression	17	(4.8)	19	(5.6)
	Discontinued due to lost to follow-up	0	(0.0)	1	(0.3)
	Discontinued due to other	3	(0.9)	2	(0.6)
	Discontinued due to radiological disease progression	75	(21.4)	154	(45.3)
	Discontinued due to subject choice	11	(3.1)	21	(6.2)
	Discontinued due to withdrawal of consent	1	(0.3)	8	(2.4)
	No visit scheduled	47	(13.4)	23	(6.8)
Week 96	**Expected to Complete Questionnaires**	**145**	**(41.3)**	**76**	**(22.4)**
	Completed	120	(34.2)	58	(17.1)
	Compliance (% in those expected to complete questionnaires)[d]	120	(82.8)	58	(76.3)
	Not completed	25	(7.1)	18	(5.3)
	Other	25	(7.1)	18	(5.3)
	Missing by Design	**206**	**(58.7)**	**264**	**(77.6)**
	Discontinued due to adverse event	46	(13.1)	36	(10.6)
	Discontinued due to clinical disease progression	17	(4.8)	19	(5.6)
	Discontinued due to lost to follow-up	0	(0.0)	1	(0.3)
	Discontinued due to other	3	(0.9)	2	(0.6)
	Discontinued due to radiological disease progression	76	(21.7)	154	(45.3)
	Discontinued due to subject choice	11	(3.1)	21	(6.2)
	Discontinued due to withdrawal of consent	1	(0.3)	8	(2.4)
	No visit scheduled	52	(14.8)	23	(6.8)
Week 99	**Expected to Complete Questionnaires**	**136**	**(38.7)**	**75**	**(22.1)**
	Completed	110	(31.3)	52	(15.3)
	Compliance (% in those expected to complete questionnaires)[d]	110	(80.9)	52	(69.3)
	Not completed	26	(7.4)	23	(6.8)
Week 99	Other	26	(7.4)	23	(6.8)
	Missing by Design	**215**	**(61.3)**	**265**	**(77.9)**
	Discontinued due to adverse event	46	(13.1)	36	(10.6)
	Discontinued due to clinical disease progression	17	(4.8)	19	(5.6)
	Discontinued due to lost to follow-up	0	(0.0)	1	(0.3)
	Discontinued due to other	3	(0.9)	2	(0.6)
	Discontinued due to radiological disease progression	79	(22.5)	154	(45.3)
	Discontinued due to subject choice	11	(3.1)	21	(6.2)
	Discontinued due to withdrawal of consent	1	(0.3)	8	(2.4)

Study: KEYNOTE 581[a]		Pembrolizumab + Lenvatinib N[b]=351		Sunitinib N[b]=340	
Treatment Visit	Questionnaire Completion Status (FKSI-DRS)[c]	n	(%)	n	(%)
	No visit scheduled	58	(16.5)	24	(7.1)
Week 102	**Expected to Complete Questionnaires**	**129**	**(36.8)**	**72**	**(21.2)**
	Completed	102	(29.1)	49	(14.4)
	Compliance (% in those expected to complete questionnaires)[d]	102	(79.1)	49	(68.1)
	Not completed	27	(7.7)	23	(6.8)
	Other	27	(7.7)	23	(6.8)
	Missing by Design	**222**	**(63.2)**	**268**	**(78.8)**
	Discontinued due to adverse event	46	(13.1)	37	(10.9)
	Discontinued due to clinical disease progression	18	(5.1)	19	(5.6)
	Discontinued due to lost to follow-up	0	(0.0)	1	(0.3)
	Discontinued due to other	3	(0.9)	2	(0.6)
	Discontinued due to radiological disease progression	83	(23.6)	156	(45.9)
	Discontinued due to subject choice	12	(3.4)	21	(6.2)
	Discontinued due to withdrawal of consent	1	(0.3)	8	(2.4)
	No visit scheduled	59	(16.8)	24	(7.1)
Week 105	**Expected to Complete Questionnaires**	**125**	**(35.6)**	**69**	**(20.3)**
	Completed	99	(28.2)	47	(13.8)
	Compliance (% in those expected to complete questionnaires)[d]	99	(79.2)	47	(68.1)
	Not completed	26	(7.4)	22	(6.5)
	Other	26	(7.4)	22	(6.5)
	Missing by Design	**226**	**(64.4)**	**271**	**(79.7)**
Week 105	Discontinued due to adverse event	47	(13.4)	37	(10.9)
	Discontinued due to clinical disease progression	18	(5.1)	19	(5.6)
	Discontinued due to lost to follow-up	0	(0.0)	1	(0.3)
	Discontinued due to other	3	(0.9)	3	(0.9)
	Discontinued due to radiological disease progression	84	(23.9)	157	(46.2)
	Discontinued due to subject choice	12	(3.4)	21	(6.2)
	Discontinued due to withdrawal of consent	1	(0.3)	8	(2.4)
	No visit scheduled	61	(17.4)	25	(7.4)
Week 108	**Expected to Complete Questionnaires**	**113**	**(32.2)**	**67**	**(19.7)**
	Completed	87	(24.8)	43	(12.6)
	Compliance (% in those expected to complete questionnaires)[d]	87	(77.0)	43	(64.2)
	Not completed	26	(7.4)	24	(7.1)
	Other	26	(7.4)	24	(7.1)

Study: KEYNOTE 581[a]		Pembrolizumab + Lenvatinib N[b]=351		Sunitinib N[b]=340	
Treatment Visit	Questionnaire Completion Status (FKSI-DRS)[c]	n	(%)	n	(%)
	Missing by Design	**238**	**(67.8)**	**273**	**(80.3)**
	Discontinued due to adverse event	48	(13.7)	37	(10.9)
	Discontinued due to clinical disease progression	18	(5.1)	19	(5.6)
	Discontinued due to lost to follow-up	0	(0.0)	1	(0.3)
	Discontinued due to other	8	(2.3)	3	(0.9)
	Discontinued due to radiological disease progression	87	(24.8)	158	(46.5)
	Discontinued due to subject choice	12	(3.4)	21	(6.2)
	Discontinued due to withdrawal of consent	1	(0.3)	8	(2.4)
	No visit scheduled	64	(18.2)	26	(7.6)
Week 111	**Expected to Complete Questionnaires**	**101**	**(28.8)**	**61**	**(17.9)**
	Completed	77	(21.9)	43	(12.6)
	Compliance (% in those expected to complete questionnaires)[d]	77	(76.2)	43	(70.5)
	Not completed	24	(6.8)	18	(5.3)
	Other	24	(6.8)	18	(5.3)
	Missing by Design	**250**	**(71.2)**	**279**	**(82.1)**
	Discontinued due to adverse event	50	(14.2)	37	(10.9)
	Discontinued due to clinical disease progression	18	(5.1)	20	(5.9)
Week 111	Discontinued due to lost to follow-up	0	(0.0)	1	(0.3)
	Discontinued due to other	9	(2.6)	3	(0.9)
	Discontinued due to radiological disease progression	88	(25.1)	159	(46.8)
	Discontinued due to subject choice	14	(4.0)	21	(6.2)
	Discontinued due to withdrawal of consent	1	(0.3)	8	(2.4)
	No visit scheduled	70	(19.9)	30	(8.8)
Week 114	**Expected to Complete Questionnaires**	**91**	**(25.9)**	**58**	**(17.1)**
	Completed	65	(18.5)	38	(11.2)
	Compliance (% in those expected to complete questionnaires)[d]	65	(71.4)	38	(65.5)
	Not completed	26	(7.4)	20	(5.9)
	Other	26	(7.4)	20	(5.9)
	Missing by Design	**260**	**(74.1)**	**282**	**(82.9)**
	Discontinued due to adverse event	51	(14.5)	37	(10.9)
	Discontinued due to clinical disease progression	18	(5.1)	20	(5.9)
	Discontinued due to lost to follow-up	0	(0.0)	1	(0.3)
	Discontinued due to other	10	(2.8)	3	(0.9)
	Discontinued due to radiological disease progression	88	(25.1)	159	(46.8)
	Discontinued due to subject choice	15	(4.3)	21	(6.2)

Study: KEYNOTE 581[a]		Pembrolizumab + Lenvatinib N[b]=351		Sunitinib N[b]=340	
Treatment Visit	Questionnaire Completion Status (FKSI-DRS)[c]	n	(%)	n	(%)
	Discontinued due to withdrawal of consent	1	(0.3)	8	(2.4)
	No visit scheduled	77	(21.9)	33	(9.7)
Week 117	**Expected to Complete Questionnaires**	**77**	**(21.9)**	**52**	**(15.3)**
	Completed	54	(15.4)	29	(8.5)
	Compliance (% in those expected to complete questionnaires)[d]	54	(70.1)	29	(55.8)
	Not completed	23	(6.6)	23	(6.8)
	Other	23	(6.6)	23	(6.8)
	Missing by Design	**274**	**(78.1)**	**288**	**(84.7)**
	Discontinued due to adverse event	53	(15.1)	37	(10.9)
	Discontinued due to clinical disease progression	18	(5.1)	20	(5.9)
	Discontinued due to lost to follow-up	0	(0.0)	1	(0.3)
	Discontinued due to other	10	(2.8)	3	(0.9)
Week 117	Discontinued due to radiological disease progression	88	(25.1)	161	(47.4)
	Discontinued due to subject choice	15	(4.3)	21	(6.2)
	Discontinued due to withdrawal of consent	1	(0.3)	8	(2.4)
	No visit scheduled	89	(25.4)	37	(10.9)
Week 120	**Expected to Complete Questionnaires**	**66**	**(18.8)**	**49**	**(14.4)**
	Completed	46	(13.1)	30	(8.8)
	Compliance (% in those expected to complete questionnaires)[d]	46	(69.7)	30	(61.2)
	Not completed	20	(5.7)	19	(5.6)
	Other	20	(5.7)	19	(5.6)
	Missing by Design	**285**	**(81.2)**	**291**	**(85.6)**
	Discontinued due to adverse event	54	(15.4)	37	(10.9)
	Discontinued due to clinical disease progression	18	(5.1)	21	(6.2)
	Discontinued due to lost to follow-up	0	(0.0)	1	(0.3)
	Discontinued due to other	10	(2.8)	3	(0.9)
	Discontinued due to radiological disease progression	90	(25.6)	161	(47.4)
	Discontinued due to subject choice	16	(4.6)	21	(6.2)
	Discontinued due to withdrawal of consent	1	(0.3)	8	(2.4)
	No visit scheduled	96	(27.4)	39	(11.5)
Week 123	**Expected to Complete Questionnaires**	**55**	**(15.7)**	**45**	**(13.2)**
	Completed	39	(11.1)	24	(7.1)
	Compliance (% in those expected to complete questionnaires)[d]	39	(70.9)	24	(53.3)
	Not completed	16	(4.6)	21	(6.2)

Study: KEYNOTE 581[a]		Pembrolizumab + Lenvatinib N[b]=351		Sunitinib N[b]=340	
Treatment Visit	Questionnaire Completion Status (FKSI-DRS)[c]	n	(%)	n	(%)
	Other	16	(4.6)	21	(6.2)
	Missing by Design	**296**	**(84.3)**	**295**	**(86.8)**
	Discontinued due to adverse event	55	(15.7)	37	(10.9)
	Discontinued due to clinical disease progression	18	(5.1)	21	(6.2)
	Discontinued due to lost to follow-up	0	(0.0)	1	(0.3)
	Discontinued due to other	12	(3.4)	3	(0.9)
	Discontinued due to radiological disease progression	91	(25.9)	163	(47.9)
	Discontinued due to subject choice	16	(4.6)	21	(6.2)
Week 123	Discontinued due to withdrawal of consent	2	(0.6)	8	(2.4)
	No visit scheduled	102	(29.1)	41	(12.1)
Week 126	**Expected to Complete Questionnaires**	**51**	**(14.5)**	**40**	**(11.8)**
	Completed	34	(9.7)	21	(6.2)
	Compliance (% in those expected to complete questionnaires)[d]	34	(66.7)	21	(52.5)
	Not completed	17	(4.8)	19	(5.6)
	Other	17	(4.8)	19	(5.6)
	Missing by Design	**300**	**(85.5)**	**300**	**(88.2)**
	Discontinued due to adverse event	56	(16.0)	37	(10.9)
	Discontinued due to clinical disease progression	18	(5.1)	21	(6.2)
	Discontinued due to lost to follow-up	0	(0.0)	1	(0.3)
	Discontinued due to other	12	(3.4)	3	(0.9)
	Discontinued due to radiological disease progression	91	(25.9)	164	(48.2)
	Discontinued due to subject choice	16	(4.6)	21	(6.2)
	Discontinued due to withdrawal of consent	2	(0.6)	8	(2.4)
	No visit scheduled	105	(29.9)	45	(13.2)
Week 129	**Expected to Complete Questionnaires**	**44**	**(12.5)**	**36**	**(10.6)**
	Completed	27	(7.7)	18	(5.3)
	Compliance (% in those expected to complete questionnaires)[d]	27	(61.4)	18	(50.0)
	Not completed	17	(4.8)	18	(5.3)
	Other	17	(4.8)	18	(5.3)
	Missing by Design	**307**	**(87.5)**	**304**	**(89.4)**
	Discontinued due to adverse event	56	(16.0)	37	(10.9)
	Discontinued due to clinical disease progression	18	(5.1)	21	(6.2)
	Discontinued due to lost to follow-up	0	(0.0)	1	(0.3)
	Discontinued due to other	12	(3.4)	3	(0.9)
	Discontinued due to radiological disease progression	91	(25.9)	164	(48.2)

Study: KEYNOTE 581[a]		Pembrolizumab + Lenvatinib N[b]=351		Sunitinib N[b]=340	
Treatment Visit	Questionnaire Completion Status (FKSI-DRS)[c]	n	(%)	n	(%)
	Discontinued due to subject choice	16	(4.6)	21	(6.2)
	Discontinued due to withdrawal of consent	2	(0.6)	8	(2.4)
	No visit scheduled	112	(31.9)	49	(14.4)
Week 132	**Expected to Complete Questionnaires**	**39**	**(11.1)**	**29**	**(8.5)**
	Completed	22	(6.3)	9	(2.6)
	Compliance (% in those expected to complete questionnaires)[d]	22	(56.4)	9	(31.0)
	Not completed	17	(4.8)	20	(5.9)
	Other	17	(4.8)	20	(5.9)
	Missing by Design	**312**	**(88.9)**	**311**	**(91.5)**
	Discontinued due to adverse event	56	(16.0)	37	(10.9)
	Discontinued due to clinical disease progression	18	(5.1)	21	(6.2)
	Discontinued due to lost to follow-up	0	(0.0)	1	(0.3)
	Discontinued due to other	12	(3.4)	3	(0.9)
	Discontinued due to radiological disease progression	91	(25.9)	166	(48.8)
	Discontinued due to subject choice	16	(4.6)	21	(6.2)
	Discontinued due to withdrawal of consent	2	(0.6)	8	(2.4)
	No visit scheduled	117	(33.3)	54	(15.9)
Week 135	**Expected to Complete Questionnaires**	**37**	**(10.5)**	**27**	**(7.9)**
	Completed	20	(5.7)	10	(2.9)
	Compliance (% in those expected to complete questionnaires)[d]	20	(54.1)	10	(37.0)
	Not completed	17	(4.8)	17	(5.0)
	Other	17	(4.8)	17	(5.0)
	Missing by Design	**314**	**(89.5)**	**313**	**(92.1)**
	Discontinued due to adverse event	56	(16.0)	37	(10.9)
	Discontinued due to clinical disease progression	18	(5.1)	21	(6.2)
	Discontinued due to lost to follow-up	0	(0.0)	1	(0.3)
	Discontinued due to other	12	(3.4)	3	(0.9)
	Discontinued due to radiological disease progression	92	(26.2)	166	(48.8)
	Discontinued due to subject choice	16	(4.6)	21	(6.2)
	Discontinued due to withdrawal of consent	2	(0.6)	8	(2.4)
	No visit scheduled	118	(33.6)	56	(16.5)
Week 138	**Expected to Complete Questionnaires**	**32**	**(9.1)**	**26**	**(7.6)**
	Completed	16	(4.6)	8	(2.4)
Week 138	Compliance (% in those expected to complete questionnaires)[d]	16	(50.0)	8	(30.8)

Study: KEYNOTE 581[a]		Pembrolizumab + Lenvatinib N[b]=351		Sunitinib N[b]=340	
Treatment Visit	Questionnaire Completion Status (FKSI-DRS)[c]	n	(%)	n	(%)
	Not completed	16	(4.6)	18	(5.3)
	Other	16	(4.6)	18	(5.3)
	Missing by Design	**319**	**(90.9)**	**314**	**(92.4)**
	Discontinued due to adverse event	56	(16.0)	37	(10.9)
	Discontinued due to clinical disease progression	18	(5.1)	21	(6.2)
	Discontinued due to lost to follow-up	0	(0.0)	1	(0.3)
	Discontinued due to other	12	(3.4)	3	(0.9)
	Discontinued due to radiological disease progression	93	(26.5)	166	(48.8)
	Discontinued due to subject choice	16	(4.6)	21	(6.2)
	Discontinued due to withdrawal of consent	2	(0.6)	8	(2.4)
	No visit scheduled	122	(34.8)	57	(16.8)
Week 141	**Expected to Complete Questionnaires**	**26**	**(7.4)**	**24**	**(7.1)**
	Completed	8	(2.3)	7	(2.1)
	Compliance (% in those expected to complete questionnaires)[d]	8	(30.8)	7	(29.2)
	Not completed	18	(5.1)	17	(5.0)
	Other	18	(5.1)	17	(5.0)
	Missing by Design	**325**	**(92.6)**	**316**	**(92.9)**
	Discontinued due to adverse event	56	(16.0)	37	(10.9)
	Discontinued due to clinical disease progression	18	(5.1)	21	(6.2)
	Discontinued due to lost to follow-up	0	(0.0)	1	(0.3)
	Discontinued due to other	12	(3.4)	3	(0.9)
	Discontinued due to radiological disease progression	93	(26.5)	166	(48.8)
	Discontinued due to subject choice	16	(4.6)	21	(6.2)
	Discontinued due to withdrawal of consent	2	(0.6)	8	(2.4)
	No visit scheduled	128	(36.5)	59	(17.4)
Week 144	**Expected to Complete Questionnaires**	**23**	**(6.6)**	**22**	**(6.5)**
	Completed	8	(2.3)	5	(1.5)
	Compliance (% in those expected to complete questionnaires)[d]	8	(34.8)	5	(22.7)
	Not completed	15	(4.3)	17	(5.0)
Week 144	Other	15	(4.3)	17	(5.0)
	Missing by Design	**328**	**(93.4)**	**318**	**(93.5)**
	Discontinued due to adverse event	56	(16.0)	37	(10.9)
	Discontinued due to clinical disease progression	18	(5.1)	21	(6.2)
	Discontinued due to lost to follow-up	0	(0.0)	1	(0.3)
	Discontinued due to other	12	(3.4)	3	(0.9)

Study: KEYNOTE 581[a]		Pembrolizumab + Lenvatinib N[b]=351		Sunitinib N[b]=340	
Treatment Visit	Questionnaire Completion Status (FKSI-DRS)[c]	n	(%)	n	(%)
	Discontinued due to radiological disease progression	93	(26.5)	167	(49.1)
	Discontinued due to subject choice	16	(4.6)	21	(6.2)
	Discontinued due to withdrawal of consent	2	(0.6)	8	(2.4)
	No visit scheduled	131	(37.3)	60	(17.6)
Week 147	**Expected to Complete Questionnaires**	**23**	**(6.6)**	**21**	**(6.2)**
	Completed	8	(2.3)	3	(0.9)
	Compliance (% in those expected to complete questionnaires)[d]	8	(34.8)	3	(14.3)
	Not completed	15	(4.3)	18	(5.3)
	Other	15	(4.3)	18	(5.3)
	Missing by Design	**328**	**(93.4)**	**319**	**(93.8)**
	Discontinued due to adverse event	56	(16.0)	37	(10.9)
	Discontinued due to clinical disease progression	18	(5.1)	21	(6.2)
	Discontinued due to lost to follow-up	0	(0.0)	1	(0.3)
	Discontinued due to other	12	(3.4)	3	(0.9)
	Discontinued due to radiological disease progression	93	(26.5)	167	(49.1)
	Discontinued due to subject choice	16	(4.6)	21	(6.2)
	Discontinued due to withdrawal of consent	2	(0.6)	8	(2.4)
	No visit scheduled	131	(37.3)	61	(17.9)
Week 150	**Expected to Complete Questionnaires**	**22**	**(6.3)**	**20**	**(5.9)**
	Completed	6	(1.7)	3	(0.9)
	Compliance (% in those expected to complete questionnaires)[d]	6	(27.3)	3	(15.0)
	Not completed	16	(4.6)	17	(5.0)
	Other	16	(4.6)	17	(5.0)
	Missing by Design	**329**	**(93.7)**	**320**	**(94.1)**
Week 150	Discontinued due to adverse event	56	(16.0)	37	(10.9)
	Discontinued due to clinical disease progression	18	(5.1)	21	(6.2)
	Discontinued due to lost to follow-up	0	(0.0)	1	(0.3)
	Discontinued due to other	12	(3.4)	3	(0.9)
	Discontinued due to radiological disease progression	94	(26.8)	167	(49.1)
	Discontinued due to subject choice	16	(4.6)	21	(6.2)
	Discontinued due to withdrawal of consent	2	(0.6)	8	(2.4)
	No visit scheduled	131	(37.3)	62	(18.2)
Week 153	**Expected to Complete Questionnaires**	**21**	**(6.0)**	**19**	**(5.6)**
	Completed	6	(1.7)	2	(0.6)
	Compliance (% in those expected to complete	6	(28.6)	2	(10.5)

Study: KEYNOTE 581[a]		Pembrolizumab + Lenvatinib N[b]=351		Sunitinib N[b]=340	
Treatment Visit	Questionnaire Completion Status (FKSI-DRS)[c]	n	(%)	n	(%)
	questionnaires)[d]				
	Not completed	15	(4.3)	17	(5.0)
	Other	15	(4.3)	17	(5.0)
	Missing by Design	**330**	**(94.0)**	**321**	**(94.4)**
	Discontinued due to adverse event	56	(16.0)	37	(10.9)
	Discontinued due to clinical disease progression	18	(5.1)	21	(6.2)
	Discontinued due to lost to follow-up	0	(0.0)	1	(0.3)
	Discontinued due to other	12	(3.4)	3	(0.9)
	Discontinued due to radiological disease progression	94	(26.8)	167	(49.1)
	Discontinued due to subject choice	16	(4.6)	21	(6.2)
	Discontinued due to withdrawal of consent	2	(0.6)	8	(2.4)
	No visit scheduled	132	(37.6)	63	(18.5)
Week 156	**Expected to Complete Questionnaires**	**19**	**(5.4)**	**19**	**(5.6)**
	Completed	4	(1.1)	1	(0.3)
	Compliance (% in those expected to complete questionnaires)[d]	4	(21.1)	1	(5.3)
	Not completed	15	(4.3)	18	(5.3)
	Other	15	(4.3)	18	(5.3)
	Missing by Design	**332**	**(94.6)**	**321**	**(94.4)**
	Discontinued due to adverse event	56	(16.0)	37	(10.9)
	Discontinued due to clinical disease progression	18	(5.1)	21	(6.2)
Week 156	Discontinued due to lost to follow-up	0	(0.0)	1	(0.3)
	Discontinued due to other	12	(3.4)	3	(0.9)
	Discontinued due to radiological disease progression	94	(26.8)	167	(49.1)
	Discontinued due to subject choice	16	(4.6)	21	(6.2)
	Discontinued due to withdrawal of consent	2	(0.6)	8	(2.4)
	No visit scheduled	134	(38.2)	63	(18.5)
Week 159	**Expected to Complete Questionnaires**	**17**	**(4.8)**	**18**	**(5.3)**
	Completed	2	(0.6)	1	(0.3)
	Compliance (% in those expected to complete questionnaires)[d]	2	(11.8)	1	(5.6)
	Not completed	15	(4.3)	17	(5.0)
	Other	15	(4.3)	17	(5.0)
	Missing by Design	**334**	**(95.2)**	**322**	**(94.7)**
	Discontinued due to adverse event	57	(16.2)	37	(10.9)
	Discontinued due to clinical disease progression	18	(5.1)	21	(6.2)
	Discontinued due to lost to follow-up	0	(0.0)	1	(0.3)

Study: KEYNOTE 581[a]		Pembrolizumab + Lenvatinib N[b]=351		Sunitinib N[b]=340	
Treatment Visit	Questionnaire Completion Status (FKSI-DRS)[c]	n	(%)	n	(%)
	Discontinued due to other	12	(3.4)	3	(0.9)
	Discontinued due to radiological disease progression	94	(26.8)	167	(49.1)
	Discontinued due to subject choice	16	(4.6)	21	(6.2)
	Discontinued due to withdrawal of consent	2	(0.6)	8	(2.4)
	No visit scheduled	135	(38.5)	64	(18.8)
Week 162	**Expected to Complete Questionnaires**	**17**	**(4.8)**	**17**	**(5.0)**
	Completed	2	(0.6)	0	(0.0)
	Compliance (% in those expected to complete questionnaires)[d]	2	(11.8)	0	(0.0)
	Not completed	15	(4.3)	17	(5.0)
	Other	15	(4.3)	17	(5.0)
	Missing by Design	**334**	**(95.2)**	**323**	**(95.0)**
	Discontinued due to adverse event	57	(16.2)	37	(10.9)
	Discontinued due to clinical disease progression	18	(5.1)	21	(6.2)
	Discontinued due to lost to follow-up	0	(0.0)	1	(0.3)
	Discontinued due to other	12	(3.4)	3	(0.9)
Week 162	Discontinued due to radiological disease progression	94	(26.8)	167	(49.1)
	Discontinued due to subject choice	16	(4.6)	21	(6.2)
	Discontinued due to withdrawal of consent	2	(0.6)	8	(2.4)
	No visit scheduled	135	(38.5)	65	(19.1)
Week 165	**Expected to Complete Questionnaires**	**17**	**(4.8)**	**17**	**(5.0)**
	Completed	2	(0.6)	0	(0.0)
	Compliance (% in those expected to complete questionnaires)[d]	2	(11.8)	0	(0.0)
	Not completed	15	(4.3)	17	(5.0)
	Other	15	(4.3)	17	(5.0)
	Missing by Design	**334**	**(95.2)**	**323**	**(95.0)**
	Discontinued due to adverse event	57	(16.2)	37	(10.9)
	Discontinued due to clinical disease progression	18	(5.1)	21	(6.2)
	Discontinued due to lost to follow-up	0	(0.0)	1	(0.3)
	Discontinued due to other	12	(3.4)	3	(0.9)
	Discontinued due to radiological disease progression	94	(26.8)	167	(49.1)
	Discontinued due to subject choice	16	(4.6)	21	(6.2)
	Discontinued due to withdrawal of consent	2	(0.6)	8	(2.4)
	No visit scheduled	135	(38.5)	65	(19.1)
Week 168	**Expected to Complete Questionnaires**	**17**	**(4.8)**	**17**	**(5.0)**
	Completed	2	(0.6)	0	(0.0)

Study: KEYNOTE 581[a]		Pembrolizumab + Lenvatinib N[b]=351		Sunitinib N[b]=340	
Treatment Visit	Questionnaire Completion Status (FKSI-DRS)[c]	n	(%)	n	(%)
	Compliance (% in those expected to complete questionnaires)[d]	2	(11.8)	0	(0.0)
	Not completed	15	(4.3)	17	(5.0)
	Other	15	(4.3)	17	(5.0)
	Missing by Design	**334**	**(95.2)**	**323**	**(95.0)**
	Discontinued due to adverse event	57	(16.2)	37	(10.9)
	Discontinued due to clinical disease progression	18	(5.1)	21	(6.2)
	Discontinued due to lost to follow-up	0	(0.0)	1	(0.3)
	Discontinued due to other	12	(3.4)	3	(0.9)
	Discontinued due to radiological disease progression	94	(26.8)	167	(49.1)
	Discontinued due to subject choice	16	(4.6)	21	(6.2)
Week 168	Discontinued due to withdrawal of consent	2	(0.6)	8	(2.4)
	No visit scheduled	135	(38.5)	65	(19.1)
Week 171	**Expected to Complete Questionnaires**	**15**	**(4.3)**	**17**	**(5.0)**
	Not completed	15	(4.3)	17	(5.0)
	Other	15	(4.3)	17	(5.0)
	Missing by Design	**336**	**(95.7)**	**323**	**(95.0)**
	Discontinued due to adverse event	57	(16.2)	37	(10.9)
	Discontinued due to clinical disease progression	18	(5.1)	21	(6.2)
	Discontinued due to lost to follow-up	0	(0.0)	1	(0.3)
	Discontinued due to other	12	(3.4)	3	(0.9)
	Discontinued due to radiological disease progression	94	(26.8)	167	(49.1)
	Discontinued due to subject choice	16	(4.6)	21	(6.2)
	Discontinued due to withdrawal of consent	2	(0.6)	8	(2.4)
	No visit scheduled	137	(39.0)	65	(19.1)
Week 174	**Expected to Complete Questionnaires**	**15**	**(4.3)**	**17**	**(5.0)**
	Not completed	15	(4.3)	17	(5.0)
	Other	15	(4.3)	17	(5.0)
	Missing by Design	**336**	**(95.7)**	**323**	**(95.0)**
	Discontinued due to adverse event	57	(16.2)	37	(10.9)
	Discontinued due to clinical disease progression	18	(5.1)	21	(6.2)
	Discontinued due to lost to follow-up	0	(0.0)	1	(0.3)
	Discontinued due to other	12	(3.4)	3	(0.9)
	Discontinued due to radiological disease progression	94	(26.8)	167	(49.1)
	Discontinued due to subject choice	16	(4.6)	21	(6.2)
	Discontinued due to withdrawal of consent	2	(0.6)	8	(2.4)
Week 174	No visit scheduled	137	(39.0)	65	(19.1)

Study: KEYNOTE 581[a]		Pembrolizumab + Lenvatinib N[b]=351		Sunitinib N[b]=340	
Treatment Visit	Questionnaire Completion Status (FKSI-DRS)[c]	n	(%)	n	(%)

a: Database Cutoff Date: 28AUG2020

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

c: Questionnaire completion status is missing by design in case of discontinuation, death, and no visit scheduled else is expected to complete questionnaires

d: Compliance Rate is defined as the number of subjects completed the questionnaire over the number of subjects expected to complete the questionnaire, excluding those missing by design

FKSI-DRS: Functional Assessment of Cancer Therapy - Kidney Symptom Index - Disease Related Symptoms

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

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

Study: KEYNOTE 581[a]		Pembrolizumab + Lenvatinib N[b]=351		Sunitinib N[b]=340	
Treatment Visit	Questionnaire Completion Status (EQ-5D)[c]	n	(%)	n	(%)
Week 0	**Expected to Complete Questionnaires**	**351**	**(100.0)**	**340**	**(100.0)**
	Completed	338	(96.3)	321	(94.4)
	Compliance (% in those expected to complete questionnaires)[d]	338	(96.3)	321	(94.4)
	Not completed	13	(3.7)	19	(5.6)
	Other	13	(3.7)	19	(5.6)
	Missing by Design	**0**	**(0.0)**	**0**	**(0.0)**
Week 3	**Expected to Complete Questionnaires**	**345**	**(98.3)**	**334**	**(98.2)**
	Completed	322	(91.7)	285	(83.8)
	Compliance (% in those expected to complete questionnaires)[d]	322	(93.3)	285	(85.3)
	Not completed	23	(6.6)	49	(14.4)
	Other	23	(6.6)	49	(14.4)
	Missing by Design	**6**	**(1.7)**	**6**	**(1.8)**
	Discontinued due to adverse event	5	(1.4)	2	(0.6)
	Discontinued due to clinical disease progression	1	(0.3)	1	(0.3)
	Discontinued due to subject choice	0	(0.0)	1	(0.3)
	Discontinued due to withdrawal of consent	0	(0.0)	2	(0.6)
Week 6	**Expected to Complete Questionnaires**	**342**	**(97.4)**	**324**	**(95.3)**

Study: KEYNOTE 581[a]		Pembrolizumab + Lenvatinib N[b]=351		Sunitinib N[b]=340	
Treatment Visit	Questionnaire Completion Status (EQ-5D)[c]	n	(%)	n	(%)
	Completed	297	(84.6)	287	(84.4)
	Compliance (% in those expected to complete questionnaires)[d]	297	(86.8)	287	(88.6)
	Not completed	45	(12.8)	37	(10.9)
	Other	45	(12.8)	37	(10.9)
	Missing by Design	**9**	**(2.6)**	**16**	**(4.7)**
	Discontinued due to adverse event	8	(2.3)	3	(0.9)
	Discontinued due to clinical disease progression	1	(0.3)	4	(1.2)
	Discontinued due to radiological disease progression	0	(0.0)	1	(0.3)
	Discontinued due to subject choice	0	(0.0)	5	(1.5)
	Discontinued due to withdrawal of consent	0	(0.0)	3	(0.9)
Week 9	**Expected to Complete Questionnaires**	**339**	**(96.6)**	**311**	**(91.5)**
	Completed	306	(87.2)	267	(78.5)
	Compliance (% in those expected to complete questionnaires)[d]	306	(90.3)	267	(85.9)
Week 9	Not completed	33	(9.4)	44	(12.9)
	Other	33	(9.4)	44	(12.9)
	Missing by Design	**12**	**(3.4)**	**29**	**(8.5)**
	Discontinued due to adverse event	10	(2.8)	7	(2.1)
	Discontinued due to clinical disease progression	1	(0.3)	5	(1.5)
	Discontinued due to radiological disease progression	1	(0.3)	8	(2.4)
	Discontinued due to subject choice	0	(0.0)	5	(1.5)
	Discontinued due to withdrawal of consent	0	(0.0)	4	(1.2)
Week 12	**Expected to Complete Questionnaires**	**331**	**(94.3)**	**285**	**(83.8)**
	Completed	299	(85.2)	255	(75.0)
	Compliance (% in those expected to complete questionnaires)[d]	299	(90.3)	255	(89.5)
	Not completed	32	(9.1)	30	(8.8)
	Other	32	(9.1)	30	(8.8)
	Missing by Design	**20**	**(5.7)**	**55**	**(16.2)**
	Discontinued due to adverse event	12	(3.4)	10	(2.9)
	Discontinued due to clinical disease progression	3	(0.9)	6	(1.8)
	Discontinued due to radiological disease progression	5	(1.4)	25	(7.4)
	Discontinued due to subject choice	0	(0.0)	10	(2.9)
	Discontinued due to withdrawal of consent	0	(0.0)	4	(1.2)
Week 15	**Expected to Complete Questionnaires**	**327**	**(93.2)**	**276**	**(81.2)**
	Completed	300	(85.5)	245	(72.1)

Study: KEYNOTE 581[a]		Pembrolizumab + Lenvatinib N[b]=351		Sunitinib N[b]=340	
Treatment Visit	Questionnaire Completion Status (EQ-5D)[c]	n	(%)	n	(%)
	Compliance (% in those expected to complete questionnaires)[d]	300	(91.7)	245	(88.8)
	Not completed	27	(7.7)	31	(9.1)
	Other	27	(7.7)	31	(9.1)
	Missing by Design	**24**	**(6.8)**	**64**	**(18.8)**
	Discontinued due to adverse event	13	(3.7)	13	(3.8)
	Discontinued due to clinical disease progression	3	(0.9)	6	(1.8)
	Discontinued due to radiological disease progression	7	(2.0)	30	(8.8)
	Discontinued due to subject choice	1	(0.3)	11	(3.2)
	Discontinued due to withdrawal of consent	0	(0.0)	4	(1.2)
Week 18	**Expected to Complete Questionnaires**	**322**	**(91.7)**	**267**	**(78.5)**
	Completed	300	(85.5)	240	(70.6)
	Compliance (% in those expected to complete questionnaires)[d]	300	(93.2)	240	(89.9)
	Not completed	22	(6.3)	27	(7.9)
	Other	22	(6.3)	27	(7.9)
	Missing by Design	**29**	**(8.3)**	**73**	**(21.5)**
	Discontinued due to adverse event	17	(4.8)	15	(4.4)
	Discontinued due to clinical disease progression	3	(0.9)	9	(2.6)
	Discontinued due to radiological disease progression	8	(2.3)	32	(9.4)
	Discontinued due to subject choice	1	(0.3)	12	(3.5)
	Discontinued due to withdrawal of consent	0	(0.0)	5	(1.5)
Week 21	**Expected to Complete Questionnaires**	**318**	**(90.6)**	**254**	**(74.7)**
	Completed	291	(82.9)	219	(64.4)
	Compliance (% in those expected to complete questionnaires)[d]	291	(91.5)	219	(86.2)
	Not completed	27	(7.7)	35	(10.3)
	Other	27	(7.7)	35	(10.3)
	Missing by Design	**33**	**(9.4)**	**86**	**(25.3)**
	Discontinued due to adverse event	19	(5.4)	17	(5.0)
	Discontinued due to clinical disease progression	3	(0.9)	9	(2.6)
	Discontinued due to other	0	(0.0)	1	(0.3)
	Discontinued due to radiological disease progression	9	(2.6)	41	(12.1)
	Discontinued due to subject choice	2	(0.6)	13	(3.8)
	Discontinued due to withdrawal of consent	0	(0.0)	5	(1.5)
Week 24	**Expected to Complete Questionnaires**	**314**	**(89.5)**	**242**	**(71.2)**
	Completed	289	(82.3)	214	(62.9)

Study: KEYNOTE 581[a]		Pembrolizumab + Lenvatinib N[b]=351		Sunitinib N[b]=340	
Treatment Visit	Questionnaire Completion Status (EQ-5D)[c]	n	(%)	n	(%)
	Compliance (% in those expected to complete questionnaires)[d]	289	(92.0)	214	(88.4)
	Not completed	25	(7.1)	28	(8.2)
	Other	25	(7.1)	28	(8.2)
	Missing by Design	**37**	**(10.5)**	**98**	**(28.8)**
	Discontinued due to adverse event	20	(5.7)	20	(5.9)
Week 24	Discontinued due to clinical disease progression	4	(1.1)	12	(3.5)
	Discontinued due to other	1	(0.3)	1	(0.3)
	Discontinued due to radiological disease progression	10	(2.8)	47	(13.8)
	Discontinued due to subject choice	2	(0.6)	13	(3.8)
	Discontinued due to withdrawal of consent	0	(0.0)	5	(1.5)
Week 27	**Expected to Complete Questionnaires**	**303**	**(86.3)**	**218**	**(64.1)**
	Completed	274	(78.1)	193	(56.8)
	Compliance (% in those expected to complete questionnaires)[d]	274	(90.4)	193	(88.5)
	Not completed	29	(8.3)	25	(7.4)
	Other	29	(8.3)	25	(7.4)
	Missing by Design	**48**	**(13.7)**	**122**	**(35.9)**
	Discontinued due to adverse event	23	(6.6)	23	(6.8)
	Discontinued due to clinical disease progression	4	(1.1)	14	(4.1)
	Discontinued due to other	1	(0.3)	1	(0.3)
	Discontinued due to radiological disease progression	15	(4.3)	65	(19.1)
	Discontinued due to subject choice	5	(1.4)	14	(4.1)
	Discontinued due to withdrawal of consent	0	(0.0)	5	(1.5)
Week 30	**Expected to Complete Questionnaires**	**297**	**(84.6)**	**206**	**(60.6)**
	Completed	277	(78.9)	181	(53.2)
	Compliance (% in those expected to complete questionnaires)[d]	277	(93.3)	181	(87.9)
	Not completed	20	(5.7)	25	(7.4)
	Other	20	(5.7)	25	(7.4)
	Missing by Design	**54**	**(15.4)**	**134**	**(39.4)**
	Discontinued due to adverse event	24	(6.8)	24	(7.1)
	Discontinued due to clinical disease progression	5	(1.4)	15	(4.4)
	Discontinued due to other	1	(0.3)	1	(0.3)
	Discontinued due to radiological disease progression	19	(5.4)	72	(21.2)
	Discontinued due to subject choice	5	(1.4)	16	(4.7)
	Discontinued due to withdrawal of consent	0	(0.0)	6	(1.8)

Study: KEYNOTE 581[a]		Pembrolizumab + Lenvatinib N[b]=351		Sunitinib N[b]=340	
Treatment Visit	Questionnaire Completion Status (EQ-5D)[c]	n	(%)	n	(%)
Week 33	**Expected to Complete Questionnaires**	**290**	**(82.6)**	**195**	**(57.4)**
Week 33	Completed	266	(75.8)	169	(49.7)
	Compliance (% in those expected to complete questionnaires)[d]	266	(91.7)	169	(86.7)
	Not completed	24	(6.8)	26	(7.6)
	Other	24	(6.8)	26	(7.6)
	Missing by Design	**61**	**(17.4)**	**145**	**(42.6)**
	Discontinued due to adverse event	27	(7.7)	26	(7.6)
	Discontinued due to clinical disease progression	5	(1.4)	15	(4.4)
	Discontinued due to other	1	(0.3)	1	(0.3)
	Discontinued due to radiological disease progression	22	(6.3)	80	(23.5)
	Discontinued due to subject choice	6	(1.7)	17	(5.0)
	Discontinued due to withdrawal of consent	0	(0.0)	6	(1.8)
Week 36	**Expected to Complete Questionnaires**	**283**	**(80.6)**	**186**	**(54.7)**
	Completed	260	(74.1)	158	(46.5)
	Compliance (% in those expected to complete questionnaires)[d]	260	(91.9)	158	(84.9)
	Not completed	23	(6.6)	28	(8.2)
	Other	23	(6.6)	28	(8.2)
	Missing by Design	**68**	**(19.4)**	**154**	**(45.3)**
	Discontinued due to adverse event	29	(8.3)	27	(7.9)
	Discontinued due to clinical disease progression	5	(1.4)	15	(4.4)
	Discontinued due to other	1	(0.3)	1	(0.3)
	Discontinued due to radiological disease progression	27	(7.7)	86	(25.3)
	Discontinued due to subject choice	6	(1.7)	18	(5.3)
	Discontinued due to withdrawal of consent	0	(0.0)	7	(2.1)
Week 39	**Expected to Complete Questionnaires**	**279**	**(79.5)**	**180**	**(52.9)**
	Completed	255	(72.6)	150	(44.1)
	Compliance (% in those expected to complete questionnaires)[d]	255	(91.4)	150	(83.3)
	Not completed	24	(6.8)	30	(8.8)
	Other	24	(6.8)	30	(8.8)
	Missing by Design	**72**	**(20.5)**	**160**	**(47.1)**
	Discontinued due to adverse event	30	(8.5)	28	(8.2)
Week 39	Discontinued due to clinical disease progression	6	(1.7)	16	(4.7)
	Discontinued due to lost to follow-up	0	(0.0)	1	(0.3)
	Discontinued due to other	1	(0.3)	1	(0.3)

Study: KEYNOTE 581[a]		Pembrolizumab + Lenvatinib N[b]=351		Sunitinib N[b]=340	
Treatment Visit	Questionnaire Completion Status (EQ-5D)[c]	n	(%)	n	(%)
	Discontinued due to radiological disease progression	29	(8.3)	89	(26.2)
	Discontinued due to subject choice	6	(1.7)	18	(5.3)
	Discontinued due to withdrawal of consent	0	(0.0)	7	(2.1)
Week 42	**Expected to Complete Questionnaires**	**273**	**(77.8)**	**174**	**(51.2)**
	Completed	248	(70.7)	146	(42.9)
	Compliance (% in those expected to complete questionnaires)[d]	248	(90.8)	146	(83.9)
	Not completed	25	(7.1)	28	(8.2)
	Other	25	(7.1)	28	(8.2)
	Missing by Design	**78**	**(22.2)**	**166**	**(48.8)**
	Discontinued due to adverse event	30	(8.5)	28	(8.2)
	Discontinued due to clinical disease progression	10	(2.8)	16	(4.7)
	Discontinued due to lost to follow-up	0	(0.0)	1	(0.3)
	Discontinued due to other	1	(0.3)	2	(0.6)
	Discontinued due to radiological disease progression	31	(8.8)	93	(27.4)
	Discontinued due to subject choice	6	(1.7)	18	(5.3)
	Discontinued due to withdrawal of consent	0	(0.0)	8	(2.4)
Week 45	**Expected to Complete Questionnaires**	**265**	**(75.5)**	**163**	**(47.9)**
	Completed	235	(67.0)	138	(40.6)
	Compliance (% in those expected to complete questionnaires)[d]	235	(88.7)	138	(84.7)
	Not completed	30	(8.5)	25	(7.4)
	Other	30	(8.5)	25	(7.4)
	Missing by Design	**86**	**(24.5)**	**177**	**(52.1)**
	Discontinued due to adverse event	32	(9.1)	28	(8.2)
	Discontinued due to clinical disease progression	10	(2.8)	16	(4.7)
	Discontinued due to lost to follow-up	0	(0.0)	1	(0.3)
	Discontinued due to other	1	(0.3)	2	(0.6)
	Discontinued due to radiological disease progression	37	(10.5)	104	(30.6)
Week 45	Discontinued due to subject choice	6	(1.7)	18	(5.3)
	Discontinued due to withdrawal of consent	0	(0.0)	8	(2.4)
Week 48	**Expected to Complete Questionnaires**	**258**	**(73.5)**	**156**	**(45.9)**
	Completed	234	(66.7)	135	(39.7)
	Compliance (% in those expected to complete questionnaires)[d]	234	(90.7)	135	(86.5)
	Not completed	24	(6.8)	21	(6.2)
	Other	24	(6.8)	21	(6.2)

Study: KEYNOTE 581[a]		Pembrolizumab + Lenvatinib N[b]=351		Sunitinib N[b]=340	
Treatment Visit	Questionnaire Completion Status (EQ-5D)[c]	n	(%)	n	(%)
	Missing by Design	**93**	**(26.5)**	**184**	**(54.1)**
	Discontinued due to adverse event	32	(9.1)	29	(8.5)
	Discontinued due to clinical disease progression	10	(2.8)	17	(5.0)
	Discontinued due to lost to follow-up	0	(0.0)	1	(0.3)
	Discontinued due to other	1	(0.3)	2	(0.6)
	Discontinued due to radiological disease progression	42	(12.0)	109	(32.1)
	Discontinued due to subject choice	7	(2.0)	18	(5.3)
	Discontinued due to withdrawal of consent	1	(0.3)	8	(2.4)
Week 51	**Expected to Complete Questionnaires**	**253**	**(72.1)**	**152**	**(44.7)**
	Completed	230	(65.5)	122	(35.9)
	Compliance (% in those expected to complete questionnaires)[d]	230	(90.9)	122	(80.3)
	Not completed	23	(6.6)	30	(8.8)
	Other	23	(6.6)	30	(8.8)
	Missing by Design	**98**	**(27.9)**	**188**	**(55.3)**
	Discontinued due to adverse event	35	(10.0)	30	(8.8)
	Discontinued due to clinical disease progression	10	(2.8)	17	(5.0)
	Discontinued due to lost to follow-up	0	(0.0)	1	(0.3)
	Discontinued due to other	1	(0.3)	2	(0.6)
	Discontinued due to radiological disease progression	44	(12.5)	112	(32.9)
	Discontinued due to subject choice	7	(2.0)	18	(5.3)
	Discontinued due to withdrawal of consent	1	(0.3)	8	(2.4)
Week 54	**Expected to Complete Questionnaires**	**250**	**(71.2)**	**142**	**(41.8)**
	Completed	219	(62.4)	113	(33.2)
Week 54	Compliance (% in those expected to complete questionnaires)[d]	219	(87.6)	113	(79.6)
	Not completed	31	(8.8)	29	(8.5)
	Other	31	(8.8)	29	(8.5)
	Missing by Design	**101**	**(28.8)**	**198**	**(58.2)**
	Discontinued due to adverse event	35	(10.0)	32	(9.4)
	Discontinued due to clinical disease progression	10	(2.8)	17	(5.0)
	Discontinued due to lost to follow-up	0	(0.0)	1	(0.3)
	Discontinued due to other	2	(0.6)	2	(0.6)
	Discontinued due to radiological disease progression	46	(13.1)	120	(35.3)
	Discontinued due to subject choice	7	(2.0)	18	(5.3)
	Discontinued due to withdrawal of consent	1	(0.3)	8	(2.4)
Week 57	**Expected to Complete Questionnaires**	**243**	**(69.2)**	**140**	**(41.2)**

Study: KEYNOTE 581[a]		Pembrolizumab + Lenvatinib N[b]=351		Sunitinib N[b]=340	
Treatment Visit	Questionnaire Completion Status (EQ-5D)[c]	n	(%)	n	(%)
	Completed	214	(61.0)	115	(33.8)
	Compliance (% in those expected to complete questionnaires)[d]	214	(88.1)	115	(82.1)
	Not completed	29	(8.3)	25	(7.4)
	Other	29	(8.3)	25	(7.4)
	Missing by Design	**108**	**(30.8)**	**200**	**(58.8)**
	Discontinued due to adverse event	37	(10.5)	32	(9.4)
	Discontinued due to clinical disease progression	12	(3.4)	17	(5.0)
	Discontinued due to lost to follow-up	0	(0.0)	1	(0.3)
	Discontinued due to other	2	(0.6)	2	(0.6)
	Discontinued due to radiological disease progression	48	(13.7)	122	(35.9)
	Discontinued due to subject choice	8	(2.3)	18	(5.3)
	Discontinued due to withdrawal of consent	1	(0.3)	8	(2.4)
Week 60	**Expected to Complete Questionnaires**	**240**	**(68.4)**	**133**	**(39.1)**
	Completed	211	(60.1)	108	(31.8)
	Compliance (% in those expected to complete questionnaires)[d]	211	(87.9)	108	(81.2)
	Not completed	29	(8.3)	25	(7.4)
	Other	29	(8.3)	25	(7.4)
	Missing by Design	**111**	**(31.6)**	**207**	**(60.9)**
Week 60	Discontinued due to adverse event	37	(10.5)	32	(9.4)
	Discontinued due to clinical disease progression	14	(4.0)	18	(5.3)
	Discontinued due to lost to follow-up	0	(0.0)	1	(0.3)
	Discontinued due to other	3	(0.9)	2	(0.6)
	Discontinued due to radiological disease progression	48	(13.7)	127	(37.4)
	Discontinued due to subject choice	8	(2.3)	18	(5.3)
	Discontinued due to withdrawal of consent	1	(0.3)	8	(2.4)
	No visit scheduled	0	(0.0)	1	(0.3)
Week 63	**Expected to Complete Questionnaires**	**229**	**(65.2)**	**128**	**(37.6)**
	Completed	204	(58.1)	100	(29.4)
	Compliance (% in those expected to complete questionnaires)[d]	204	(89.1)	100	(78.1)
	Not completed	25	(7.1)	28	(8.2)
	Other	25	(7.1)	28	(8.2)
	Missing by Design	**122**	**(34.8)**	**212**	**(62.4)**
	Discontinued due to adverse event	37	(10.5)	33	(9.7)
	Discontinued due to clinical disease progression	14	(4.0)	18	(5.3)

Study: KEYNOTE 581[a]		Pembrolizumab + Lenvatinib N[b]=351		Sunitinib N[b]=340	
Treatment Visit	Questionnaire Completion Status (EQ-5D)[c]	n	(%)	n	(%)
	Discontinued due to lost to follow-up	0	(0.0)	1	(0.3)
	Discontinued due to other	3	(0.9)	2	(0.6)
	Discontinued due to radiological disease progression	50	(14.2)	127	(37.4)
	Discontinued due to subject choice	9	(2.6)	19	(5.6)
	Discontinued due to withdrawal of consent	1	(0.3)	8	(2.4)
	No visit scheduled	8	(2.3)	4	(1.2)
Week 66	**Expected to Complete Questionnaires**	**216**	**(61.5)**	**123**	**(36.2)**
	Completed	192	(54.7)	99	(29.1)
	Compliance (% in those expected to complete questionnaires)[d]	192	(88.9)	99	(80.5)
	Not completed	24	(6.8)	24	(7.1)
	Other	24	(6.8)	24	(7.1)
	Missing by Design	**135**	**(38.5)**	**217**	**(63.8)**
	Discontinued due to adverse event	40	(11.4)	33	(9.7)
	Discontinued due to clinical disease progression	14	(4.0)	18	(5.3)
Week 66	Discontinued due to lost to follow-up	0	(0.0)	1	(0.3)
	Discontinued due to other	3	(0.9)	2	(0.6)
	Discontinued due to radiological disease progression	53	(15.1)	130	(38.2)
	Discontinued due to subject choice	10	(2.8)	19	(5.6)
	Discontinued due to withdrawal of consent	1	(0.3)	8	(2.4)
	No visit scheduled	14	(4.0)	6	(1.8)
Week 69	**Expected to Complete Questionnaires**	**207**	**(59.0)**	**118**	**(34.7)**
	Completed	185	(52.7)	93	(27.4)
	Compliance (% in those expected to complete questionnaires)[d]	185	(89.4)	93	(78.8)
	Not completed	22	(6.3)	25	(7.4)
	Other	22	(6.3)	25	(7.4)
	Missing by Design	**144**	**(41.0)**	**222**	**(65.3)**
	Discontinued due to adverse event	40	(11.4)	34	(10.0)
	Discontinued due to clinical disease progression	15	(4.3)	19	(5.6)
	Discontinued due to lost to follow-up	0	(0.0)	1	(0.3)
	Discontinued due to other	3	(0.9)	2	(0.6)
	Discontinued due to radiological disease progression	56	(16.0)	131	(38.5)
	Discontinued due to subject choice	10	(2.8)	19	(5.6)
	Discontinued due to withdrawal of consent	1	(0.3)	8	(2.4)
	No visit scheduled	19	(5.4)	8	(2.4)
Week 72	**Expected to Complete Questionnaires**	**201**	**(57.3)**	**112**	**(32.9)**

Study: KEYNOTE 581[a]		Pembrolizumab + Lenvatinib N[b]=351		Sunitinib N[b]=340	
Treatment Visit	Questionnaire Completion Status (EQ-5D)[c]	n	(%)	n	(%)
	Completed	179	(51.0)	89	(26.2)
	Compliance (% in those expected to complete questionnaires)[d]	179	(89.1)	89	(79.5)
	Not completed	22	(6.3)	23	(6.8)
	Other	22	(6.3)	23	(6.8)
	Missing by Design	**150**	**(42.7)**	**228**	**(67.1)**
	Discontinued due to adverse event	41	(11.7)	35	(10.3)
	Discontinued due to clinical disease progression	15	(4.3)	19	(5.6)
	Discontinued due to lost to follow-up	0	(0.0)	1	(0.3)
	Discontinued due to other	3	(0.9)	2	(0.6)
Week 72	Discontinued due to radiological disease progression	58	(16.5)	134	(39.4)
	Discontinued due to subject choice	10	(2.8)	19	(5.6)
	Discontinued due to withdrawal of consent	1	(0.3)	8	(2.4)
	No visit scheduled	22	(6.3)	10	(2.9)
Week 75	**Expected to Complete Questionnaires**	**188**	**(53.6)**	**108**	**(31.8)**
	Completed	166	(47.3)	82	(24.1)
	Compliance (% in those expected to complete questionnaires)[d]	166	(88.3)	82	(75.9)
	Not completed	22	(6.3)	26	(7.6)
	Other	22	(6.3)	26	(7.6)
	Missing by Design	**163**	**(46.4)**	**232**	**(68.2)**
	Discontinued due to adverse event	41	(11.7)	35	(10.3)
	Discontinued due to clinical disease progression	15	(4.3)	19	(5.6)
	Discontinued due to lost to follow-up	0	(0.0)	1	(0.3)
	Discontinued due to other	3	(0.9)	2	(0.6)
	Discontinued due to radiological disease progression	62	(17.7)	136	(40.0)
	Discontinued due to subject choice	10	(2.8)	19	(5.6)
	Discontinued due to withdrawal of consent	1	(0.3)	8	(2.4)
	No visit scheduled	31	(8.8)	12	(3.5)
Week 78	**Expected to Complete Questionnaires**	**180**	**(51.3)**	**104**	**(30.6)**
	Completed	158	(45.0)	82	(24.1)
	Compliance (% in those expected to complete questionnaires)[d]	158	(87.8)	82	(78.8)
	Not completed	22	(6.3)	22	(6.5)
	Other	22	(6.3)	22	(6.5)
	Missing by Design	**171**	**(48.7)**	**236**	**(69.4)**
	Discontinued due to adverse event	43	(12.3)	35	(10.3)

Study: KEYNOTE 581[a]		Pembrolizumab + Lenvatinib N[b]=351		Sunitinib N[b]=340	
Treatment Visit	Questionnaire Completion Status (EQ-5D)[c]	n	(%)	n	(%)
	Discontinued due to clinical disease progression	16	(4.6)	19	(5.6)
	Discontinued due to lost to follow-up	0	(0.0)	1	(0.3)
	Discontinued due to other	3	(0.9)	2	(0.6)
	Discontinued due to radiological disease progression	66	(18.8)	140	(41.2)
	Discontinued due to subject choice	10	(2.8)	19	(5.6)
Week 78	Discontinued due to withdrawal of consent	1	(0.3)	8	(2.4)
	No visit scheduled	32	(9.1)	12	(3.5)
Week 81	**Expected to Complete Questionnaires**	**175**	**(49.9)**	**101**	**(29.7)**
	Completed	159	(45.3)	78	(22.9)
	Compliance (% in those expected to complete questionnaires)[d]	159	(90.9)	78	(77.2)
	Not completed	16	(4.6)	23	(6.8)
	Other	16	(4.6)	23	(6.8)
	Missing by Design	**176**	**(50.1)**	**239**	**(70.3)**
	Discontinued due to adverse event	44	(12.5)	35	(10.3)
	Discontinued due to clinical disease progression	16	(4.6)	19	(5.6)
	Discontinued due to lost to follow-up	0	(0.0)	1	(0.3)
	Discontinued due to other	3	(0.9)	2	(0.6)
	Discontinued due to radiological disease progression	66	(18.8)	141	(41.5)
	Discontinued due to subject choice	10	(2.8)	19	(5.6)
	Discontinued due to withdrawal of consent	1	(0.3)	9	(2.6)
	No visit scheduled	36	(10.3)	13	(3.8)
Week 84	**Expected to Complete Questionnaires**	**169**	**(48.1)**	**93**	**(27.4)**
	Completed	151	(43.0)	73	(21.5)
	Compliance (% in those expected to complete questionnaires)[d]	151	(89.3)	73	(78.5)
	Not completed	18	(5.1)	20	(5.9)
	Other	18	(5.1)	20	(5.9)
	Missing by Design	**182**	**(51.9)**	**247**	**(72.6)**
	Discontinued due to adverse event	45	(12.8)	36	(10.6)
	Discontinued due to clinical disease progression	17	(4.8)	19	(5.6)
	Discontinued due to lost to follow-up	0	(0.0)	1	(0.3)
	Discontinued due to other	3	(0.9)	2	(0.6)
	Discontinued due to radiological disease progression	68	(19.4)	145	(42.6)
	Discontinued due to subject choice	11	(3.1)	20	(5.9)
	Discontinued due to withdrawal of consent	1	(0.3)	9	(2.6)
	No visit scheduled	37	(10.5)	15	(4.4)

Study: KEYNOTE 581[a]		Pembrolizumab + Lenvatinib N[b]=351		Sunitinib N[b]=340	
Treatment Visit	Questionnaire Completion Status (EQ-5D)[c]	n	(%)	n	(%)
Week 87	**Expected to Complete Questionnaires**	**166**	**(47.3)**	**88**	**(25.9)**
	Completed	144	(41.0)	65	(19.1)
	Compliance (% in those expected to complete questionnaires)[d]	144	(86.7)	65	(73.9)
	Not completed	22	(6.3)	23	(6.8)
	Other	22	(6.3)	23	(6.8)
	Missing by Design	**185**	**(52.7)**	**252**	**(74.1)**
	Discontinued due to adverse event	46	(13.1)	37	(10.9)
	Discontinued due to clinical disease progression	17	(4.8)	19	(5.6)
	Discontinued due to lost to follow-up	0	(0.0)	1	(0.3)
	Discontinued due to other	3	(0.9)	2	(0.6)
	Discontinued due to radiological disease progression	68	(19.4)	146	(42.9)
	Discontinued due to subject choice	11	(3.1)	20	(5.9)
	Discontinued due to withdrawal of consent	1	(0.3)	9	(2.6)
	No visit scheduled	39	(11.1)	18	(5.3)
Week 90	**Expected to Complete Questionnaires**	**161**	**(45.9)**	**83**	**(24.4)**
	Completed	138	(39.3)	62	(18.2)
	Compliance (% in those expected to complete questionnaires)[d]	138	(85.7)	62	(74.7)
	Not completed	23	(6.6)	21	(6.2)
	Other	23	(6.6)	21	(6.2)
	Missing by Design	**190**	**(54.1)**	**257**	**(75.6)**
	Discontinued due to adverse event	46	(13.1)	38	(11.2)
	Discontinued due to clinical disease progression	17	(4.8)	19	(5.6)
	Discontinued due to lost to follow-up	0	(0.0)	1	(0.3)
	Discontinued due to other	3	(0.9)	2	(0.6)
	Discontinued due to radiological disease progression	69	(19.7)	148	(43.5)
	Discontinued due to subject choice	11	(3.1)	21	(6.2)
	Discontinued due to withdrawal of consent	1	(0.3)	9	(2.6)
	No visit scheduled	43	(12.3)	19	(5.6)
Week 93	**Expected to Complete Questionnaires**	**151**	**(43.0)**	**77**	**(22.6)**
	Completed	123	(35.0)	54	(15.9)
Week 93	Compliance (% in those expected to complete questionnaires)[d]	123	(81.5)	54	(70.1)
	Not completed	28	(8.0)	23	(6.8)
	Other	28	(8.0)	23	(6.8)
	Missing by Design	**200**	**(57.0)**	**263**	**(77.4)**

Study: KEYNOTE 581[a]		Pembrolizumab + Lenvatinib N[b]=351		Sunitinib N[b]=340	
Treatment Visit	Questionnaire Completion Status (EQ-5D)[c]	n	(%)	n	(%)
	Discontinued due to adverse event	46	(13.1)	38	(11.2)
	Discontinued due to clinical disease progression	17	(4.8)	19	(5.6)
	Discontinued due to lost to follow-up	0	(0.0)	1	(0.3)
	Discontinued due to other	3	(0.9)	2	(0.6)
	Discontinued due to radiological disease progression	75	(21.4)	151	(44.4)
	Discontinued due to subject choice	11	(3.1)	21	(6.2)
	Discontinued due to withdrawal of consent	1	(0.3)	9	(2.6)
	No visit scheduled	47	(13.4)	22	(6.5)
Week 96	**Expected to Complete Questionnaires**	**144**	**(41.0)**	**77**	**(22.6)**
	Completed	121	(34.5)	57	(16.8)
	Compliance (% in those expected to complete questionnaires)[d]	121	(84.0)	57	(74.0)
	Not completed	23	(6.6)	20	(5.9)
	Other	23	(6.6)	20	(5.9)
	Missing by Design	**207**	**(59.0)**	**263**	**(77.4)**
	Discontinued due to adverse event	46	(13.1)	38	(11.2)
	Discontinued due to clinical disease progression	17	(4.8)	19	(5.6)
	Discontinued due to lost to follow-up	0	(0.0)	1	(0.3)
	Discontinued due to other	3	(0.9)	2	(0.6)
	Discontinued due to radiological disease progression	76	(21.7)	151	(44.4)
	Discontinued due to subject choice	12	(3.4)	21	(6.2)
	Discontinued due to withdrawal of consent	1	(0.3)	9	(2.6)
	No visit scheduled	52	(14.8)	22	(6.5)
Week 99	**Expected to Complete Questionnaires**	**135**	**(38.5)**	**76**	**(22.4)**
	Completed	111	(31.6)	51	(15.0)
	Compliance (% in those expected to complete questionnaires)[d]	111	(82.2)	51	(67.1)
	Not completed	24	(6.8)	25	(7.4)
Week 99	Other	24	(6.8)	25	(7.4)
	Missing by Design	**216**	**(61.5)**	**264**	**(77.6)**
	Discontinued due to adverse event	46	(13.1)	38	(11.2)
	Discontinued due to clinical disease progression	17	(4.8)	19	(5.6)
	Discontinued due to lost to follow-up	0	(0.0)	1	(0.3)
	Discontinued due to other	3	(0.9)	2	(0.6)
	Discontinued due to radiological disease progression	79	(22.5)	151	(44.4)
	Discontinued due to subject choice	12	(3.4)	21	(6.2)
	Discontinued due to withdrawal of consent	1	(0.3)	9	(2.6)

Study: KEYNOTE 581[a]		Pembrolizumab + Lenvatinib N[b]=351		Sunitinib N[b]=340	
Treatment Visit	Questionnaire Completion Status (EQ-5D)[c]	n	(%)	n	(%)
	No visit scheduled	58	(16.5)	23	(6.8)
Week 102	**Expected to Complete Questionnaires**	**128**	**(36.5)**	**73**	**(21.5)**
	Completed	100	(28.5)	48	(14.1)
	Compliance (% in those expected to complete questionnaires)[d]	100	(78.1)	48	(65.8)
	Not completed	28	(8.0)	25	(7.4)
	Other	28	(8.0)	25	(7.4)
	Missing by Design	**223**	**(63.5)**	**267**	**(78.5)**
	Discontinued due to adverse event	46	(13.1)	39	(11.5)
	Discontinued due to clinical disease progression	18	(5.1)	19	(5.6)
	Discontinued due to lost to follow-up	0	(0.0)	1	(0.3)
	Discontinued due to other	3	(0.9)	2	(0.6)
	Discontinued due to radiological disease progression	83	(23.6)	153	(45.0)
	Discontinued due to subject choice	13	(3.7)	21	(6.2)
	Discontinued due to withdrawal of consent	1	(0.3)	9	(2.6)
	No visit scheduled	59	(16.8)	23	(6.8)
Week 105	**Expected to Complete Questionnaires**	**124**	**(35.3)**	**70**	**(20.6)**
	Completed	98	(27.9)	46	(13.5)
	Compliance (% in those expected to complete questionnaires)[d]	98	(79.0)	46	(65.7)
	Not completed	26	(7.4)	24	(7.1)
	Other	26	(7.4)	24	(7.1)
	Missing by Design	**227**	**(64.7)**	**270**	**(79.4)**
Week 105	Discontinued due to adverse event	47	(13.4)	39	(11.5)
	Discontinued due to clinical disease progression	18	(5.1)	19	(5.6)
	Discontinued due to lost to follow-up	0	(0.0)	1	(0.3)
	Discontinued due to other	3	(0.9)	3	(0.9)
	Discontinued due to radiological disease progression	84	(23.9)	154	(45.3)
	Discontinued due to subject choice	13	(3.7)	21	(6.2)
	Discontinued due to withdrawal of consent	1	(0.3)	9	(2.6)
	No visit scheduled	61	(17.4)	24	(7.1)
Week 108	**Expected to Complete Questionnaires**	**112**	**(31.9)**	**68**	**(20.0)**
	Completed	86	(24.5)	42	(12.4)
	Compliance (% in those expected to complete questionnaires)[d]	86	(76.8)	42	(61.8)
	Not completed	26	(7.4)	26	(7.6)
	Other	26	(7.4)	26	(7.6)

Study: KEYNOTE 581[a]		Pembrolizumab + Lenvatinib N[b]=351		Sunitinib N[b]=340	
Treatment Visit	Questionnaire Completion Status (EQ-5D)[c]	n	(%)	n	(%)
	Missing by Design	**239**	**(68.1)**	**272**	**(80.0)**
	Discontinued due to adverse event	48	(13.7)	39	(11.5)
	Discontinued due to clinical disease progression	18	(5.1)	19	(5.6)
	Discontinued due to lost to follow-up	0	(0.0)	1	(0.3)
	Discontinued due to other	8	(2.3)	3	(0.9)
	Discontinued due to radiological disease progression	87	(24.8)	155	(45.6)
	Discontinued due to subject choice	13	(3.7)	21	(6.2)
	Discontinued due to withdrawal of consent	1	(0.3)	9	(2.6)
	No visit scheduled	64	(18.2)	25	(7.4)
Week 111	**Expected to Complete Questionnaires**	**100**	**(28.5)**	**62**	**(18.2)**
	Completed	78	(22.2)	42	(12.4)
	Compliance (% in those expected to complete questionnaires)[d]	78	(78.0)	42	(67.7)
	Not completed	22	(6.3)	20	(5.9)
	Other	22	(6.3)	20	(5.9)
	Missing by Design	**251**	**(71.5)**	**278**	**(81.8)**
	Discontinued due to adverse event	50	(14.2)	39	(11.5)
	Discontinued due to clinical disease progression	18	(5.1)	20	(5.9)
Week 111	Discontinued due to lost to follow-up	0	(0.0)	1	(0.3)
	Discontinued due to other	9	(2.6)	3	(0.9)
	Discontinued due to radiological disease progression	88	(25.1)	156	(45.9)
	Discontinued due to subject choice	15	(4.3)	21	(6.2)
	Discontinued due to withdrawal of consent	1	(0.3)	9	(2.6)
	No visit scheduled	70	(19.9)	29	(8.5)
Week 114	**Expected to Complete Questionnaires**	**90**	**(25.6)**	**59**	**(17.4)**
	Completed	65	(18.5)	37	(10.9)
	Compliance (% in those expected to complete questionnaires)[d]	65	(72.2)	37	(62.7)
	Not completed	25	(7.1)	22	(6.5)
	Other	25	(7.1)	22	(6.5)
	Missing by Design	**261**	**(74.4)**	**281**	**(82.6)**
	Discontinued due to adverse event	51	(14.5)	39	(11.5)
	Discontinued due to clinical disease progression	18	(5.1)	20	(5.9)
	Discontinued due to lost to follow-up	0	(0.0)	1	(0.3)
	Discontinued due to other	10	(2.8)	3	(0.9)
	Discontinued due to radiological disease progression	88	(25.1)	156	(45.9)
	Discontinued due to subject choice	16	(4.6)	21	(6.2)

Study: KEYNOTE 581[a]		Pembrolizumab + Lenvatinib N[b]=351		Sunitinib N[b]=340	
Treatment Visit	Questionnaire Completion Status (EQ-5D)[c]	n	(%)	n	(%)
	Discontinued due to withdrawal of consent	1	(0.3)	9	(2.6)
	No visit scheduled	77	(21.9)	32	(9.4)
Week 117	**Expected to Complete Questionnaires**	**76**	**(21.7)**	**53**	**(15.6)**
	Completed	55	(15.7)	28	(8.2)
	Compliance (% in those expected to complete questionnaires)[d]	55	(72.4)	28	(52.8)
	Not completed	21	(6.0)	25	(7.4)
	Other	21	(6.0)	25	(7.4)
	Missing by Design	**275**	**(78.3)**	**287**	**(84.4)**
	Discontinued due to adverse event	53	(15.1)	39	(11.5)
	Discontinued due to clinical disease progression	18	(5.1)	20	(5.9)
	Discontinued due to lost to follow-up	0	(0.0)	1	(0.3)
	Discontinued due to other	10	(2.8)	3	(0.9)
Week 117	Discontinued due to radiological disease progression	88	(25.1)	158	(46.5)
	Discontinued due to subject choice	16	(4.6)	21	(6.2)
	Discontinued due to withdrawal of consent	1	(0.3)	9	(2.6)
	No visit scheduled	89	(25.4)	36	(10.6)
Week 120	**Expected to Complete Questionnaires**	**65**	**(18.5)**	**50**	**(14.7)**
	Completed	48	(13.7)	29	(8.5)
	Compliance (% in those expected to complete questionnaires)[d]	48	(73.8)	29	(58.0)
	Not completed	17	(4.8)	21	(6.2)
	Other	17	(4.8)	21	(6.2)
	Missing by Design	**286**	**(81.5)**	**290**	**(85.3)**
	Discontinued due to adverse event	54	(15.4)	39	(11.5)
	Discontinued due to clinical disease progression	18	(5.1)	21	(6.2)
	Discontinued due to lost to follow-up	0	(0.0)	1	(0.3)
	Discontinued due to other	10	(2.8)	3	(0.9)
	Discontinued due to radiological disease progression	90	(25.6)	158	(46.5)
	Discontinued due to subject choice	17	(4.8)	21	(6.2)
	Discontinued due to withdrawal of consent	1	(0.3)	9	(2.6)
	No visit scheduled	96	(27.4)	38	(11.2)
Week 123	**Expected to Complete Questionnaires**	**54**	**(15.4)**	**46**	**(13.5)**
	Completed	40	(11.4)	23	(6.8)
	Compliance (% in those expected to complete questionnaires)[d]	40	(74.1)	23	(50.0)
	Not completed	14	(4.0)	23	(6.8)

Study: KEYNOTE 581[a]		Pembrolizumab + Lenvatinib N[b]=351		Sunitinib N[b]=340	
Treatment Visit	Questionnaire Completion Status (EQ-5D)[c]	n	(%)	n	(%)
	Other	14	(4.0)	23	(6.8)
	Missing by Design	**297**	**(84.6)**	**294**	**(86.5)**
	Discontinued due to adverse event	55	(15.7)	39	(11.5)
	Discontinued due to clinical disease progression	18	(5.1)	21	(6.2)
	Discontinued due to lost to follow-up	0	(0.0)	1	(0.3)
	Discontinued due to other	12	(3.4)	3	(0.9)
	Discontinued due to radiological disease progression	91	(25.9)	160	(47.1)
	Discontinued due to subject choice	17	(4.8)	21	(6.2)
Week 123	Discontinued due to withdrawal of consent	2	(0.6)	9	(2.6)
	No visit scheduled	102	(29.1)	40	(11.8)
Week 126	**Expected to Complete Questionnaires**	**50**	**(14.2)**	**41**	**(12.1)**
	Completed	35	(10.0)	20	(5.9)
	Compliance (% in those expected to complete questionnaires)[d]	35	(70.0)	20	(48.8)
	Not completed	15	(4.3)	21	(6.2)
	Other	15	(4.3)	21	(6.2)
	Missing by Design	**301**	**(85.8)**	**299**	**(87.9)**
	Discontinued due to adverse event	56	(16.0)	39	(11.5)
	Discontinued due to clinical disease progression	18	(5.1)	21	(6.2)
	Discontinued due to lost to follow-up	0	(0.0)	1	(0.3)
	Discontinued due to other	12	(3.4)	3	(0.9)
	Discontinued due to radiological disease progression	91	(25.9)	161	(47.4)
	Discontinued due to subject choice	17	(4.8)	21	(6.2)
	Discontinued due to withdrawal of consent	2	(0.6)	9	(2.6)
	No visit scheduled	105	(29.9)	44	(12.9)
Week 129	**Expected to Complete Questionnaires**	**43**	**(12.3)**	**37**	**(10.9)**
	Completed	28	(8.0)	17	(5.0)
	Compliance (% in those expected to complete questionnaires)[d]	28	(65.1)	17	(45.9)
	Not completed	15	(4.3)	20	(5.9)
	Other	15	(4.3)	20	(5.9)
	Missing by Design	**308**	**(87.7)**	**303**	**(89.1)**
	Discontinued due to adverse event	56	(16.0)	39	(11.5)
	Discontinued due to clinical disease progression	18	(5.1)	21	(6.2)
	Discontinued due to lost to follow-up	0	(0.0)	1	(0.3)
	Discontinued due to other	12	(3.4)	3	(0.9)
	Discontinued due to radiological disease progression	91	(25.9)	161	(47.4)

Study: KEYNOTE 581[a]		Pembrolizumab + Lenvatinib N[b]=351		Sunitinib N[b]=340	
Treatment Visit	Questionnaire Completion Status (EQ-5D)[c]	n	(%)	n	(%)
	Discontinued due to subject choice	17	(4.8)	21	(6.2)
	Discontinued due to withdrawal of consent	2	(0.6)	9	(2.6)
	No visit scheduled	112	(31.9)	48	(14.1)
Week 132	**Expected to Complete Questionnaires**	**38**	**(10.8)**	**30**	**(8.8)**
	Completed	23	(6.6)	8	(2.4)
	Compliance (% in those expected to complete questionnaires)[d]	23	(60.5)	8	(26.7)
	Not completed	15	(4.3)	22	(6.5)
	Other	15	(4.3)	22	(6.5)
	Missing by Design	**313**	**(89.2)**	**310**	**(91.2)**
	Discontinued due to adverse event	56	(16.0)	39	(11.5)
	Discontinued due to clinical disease progression	18	(5.1)	21	(6.2)
	Discontinued due to lost to follow-up	0	(0.0)	1	(0.3)
	Discontinued due to other	12	(3.4)	3	(0.9)
	Discontinued due to radiological disease progression	91	(25.9)	163	(47.9)
	Discontinued due to subject choice	17	(4.8)	21	(6.2)
	Discontinued due to withdrawal of consent	2	(0.6)	9	(2.6)
	No visit scheduled	117	(33.3)	53	(15.6)
Week 135	**Expected to Complete Questionnaires**	**35**	**(10.0)**	**29**	**(8.5)**
	Completed	20	(5.7)	10	(2.9)
	Compliance (% in those expected to complete questionnaires)[d]	20	(57.1)	10	(34.5)
	Not completed	15	(4.3)	19	(5.6)
	Other	15	(4.3)	19	(5.6)
	Missing by Design	**316**	**(90.0)**	**311**	**(91.5)**
	Discontinued due to adverse event	56	(16.0)	39	(11.5)
	Discontinued due to clinical disease progression	18	(5.1)	21	(6.2)
	Discontinued due to lost to follow-up	0	(0.0)	1	(0.3)
	Discontinued due to other	12	(3.4)	3	(0.9)
	Discontinued due to radiological disease progression	92	(26.2)	163	(47.9)
	Discontinued due to subject choice	17	(4.8)	21	(6.2)
	Discontinued due to withdrawal of consent	2	(0.6)	9	(2.6)
	No visit scheduled	119	(33.9)	54	(15.9)
Week 138	**Expected to Complete Questionnaires**	**30**	**(8.5)**	**28**	**(8.2)**
	Completed	16	(4.6)	8	(2.4)
Week 138	Compliance (% in those expected to complete questionnaires)[d]	16	(53.3)	8	(28.6)

Study: KEYNOTE 581[a]		Pembrolizumab + Lenvatinib N[b]=351		Sunitinib N[b]=340	
Treatment Visit	Questionnaire Completion Status (EQ-5D)[c]	n	(%)	n	(%)
	Not completed	14	(4.0)	20	(5.9)
	Other	14	(4.0)	20	(5.9)
	Missing by Design	**321**	**(91.5)**	**312**	**(91.8)**
	Discontinued due to adverse event	56	(16.0)	39	(11.5)
	Discontinued due to clinical disease progression	18	(5.1)	21	(6.2)
	Discontinued due to lost to follow-up	0	(0.0)	1	(0.3)
	Discontinued due to other	12	(3.4)	3	(0.9)
	Discontinued due to radiological disease progression	93	(26.5)	163	(47.9)
	Discontinued due to subject choice	17	(4.8)	21	(6.2)
	Discontinued due to withdrawal of consent	2	(0.6)	9	(2.6)
	No visit scheduled	123	(35.0)	55	(16.2)
Week 141	**Expected to Complete Questionnaires**	**24**	**(6.8)**	**26**	**(7.6)**
	Completed	8	(2.3)	7	(2.1)
	Compliance (% in those expected to complete questionnaires)[d]	8	(33.3)	7	(26.9)
	Not completed	16	(4.6)	19	(5.6)
	Other	16	(4.6)	19	(5.6)
	Missing by Design	**327**	**(93.2)**	**314**	**(92.4)**
	Discontinued due to adverse event	56	(16.0)	39	(11.5)
	Discontinued due to clinical disease progression	18	(5.1)	21	(6.2)
	Discontinued due to lost to follow-up	0	(0.0)	1	(0.3)
	Discontinued due to other	12	(3.4)	3	(0.9)
	Discontinued due to radiological disease progression	93	(26.5)	163	(47.9)
	Discontinued due to subject choice	17	(4.8)	21	(6.2)
	Discontinued due to withdrawal of consent	2	(0.6)	9	(2.6)
	No visit scheduled	129	(36.8)	57	(16.8)
Week 144	**Expected to Complete Questionnaires**	**21**	**(6.0)**	**24**	**(7.1)**
	Completed	8	(2.3)	5	(1.5)
	Compliance (% in those expected to complete questionnaires)[d]	8	(38.1)	5	(20.8)
	Not completed	13	(3.7)	19	(5.6)
Week 144	Other	13	(3.7)	19	(5.6)
	Missing by Design	**330**	**(94.0)**	**316**	**(92.9)**
	Discontinued due to adverse event	56	(16.0)	39	(11.5)
	Discontinued due to clinical disease progression	18	(5.1)	21	(6.2)
	Discontinued due to lost to follow-up	0	(0.0)	1	(0.3)
	Discontinued due to other	12	(3.4)	3	(0.9)

Study: KEYNOTE 581[a]		Pembrolizumab + Lenvatinib N[b]=351		Sunitinib N[b]=340	
Treatment Visit	Questionnaire Completion Status (EQ-5D)[c]	n	(%)	n	(%)
	Discontinued due to radiological disease progression	93	(26.5)	164	(48.2)
	Discontinued due to subject choice	17	(4.8)	21	(6.2)
	Discontinued due to withdrawal of consent	2	(0.6)	9	(2.6)
	No visit scheduled	132	(37.6)	58	(17.1)
Week 147	**Expected to Complete Questionnaires**	**21**	**(6.0)**	**23**	**(6.8)**
	Completed	8	(2.3)	3	(0.9)
	Compliance (% in those expected to complete questionnaires)[d]	8	(38.1)	3	(13.0)
	Not completed	13	(3.7)	20	(5.9)
	Other	13	(3.7)	20	(5.9)
	Missing by Design	**330**	**(94.0)**	**317**	**(93.2)**
	Discontinued due to adverse event	56	(16.0)	39	(11.5)
	Discontinued due to clinical disease progression	18	(5.1)	21	(6.2)
	Discontinued due to lost to follow-up	0	(0.0)	1	(0.3)
	Discontinued due to other	12	(3.4)	3	(0.9)
	Discontinued due to radiological disease progression	93	(26.5)	164	(48.2)
	Discontinued due to subject choice	17	(4.8)	21	(6.2)
	Discontinued due to withdrawal of consent	2	(0.6)	9	(2.6)
	No visit scheduled	132	(37.6)	59	(17.4)
Week 150	**Expected to Complete Questionnaires**	**20**	**(5.7)**	**22**	**(6.5)**
	Completed	7	(2.0)	3	(0.9)
	Compliance (% in those expected to complete questionnaires)[d]	7	(35.0)	3	(13.6)
	Not completed	13	(3.7)	19	(5.6)
	Other	13	(3.7)	19	(5.6)
	Missing by Design	**331**	**(94.3)**	**318**	**(93.5)**
Week 150	Discontinued due to adverse event	56	(16.0)	39	(11.5)
	Discontinued due to clinical disease progression	18	(5.1)	21	(6.2)
	Discontinued due to lost to follow-up	0	(0.0)	1	(0.3)
	Discontinued due to other	12	(3.4)	3	(0.9)
	Discontinued due to radiological disease progression	94	(26.8)	164	(48.2)
	Discontinued due to subject choice	17	(4.8)	21	(6.2)
	Discontinued due to withdrawal of consent	2	(0.6)	9	(2.6)
	No visit scheduled	132	(37.6)	60	(17.6)
Week 153	**Expected to Complete Questionnaires**	**19**	**(5.4)**	**21**	**(6.2)**
	Completed	6	(1.7)	2	(0.6)
	Compliance (% in those expected to complete	6	(31.6)	2	(9.5)

Study: KEYNOTE 581[a]		Pembrolizumab + Lenvatinib N[b]=351		Sunitinib N[b]=340	
Treatment Visit	Questionnaire Completion Status (EQ-5D)[c]	n	(%)	n	(%)
	questionnaires)[d]				
	Not completed	13	(3.7)	19	(5.6)
	Other	13	(3.7)	19	(5.6)
	Missing by Design	**332**	**(94.6)**	**319**	**(93.8)**
	Discontinued due to adverse event	56	(16.0)	39	(11.5)
	Discontinued due to clinical disease progression	18	(5.1)	21	(6.2)
	Discontinued due to lost to follow-up	0	(0.0)	1	(0.3)
	Discontinued due to other	12	(3.4)	3	(0.9)
	Discontinued due to radiological disease progression	94	(26.8)	164	(48.2)
	Discontinued due to subject choice	17	(4.8)	21	(6.2)
	Discontinued due to withdrawal of consent	2	(0.6)	9	(2.6)
	No visit scheduled	133	(37.9)	61	(17.9)
Week 156	**Expected to Complete Questionnaires**	**17**	**(4.8)**	**21**	**(6.2)**
	Completed	4	(1.1)	1	(0.3)
	Compliance (% in those expected to complete questionnaires)[d]	4	(23.5)	1	(4.8)
	Not completed	13	(3.7)	20	(5.9)
	Other	13	(3.7)	20	(5.9)
	Missing by Design	**334**	**(95.2)**	**319**	**(93.8)**
	Discontinued due to adverse event	56	(16.0)	39	(11.5)
	Discontinued due to clinical disease progression	18	(5.1)	21	(6.2)
Week 156	Discontinued due to lost to follow-up	0	(0.0)	1	(0.3)
	Discontinued due to other	12	(3.4)	3	(0.9)
	Discontinued due to radiological disease progression	94	(26.8)	164	(48.2)
	Discontinued due to subject choice	17	(4.8)	21	(6.2)
	Discontinued due to withdrawal of consent	2	(0.6)	9	(2.6)
	No visit scheduled	135	(38.5)	61	(17.9)
Week 159	**Expected to Complete Questionnaires**	**15**	**(4.3)**	**20**	**(5.9)**
	Completed	2	(0.6)	1	(0.3)
	Compliance (% in those expected to complete questionnaires)[d]	2	(13.3)	1	(5.0)
	Not completed	13	(3.7)	19	(5.6)
	Other	13	(3.7)	19	(5.6)
	Missing by Design	**336**	**(95.7)**	**320**	**(94.1)**
	Discontinued due to adverse event	57	(16.2)	39	(11.5)
	Discontinued due to clinical disease progression	18	(5.1)	21	(6.2)
	Discontinued due to lost to follow-up	0	(0.0)	1	(0.3)

Study: KEYNOTE 581[a]		Pembrolizumab + Lenvatinib N[b]=351		Sunitinib N[b]=340	
Treatment Visit	Questionnaire Completion Status (EQ-5D)[c]	n	(%)	n	(%)
	Discontinued due to other	12	(3.4)	3	(0.9)
	Discontinued due to radiological disease progression	94	(26.8)	164	(48.2)
	Discontinued due to subject choice	17	(4.8)	21	(6.2)
	Discontinued due to withdrawal of consent	2	(0.6)	9	(2.6)
	No visit scheduled	136	(38.7)	62	(18.2)
Week 162	**Expected to Complete Questionnaires**	**15**	**(4.3)**	**19**	**(5.6)**
	Completed	2	(0.6)	0	(0.0)
	Compliance (% in those expected to complete questionnaires)[d]	2	(13.3)	0	(0.0)
	Not completed	13	(3.7)	19	(5.6)
	Other	13	(3.7)	19	(5.6)
	Missing by Design	**336**	**(95.7)**	**321**	**(94.4)**
	Discontinued due to adverse event	57	(16.2)	39	(11.5)
	Discontinued due to clinical disease progression	18	(5.1)	21	(6.2)
	Discontinued due to lost to follow-up	0	(0.0)	1	(0.3)
	Discontinued due to other	12	(3.4)	3	(0.9)
Week 162	Discontinued due to radiological disease progression	94	(26.8)	164	(48.2)
	Discontinued due to subject choice	17	(4.8)	21	(6.2)
	Discontinued due to withdrawal of consent	2	(0.6)	9	(2.6)
	No visit scheduled	136	(38.7)	63	(18.5)
Week 165	**Expected to Complete Questionnaires**	**15**	**(4.3)**	**19**	**(5.6)**
	Completed	2	(0.6)	0	(0.0)
	Compliance (% in those expected to complete questionnaires)[d]	2	(13.3)	0	(0.0)
	Not completed	13	(3.7)	19	(5.6)
	Other	13	(3.7)	19	(5.6)
	Missing by Design	**336**	**(95.7)**	**321**	**(94.4)**
	Discontinued due to adverse event	57	(16.2)	39	(11.5)
	Discontinued due to clinical disease progression	18	(5.1)	21	(6.2)
	Discontinued due to lost to follow-up	0	(0.0)	1	(0.3)
	Discontinued due to other	12	(3.4)	3	(0.9)
	Discontinued due to radiological disease progression	94	(26.8)	164	(48.2)
	Discontinued due to subject choice	17	(4.8)	21	(6.2)
	Discontinued due to withdrawal of consent	2	(0.6)	9	(2.6)
	No visit scheduled	136	(38.7)	63	(18.5)
Week 168	**Expected to Complete Questionnaires**	**15**	**(4.3)**	**19**	**(5.6)**
	Completed	2	(0.6)	0	(0.0)

Study: KEYNOTE 581[a]		Pembrolizumab + Lenvatinib N[b]=351		Sunitinib N[b]=340	
Treatment Visit	Questionnaire Completion Status (EQ-5D)[c]	n	(%)	n	(%)
	Compliance (% in those expected to complete questionnaires)[d]	2	(13.3)	0	(0.0)
	Not completed	13	(3.7)	19	(5.6)
	Other	13	(3.7)	19	(5.6)
	Missing by Design	**336**	**(95.7)**	**321**	**(94.4)**
	Discontinued due to adverse event	57	(16.2)	39	(11.5)
	Discontinued due to clinical disease progression	18	(5.1)	21	(6.2)
	Discontinued due to lost to follow-up	0	(0.0)	1	(0.3)
	Discontinued due to other	12	(3.4)	3	(0.9)
	Discontinued due to radiological disease progression	94	(26.8)	164	(48.2)
	Discontinued due to subject choice	17	(4.8)	21	(6.2)
Week 168	Discontinued due to withdrawal of consent	2	(0.6)	9	(2.6)
	No visit scheduled	136	(38.7)	63	(18.5)
Week 171	**Expected to Complete Questionnaires**	**13**	**(3.7)**	**19**	**(5.6)**
	Not completed	13	(3.7)	19	(5.6)
	Other	13	(3.7)	19	(5.6)
	Missing by Design	**338**	**(96.3)**	**321**	**(94.4)**
	Discontinued due to adverse event	57	(16.2)	39	(11.5)
	Discontinued due to clinical disease progression	18	(5.1)	21	(6.2)
	Discontinued due to lost to follow-up	0	(0.0)	1	(0.3)
	Discontinued due to other	12	(3.4)	3	(0.9)
	Discontinued due to radiological disease progression	94	(26.8)	164	(48.2)
	Discontinued due to subject choice	17	(4.8)	21	(6.2)
	Discontinued due to withdrawal of consent	2	(0.6)	9	(2.6)
	No visit scheduled	138	(39.3)	63	(18.5)
Week 174	**Expected to Complete Questionnaires**	**13**	**(3.7)**	**19**	**(5.6)**
	Not completed	13	(3.7)	19	(5.6)
	Other	13	(3.7)	19	(5.6)
	Missing by Design	**338**	**(96.3)**	**321**	**(94.4)**
	Discontinued due to adverse event	57	(16.2)	39	(11.5)
	Discontinued due to clinical disease progression	18	(5.1)	21	(6.2)
	Discontinued due to lost to follow-up	0	(0.0)	1	(0.3)
	Discontinued due to other	12	(3.4)	3	(0.9)
	Discontinued due to radiological disease progression	94	(26.8)	164	(48.2)
	Discontinued due to subject choice	17	(4.8)	21	(6.2)
	Discontinued due to withdrawal of consent	2	(0.6)	9	(2.6)
Week 174	No visit scheduled	138	(39.3)	63	(18.5)

Study: KEYNOTE 581[a]		Pembrolizumab + Lenvatinib		Sunitinib	
		N[b]=351		N[b]=340	
Treatment Visit	Questionnaire Completion Status (EQ-5D)[c]	n	(%)	n	(%)

a: Database Cutoff Date: 28AUG2020

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

c: Questionnaire completion status is missing by design in case of discontinuation, death, and no visit scheduled else is expected to complete questionnaires

d: Compliance Rate is defined as the number of subjects completed the questionnaire over the number of subjects expected to complete the questionnaire, excluding those missing by design

EQ-5D: European Quality of Life 5 Dimension

Anhang 4-G2: Kaplan-Meier-Kurven der Subgruppen mit signifikantem Interaktionstest (p < 0,05) der Studie KEYNOTE 581/CLEAR

Im Folgenden werden ergänzend zu Abschnitt 4.3.1.3.2 des Moduls 4 A die Kaplan-Meier-Kurven der Subgruppenanalysen, für die ein signifikanter Interaktionstest (p < 0,05) vorliegt, dargestellt.

Alle Ergebnisse beziehen sich auf den Datenschnitt vom 28. August 2020.

Mortalität

Gesamtüberleben

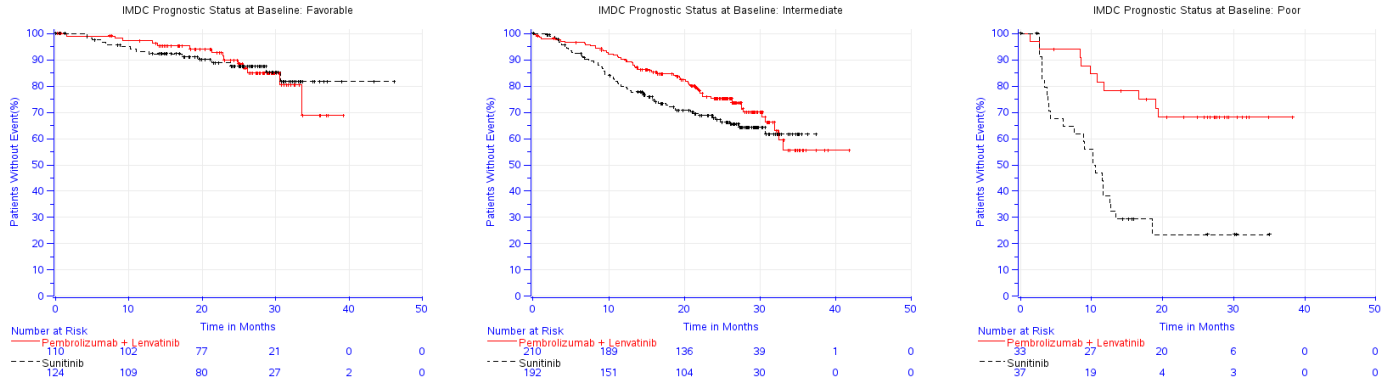


Abbildung 4G-1: Kaplan-Meier-Kurve für die Subgruppenanalyse nach IMDC Risikogruppe (günstig, intermediär, ungünstig) zu Studienbeginn für das Gesamtüberleben der Studie KEYNOTE 581/CLEAR

Morbidität

Krankheitssymptomatik und Gesundheitszustand

EORTC QLQ-C30: Symptomskala Schmerzen

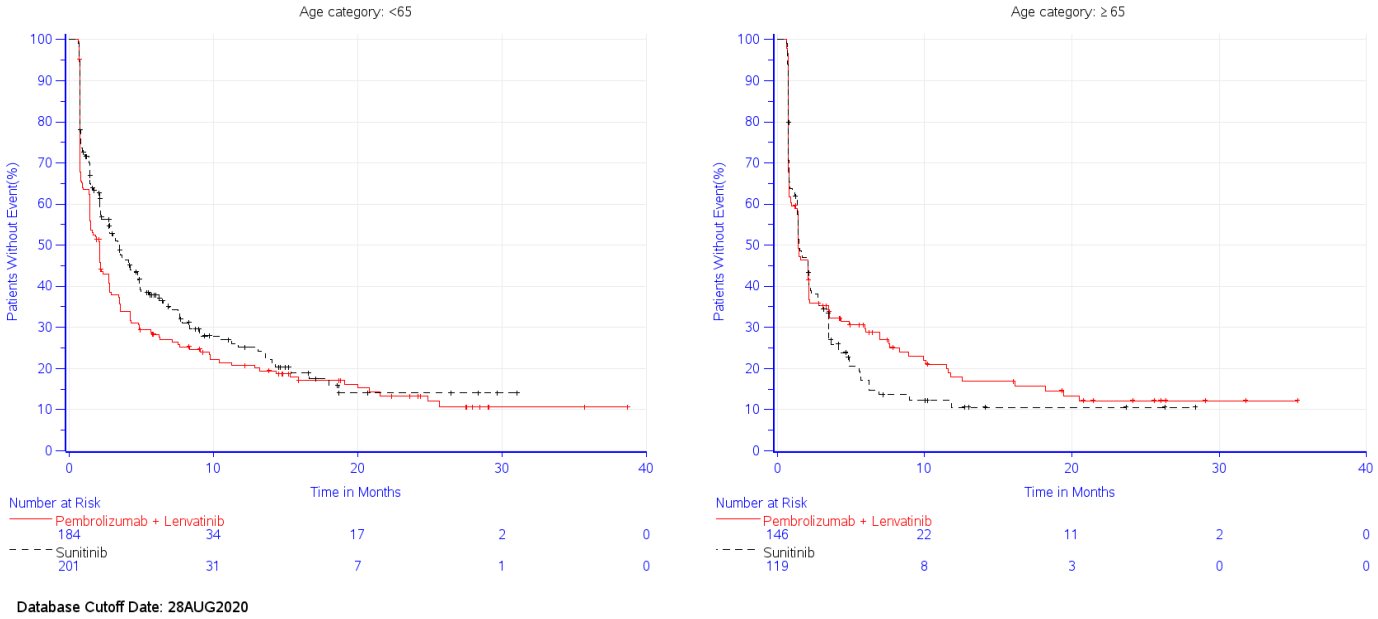
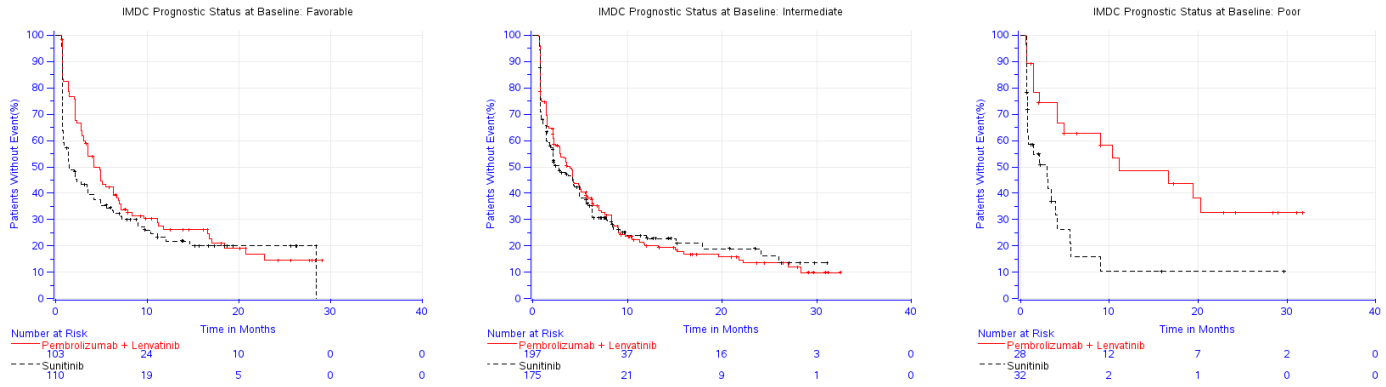


Abbildung 4G-2: Kaplan-Meier-Kurve für die Subgruppenanalyse nach Alter (< 65 vs. ≥65) für die Symptomskala Schmerzen des EORTC QLQ-C30 der Studie KEYNOTE 581/CLEAR

EORTC QLQ-C30: Symptomskala Appetitverlust



Database Cutoff Date: 28AUG2020

Abbildung 4G-3: Kaplan-Meier-Kurve für die Subgruppenanalyse nach IMDC Risikogruppe (günstig, intermediär, ungünstig) zu Studienbeginn für die Symptomskala Appetitverlust des EORTC QLQ-C30 der Studie KEYNOTE 581/CLEAR

FKSI-DRS Gesamtscore (3 Punkte): Region

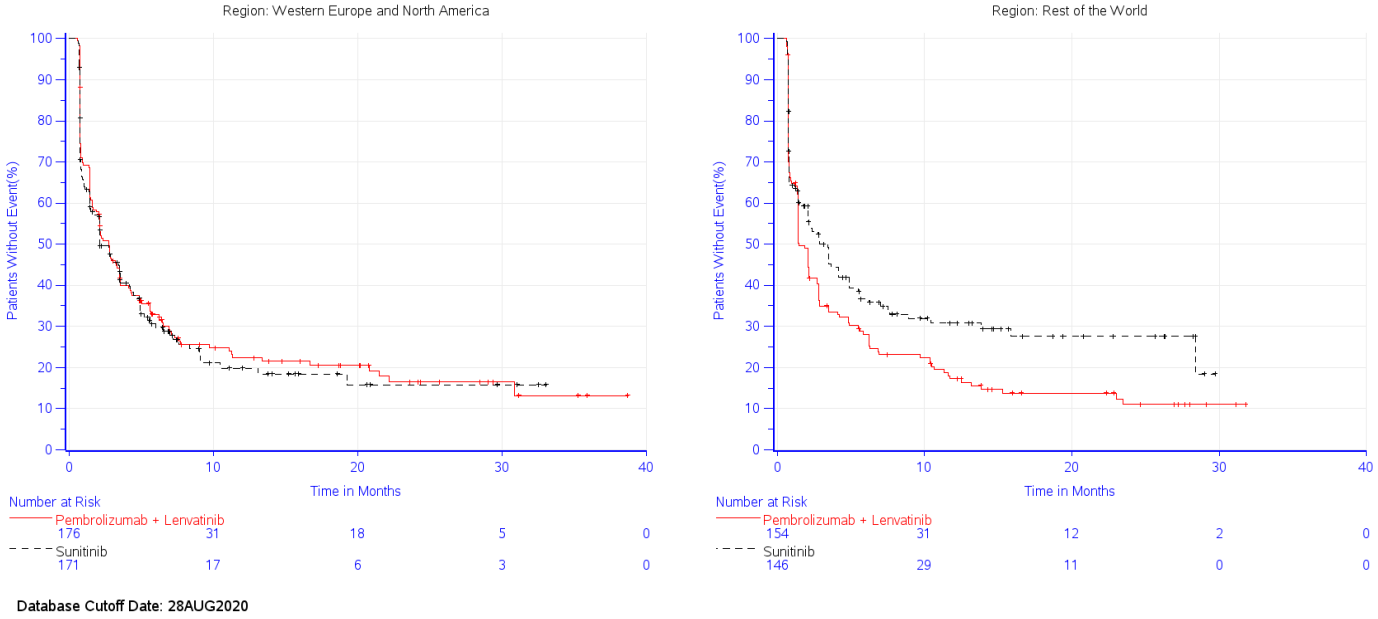


Abbildung 4G-4: Kaplan-Meier-Kurve für die Subgruppenanalyse nach Region für den Endpunkt Gesundheitszustand des FKSI-DRS (3 Punkte) der Studie KEYNOTE 581/CLEAR

FKSI-DRS Gesamtscore (4 Punkte): Region

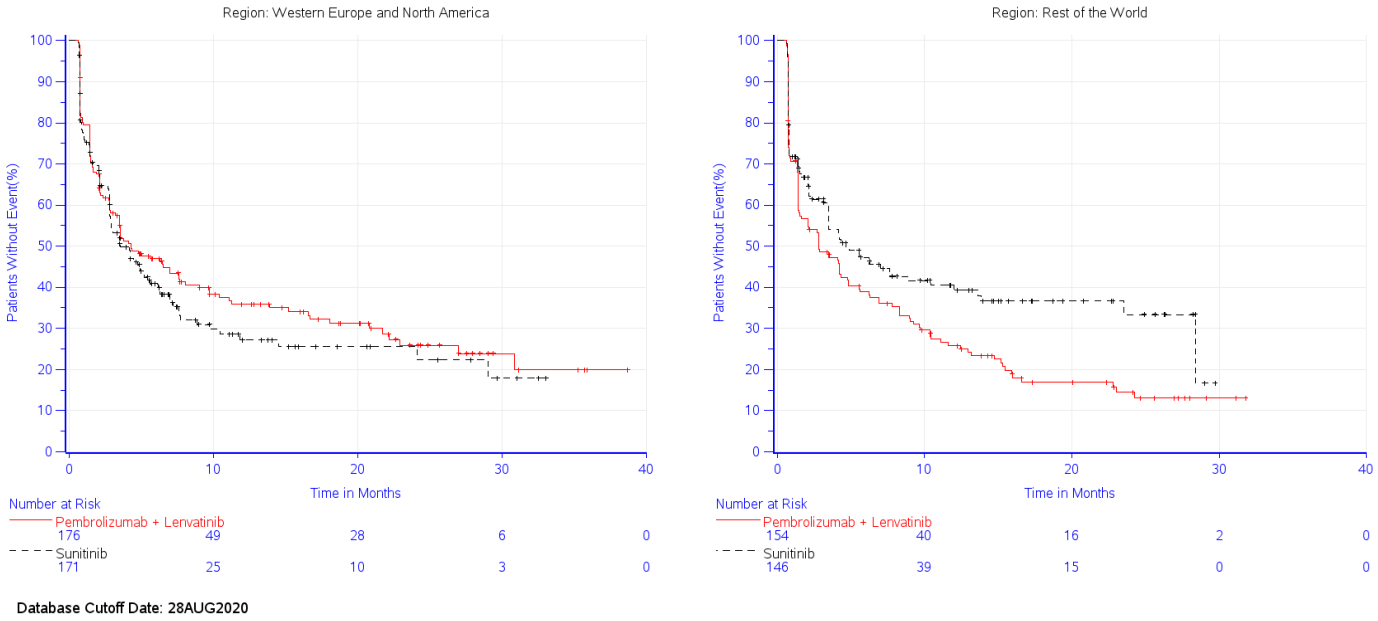


Abbildung 4G-5: Kaplan-Meier-Kurve für die Subgruppenanalyse nach Region für den Endpunkt Gesundheitszustand des FKSI-DRS (4 Punkte) der Studie KEYNOTE 581/CLEAR

EQ-5D VAS (7 Punkte): Alter (< 65 vs. ≥65)

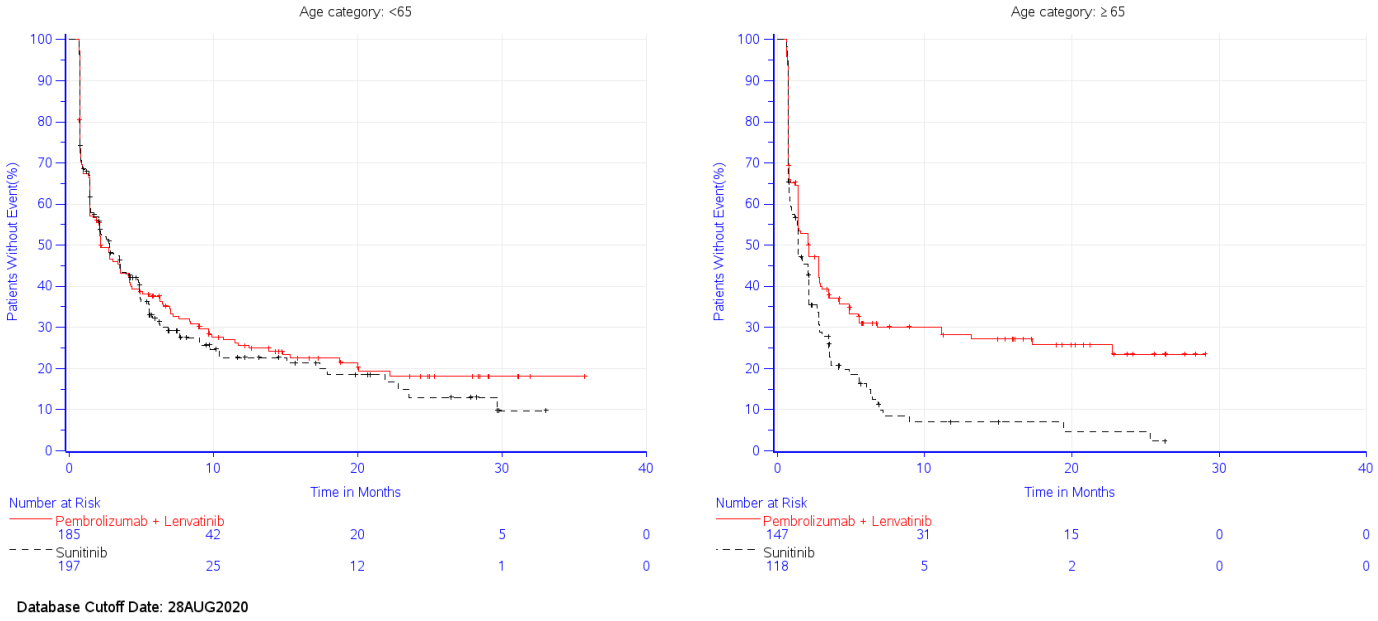


Abbildung 4G-6: Kaplan-Meier-Kurve für die Subgruppenanalyse nach Alter (< 65 vs. ≥65) für den Endpunkt Gesundheitszustand für die EQ-5D VAS (7 Punkte) der Studie KEYNOTE 581/CLEAR

EQ-5D VAS (7 Punkte): KPS Score zu Studienbeginn (100-90 vs. 80-70)

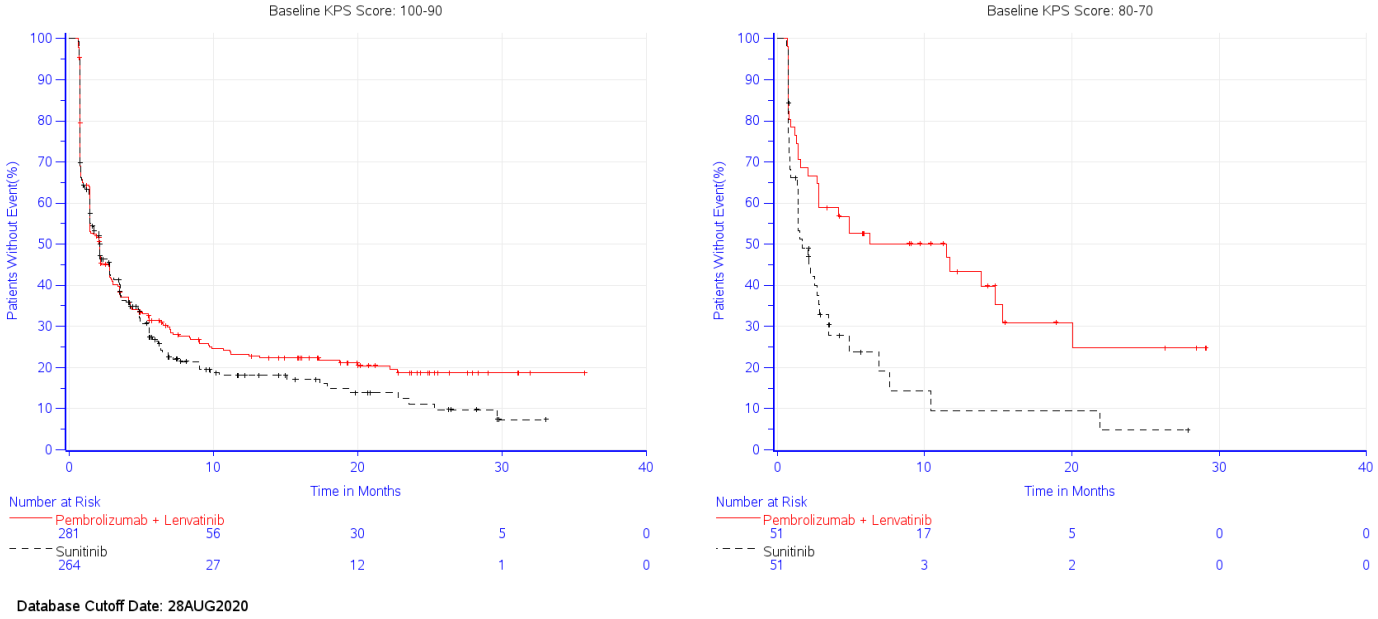


Abbildung 4G-7: Kaplan-Meier-Kurve für die Subgruppenanalyse nach KPS Score zu Studienbeginn (100-90 vs. 80-70) für den Endpunkt Gesundheitszustand für die EQ-5D VAS (7 Punkte) der Studie KEYNOTE 581/CLEAR

EQ-5D VAS (7 Punkte): Region

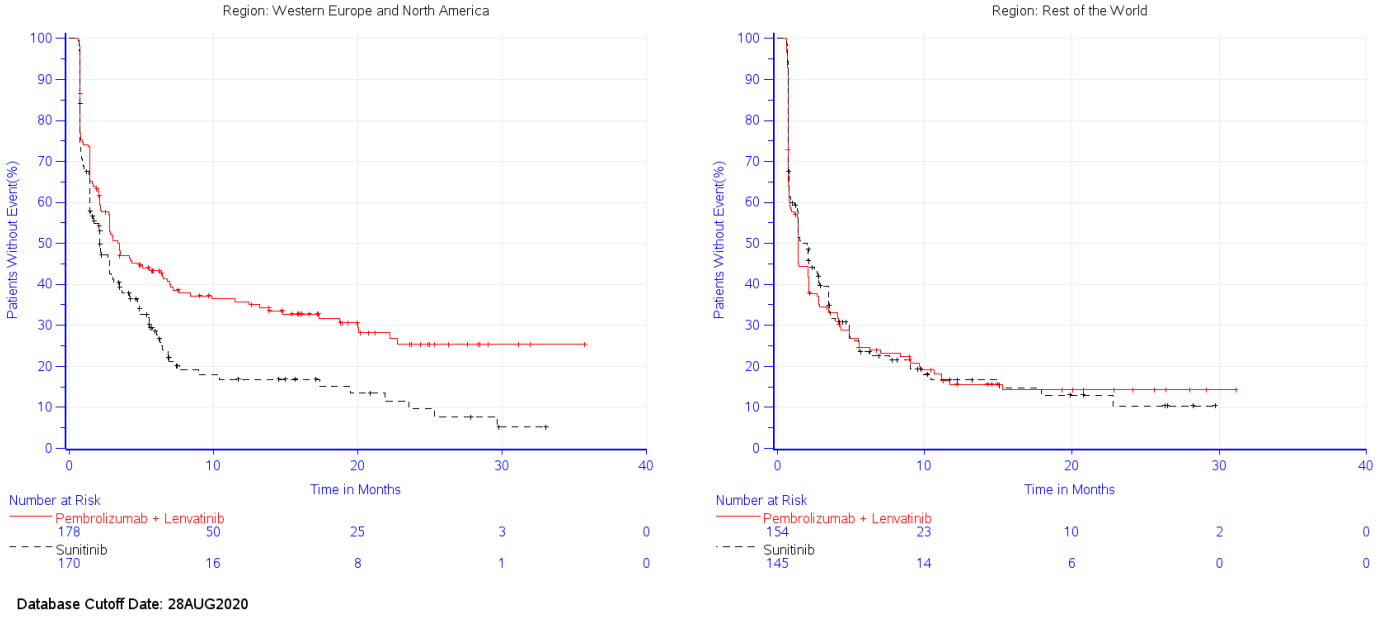


Abbildung 4G-8: Kaplan-Meier-Kurve für die Subgruppenanalyse nach Region für den Endpunkt Gesundheitszustand für die EQ-5D VAS (7 Punkte) der Studie KEYNOTE 581/CLEAR

EQ-5D VAS (10 Punkte): Alter (< 65 vs. ≥65)

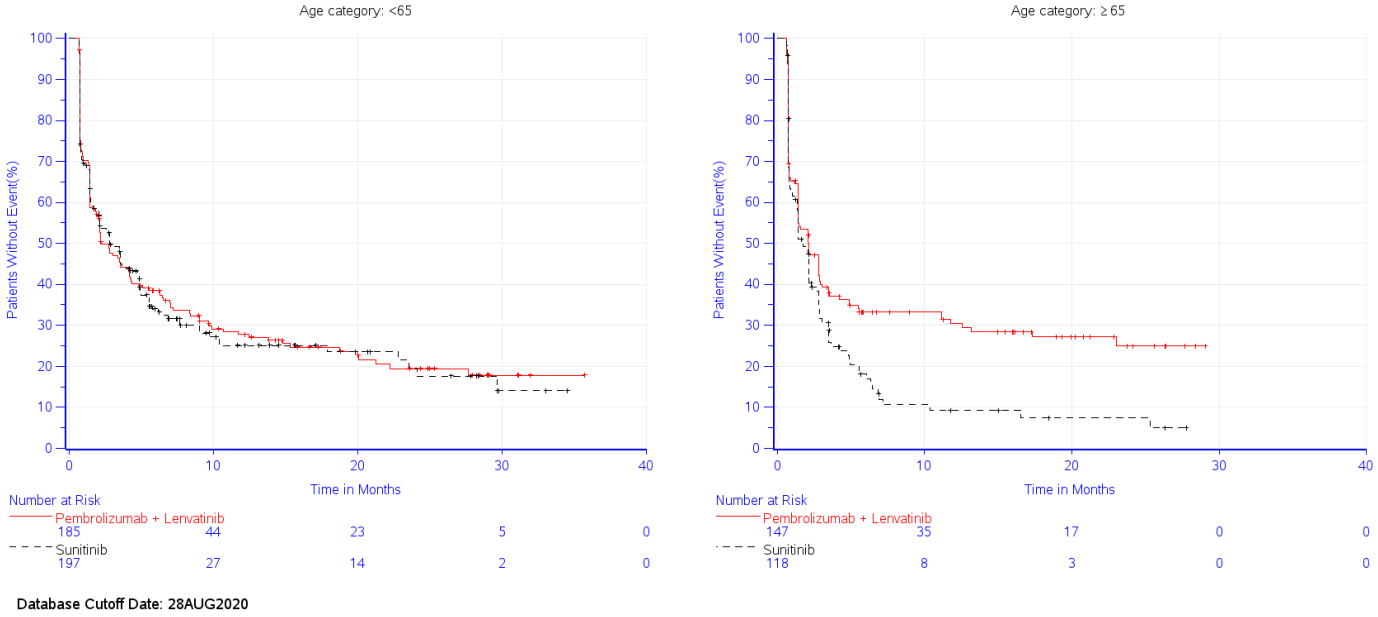


Abbildung 4G-9: Kaplan-Meier-Kurve für die Subgruppenanalyse nach Alter (< 65 vs. ≥65) für den Endpunkt Gesundheitszustand für die EQ-5D VAS (10 Punkte) der Studie KEYNOTE 581/CLEAR

EQ-5D VAS (10 Punkte): KPS Score zu Studienbeginn (100-90 vs. 80-70)

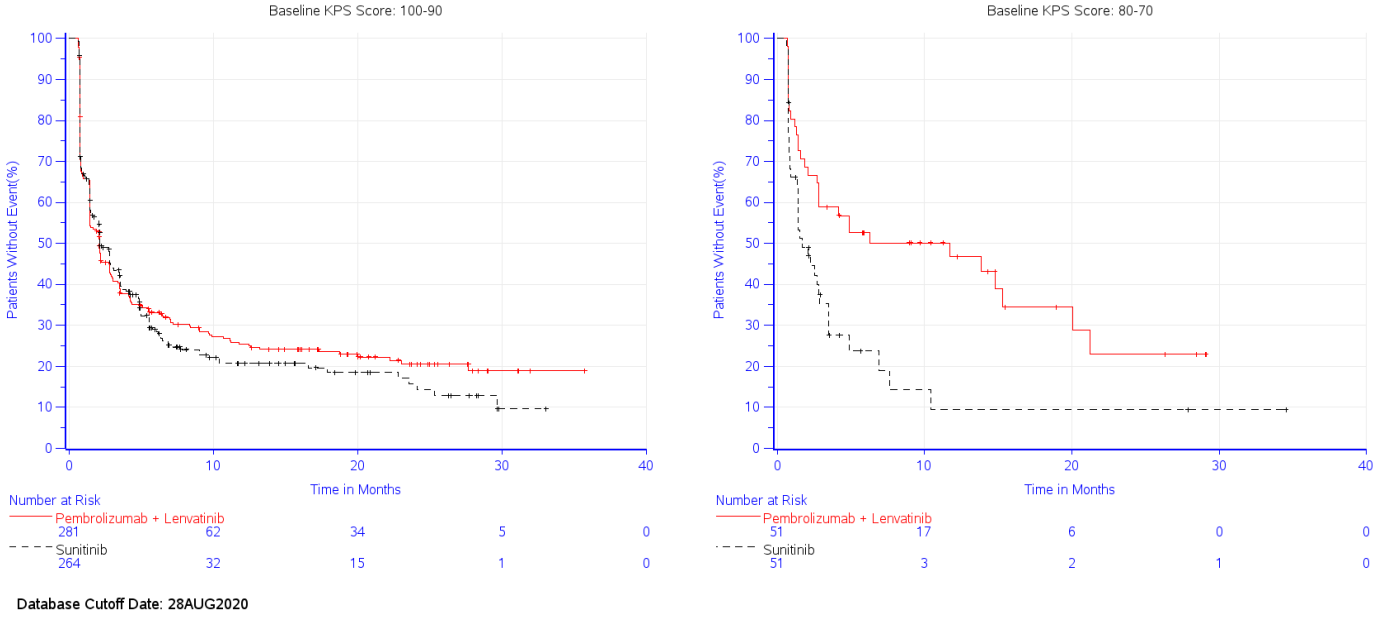


Abbildung 4G-10: Kaplan-Meier-Kurve für die Subgruppenanalyse nach KPS Score zu Studienbeginn (100-90 vs. 80-70) für den Endpunkt Gesundheitszustand für die EQ-5D VAS (10 Punkte) der Studie KEYNOTE 581/CLEAR

EQ-5D VAS (10 Punkte): Region

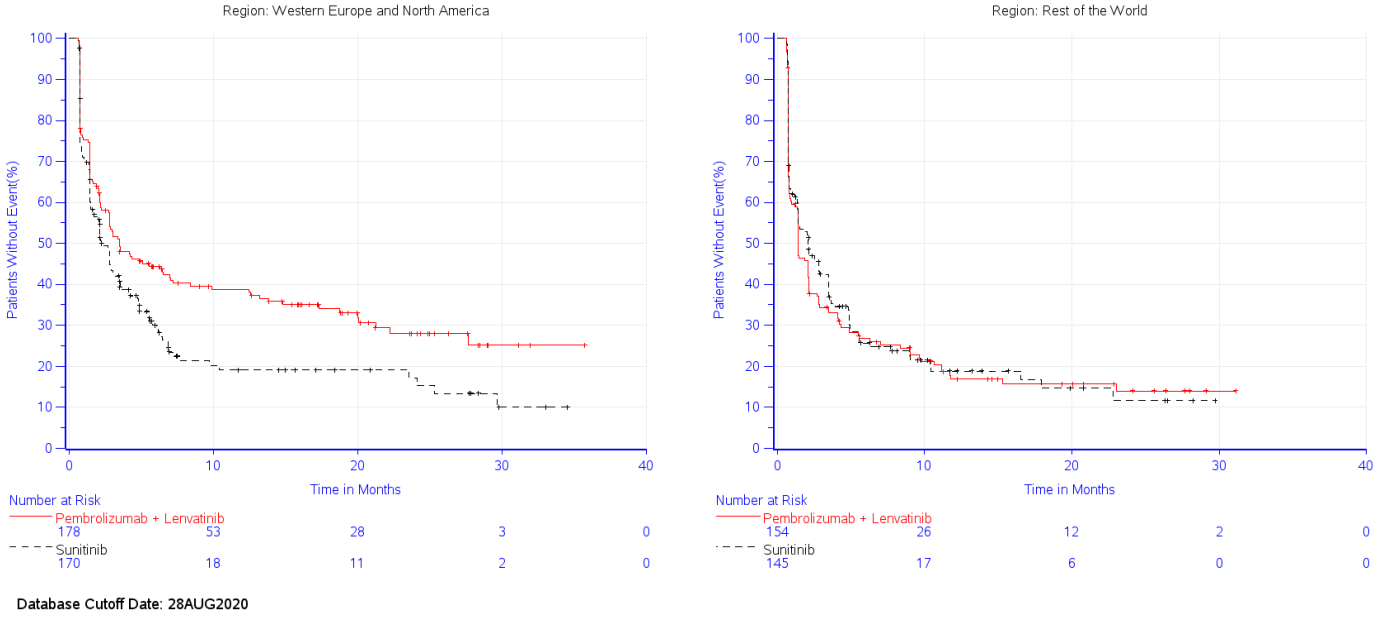


Abbildung 4G-11: Kaplan-Meier-Kurve für die Subgruppenanalyse nach Region für den Endpunkt Gesundheitszustand für die EQ-5D VAS (10 Punkte) der Studie KEYNOTE 581/CLEAR

Gesundheitsbezogene Lebensqualität

EORTC QLQ-C30: Globaler Gesundheitsstatus

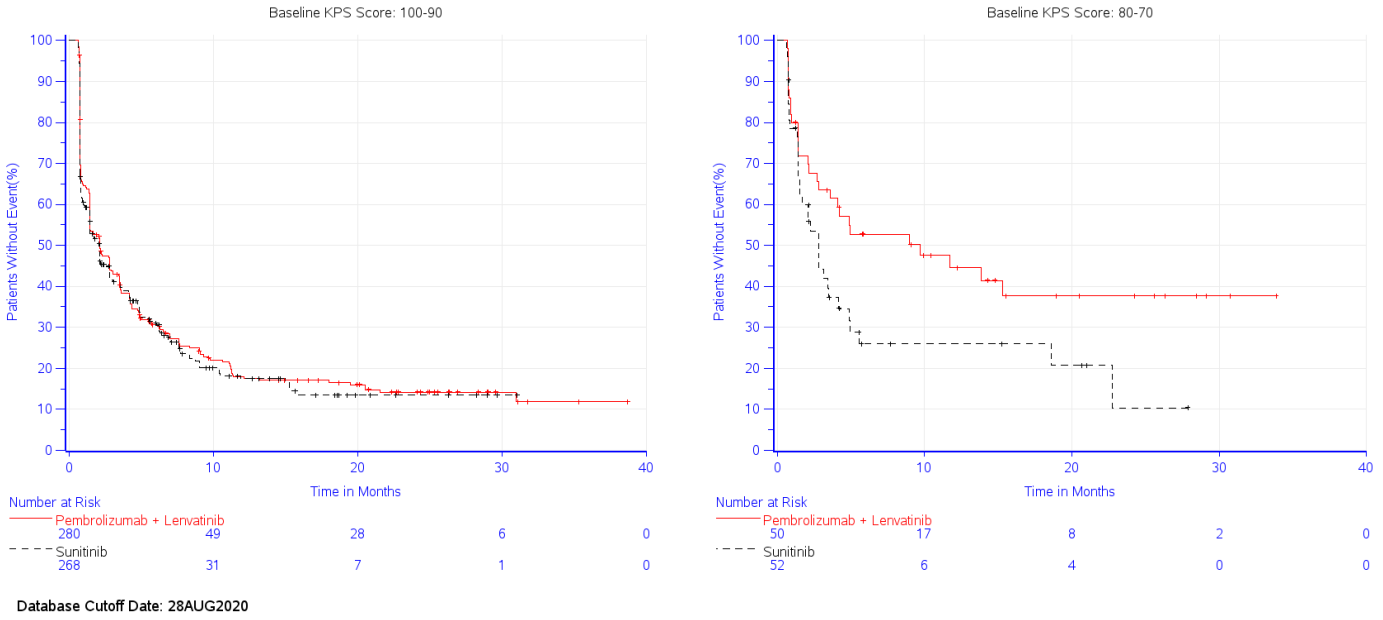


Abbildung 4G- 12: Kaplan-Meier-Kurve für die Subgruppenanalyse nach KPS Score zu Studienbeginn (100-90 vs. 80-70) für den globalen Gesundheitsstatus des EORTC QLQ-C30 der Studie KEYNOTE 581/CLEAR

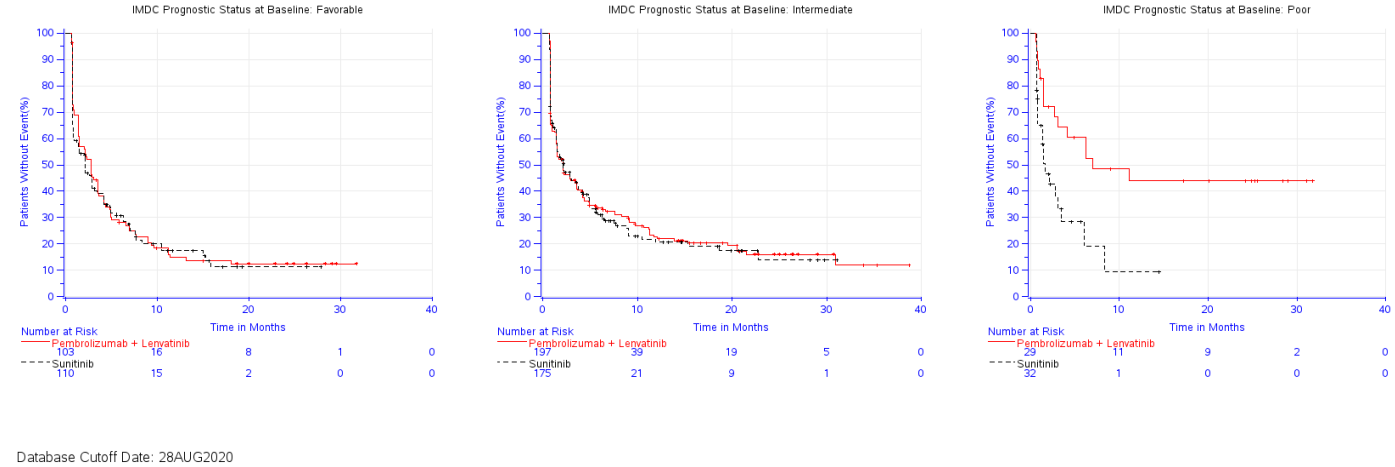


Abbildung 4G-13: Kaplan-Meier-Kurve für die Subgruppenanalyse IMDC Risikogruppe zu Studienbeginn (günstig vs. intermediär vs. ungünstig) für den globalen Gesundheitsstatus des EORTC QLQ-C30 der Studie KEYNOTE 581/CLEAR

EORTC QLQ-C30: Funktionsskala Kognitive Funktion

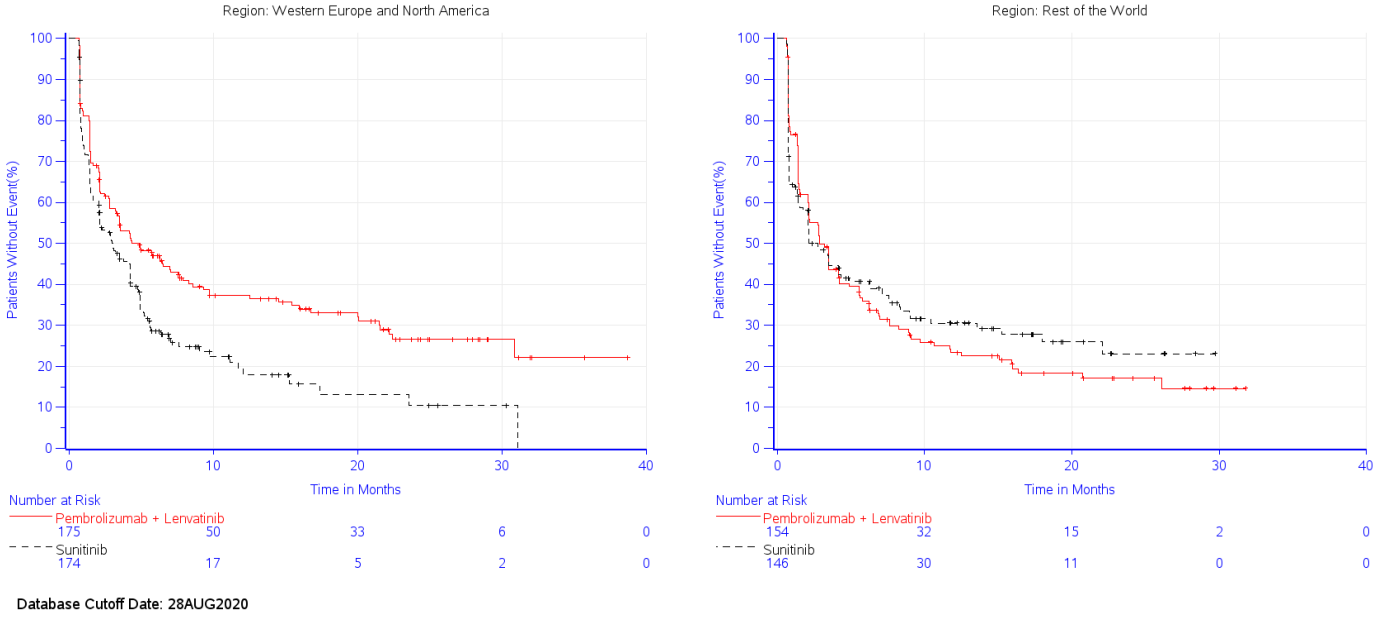


Abbildung 4G-14: Kaplan-Meier-Kurve für die Subgruppenanalyse nach Region für die Funktionsskala Kognitive Funktion des EORTC QLQ-C30 der Studie KEYNOTE 581/CLEAR

EORTC QLQ-C30: Funktionsskala Körperliche Funktion

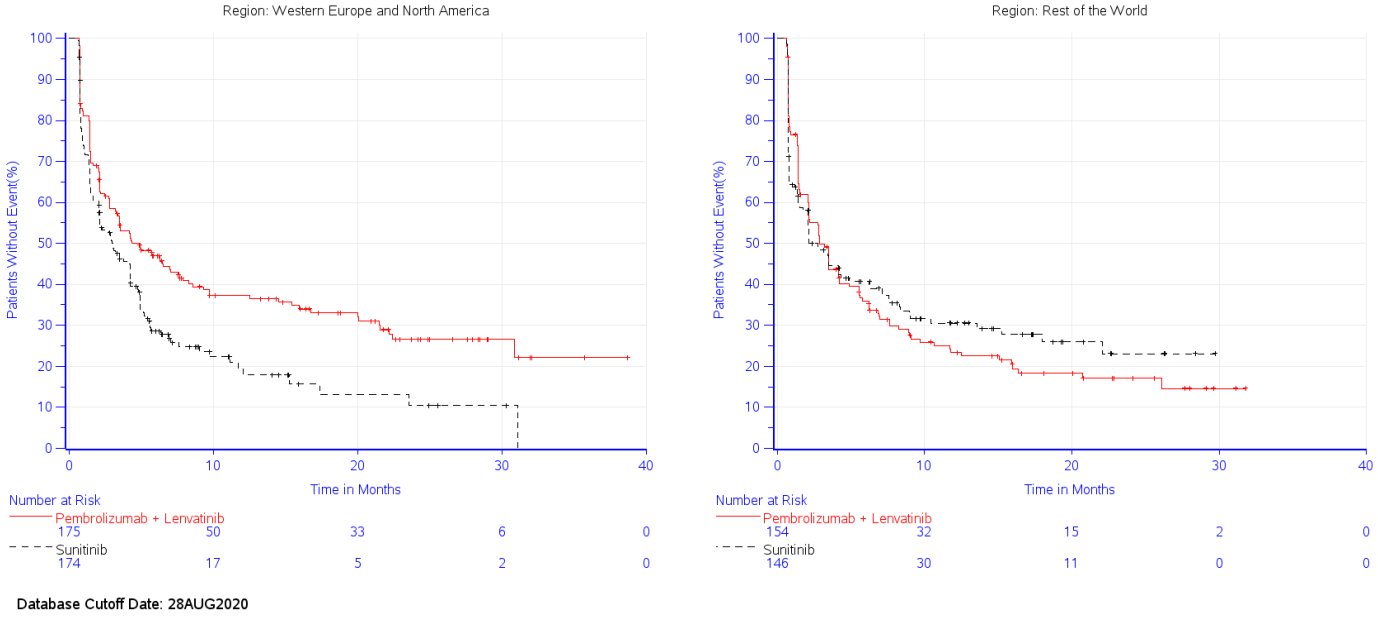


Abbildung 4G-15: Kaplan-Meier-Kurve für die Subgruppenanalyse nach Region für die Funktionsskala Körperliche Funktion des EORTC QLQ-C30 der Studie KEYNOTE 581/CLEAR

Nebenwirkungen

Unerwünschte Ereignisse

Therapieabbruch wegen unerwünschter Ereignisse

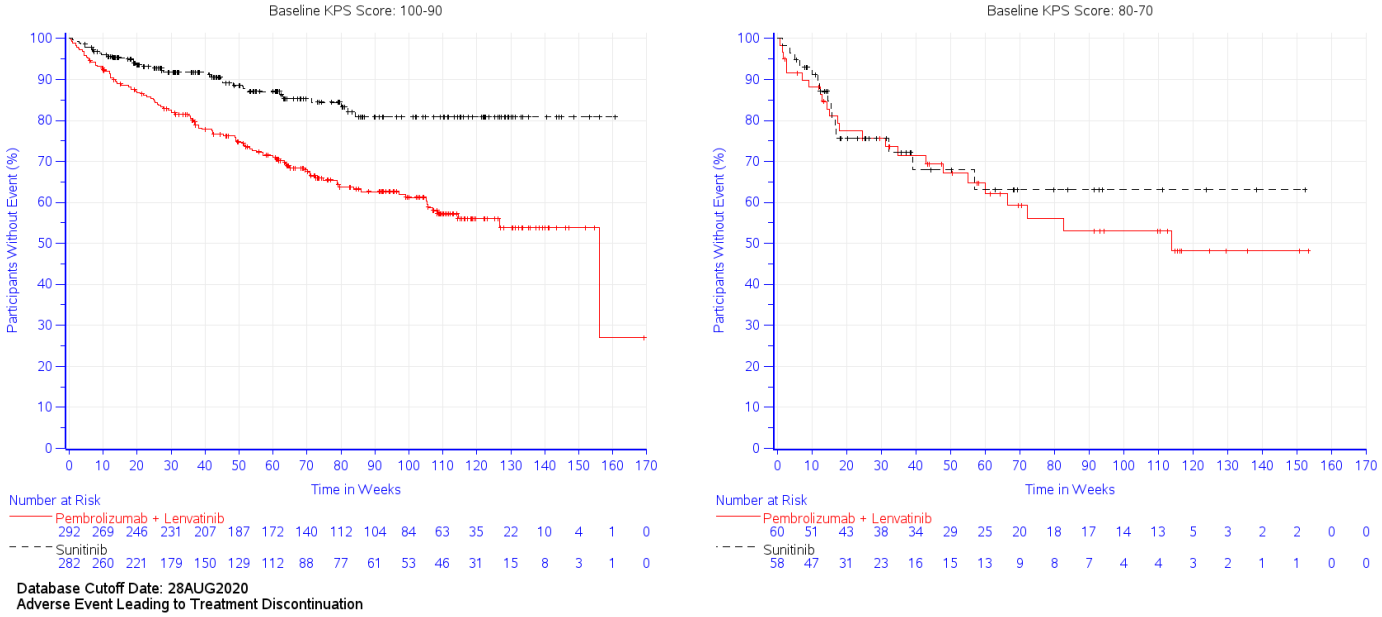


Abbildung 4G-16: Kaplan-Meier-Kurve für die Subgruppenanalyse nach KPS Score zu Studienbeginn (100-90 vs. 80-70) für den Endpunkt Therapieabbruch wegen unerwünschter Ereignisse der Studie KEYNOTE 581/CLEAR

Unerwünschte Ereignisse (gegliedert nach SOC und PT)

Unerwünschte Ereignisse gesamt (SOC und PT)

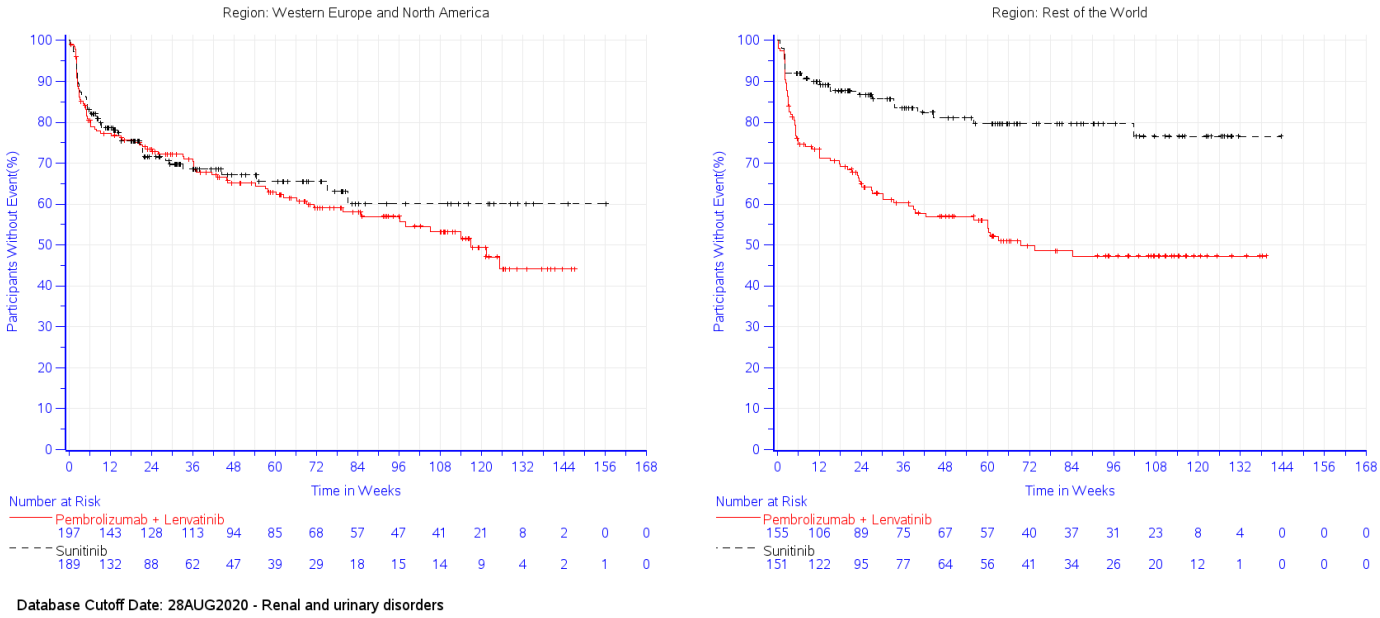


Abbildung 4G-17: Kaplan-Meier-Kurve für die Subgruppenanalyse nach Region für den Endpunkt Unerwünschte Ereignisse gesamt (SOC und PT) für die SOC „Erkrankungen der Nieren und Harnwege“ der Studie KEYNOTE 581/CLEAR

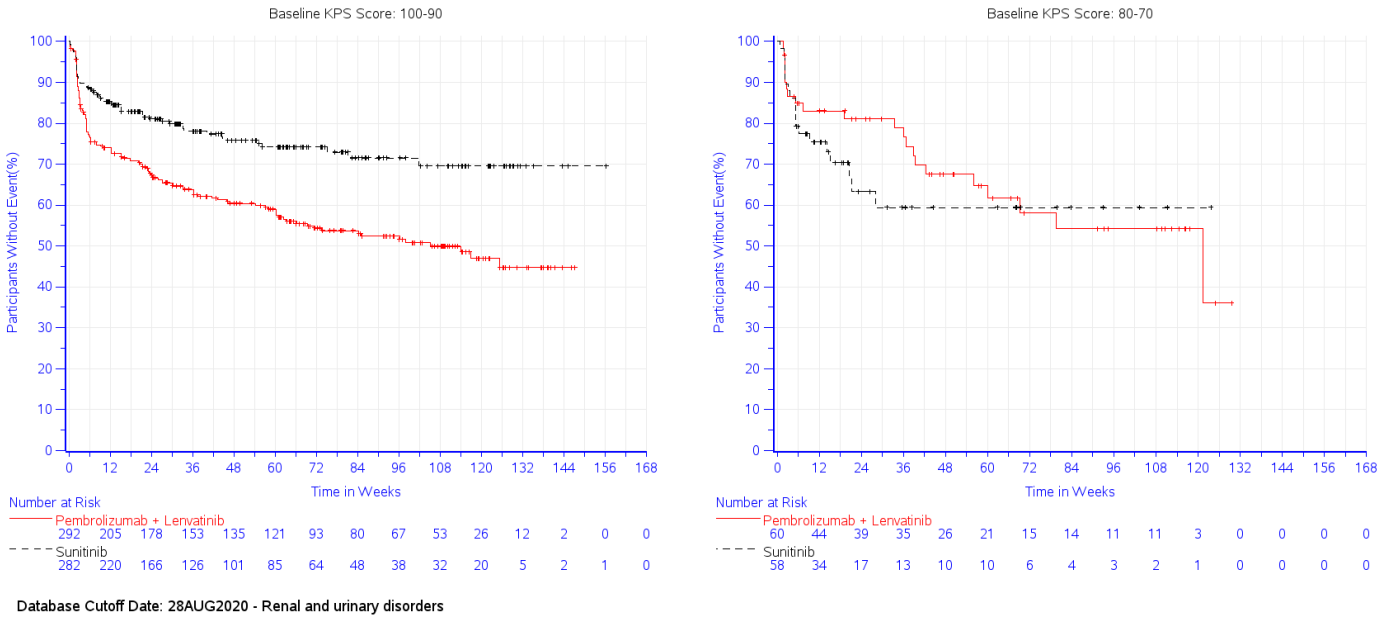


Abbildung 4G-18: Kaplan-Meier-Kurve für die Subgruppenanalyse nach KPS Score zu Studienbeginn (100-90 vs. 80-70) für den Endpunkt Unerwünschte Ereignisse gesamt (SOC und PT) für die SOC „Erkrankungen der Nieren und Harnwege“ der Studie KEYNOTE 581/CLEAR

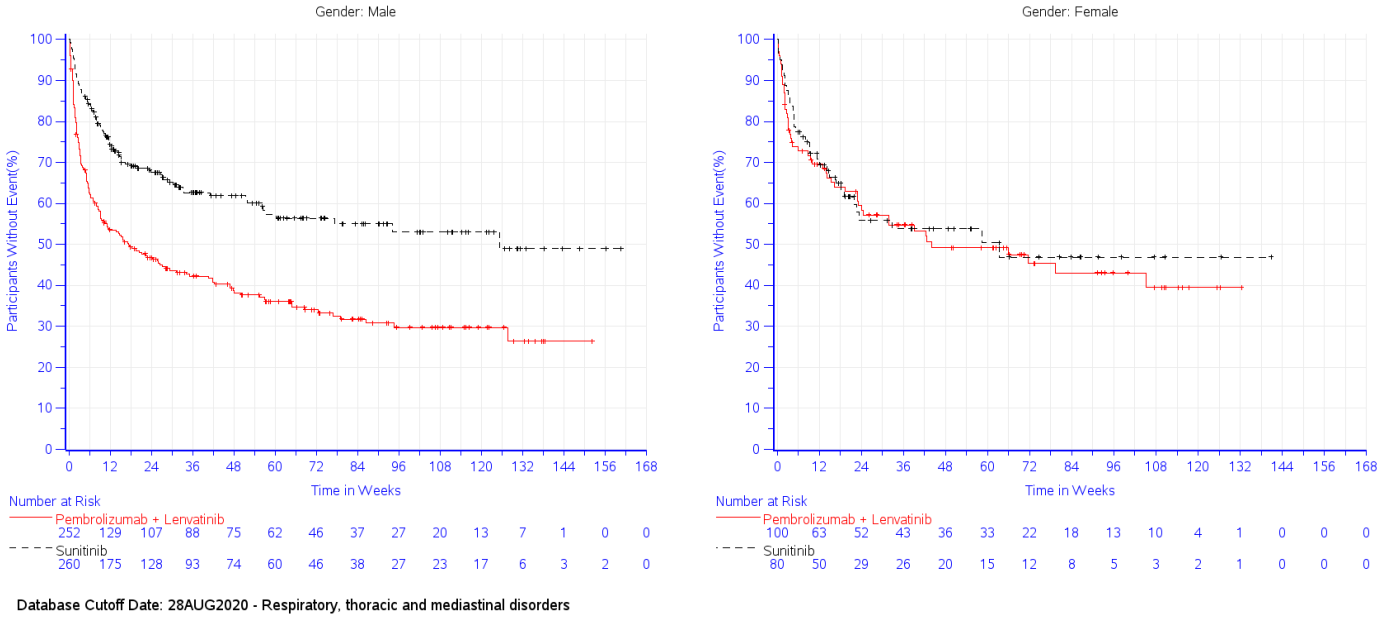


Abbildung 4G-19: Kaplan-Meier-Kurve für die Subgruppenanalyse nach Geschlecht für den Endpunkt Unerwünschte Ereignisse gesamt (SOC und PT) für die SOC „Erkrankungen der Atemwege, des Brustraums und Mediastinums“ der Studie KEYNOTE 581/CLEAR

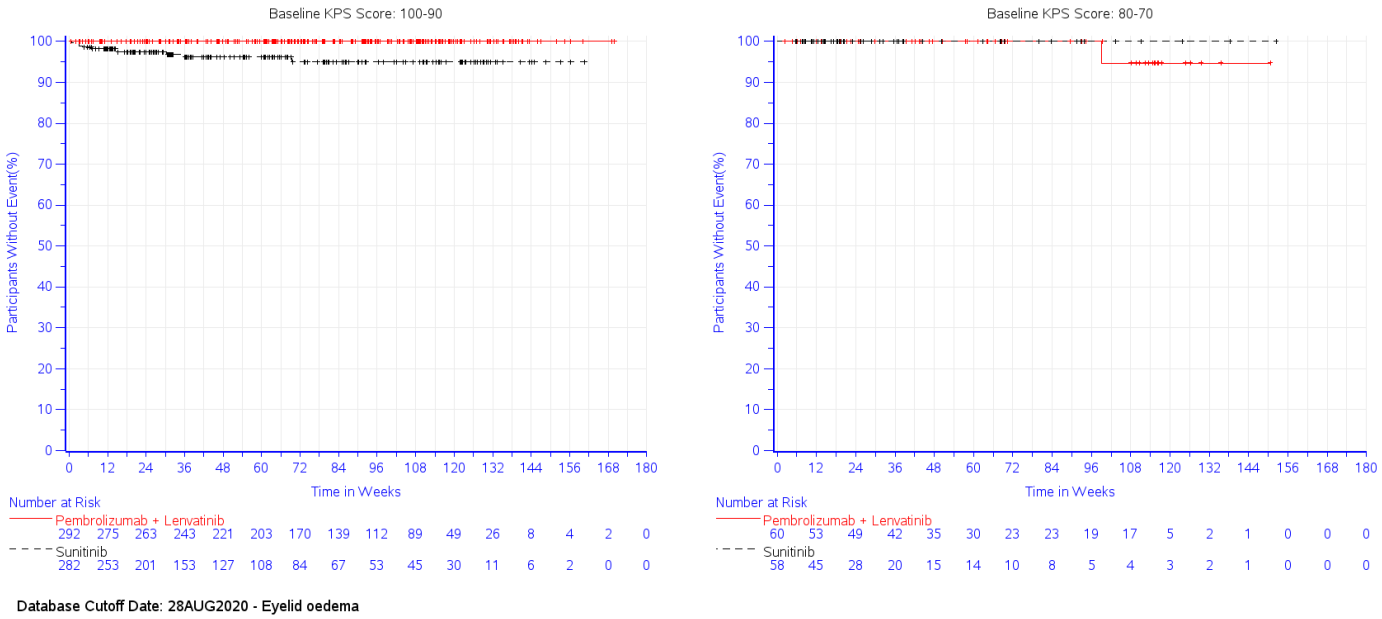


Abbildung 4G-20: Kaplan-Meier-Kurve für die Subgruppenanalyse nach KPS Score zu Studienbeginn (100-90 vs. 80-70) für den Endpunkt Unerwünschte Ereignisse gesamt (SOC und PT) für den PT „Augenlidödem“ der Studie KEYNOTE 581/CLEAR

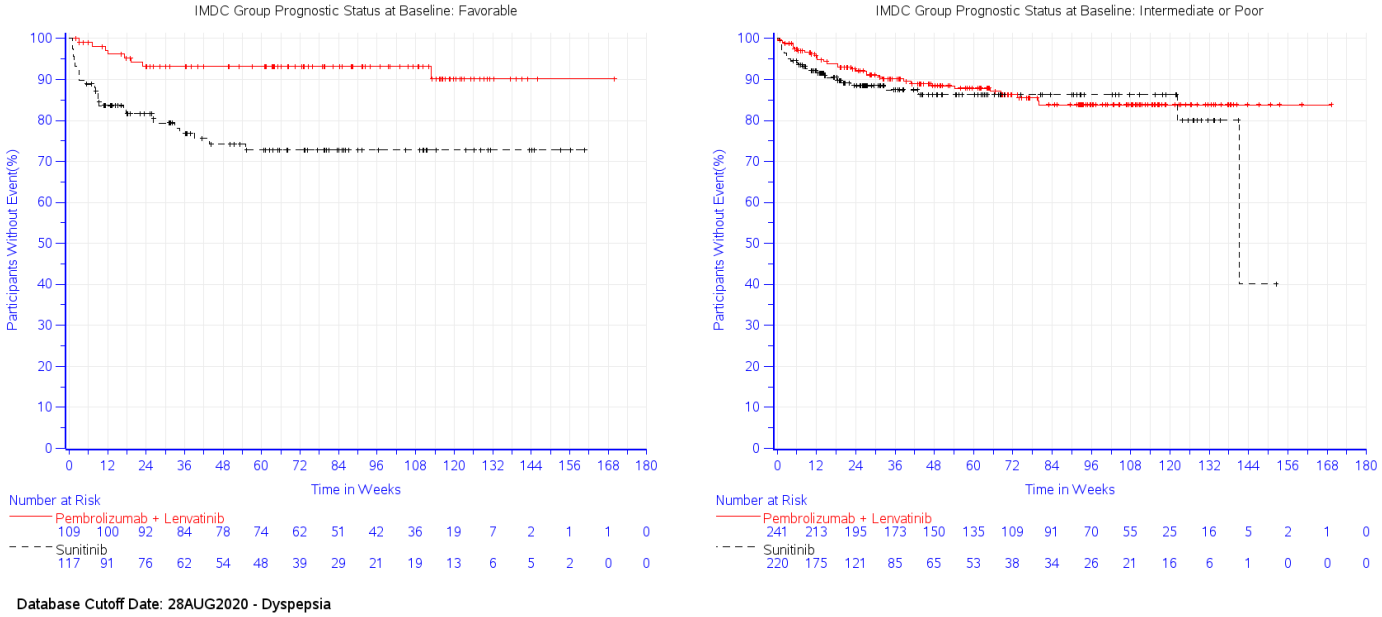


Abbildung 4G-21: Kaplan-Meier-Kurve für die Subgruppenanalyse nach IMDC Risikogruppe zu Studienbeginn (günstig vs. intermediär und ungünstig) für den Endpunkt Unerwünschte Ereignisse gesamt (SOC und PT) für den PT „Dyspepsie“ der Studie KEYNOTE 581/CLEAR

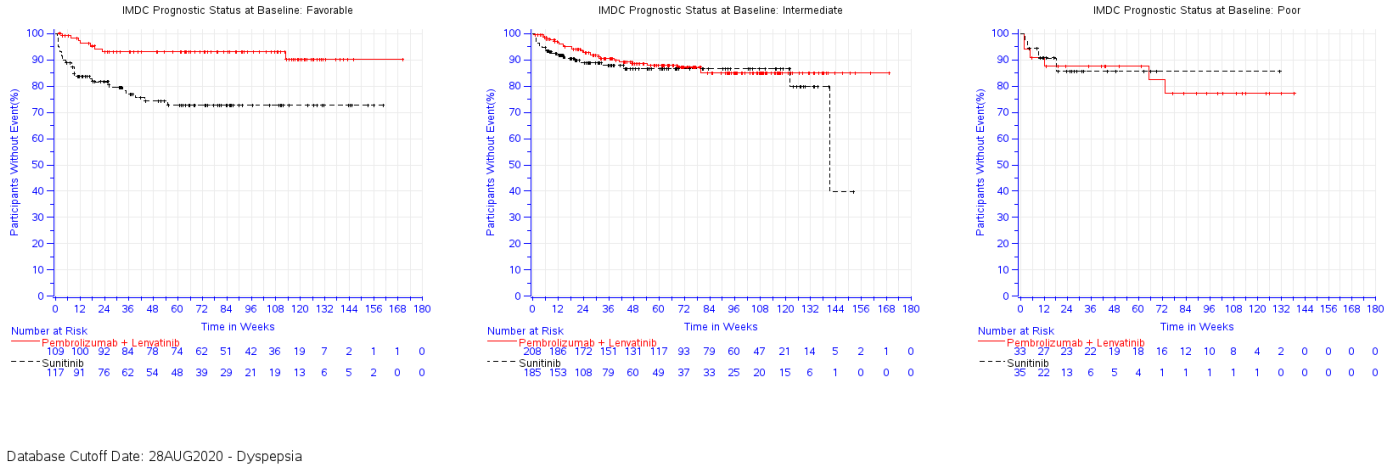


Abbildung 4G-22: Kaplan-Meier-Kurve für die Subgruppenanalyse nach IMDC Risikogruppe zu Studienbeginn (günstig vs. intermediär vs. ungünstig) für den Endpunkt Unerwünschte Ereignisse gesamt (SOC und PT) für den PT „Dyspepsie“ der Studie KEYNOTE 581/CLEAR

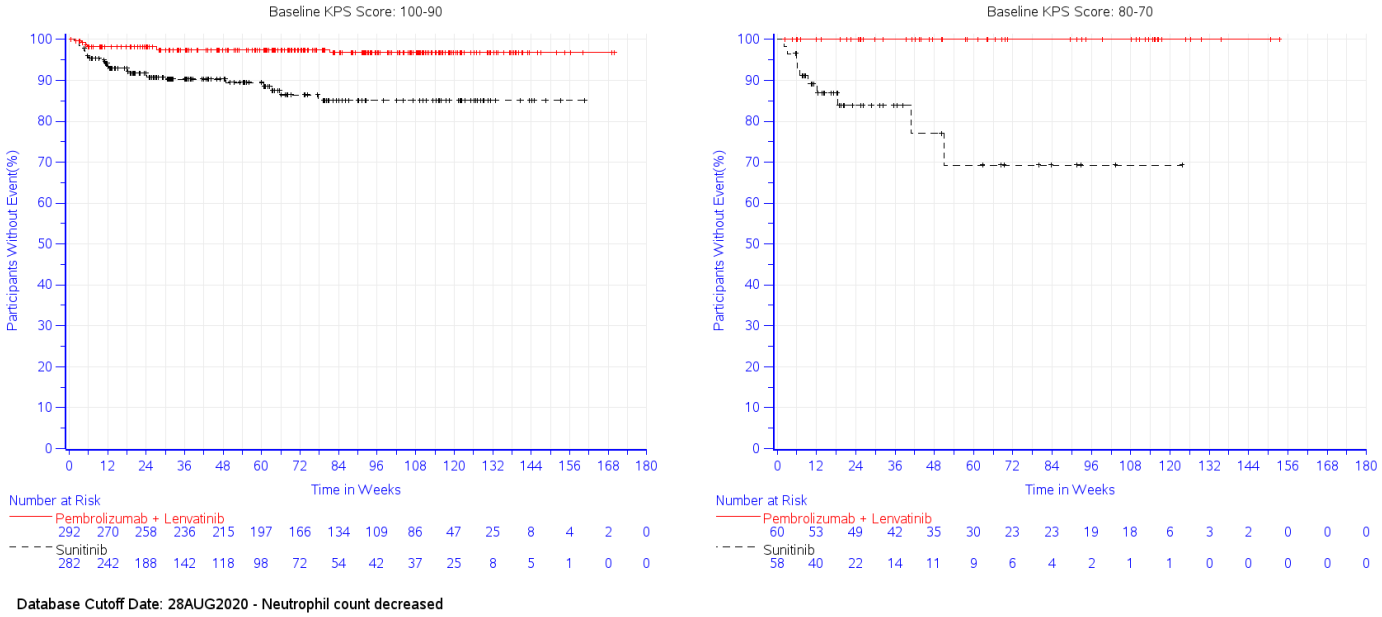


Abbildung 4G-23: Kaplan-Meier-Kurve für die Subgruppenanalyse nach KPS Score zu Studienbeginn (100-90 vs. 80-70) für den Endpunkt Unerwünschte Ereignisse gesamt (SOC und PT) für den PT „Neutrophilenzahl erniedrigt“ der Studie KEYNOTE 581/CLEAR

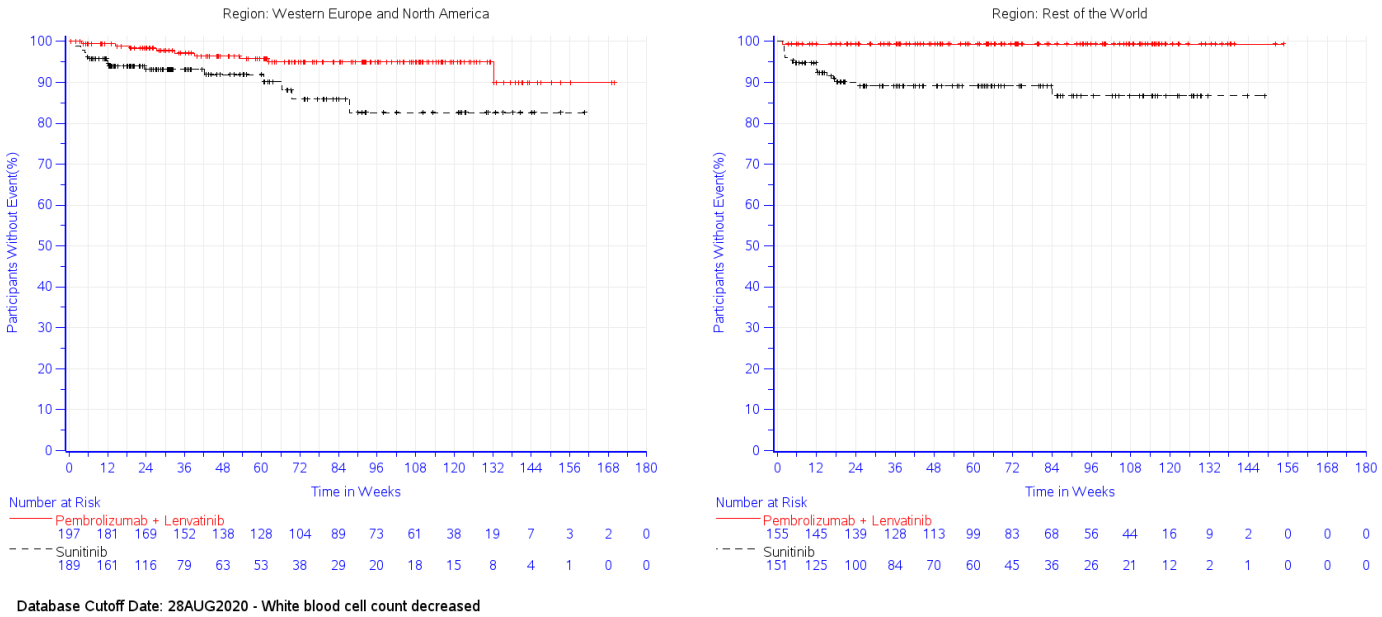


Abbildung 4G-24: Kaplan-Meier-Kurve für die Subgruppenanalyse nach Region für den Endpunkt Unerwünschte Ereignisse gesamt (SOC und PT) für den PT „Leukozytenzahl erniedrigt“ der Studie KEYNOTE 581/CLEAR

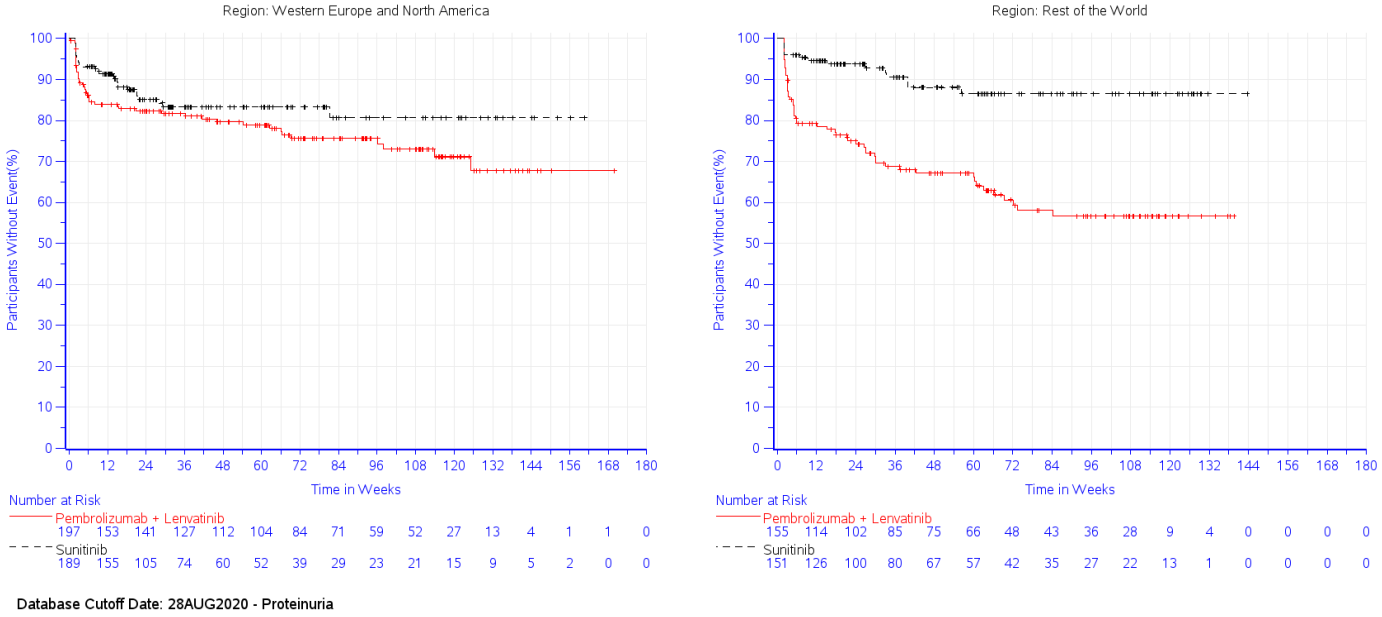


Abbildung 4G-25: Kaplan-Meier-Kurve für die Subgruppenanalyse nach Region für den Endpunkt Unerwünschte Ereignisse gesamt (SOC und PT) für den PT „Proteinurie“ der Studie KEYNOTE 581/CLEAR

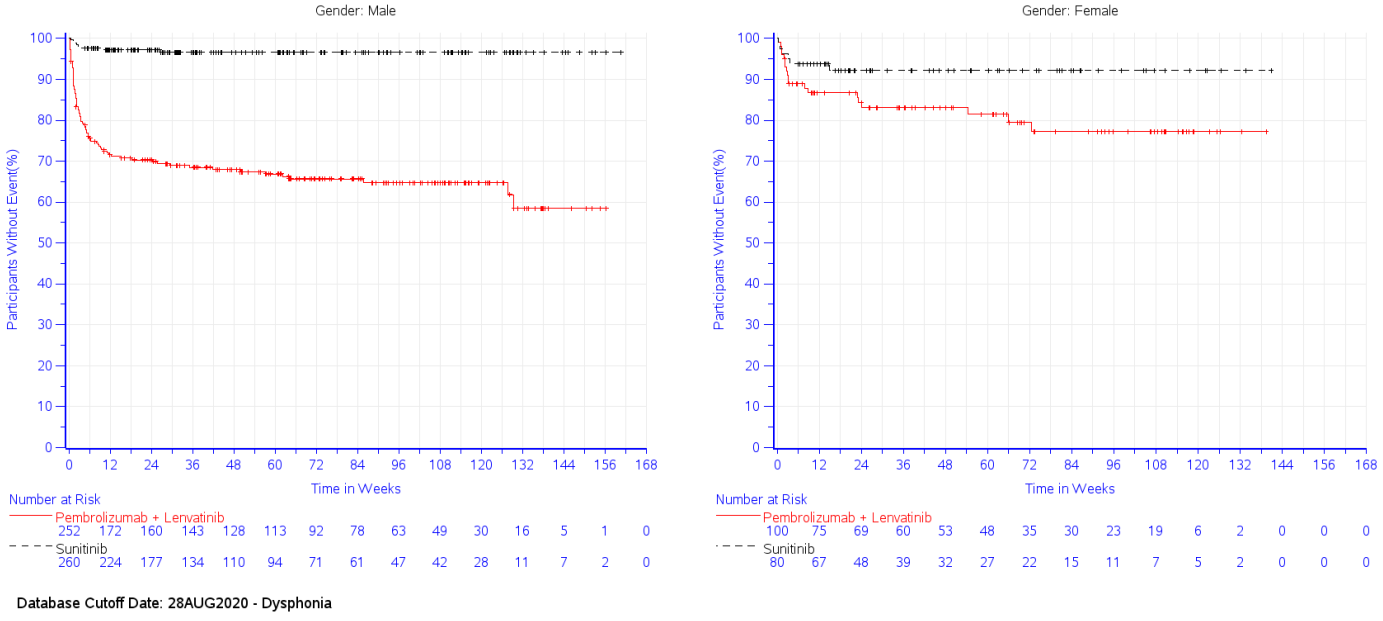


Abbildung 4G-26: Kaplan-Meier-Kurve für die Subgruppenanalyse nach Geschlecht für den Endpunkt Unerwünschte Ereignisse gesamt (SOC und PT) für den PT „Dysphonie“ der Studie KEYNOTE 581/CLEAR

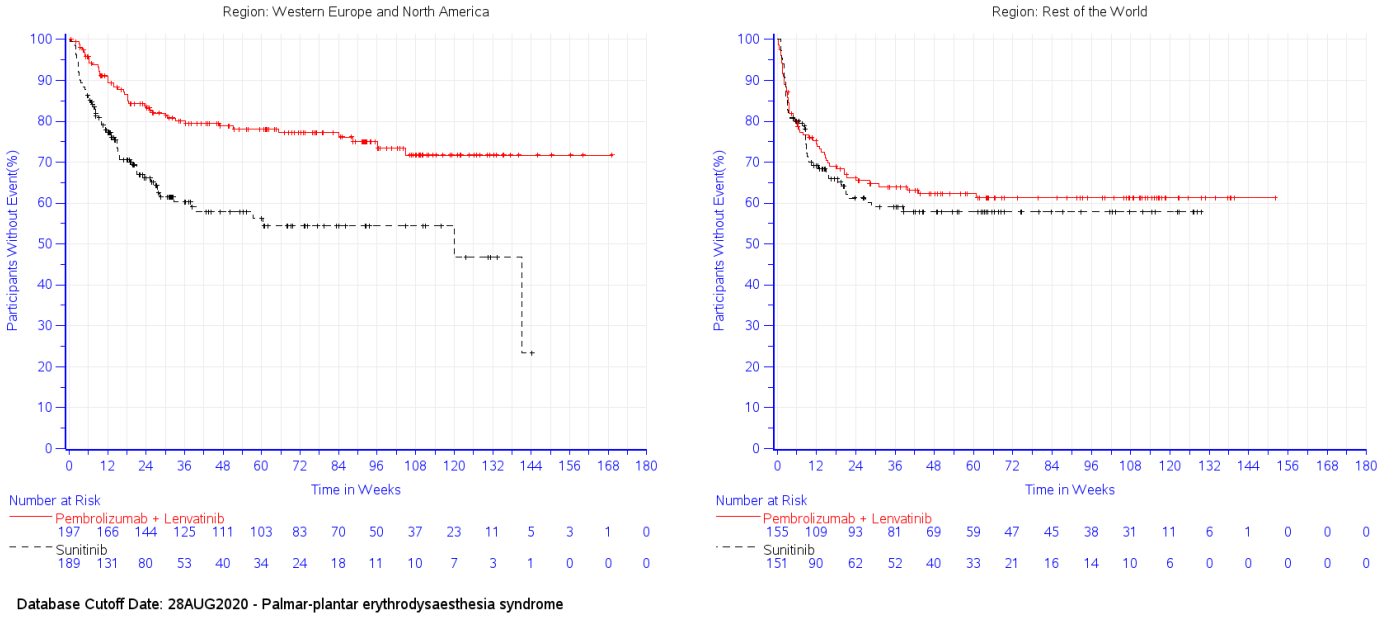


Abbildung 4G-27: Kaplan-Meier-Kurve für die Subgruppenanalyse nach Region für den Endpunkt Unerwünschte Ereignisse gesamt (SOC und PT) für den PT „Palmar-plantares Erythrodysästhesie-Syndrom“ der Studie KEYNOTE 581/CLEAR

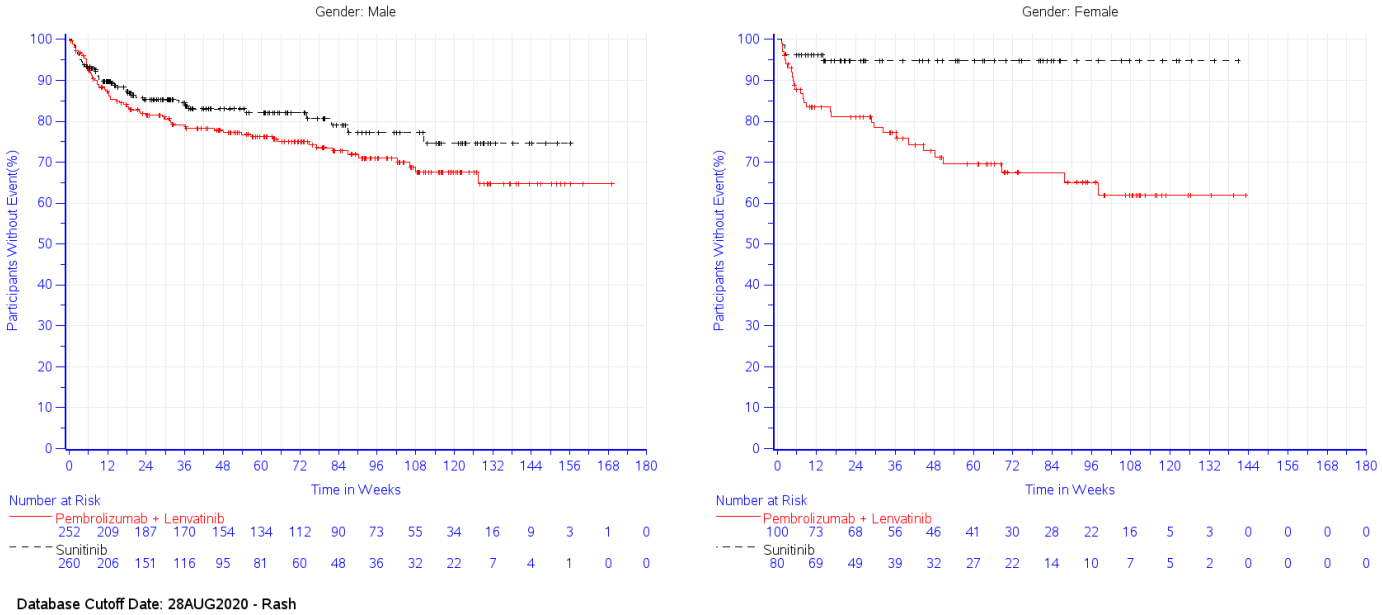


Abbildung 4G-28: Kaplan-Meier-Kurve für die Subgruppenanalyse nach Geschlecht für den Endpunkt Unerwünschte Ereignisse gesamt (SOC und PT) für den PT „Ausschlag“ der Studie KEYNOTE 581/CLEAR

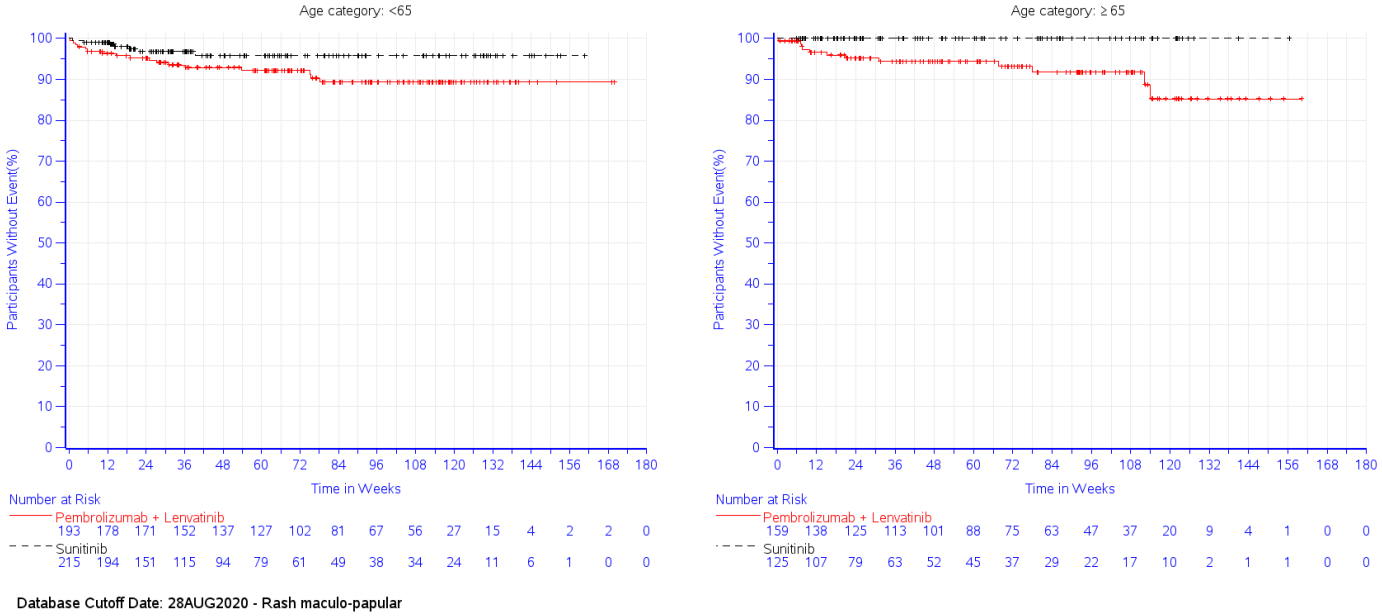


Abbildung 4G-29: Kaplan-Meier-Kurve für die Subgruppenanalyse nach Alter (< 65 vs. ≥65) für den Endpunkt Unerwünschte Ereignisse gesamt (SOC und PT) für den PT „makulapapulöser Ausschlag“ der Studie KEYNOTE 581/CLEAR

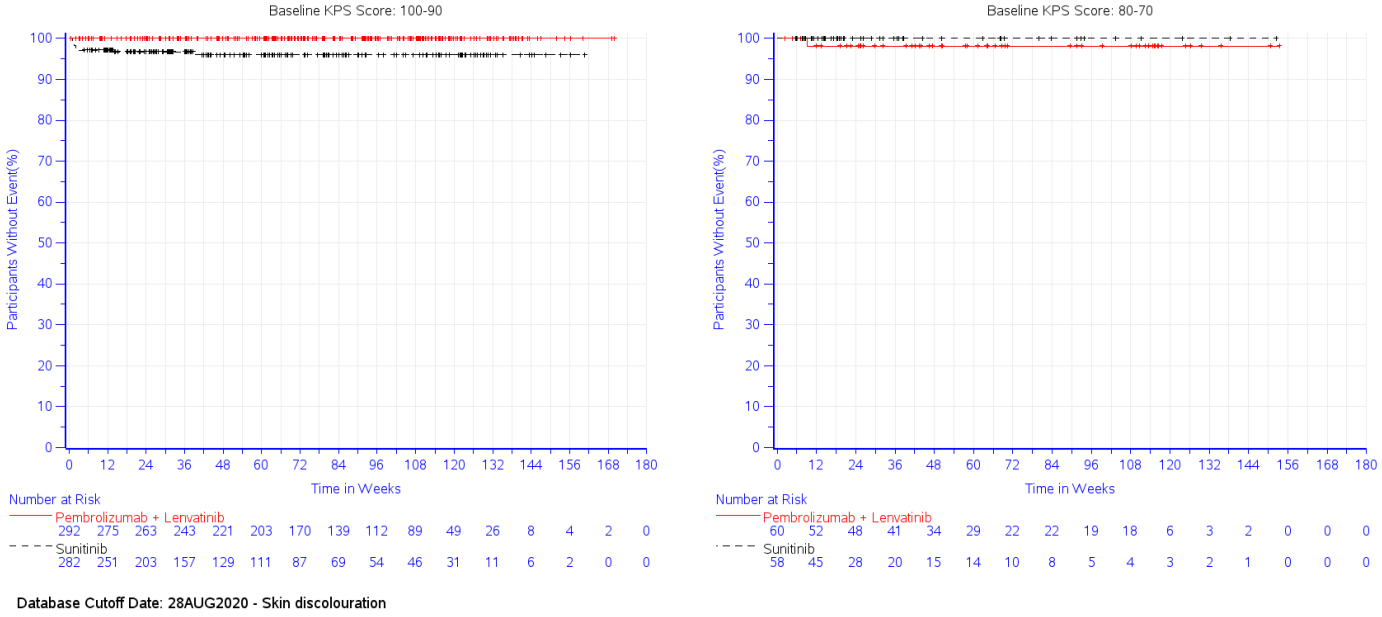


Abbildung 4G-30: Kaplan-Meier-Kurve für die Subgruppenanalyse nach KPS Score zu Studienbeginn (100-90 vs. 80-70) für den Endpunkt Unerwünschte Ereignisse gesamt (SOC und PT) für den PT „Hautverfärbung“ der Studie KEYNOTE 581/CLEAR

Schwerwiegende unerwünschte Ereignisse (SOC und PT)

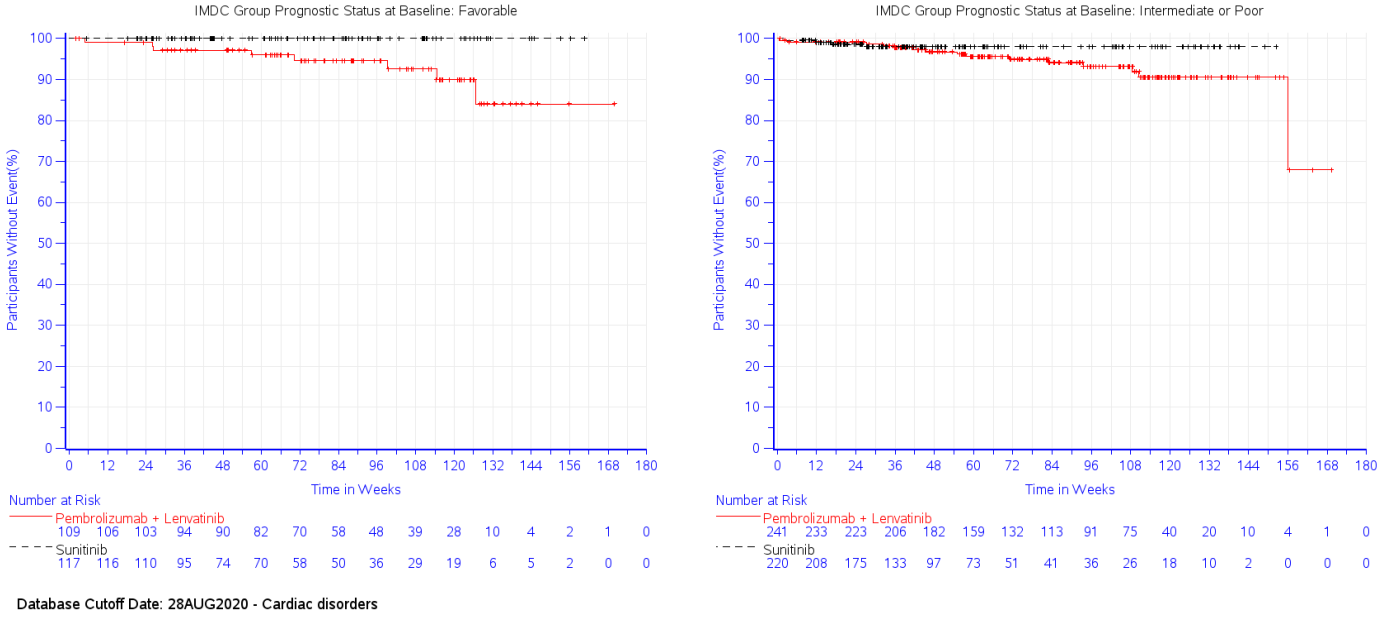


Abbildung 4G-31: Kaplan-Meier-Kurve für die Subgruppenanalyse nach IMDC Risikogruppe zu Studienbeginn (günstig vs. intermediär und ungünstig) für den Endpunkt Schwerwiegende unerwünschte Ereignisse gesamt (SOC und PT) für den SOC „Herzerkrankungen“ der Studie KEYNOTE 581/CLEAR

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

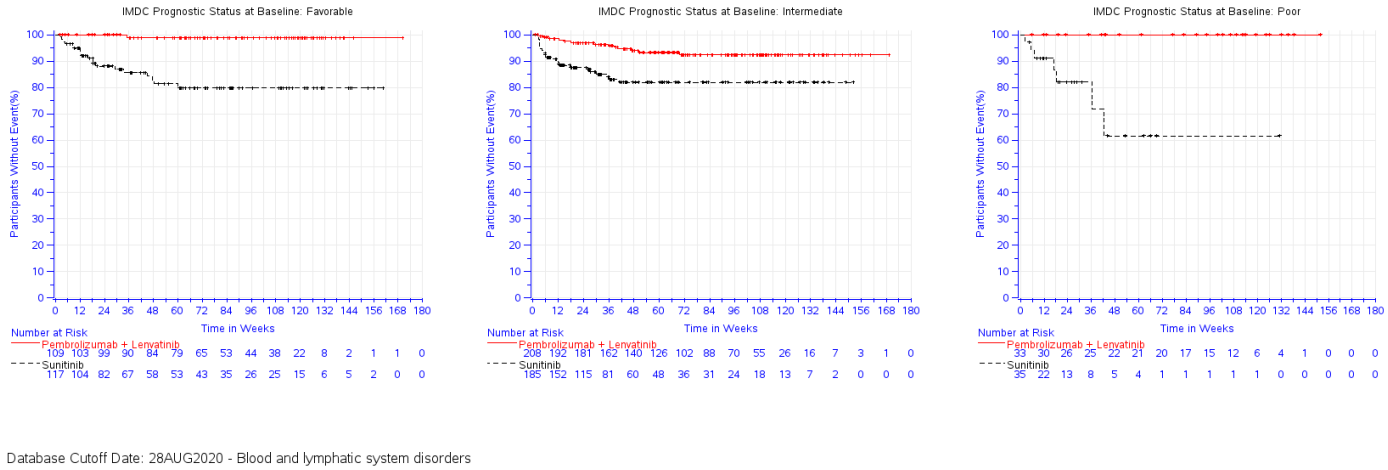


Abbildung 4G-32: Kaplan-Meier-Kurve für die Subgruppenanalyse nach IMDC Risikogruppe zu Studienbeginn (günstig vs. intermediär vs. ungünstig) für den Endpunkt Schwere unerwünschte Ereignisse (CTCAE-Grad 3-5) (SOC und PT) für den SOC „Erkrankungen des Blutes und des Lymphsystems“ der Studie KEYNOTE 581/CLEAR

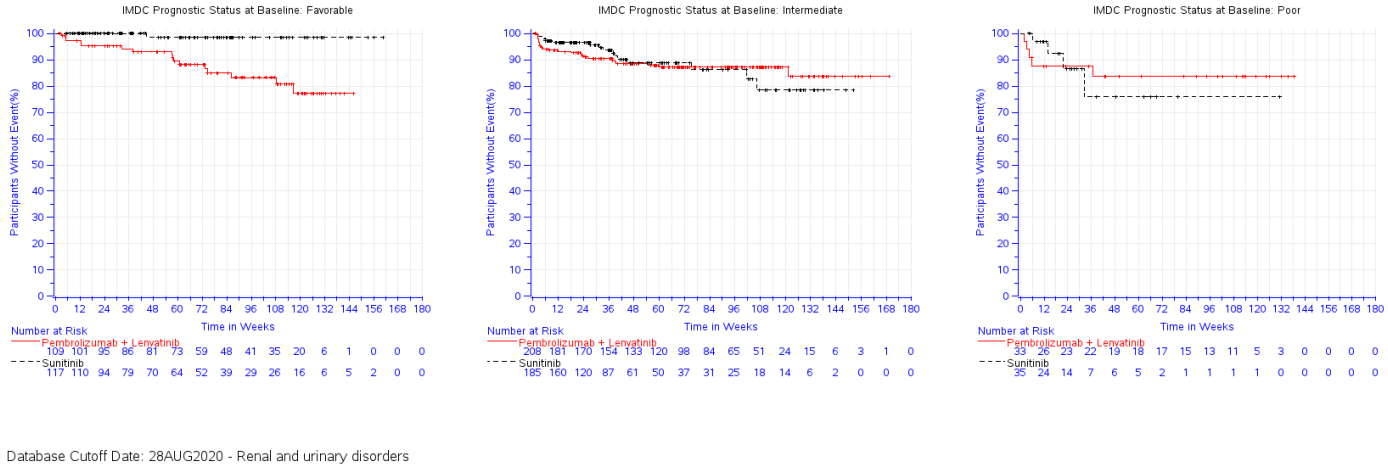


Abbildung 4G-33: Kaplan-Meier-Kurve für die Subgruppenanalyse nach IMDC Risikogruppe zu Studienbeginn (günstig vs. intermediär vs. ungünstig) für den Endpunkt Schwere unerwünschte Ereignisse (CTCAE-Grad 3-5) (SOC und PT) für den SOC „Erkrankungen der Nieren und Harnwege“ der Studie KEYNOTE 581/CLEAR

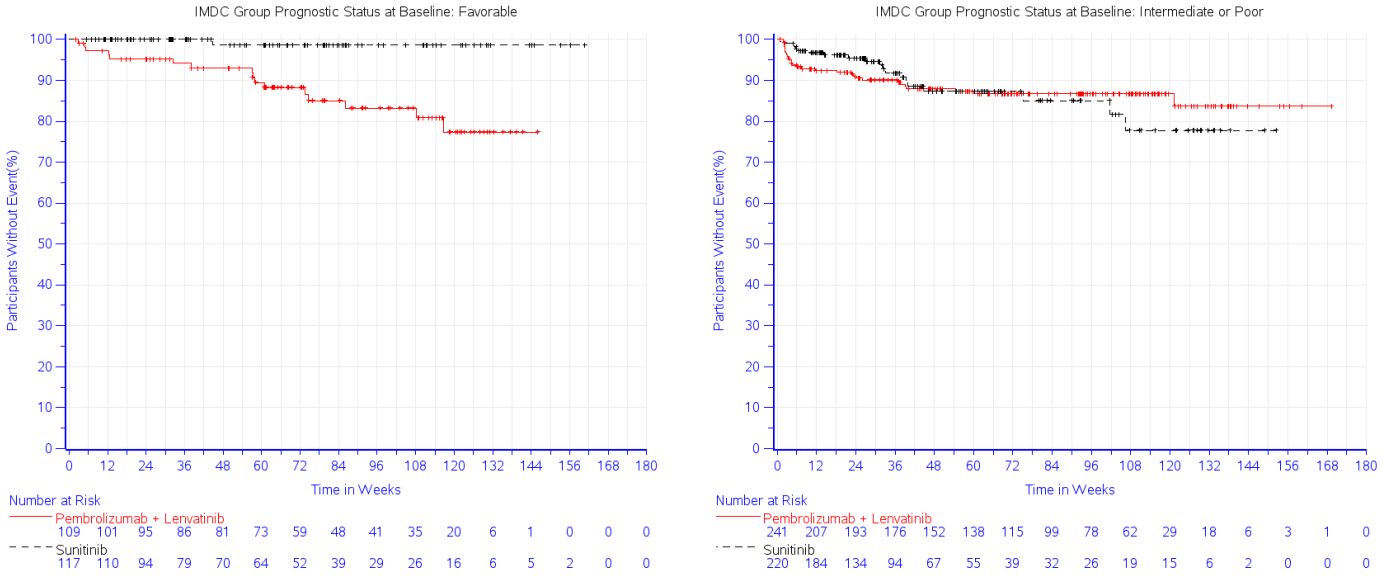


Abbildung 4G-34: Kaplan-Meier-Kurve für die Subgruppenanalyse nach IMDC Risikogruppe zu Studienbeginn (günstig vs. intermediär und ungünstig) für den Endpunkt Schwere unerwünschte Ereignisse (CTCAE-Grad 3-5) (SOC und PT) für den SOC „Erkrankungen der Nieren und Harnwege“ der Studie KEYNOTE 581/CLEAR

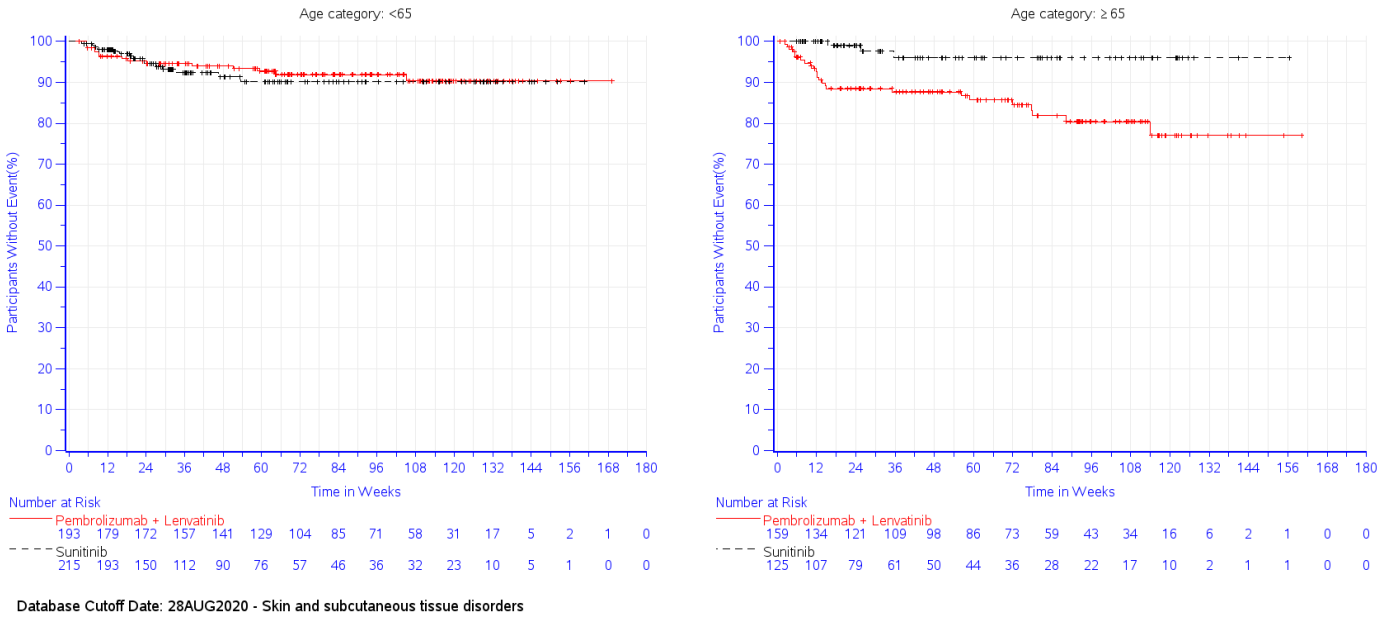


Abbildung 4G-35: Kaplan-Meier-Kurve für die Subgruppenanalyse nach Alter (< 65 vs. ≥65) für den Endpunkt Schwere unerwünschte Ereignisse (CTCAE-Grad 3-5) (SOC und PT) für den SOC „Erkrankungen der Haut und des Unterhautgewebes“ der Studie KEYNOTE 581/CLEAR

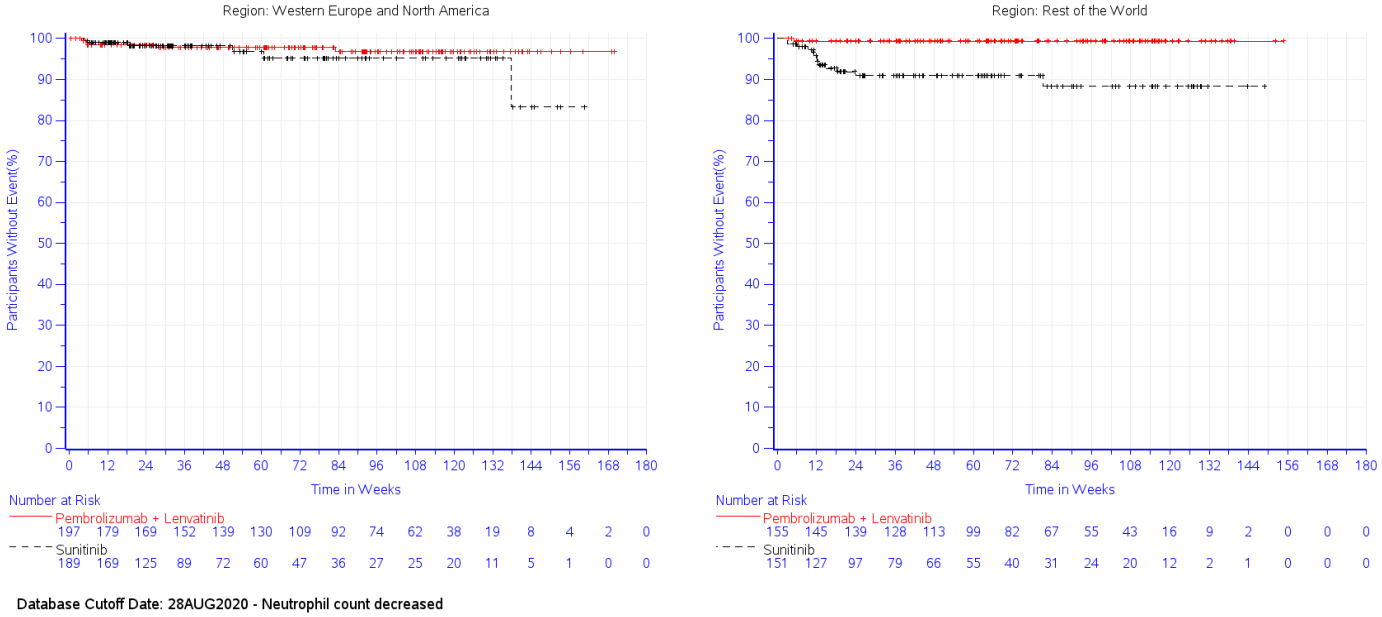


Abbildung 4G-36: Kaplan-Meier-Kurve für die Subgruppenanalyse nach Region für den Endpunkt Schwere unerwünschte Ereignisse (CTCAE-Grad 3-5) (SOC und PT) für den SOC „Neutrophilenzahl erniedrigt“ der Studie KEYNOTE 581/CLEAR

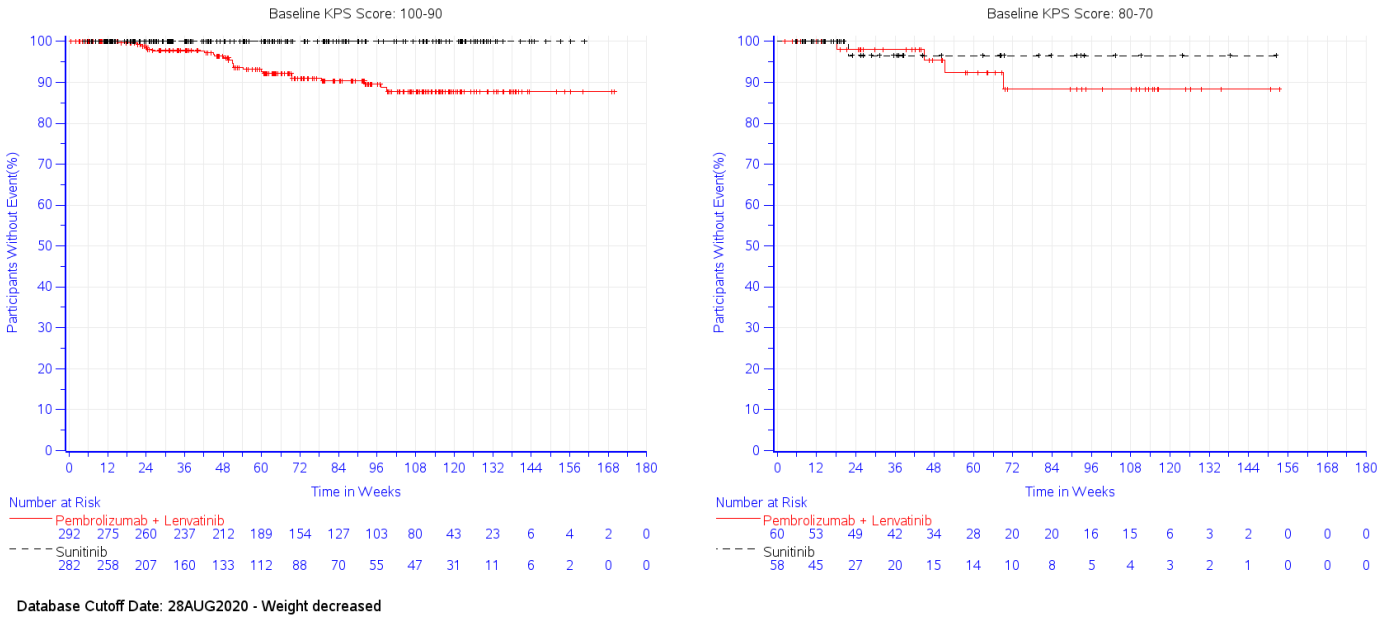


Abbildung 4G-37: Kaplan-Meier-Kurve für die Subgruppenanalyse nach KPS Score zu Studienbeginn (100-90 vs. 80-70) für den Endpunkt Schwere unerwünschte Ereignisse (CTCAE-Grad 3-5) (SOC und PT) für den SOC „Gewicht erniedrigt“ der Studie KEYNOTE 581/CLEAR

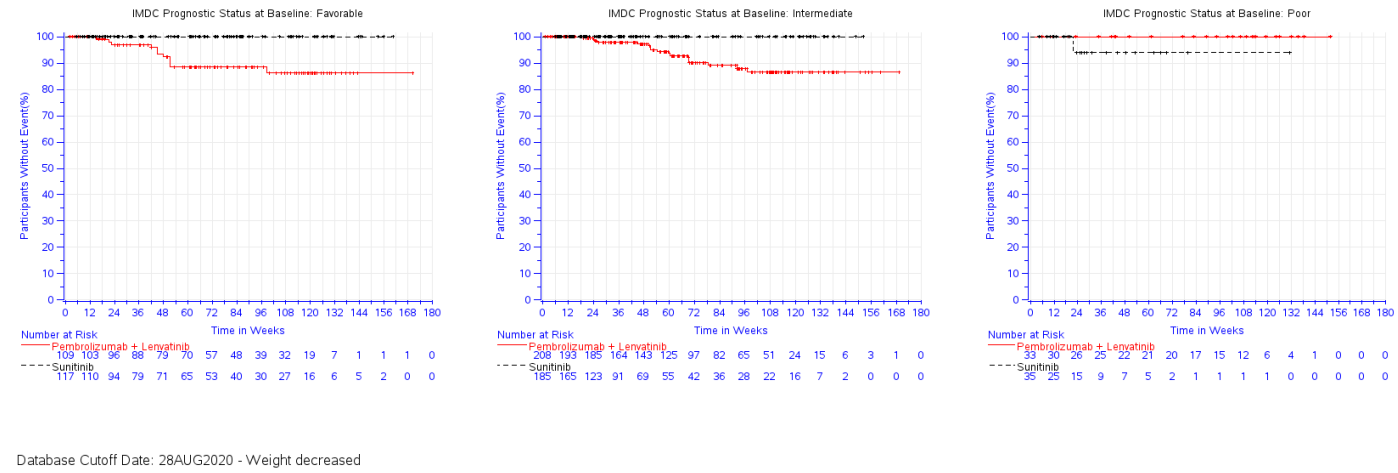


Abbildung 4G-38: Kaplan-Meier-Kurve für die Subgruppenanalyse nach IMDC Risikogruppe zu Studienbeginn (günstig vs. intermediär vs. ungünstig) für den Endpunkt Schwere unerwünschte Ereignisse (CTCAE-Grad 3-5) (SOC und PT) für den SOC „Gewicht erniedrigt“ der Studie KEYNOTE 581/CLEAR

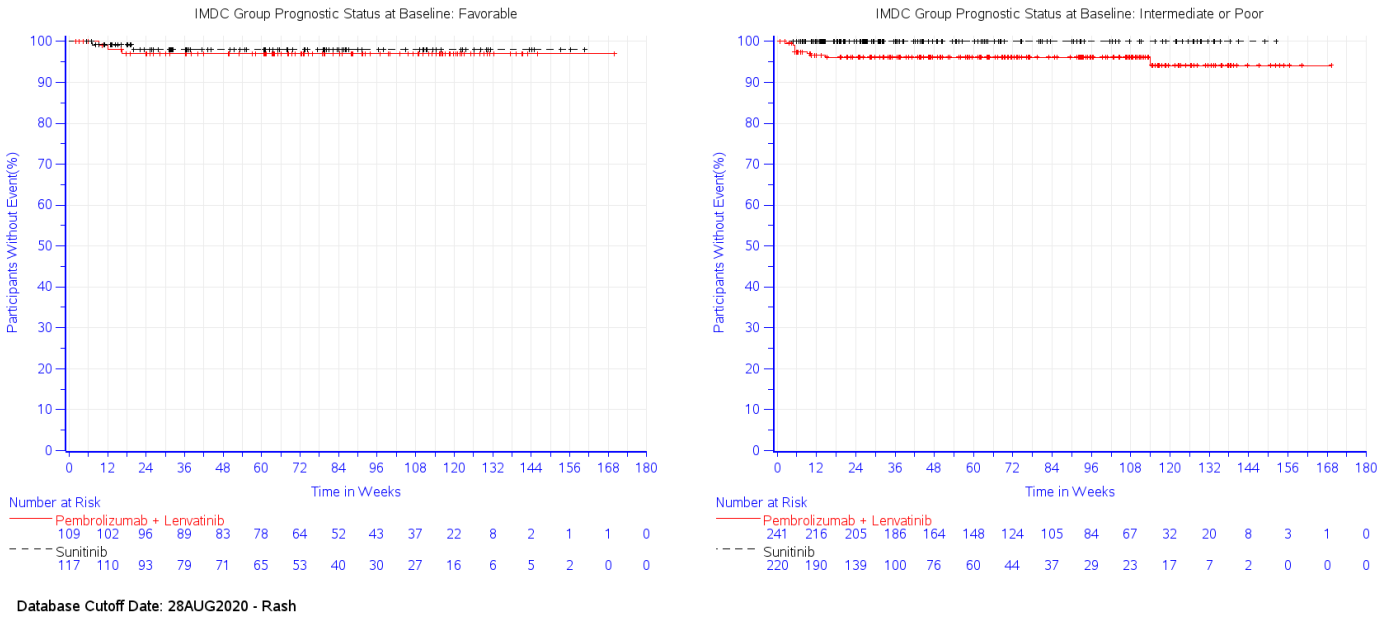


Abbildung 4G-39: Kaplan-Meier-Kurve für die Subgruppenanalyse nach IMDC Risikogruppe zu Studienbeginn (günstig vs. intermediär und ungünstig) für den Endpunkt Schwere unerwünschte Ereignisse (CTCAE-Grad 3-5) (SOC und PT) für den SOC „Ausschlag“ der Studie KEYNOTE 581/CLEAR

Anhang 4-G3: Ergebnisse der Subgruppen mit nicht signifikantem Interaktionstest (p ≥ 0,05) der Studie KEYNOTE 581/CLEAR

Im Folgenden werden ergänzend zu Abschnitt 4.3.1.3.2 des Moduls 4 A die Ergebnisse der Subgruppenanalysen, für die ein nicht signifikanter Interaktionstest (p ≥ 0,05) vorliegt, dargestellt.

Alle Ergebnisse beziehen sich auf den Datenschnitt vom 28. August 2020

Mortalität

Gesamtüberleben

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

Study: KEYNOTE 581[a]	Pembrolizumab + Lenvatinib			Sunitinib			Pembrolizumab + Lenvatinib vs. Sunitinib		
Overall Survival	N[b]	Participants with Event n (%)	Median Time[c] in Months [95 %-CI]	N[b]	Participants with Event n (%)	Median Time[c] in Months [95 %-CI]	Hazard Ratio [95 %-CI][d]	p-Value[d,e]	p-Value for Interaction Test[f]
Age category									
<65	194	41 (21.1)	Not reached [-; -]	225	57 (25.3)	Not reached [-; -]	0.63 [0.41; 0.95]	0.026	0.829
≥65	161	39 (24.2)	Not reached [32.4; -]	132	44 (33.3)	Not reached [30.6; -]	0.61 [0.40; 0.95]	0.028	
Gender									
Male	255	59 (23.1)	Not reached [33.6; -]	275	71 (25.8)	Not reached [-; -]	0.70 [0.49; 0.99]	0.044	0.391
Female	100	21 (21.0)	Not reached [31.9; -]	82	30 (36.6)	Not reached [23.9; -]	0.54 [0.30; 0.94]	0.031	
Baseline KPS Score									
100-90	295	62 (21.0)	Not reached [33.6; -]	294	72 (24.5)	Not reached [-; -]	0.73 [0.52; 1.03]	0.073	0.112
80-70	60	18 (30.0)	Not reached [-; -]	62	29 (46.8)	17.9 [10.8; -]	0.48 [0.26; 0.87]	0.016	
Region									
Western Europe and North America	199	46 (23.1)	Not reached [33.6; -]	199	57 (28.6)	Not reached [-; -]	0.68 [0.46; 1.00]	0.050	0.851
Rest of the World	156	34 (21.8)	Not reached [-; -]	158	44 (27.8)	Not reached [-; -]	0.64 [0.40; 1.00]	0.050	
IMDC Group Prognostic Status at Baseline									
Favorable	110	14 (12.7)	Not reached [33.6; -]	124	15 (12.1)	Not reached [-; -]	1.15 [0.55; 2.40]	0.717	0.146
Intermediate or Poor	243	66 (27.2)	Not reached [32.4; -]	229	85 (37.1)	Not reached [30.7; -]	0.58 [0.42; 0.80]	< 0.001	

Study: KEYNOTE 581[a]	Pembrolizumab + Lenvatinib			Sunitinib			Pembrolizumab + Lenvatinib vs. Sunitinib		
Overall Survival	N[b]	Participants with Event n (%)	Median Time[c] in Months [95 %-CI]	N[b]	Participants with Event n (%)	Median Time[c] in Months [95 %-CI]	Hazard Ratio [95 %-CI][d]	p-Value[d,e]	p-Value for Interaction Test[f]
MSKCC Category									
Favorable	101	12 (11.9)	Not reached [33.6; -]	95	12 (12.6)	Not reached [-; -]	0.92 [0.40; 2.09]	0.841	0.425
Intermediate	222	56 (25.2)	Not reached [33.1; -]	231	74 (32.0)	Not reached [-; -]	0.67 [0.47; 0.95]	0.024	
Poor	32	12 (37.5)	Not reached [16.6; -]	31	15 (48.4)	11.5 [6.0; -]	0.44 [0.20; 0.98]	0.043	
PD-L1									
CPS ≥1	107	28 (26.2)	Not reached [31.9; -]	119	36 (30.3)	Not reached [30.6; -]	0.76 [0.46; 1.27]	0.300	0.262
CPS < 1	112	21 (18.8)	Not reached [-; -]	103	31 (30.1)	Not reached [-; -]	0.50 [0.28; 0.89]	0.017	
Number of Metastatic sites									
0	5	0 (0.0)	Not reached [-; -]	6	2 (33.3)	30.7 [20.8; -]	n.a. [n.a.; n.a.]	n.a.	0.185
1	119	15 (12.6)	Not reached [-; -]	114	18 (15.8)	Not reached [-; -]	0.75 [0.38; 1.50]	0.421	
2	129	22 (17.1)	Not reached [-; -]	127	37 (29.1)	Not reached [-; -]	0.46 [0.27; 0.78]	0.004	
≥3	102	43 (42.2)	32.4 [26.3; -]	109	44 (40.4)	30.6 [21.1; -]	0.76 [0.49; 1.17]	0.218	
Race Category									
White	263	63 (24.0)	Not reached [33.6; -]	270	80 (29.6)	Not reached [-; -]	0.67 [0.48; 0.93]	0.017	0.581
Asian	81	15 (18.5)	Not reached [-; -]	67	13 (19.4)	Not reached [30.6; -]	0.65 [0.28; 1.54]	0.330	
All Others	6	1 (16.7)	Not reached [24.9; -]	10	5 (50.0)	17.9 [7.5; -]	n.a. [n.a.; n.a.]	> 0.999	
Baseline bone metastasis									
Yes	80	29 (36.3)	32.4 [27.6; -]	89	39 (43.8)	28.6 [17.2; -]	0.62 [0.38; 1.02]	0.061	0.742
No	275	51 (18.5)	Not reached [-; -]	267	62 (23.2)	Not reached [-; -]	0.69 [0.47; 1.00]	0.049	
Baseline liver metastasis									
Yes	63	25 (39.7)	31.9 [23.5; -]	70	28 (40.0)	30.6 [24.8; -]	0.89 [0.51; 1.57]	0.698	0.150
No	292	55 (18.8)	Not reached [-; -]	286	73 (25.5)	Not reached [-; -]	0.58 [0.41; 0.83]	0.003	

Study: KEYNOTE 581[a]	Pembrolizumab + Lenvatinib			Sunitinib			Pembrolizumab + Lenvatinib vs. Sunitinib		
Overall Survival	N[b]	Participants with Event n (%)	Median Time[c] in Months [95 %-CI]	N[b]	Participants with Event n (%)	Median Time[c] in Months [95 %-CI]	Hazard Ratio [95 %-CI][d]	p-Value[d,e]	p-Value for Interaction Test[f]
Baseline lung metastasis									
Yes	252	65 (25.8)	Not reached [33.1; -]	228	68 (29.8)	Not reached [-; -]	0.63 [0.45; 0.89]	0.009	0.658
No	103	15 (14.6)	Not reached [-; -]	128	33 (25.8)	Not reached [30.7; -]	0.58 [0.31; 1.07]	0.082	
Prior Nephrectomy									
Yes	262	50 (19.1)	Not reached [-; -]	275	66 (24.0)	Not reached [-; -]	0.71 [0.49; 1.03]	0.069	0.248
No	93	30 (32.3)	33.1 [30.3; -]	82	35 (42.7)	24.0 [12.4; -]	0.52 [0.31; 0.86]	0.012	
RCC Sarcomatoid Component by Histology									
Yes	28	9 (32.1)	Not reached [18.9; -]	21	7 (33.3)	Not reached [15.7; -]	0.91 [0.32; 2.58]	0.855	0.512
No	327	71 (21.7)	Not reached [33.6; -]	336	94 (28.0)	Not reached [-; -]	0.64 [0.47; 0.87]	0.004	

a: Database Cutoff Date: 28AUG2020

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

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

d: Based on Cox regression model with treatment as a covariate stratified by geographic region (Region 1: Western Europe and North America, Region 2: Rest of the World) and MSKCC prognostic groups (favourable, intermediate and poor risk) using Wald confidence interval

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

f: Based on Cox regression model with geographic region (Region 1: Western Europe and North America, Region 2: Rest of the World), MSKCC prognostic groups (favorable, intermediate and poor risk) in IxRS, 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; IMDC: International Metastatic Renal Cell Carcinoma Database Consortium; KPS: Karnofsky Performance Status; MSKCC: Memorial Sloan Kettering Cancer Center; n.a.: not applicable (when estimation not possible); PD-L1: Programmed Cell Death - Ligand 1; RCC: Renal Cell Carcinoma

Morbidität

Zeit bis zur ersten Folgetherapie (oder Tod)

Zeit bis zur ersten Folgetherapie oder Tod

Tabelle 4G-5: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für den Endpunkt Zeit bis zur ersten Folgetherapie oder Tod aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE 581[a]	**Pembrolizumab + Lenvatinib**			**Sunitinib**			**Pembrolizumab + Lenvatinib vs. Sunitinib**		
Subsequent Oncologic Therapy or Death	**N[b]**	**Participants with Event n (%)**	**Median Time[c] in Months [95 %-CI]**	**N[b]**	**Participants with Event n (%)**	**Median Time[c] in Months [95 %-CI]**	**Hazard Ratio [95 %-CI][d]**	**p-Value[d,e]**	**p-Value for Interaction Test[f]**
Age category									
<65	194	82 (42.3)	30.6 [24.2; -]	225	148 (65.8)	11.5 [9.2; 13.3]	0.38 [0.28; 0.50]	< 0.001	0.573
≥65	161	74 (46.0)	28.6 [20.8; -]	132	90 (68.2)	10.7 [8.0; 13.0]	0.43 [0.32; 0.60]	< 0.001	
Gender									
Male	255	117 (45.9)	30.3 [23.5; -]	275	178 (64.7)	11.1 [9.4; 13.1]	0.41 [0.33; 0.53]	< 0.001	0.523
Female	100	39 (39.0)	Not reached [22.5; -]	82	60 (73.2)	10.0 [6.3; 12.6]	0.41 [0.27; 0.62]	< 0.001	
Baseline KPS Score									
100-90	295	126 (42.7)	30.6 [25.1; -]	294	193 (65.6)	11.6 [9.9; 13.4]	0.40 [0.32; 0.51]	< 0.001	0.784
80-70	60	30 (50.0)	21.0 [14.8; -]	62	45 (72.6)	9.0 [4.4; 10.0]	0.41 [0.25; 0.65]	< 0.001	
Region									
Western Europe and North America	199	90 (45.2)	30.3 [22.9; -]	199	136 (68.3)	9.4 [7.4; 11.6]	0.40 [0.30; 0.52]	< 0.001	0.630
Rest of the World	156	66 (42.3)	28.6 [23.5; -]	158	102 (64.6)	12.3 [10.2; 16.7]	0.42 [0.31; 0.58]	< 0.001	
IMDC Group Prognostic Status at Baseline									
Favorable	110	34 (30.9)	Not reached [30.6; -]	124	65 (52.4)	18.2 [13.3; 27.6]	0.42 [0.28; 0.64]	< 0.001	0.598
Intermediate or Poor	243	121 (49.8)	24.4 [20.9; 31.1]	229	172 (75.1)	9.4 [7.0; 10.2]	0.38 [0.30; 0.48]	< 0.001	

Study: KEYNOTE 581[a]	Pembrolizumab + Lenvatinib			Sunitinib			Pembrolizumab + Lenvatinib vs. Sunitinib		
Subsequent Oncologic Therapy or Death	N[b]	Participants with Event n (%)	Median Time[c] in Months [95 %-CI]	N[b]	Participants with Event n (%)	Median Time[c] in Months [95 %-CI]	Hazard Ratio [95 %-CI][d]	p-Value[d,e]	p-Value for Interaction Test[f]
IMDC Prognostic Status at Baseline									
Favorable	110	34 (30.9)	Not reached [30.6; -]	124	65 (52.4)	18.2 [13.3; 27.6]	0.42 [0.28; 0.64]	< 0.001	0.124
Intermediate	210	106 (50.5)	24.2 [20.5; 30.6]	192	142 (74.0)	9.5 [7.8; 11.5]	0.42 [0.32; 0.54]	< 0.001	
Poor	33	15 (45.5)	Not reached [11.8; -]	37	30 (81.1)	5.7 [3.8; 8.8]	0.25 [0.12; 0.51]	< 0.001	

a: Database Cutoff Date: 28AUG2020

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

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

d: Based on Cox regression model with treatment as a covariate stratified by geographic region (Region 1: Western Europe and North America, Region 2: Rest of the World) and MSKCC prognostic groups (favourable, intermediate and poor risk) using Wald confidence interval

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

f: Based on Cox regression model with geographic region (Region 1: Western Europe and North America, Region 2: Rest of the World), MSKCC prognostic groups (favorable, intermediate and poor risk) in IxRS, treatment and subgroup as covariates , and treatment-by-subgroup interaction (p-value of likelihood ratio test for interaction term)

CI: Confidence Interval; IMDC: International Metastatic Renal Cell Carcinoma Database Consortium; KPS: Karnofsky Performance Status; MSKCC: Memorial Sloan Kettering Cancer Center

Krankheitssymptomatik und Gesundheitszustand

EORTC QLQ-C30: Symptomskala Erschöpfung

Tabelle 4G-6: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für die Symptomskala Erschöpfung aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE 581[a]	Pembrolizumab + Lenvatinib			Sunitinib			Pembrolizumab + Lenvatinib vs. Sunitinib		
Time to first deterioration	N[b]	Participants with Event[c] n (%)	Median Time[d] in Months [95 %-CI]	N[b]	Participants with Event[c] n (%)	Median Time[d] in Months [95 %-CI]	Hazard Ratio[e] [95 %-CI][e]	p-Value[e,f]	p-Value for Interaction Test[g]
Age category									
<65	183	150 (82.0)	1.4 [1.0; 2.1]	201	153 (76.1)	1.4 [0.9; 2.1]	1.03 [0.81; 1.29]	0.833	0.056
≥65	146	129 (88.4)	1.4 [0.8; 1.6]	119	112 (94.1)	0.8 [0.8; 1.4]	0.75 [0.58; 0.98]	0.035	
Gender									
Male	234	202 (86.3)	1.4 [0.8; 1.4]	245	200 (81.6)	1.3 [0.8; 1.4]	0.94 [0.77; 1.14]	0.512	0.873
Female	95	77 (81.1)	1.5 [0.8; 2.1]	75	65 (86.7)	1.4 [0.8; 2.1]	0.88 [0.62; 1.24]	0.468	
Baseline KPS Score									

Study: KEYNOTE 581[a]	Pembrolizumab + Lenvatinib			Sunitinib			Pembrolizumab + Lenvatinib vs. Sunitinib		p-Value for Interaction Test[g]
Time to first deterioration	N[b]	Participants with Event[c] n (%)	Median Time[d] in Months [95 %-CI]	N[b]	Participants with Event[c] n (%)	Median Time[d] in Months [95 %-CI]	Hazard Ratio[e] [95 %-CI][e]	p-Value[e,f]	
100-90	280	241 (86.1)	1.4 [0.8; 1.4]	268	222 (82.8)	1.3 [0.8; 1.4]	0.97 [0.81; 1.17]	0.786	0.122
80-70	49	38 (77.6)	2.1 [1.0; 3.2]	52	43 (82.7)	1.4 [0.8; 1.5]	0.62 [0.39; 0.98]	0.042	
Region									
Western Europe and North America	175	148 (84.6)	1.4 [0.8; 1.8]	174	149 (85.6)	1.3 [0.8; 1.4]	0.84 [0.66; 1.05]	0.130	0.198
Rest of the World	154	131 (85.1)	1.4 [1.0; 2.1]	146	116 (79.5)	1.4 [0.8; 1.7]	1.04 [0.81; 1.34]	0.740	
IMDC Group Prognostic Status at Baseline									
Favorable	103	92 (89.3)	1.4 [0.8; 2.1]	110	93 (84.5)	0.8 [0.8; 1.4]	0.99 [0.74; 1.33]	0.960	0.742
Intermediate or Poor	225	186 (82.7)	1.4 [0.9; 1.8]	207	170 (82.1)	1.4 [0.9; 1.4]	0.90 [0.73; 1.12]	0.341	
IMDC Prognostic Status at Baseline									
Favorable	103	92 (89.3)	1.4 [0.8; 2.1]	110	93 (84.5)	0.8 [0.8; 1.4]	0.99 [0.74; 1.33]	0.960	0.394
Intermediate	197	167 (84.8)	1.4 [0.8; 1.5]	175	146 (83.4)	1.2 [0.8; 1.4]	0.95 [0.76; 1.19]	0.673	
Poor	28	19 (67.9)	2.8 [1.4; 20.8]	32	24 (75.0)	1.7 [0.8; 3.1]	0.56 [0.29; 1.08]	0.084	

a: Database Cutoff Date: 28AUG2020

b: Number of participants: full-analysis-set population, participants with data for the specific endpoint in each row recorded at baseline and at least at one post-baseline visit

c: Time to first deterioration is defined as the time from the date of randomization to the first onset of a pre-specified number of points or more decrease from baseline

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

e: Based on Cox regression model with treatment as a covariate stratified by geographic region (Region 1: Western Europe and North America, Region 2: Rest of the World) and MSKCC prognostic groups (favourable, intermediate and poor risk) 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 regression model with geographic region (Region 1: Western Europe and North America, Region 2: Rest of the World), MSKCC prognostic groups (favorable, intermediate and poor risk) in IxRS, treatment and subgroup as covariates, and treatment-by-subgroup interaction (p-value of likelihood ratio test for interaction term)

CI: Confidence Interval; IMDC: International Metastatic Renal Cell Carcinoma Database Consortium; KPS: Karnofsky Performance Status; MSKCC: Memorial Sloan Kettering Cancer Center

EORTC QLQ-C30: Symptomskala Übelkeit und Erbrechen

Tabelle 4G-7: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für die Symptomskala Übelkeit und Erbrechen aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE 581[a]	**Pembrolizumab + Lenvatinib**			**Sunitinib**			**Pembrolizumab + Lenvatinib vs. Sunitinib**		**p-Value for Interaction Test[g]**
Time to first deterioration	**N[b]**	**Participants with Event[c] n (%)**	**Median Time[d] in Months [95 %-CI]**	**N[b]**	**Participants with Event[c] n (%)**	**Median Time[d] in Months [95 %-CI]**	**Hazard Ratio[e] [95 %-CI][e]**	**p-Value[e,f]**	
Age category									
<65	183	131 (71.6)	5.6 [4.2; 8.5]	201	128 (63.7)	4.2 [2.8; 5.0]	0.90 [0.70; 1.15]	0.392	0.608
≥65	146	110 (75.3)	4.2 [2.8; 6.1]	119	75 (63.0)	3.5 [2.1; 6.2]	1.03 [0.77; 1.39]	0.828	
Gender									
Male	234	170 (72.6)	6.2 [4.2; 8.3]	245	155 (63.3)	4.0 [3.1; 5.0]	0.88 [0.71; 1.10]	0.276	0.252
Female	95	71 (74.7)	3.3 [1.4; 4.9]	75	48 (64.0)	2.2 [1.1; 6.5]	1.15 [0.79; 1.68]	0.463	
Baseline KPS Score									
100-90	280	203 (72.5)	4.3 [4.2; 6.2]	268	170 (63.4)	4.2 [2.9; 5.2]	0.99 [0.81; 1.21]	0.914	0.547
80-70	49	38 (77.6)	6.2 [2.8; 9.0]	52	33 (63.5)	2.8 [2.1; 4.4]	0.85 [0.51; 1.39]	0.508	
Region									
Western Europe and North America	175	130 (74.3)	4.9 [3.5; 6.3]	174	115 (66.1)	4.2 [3.2; 5.2]	0.98 [0.76; 1.27]	0.906	0.768
Rest of the World	154	111 (72.1)	4.9 [4.2; 9.0]	146	88 (60.3)	2.9 [2.1; 6.5]	0.94 [0.71; 1.24]	0.654	
IMDC Group Prognostic Status at Baseline									
Favorable	103	73 (70.9)	6.3 [4.2; 10.4]	110	70 (63.6)	4.2 [2.8; 6.4]	0.91 [0.65; 1.27]	0.585	0.982
Intermediate or Poor	225	168 (74.7)	4.2 [3.5; 6.1]	207	131 (63.3)	3.5 [2.1; 5.0]	0.97 [0.77; 1.23]	0.819	
IMDC Prognostic Status at Baseline									
Favorable	103	73 (70.9)	6.3 [4.2; 10.4]	110	70 (63.6)	4.2 [2.8; 6.4]	0.91 [0.65; 1.27]	0.585	0.674
Intermediate	197	147 (74.6)	4.2 [3.5; 6.2]	175	109 (62.3)	4.1 [2.1; 6.5]	1.03 [0.80; 1.33]	0.808	
Poor	28	21 (75.0)	4.2 [1.4; 9.0]	32	22 (68.8)	2.3 [0.8; 4.6]	0.54 [0.27; 1.06]	0.071	

a: Database Cutoff Date: 28AUG2020

b: Number of participants: full-analysis-set population, participants with data for the specific endpoint in each row recorded at baseline and at least at one post-baseline visit

c: Time to first deterioration is defined as the time from the date of randomization to the first onset of a pre-specified number of points or more decrease from baseline

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

e: Based on Cox regression model with treatment as a covariate stratified by geographic region (Region 1: Western Europe and North America, Region 2: Rest of the World) and MSKCC prognostic groups (favourable, intermediate and poor risk) using Wald confidence interval

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

Study: KEYNOTE 581[a]	Pembrolizumab + Lenvatinib			Sunitinib			Pembrolizumab + Lenvatinib vs. Sunitinib		
Time to first deterioration	N[b]	Participants with Event[c] n (%)	Median Time[d] in Months [95 %-CI]	N[b]	Participants with Event[c] n (%)	Median Time[d] in Months [95 %-CI]	Hazard Ratio[e] [95 %-CI][e]	p-Value[e,f]	p-Value for Interaction Test[g]
g: Based on Cox regression model with geographic region (Region 1: Western Europe and North America, Region 2: Rest of the World), MSKCC prognostic groups (favorable, intermediate and poor risk) in IxRS, treatment and subgroup as covariates, and treatment-by-subgroup interaction (p-value of likelihood ratio test for interaction term)									
CI: Confidence Interval; IMDC: International Metastatic Renal Cell Carcinoma Database Consortium; KPS: Karnofsky Performance Status; MSKCC: Memorial Sloan Kettering Cancer Center									

EORTC QLQ-C30: Symptomskala Schmerzen

Tabelle 4G-8: Subgruppenanalysen mit nicht signifikantem Interaktionstest ($p \geq 0,05$) für die Symptomskala Schmerzen aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE 581[a]	Pembrolizumab + Lenvatinib			Sunitinib			Pembrolizumab + Lenvatinib vs. Sunitinib		
Time to first deterioration	N[b]	Participants with Event[c] n (%)	Median Time[d] in Months [95 %-CI]	N[b]	Participants with Event[c] n (%)	Median Time[d] in Months [95 %-CI]	Hazard Ratio[e] [95 %-CI][e]	p-Value[e,f]	p-Value for Interaction Test[g]
Gender									
Male	234	191 (81.6)	2.1 [1.4; 2.2]	245	185 (75.5)	2.8 [2.1; 3.5]	1.05 [0.86; 1.30]	0.618	0.460
Female	96	80 (83.3)	1.5 [0.9; 2.1]	75	55 (73.3)	2.1 [1.4; 3.6]	1.20 [0.84; 1.71]	0.325	
Baseline KPS Score									
100-90	280	233 (83.2)	1.5 [1.4; 2.1]	268	202 (75.4)	2.3 [2.1; 3.5]	1.15 [0.95; 1.40]	0.143	0.097
80-70	50	38 (76.0)	2.8 [1.5; 6.2]	52	38 (73.1)	2.2 [1.4; 4.2]	0.79 [0.50; 1.27]	0.339	
Region									
Western Europe and North America	176	141 (80.1)	2.1 [1.5; 2.8]	174	132 (75.9)	2.8 [2.1; 3.5]	1.01 [0.79; 1.29]	0.936	0.412
Rest of the World	154	130 (84.4)	1.4 [1.4; 2.1]	146	108 (74.0)	2.1 [1.4; 3.5]	1.17 [0.90; 1.52]	0.231	
IMDC Group Prognostic Status at Baseline									
Favorable	103	89 (86.4)	1.4 [0.8; 2.1]	110	89 (80.9)	2.8 [2.1; 3.5]	1.17 [0.86; 1.60]	0.303	0.414
Intermediate or Poor	226	181 (80.1)	2.1 [1.4; 2.2]	207	149 (72.0)	2.2 [1.5; 3.5]	1.03 [0.82; 1.28]	0.823	
IMDC Prognostic Status at Baseline									
Favorable	103	89 (86.4)	1.4 [0.8; 2.1]	110	89 (80.9)	2.8 [2.1; 3.5]	1.17 [0.86; 1.60]	0.303	0.651
Intermediate	197	162 (82.2)	1.6 [1.4; 2.1]	175	132 (75.4)	2.1 [1.4; 2.8]	1.03 [0.81; 1.30]	0.815	
Poor	29	19 (65.5)	7.0 [1.4; 18.2]	32	17 (53.1)	7.5 [2.2; 8.3]	0.79 [0.38; 1.62]	0.518	

Study: KEYNOTE 581[a]	Pembrolizumab + Lenvatinib			Sunitinib			Pembrolizumab + Lenvatinib vs. Sunitinib		p-Value for Interaction Test[g]
Time to first deterioration	N[b]	Participants with Event[c] n (%)	Median Time[d] in Months [95 %-CI]	N[b]	Participants with Event[c] n (%)	Median Time[d] in Months [95 %-CI]	Hazard Ratio[e] [95 %-CI][e]	p-Value[e,f]	
a: Database Cutoff Date: 28AUG2020									
b: Number of participants: full-analysis-set population, participants with data for the specific endpoint in each row recorded at baseline and at least at one post-baseline visit									
c: Time to first deterioration is defined as the time from the date of randomization to the first onset of a pre-specified number of points or more decrease from baseline									
d: From product-limit (Kaplan-Meier) method for censored data									
e: Based on Cox regression model with treatment as a covariate stratified by geographic region (Region 1: Western Europe and North America, Region 2: Rest of the World) and MSKCC prognostic groups (favourable, intermediate and poor risk) 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 regression model with geographic region (Region 1: Western Europe and North America, Region 2: Rest of the World), MSKCC prognostic groups (favorable, intermediate and poor risk) in IxRS, treatment and subgroup as covariates, and treatment-by-subgroup interaction (p-value of likelihood ratio test for interaction term)									
CI: Confidence Interval; IMDC: International Metastatic Renal Cell Carcinoma Database Consortium; KPS: Karnofsky Performance Status; MSKCC: Memorial Sloan Kettering Cancer Center									

EORTC QLQ-C30: Symptomskala Dyspnoe

Tabelle 4G-9: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für die Symptomskala Dyspnoe aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE 581[a]	Pembrolizumab + Lenvatinib			Sunitinib			Pembrolizumab + Lenvatinib vs. Sunitinib		p-Value for Interaction Test[g]
Time to first deterioration	N[b]	Participants with Event[c] n (%)	Median Time[d] in Months [95 %-CI]	N[b]	Participants with Event[c] n (%)	Median Time[d] in Months [95 %-CI]	Hazard Ratio[e] [95 %-CI][e]	p-Value[e,f]	
Age category									
<65	183	105 (57.4)	9.3 [5.6; 15.9]	200	109 (54.5)	7.5 [4.1; 12.4]	0.86 [0.66; 1.13]	0.285	0.269
≥65	146	85 (58.2)	8.4 [4.2; 11.8]	119	80 (67.2)	3.6 [2.9; 4.9]	0.69 [0.50; 0.94]	0.020	
Gender									
Male	234	138 (59.0)	9.7 [5.6; 11.8]	244	144 (59.0)	5.6 [3.8; 9.0]	0.80 [0.63; 1.02]	0.066	0.685
Female	95	52 (54.7)	7.7 [4.2; 20.0]	75	45 (60.0)	3.5 [2.1; 5.3]	0.73 [0.48; 1.10]	0.128	
Baseline KPS Score									
100-90	280	159 (56.8)	9.7 [5.7; 13.2]	267	160 (59.9)	4.9 [3.5; 7.0]	0.75 [0.60; 0.94]	0.014	0.302
80-70	49	31 (63.3)	5.8 [2.1; 11.8]	52	29 (55.8)	4.2 [3.1; 15.8]	1.07 [0.63; 1.80]	0.808	
Region									
Western Europe and North America	175	102 (58.3)	7.1 [4.9; 11.3]	174	100 (57.5)	5.1 [4.1; 9.0]	0.83 [0.63; 1.10]	0.201	0.470
Rest of the World	154	88	10.4	145	89	3.5	0.74	0.044	

Study: KEYNOTE 581[a]	Pembrolizumab + Lenvatinib			Sunitinib			Pembrolizumab + Lenvatinib vs. Sunitinib		
Time to first deterioration	N[b]	Participants with Event[c] n (%)	Median Time[d] in Months [95 %-CI]	N[b]	Participants with Event[c] n (%)	Median Time[d] in Months [95 %-CI]	Hazard Ratio[e] [95 %-CI][e]	p-Value[e,f]	p-Value for Interaction Test[g]
		(57.1)	[5.6; 15.9]		(61.4)	[2.8; 8.3]	[0.55; 0.99]		
IMDC Group Prognostic Status at Baseline									
Favorable	103	58 (56.3)	11.1 [4.9; 26.3]	109	71 (65.1)	5.1 [2.9; 9.7]	0.67 [0.47; 0.95]	0.026	0.297
Intermediate or Poor	225	131 (58.2)	8.3 [5.1; 11.8]	207	115 (55.6)	4.8 [3.5; 8.3]	0.86 [0.67; 1.11]	0.250	
IMDC Prognostic Status at Baseline									
Favorable	103	58 (56.3)	11.1 [4.9; 26.3]	109	71 (65.1)	5.1 [2.9; 9.7]	0.67 [0.47; 0.95]	0.026	0.516
Intermediate	197	116 (58.9)	6.9 [4.9; 11.2]	175	100 (57.1)	4.8 [3.5; 8.9]	0.87 [0.66; 1.15]	0.324	
Poor	28	15 (53.6)	20.8 [3.2; -]	32	15 (46.9)	4.2 [3.0; -]	0.71 [0.33; 1.53]	0.383	

a: Database Cutoff Date: 28AUG2020

b: Number of participants: full-analysis-set population, participants with data for the specific endpoint in each row recorded at baseline and at least at one post-baseline visit

c: Time to first deterioration is defined as the time from the date of randomization to the first onset of a pre-specified number of points or more decrease from baseline

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

e: Based on Cox regression model with treatment as a covariate stratified by geographic region (Region 1: Western Europe and North America, Region 2: Rest of the World) and MSKCC prognostic groups (favourable, intermediate and poor risk) 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 regression model with geographic region (Region 1: Western Europe and North America, Region 2: Rest of the World), MSKCC prognostic groups (favorable, intermediate and poor risk) in IxRS, treatment and subgroup as covariates, and treatment-by-subgroup interaction (p-value of likelihood ratio test for interaction term)

CI: Confidence Interval; IMDC: International Metastatic Renal Cell Carcinoma Database Consortium; KPS: Karnofsky Performance Status; MSKCC: Memorial Sloan Kettering Cancer Center

EORTC QLQ-C30: Symptomskala Schlaflosigkeit

Tabelle 4G-10: Subgruppenanalysen mit nicht signifikantem Interaktionstest ($p \geq 0,05$) für die Symptomskala Schlaflosigkeit aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE 581[a]	Pembrolizumab + Lenvatinib			Sunitinib			Pembrolizumab + Lenvatinib vs. Sunitinib		
Time to first deterioration	N[b]	Participants with Event[c] n (%)	Median Time[d] in Months [95 %-CI]	N[b]	Participants with Event[c] n (%)	Median Time[d] in Months [95 %-CI]	Hazard Ratio[e] [95 %-CI][e]	p-Value[e,f]	p-Value for Interaction Test[g]
Age category									
<65	182	118 (64.8)	5.8 [3.5; 9.0]	201	105 (52.2)	6.9 [3.5; 11.2]	1.06 [0.81; 1.39]	0.659	0.383
≥65	146	99 (67.8)	4.2 [2.4; 5.5]	119	79 (66.4)	3.5 [2.4; 4.9]	0.93 [0.69; 1.26]	0.637	
Gender									

Study: KEYNOTE 581[a]	Pembrolizumab + Lenvatinib			Sunitinib			Pembrolizumab + Lenvatinib vs. Sunitinib		
Time to first deterioration	N[b]	Participants with Event[c] n (%)	Median Time[d] in Months [95 %-CI]	N[b]	Participants with Event[c] n (%)	Median Time[d] in Months [95 %-CI]	Hazard Ratio[e] [95 %-CI][e]	p-Value[e,f]	p-Value for Interaction Test[g]
Male	233	155 (66.5)	4.9 [3.5; 7.0]	245	140 (57.1)	4.9 [3.3; 7.7]	1.00 [0.80; 1.26]	0.985	0.868
Female	95	62 (65.3)	4.9 [2.2; 9.0]	75	44 (58.7)	4.2 [2.7; 7.6]	0.99 [0.67; 1.47]	0.968	
Baseline KPS Score									
100-90	279	181 (64.9)	5.0 [3.5; 7.0]	268	152 (56.7)	6.0 [3.5; 9.7]	1.03 [0.83; 1.28]	0.793	0.627
80-70	49	36 (73.5)	4.2 [1.6; 9.7]	52	32 (61.5)	2.8 [2.2; 4.2]	0.85 [0.51; 1.43]	0.545	
Region									
Western Europe and North America	174	113 (64.9)	4.9 [2.9; 8.7]	174	99 (56.9)	4.9 [3.4; 7.7]	1.01 [0.77; 1.32]	0.948	0.985
Rest of the World	154	104 (67.5)	4.9 [3.4; 7.0]	146	85 (58.2)	4.2 [2.7; 9.8]	1.01 [0.76; 1.35]	0.926	
IMDC Group Prognostic Status at Baseline									
Favorable	103	66 (64.1)	7.0 [4.9; 9.7]	110	60 (54.5)	7.7 [3.5; 19.4]	1.10 [0.77; 1.57]	0.606	0.714
Intermediate or Poor	224	150 (67.0)	4.2 [2.8; 5.6]	207	122 (58.9)	3.5 [2.8; 5.0]	0.99 [0.77; 1.26]	0.918	
IMDC Prognostic Status at Baseline									
Favorable	103	66 (64.1)	7.0 [4.9; 9.7]	110	60 (54.5)	7.7 [3.5; 19.4]	1.10 [0.77; 1.57]	0.606	0.714
Intermediate	196	134 (68.4)	3.5 [2.4; 5.0]	175	106 (60.6)	3.5 [2.7; 6.2]	1.02 [0.79; 1.32]	0.874	
Poor	28	16 (57.1)	11.8 [2.2; -]	32	16 (50.0)	3.1 [2.2; -]	0.66 [0.31; 1.41]	0.284	

a: Database Cutoff Date: 28AUG2020

b: Number of participants: full-analysis-set population, participants with data for the specific endpoint in each row recorded at baseline and at least at one post-baseline visit

c: Time to first deterioration is defined as the time from the date of randomization to the first onset of a pre-specified number of points or more decrease from baseline

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

e: Based on Cox regression model with treatment as a covariate stratified by geographic region (Region 1: Western Europe and North America, Region 2: Rest of the World) and MSKCC prognostic groups (favourable, intermediate and poor risk) 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 regression model with geographic region (Region 1: Western Europe and North America, Region 2: Rest of the World), MSKCC prognostic groups (favorable, intermediate and poor risk) in IxRS, treatment and subgroup as covariates, and treatment-by-subgroup interaction (p-value of likelihood ratio test for interaction term)

CI: Confidence Interval; IMDC: International Metastatic Renal Cell Carcinoma Database Consortium; KPS: Karnofsky Performance Status; MSKCC: Memorial Sloan Kettering Cancer Center

EORTC QLQ-C30: Symptomskala Appetitverlust

Tabelle 4G-11: Subgruppenanalysen mit nicht signifikantem Interaktionstest ($p \geq 0,05$) für die Symptomskala Appetitverlust aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE 581[a]	**Pembrolizumab + Lenvatinib**			**Sunitinib**			**Pembrolizumab + Lenvatinib vs. Sunitinib**		
Time to first deterioration	**N[b]**	**Participants with Event[c] n (%)**	**Median Time[d] in Months [95 %-CI]**	**N[b]**	**Participants with Event[c] n (%)**	**Median Time[d] in Months [95 %-CI]**	**Hazard Ratio[e] [95 %-CI][e]**	**p-Value[e,f]**	**p-Value for Interaction Test[g]**
Age category									
<65	183	136 (74.3)	5.1 [4.2; 7.2]	201	134 (66.7)	4.2 [2.1; 5.6]	0.87 [0.69; 1.11]	0.271	0.161
≥65	146	115 (78.8)	2.8 [2.1; 4.1]	119	99 (83.2)	1.4 [1.0; 2.2]	0.69 [0.52; 0.91]	0.009	
Gender									
Male	234	181 (77.4)	4.8 [4.1; 6.3]	245	173 (70.6)	2.8 [1.4; 4.2]	0.79 [0.64; 0.98]	0.032	0.888
Female	95	70 (73.7)	3.1 [2.1; 4.2]	75	60 (80.0)	2.1 [1.0; 3.5]	0.87 [0.60; 1.25]	0.441	
Baseline KPS Score									
100-90	280	215 (76.8)	4.2 [3.5; 5.0]	268	197 (73.5)	2.1 [1.4; 4.2]	0.83 [0.69; 1.01]	0.067	0.536
80-70	49	36 (73.5)	3.9 [2.1; 9.0]	52	36 (69.2)	2.1 [1.4; 3.7]	0.72 [0.44; 1.17]	0.185	
Region									
Western Europe and North America	175	133 (76.0)	4.2 [3.3; 5.1]	174	133 (76.4)	2.3 [1.4; 3.7]	0.76 [0.59; 0.97]	0.025	0.536
Rest of the World	154	118 (76.6)	4.2 [2.8; 6.2]	146	100 (68.5)	2.1 [1.4; 4.2]	0.88 [0.67; 1.15]	0.342	
IMDC Group Prognostic Status at Baseline									
Favorable	103	78 (75.7)	4.2 [3.1; 6.2]	110	83 (75.5)	1.4 [0.9; 3.5]	0.79 [0.57; 1.08]	0.138	0.672
Intermediate or Poor	225	173 (76.9)	4.2 [2.9; 5.1]	207	148 (71.5)	2.8 [1.8; 4.2]	0.84 [0.68; 1.05]	0.134	

a: Database Cutoff Date: 28AUG2020

b: Number of participants: full-analysis-set population, participants with data for the specific endpoint in each row recorded at baseline and at least at one post-baseline visit

c: Time to first deterioration is defined as the time from the date of randomization to the first onset of a pre-specified number of points or more decrease from baseline

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

e: Based on Cox regression model with treatment as a covariate stratified by geographic region (Region 1: Western Europe and North America, Region 2: Rest of the World) and MSKCC prognostic groups (favourable, intermediate and poor risk) 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 regression model with geographic region (Region 1: Western Europe and North America, Region 2: Rest of the World), MSKCC prognostic groups (favorable, intermediate and poor risk) in IxRS, treatment and subgroup as covariates, and treatment-by-subgroup interaction (p-value of likelihood ratio test for interaction term)

CI: Confidence Interval; IMDC: International Metastatic Renal Cell Carcinoma Database Consortium; KPS: Karnofsky Performance Status; MSKCC: Memorial Sloan Kettering Cancer Center

EORTC QLQ-C30: Symptomskala Verstopfung

Tabelle 4G-12: Subgruppenanalysen mit nicht signifikantem Interaktionstest ($p \geq 0,05$) für die Symptomskala Verstopfung aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE 581[a]	**Pembrolizumab + Lenvatinib**			**Sunitinib**			**Pembrolizumab + Lenvatinib vs. Sunitinib**		
Time to first deterioration	**N[b]**	**Participants with Event[c] n (%)**	**Median Time[d] in Months [95 %-CI]**	**N[b]**	**Participants with Event[c] n (%)**	**Median Time[d] in Months [95 %-CI]**	**Hazard Ratio[e] [95 %-CI][e]**	**p-Value[e,f]**	**p-Value for Interaction Test[g]**
Age category									
<65	183	106 (57.9)	8.3 [5.6; 18.4]	201	95 (47.3)	11.3 [6.9; 21.4]	1.07 [0.81; 1.43]	0.619	0.119
≥65	146	86 (58.9)	7.0 [3.6; 19.4]	119	71 (59.7)	4.1 [3.1; 6.2]	0.82 [0.59; 1.12]	0.212	
Gender									
Male	234	137 (58.5)	7.9 [5.6; 18.7]	245	126 (51.4)	8.3 [5.6; 15.2]	0.96 [0.75; 1.23]	0.747	0.824
Female	95	55 (57.9)	6.9 [3.5; 18.4]	75	40 (53.3)	4.2 [2.8; -]	0.85 [0.55; 1.30]	0.450	
Baseline KPS Score									
100-90	280	162 (57.9)	7.0 [5.4; 15.2]	268	135 (50.4)	8.5 [5.7; 18.7]	1.03 [0.82; 1.30]	0.783	0.128
80-70	49	30 (61.2)	7.9 [4.1; 21.7]	52	31 (59.6)	4.1 [2.2; 9.0]	0.65 [0.38; 1.11]	0.112	
Region									
Western Europe and North America	175	95 (54.3)	12.8 [6.2; 21.7]	174	88 (50.6)	6.4 [4.2; 21.4]	0.85 [0.63; 1.14]	0.280	0.224
Rest of the World	154	97 (63.0)	5.6 [3.5; 9.7]	146	78 (53.4)	8.3 [5.6; 15.2]	1.09 [0.80; 1.47]	0.584	
IMDC Group Prognostic Status at Baseline									
Favorable	103	61 (59.2)	6.3 [3.5; 18.7]	110	67 (60.9)	4.9 [3.2; 11.1]	0.81 [0.57; 1.15]	0.243	0.155
Intermediate or Poor	225	130 (57.8)	8.5 [5.1; 15.3]	207	98 (47.3)	9.7 [6.0; 21.4]	1.09 [0.83; 1.42]	0.544	
IMDC Prognostic Status at Baseline									
Favorable	103	61 (59.2)	6.3 [3.5; 18.7]	110	67 (60.9)	4.9 [3.2; 11.1]	0.81 [0.57; 1.15]	0.243	0.071
Intermediate	197	114 (57.9)	7.9 [4.9; 15.3]	175	78 (44.6)	11.7 [6.8; -]	1.24 [0.92; 1.67]	0.150	
Poor	28	16 (57.1)	11.8 [2.7; -]	32	20 (62.5)	4.2 [2.3; 7.5]	0.56 [0.27; 1.17]	0.124	

a: Database Cutoff Date: 28AUG2020

b: Number of participants: full-analysis-set population, participants with data for the specific endpoint in each row recorded at baseline and at least at one post-baseline visit

c: Time to first deterioration is defined as the time from the date of randomization to the first onset of a pre-specified number of points or more decrease from baseline

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

e: Based on Cox regression model with treatment as a covariate stratified by geographic region (Region 1: Western Europe and North America, Region 2: Rest of the World) and MSKCC prognostic groups (favourable, intermediate and poor risk) using Wald confidence interval

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

Study: KEYNOTE 581[a]	Pembrolizumab + Lenvatinib			Sunitinib			Pembrolizumab + Lenvatinib vs. Sunitinib		p-Value for Interaction Test[g]
Time to first deterioration	N[b]	Participants with Event[c] n (%)	Median Time[d] in Months [95 %-CI]	N[b]	Participants with Event[c] n (%)	Median Time[d] in Months [95 %-CI]	Hazard Ratio[e] [95 %-CI][e]	p-Value[e,f]	
g: Based on Cox regression model with geographic region (Region 1: Western Europe and North America, Region 2: Rest of the World), MSKCC prognostic groups (favorable, intermediate and poor risk) in IxRS, treatment and subgroup as covariates, and treatment-by-subgroup interaction (p-value of likelihood ratio test for interaction term)									
CI: Confidence Interval; IMDC: International Metastatic Renal Cell Carcinoma Database Consortium; KPS: Karnofsky Performance Status; MSKCC: Memorial Sloan Kettering Cancer Center									

EORTC QLQ-C30: Symptomskala Diarrhö

Tabelle 4G-13: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für die Symptomskala Diarrhö aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE 581[a]	Pembrolizumab + Lenvatinib			Sunitinib			Pembrolizumab + Lenvatinib vs. Sunitinib		p-Value for Interaction Test[g]
Time to first deterioration	N[b]	Participants with Event[c] n (%)	Median Time[d] in Months [95 %-CI]	N[b]	Participants with Event[c] n (%)	Median Time[d] in Months [95 %-CI]	Hazard Ratio[e] [95 %-CI][e]	p-Value[e,f]	
Age category									
<65	183	156 (85.2)	3.5 [2.8; 4.2]	201	144 (71.6)	3.1 [2.2; 3.5]	0.94 [0.75; 1.19]	0.609	0.426
≥65	146	110 (75.3)	4.3 [2.9; 5.5]	119	88 (73.9)	3.5 [2.7; 4.9]	0.82 [0.62; 1.10]	0.182	
Gender									
Male	233	194 (83.3)	3.5 [2.8; 4.3]	245	178 (72.7)	3.5 [2.8; 4.2]	0.96 [0.78; 1.18]	0.673	0.116
Female	96	72 (75.0)	4.2 [2.8; 5.7]	75	54 (72.0)	2.2 [1.5; 3.5]	0.59 [0.41; 0.86]	0.006	
Baseline KPS Score									
100-90	279	226 (81.0)	4.2 [3.5; 4.9]	268	196 (73.1)	3.5 [2.8; 3.5]	0.84 [0.69; 1.02]	0.073	0.313
80-70	50	40 (80.0)	2.3 [1.6; 4.2]	52	36 (69.2)	3.5 [2.2; 4.2]	1.24 [0.76; 2.01]	0.394	
Region									
Western Europe and North America	175	141 (80.6)	4.1 [2.9; 4.9]	174	132 (75.9)	2.8 [2.1; 3.5]	0.75 [0.59; 0.96]	0.020	0.051
Rest of the World	154	125 (81.2)	3.5 [2.8; 4.9]	146	100 (68.5)	4.1 [3.5; 5.6]	1.04 [0.80; 1.36]	0.764	
IMDC Group Prognostic Status at Baseline									
Favorable	103	83 (80.6)	4.2 [2.8; 6.5]	110	77 (70.0)	3.5 [2.8; 6.2]	0.96 [0.70; 1.33]	0.826	0.302
Intermediate or Poor	225	182 (80.9)	3.5 [2.8; 4.8]	207	153 (73.9)	3.1 [2.2; 3.5]	0.82 [0.66; 1.03]	0.085	
IMDC Prognostic Status at Baseline									

Study: KEYNOTE 581[a]	Pembrolizumab + Lenvatinib			Sunitinib			Pembrolizumab + Lenvatinib vs. Sunitinib		p-Value for Interaction Test[g]
Time to first deterioration	N[b]	Participants with Event[c] n (%)	Median Time[d] in Months [95 %-CI]	N[b]	Participants with Event[c] n (%)	Median Time[d] in Months [95 %-CI]	Hazard Ratio[e] [95 %-CI][e]	p-Value[e,f]	
Favorable	103	83 (80.6)	4.2 [2.8; 6.5]	110	77 (70.0)	3.5 [2.8; 6.2]	0.96 [0.70; 1.33]	0.826	0.561
Intermediate	197	158 (80.2)	3.5 [2.8; 4.8]	175	133 (76.0)	3.1 [2.2; 3.5]	0.82 [0.65; 1.04]	0.104	
Poor	28	24 (85.7)	3.5 [2.1; 6.9]	32	20 (62.5)	3.5 [2.1; 4.3]	0.71 [0.36; 1.41]	0.328	

a: Database Cutoff Date: 28AUG2020

b: Number of participants: full-analysis-set population, participants with data for the specific endpoint in each row recorded at baseline and at least at one post-baseline visit

c: Time to first deterioration is defined as the time from the date of randomization to the first onset of a pre-specified number of points or more decrease from baseline

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

e: Based on Cox regression model with treatment as a covariate stratified by geographic region (Region 1: Western Europe and North America, Region 2: Rest of the World) and MSKCC prognostic groups (favourable, intermediate and poor risk) 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 regression model with geographic region (Region 1: Western Europe and North America, Region 2: Rest of the World), MSKCC prognostic groups (favorable, intermediate and poor risk) in IxRS, treatment and subgroup as covariates, and treatment-by-subgroup interaction (p-value of likelihood ratio test for interaction term)

CI: Confidence Interval; IMDC: International Metastatic Renal Cell Carcinoma Database Consortium; KPS: Karnofsky Performance Status; MSKCC: Memorial Sloan Kettering Cancer Center

FKSI-DRS Gesamtscore (3 Punkte)

Tabelle 4G-14: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für den FKSI-DRS Gesamtscore (3 Punkte) aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE 581[a]	Pembrolizumab + Lenvatinib			Sunitinib			Pembrolizumab + Lenvatinib vs. Sunitinib		p-Value for Interaction Test[g]
Time to first deterioration	N[b]	Participants with Event[c] n (%)	Median Time[d] in Months [95 %-CI]	N[b]	Participants with Event[c] n (%)	Median Time[d] in Months [95 %-CI]	Hazard Ratio[e] [95 %-CI][e]	p-Value[e,f]	
Age category									
<65	184	148 (80.4)	2.7 [1.9; 3.5]	200	126 (63.0)	3.5 [2.1; 4.9]	1.30 [1.02; 1.65]	0.034	0.060
≥65	146	117 (80.1)	1.6 [1.4; 2.2]	117	92 (78.6)	2.1 [1.0; 2.8]	0.91 [0.69; 1.21]	0.513	
Gender									
Male	234	197 (84.2)	2.1 [1.4; 2.7]	243	168 (69.1)	2.8 [2.1; 3.5]	1.19 [0.96; 1.46]	0.107	0.319
Female	96	68 (70.8)	2.8 [1.4; 4.1]	74	50 (67.6)	2.9 [1.4; 4.9]	1.01 [0.69; 1.47]	0.960	
Baseline KPS Score									
100-90	280	230 (82.1)	2.1 [1.4; 2.7]	266	188 (70.7)	2.8 [2.1; 3.5]	1.15 [0.95; 1.40]	0.151	0.458
80-70	50	35	3.2	51	30	2.8	1.01	0.955	

Study: KEYNOTE 581[a]	Pembrolizumab + Lenvatinib			Sunitinib			Pembrolizumab + Lenvatinib vs. Sunitinib		p-Value for Interaction Test[g]
Time to first deterioration	N[b]	Participants with Event[c] n (%)	Median Time[d] in Months [95 %-CI]	N[b]	Participants with Event[c] n (%)	Median Time[d] in Months [95 %-CI]	Hazard Ratio[e] [95 %-CI][e]	p-Value[e,f]	
		(70.0)	[1.4; 6.3]		(58.8)	[1.4; 4.9]	[0.62; 1.67]		
IMDC Group Prognostic Status at Baseline									
Favorable	104	89 (85.6)	2.1 [1.4; 2.9]	110	78 (70.9)	2.9 [1.4; 4.9]	1.18 [0.86; 1.61]	0.303	0.652
Intermediate or Poor	225	175 (77.8)	2.1 [1.5; 2.8]	204	138 (67.6)	2.4 [2.1; 3.5]	1.10 [0.88; 1.38]	0.419	
IMDC Prognostic Status at Baseline									
Favorable	104	89 (85.6)	2.1 [1.4; 2.9]	110	78 (70.9)	2.9 [1.4; 4.9]	1.18 [0.86; 1.61]	0.303	0.460
Intermediate	196	161 (82.1)	2.1 [1.4; 2.2]	173	124 (71.7)	2.1 [1.7; 3.5]	1.16 [0.91; 1.48]	0.233	
Poor	29	14 (48.3)	21.5 [2.8; -]	31	14 (45.2)	5.2 [1.7; -]	0.82 [0.37; 1.81]	0.629	

a: Database Cutoff Date: 28AUG2020

b: Number of participants: full-analysis-set population, participants with data for the specific endpoint in each row recorded at baseline and at least at one post-baseline visit

c: Time to first deterioration is defined as the time from the date of randomization to the first onset of a pre-specified number of points or more decrease from baseline

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

e: Based on Cox regression model with treatment as a covariate stratified by geographic region (Region 1: Western Europe and North America, Region 2: Rest of the World) and MSKCC prognostic groups (favourable, intermediate and poor risk) 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 regression model with geographic region (Region 1: Western Europe and North America, Region 2: Rest of the World), MSKCC prognostic groups (favorable, intermediate and poor risk) in IxRS, treatment and subgroup as covariates, and treatment-by-subgroup interaction (p-value of likelihood ratio test for interaction term)

CI: Confidence Interval; IMDC: International Metastatic Renal Cell Carcinoma Database Consortium; KPS: Karnofsky Performance Status; MSKCC: Memorial Sloan Kettering Cancer Center

FKSI-DRS Gesamtscore (4 Punkte)

Tabelle 4G-15: Subgruppenanalysen mit nicht signifikantem Interaktionstest ($p \geq 0,05$) für den FKSI-DRS Gesamtscore (4 Punkte) aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE 581[a]	Pembrolizumab + Lenvatinib			Sunitinib			Pembrolizumab + Lenvatinib vs. Sunitinib		p-Value for Interaction Test[g]
Time to first deterioration	N[b]	Participants with Event[c] n (%)	Median Time[d] in Months [95 %-CI]	N[b]	Participants with Event[c] n (%)	Median Time[d] in Months [95 %-CI]	Hazard Ratio[e] [95 %-CI][e]	p-Value[e,f]	
Age category									
<65	184	132 (71.7)	4.8 [3.5; 7.6]	200	110 (55.0)	6.3 [4.2; 10.4]	1.25 [0.97; 1.61]	0.091	0.097
≥65	146	108 (74.0)	2.8 [1.5; 4.1]	117	84 (71.8)	2.9 [2.1; 3.5]	0.93 [0.69; 1.25]	0.627	
Gender									

Study: KEYNOTE 581[a]	Pembrolizumab + Lenvatinib			Sunitinib			Pembrolizumab + Lenvatinib vs. Sunitinib		p-Value for Interaction Test[g]
Time to first deterioration	N[b]	Participants with Event[c] n (%)	Median Time[d] in Months [95 %-CI]	N[b]	Participants with Event[c] n (%)	Median Time[d] in Months [95 %-CI]	Hazard Ratio[e] [95 %-CI][e]	p-Value[e,f]	
Male	234	176 (75.2)	3.5 [2.2; 4.8]	243	149 (61.3)	4.2 [3.4; 6.2]	1.14 [0.91; 1.42]	0.245	0.458
Female	96	64 (66.7)	5.6 [2.8; 9.0]	74	45 (60.8)	4.2 [2.1; 7.0]	1.01 [0.68; 1.50]	0.942	
Baseline KPS Score									
100-90	280	207 (73.9)	3.5 [2.8; 4.8]	266	165 (62.0)	4.2 [3.5; 6.2]	1.12 [0.91; 1.38]	0.278	0.423
80-70	50	33 (66.0)	6.3 [2.7; 10.4]	51	29 (56.9)	4.2 [2.8; 6.3]	0.97 [0.58; 1.63]	0.913	
IMDC Group Prognostic Status at Baseline									
Favorable	104	82 (78.8)	3.5 [2.1; 7.8]	110	68 (61.8)	4.9 [2.8; 7.0]	1.15 [0.82; 1.59]	0.420	0.560
Intermediate or Poor	225	157 (69.8)	4.1 [2.8; 5.0]	204	124 (60.8)	4.2 [2.9; 5.6]	1.07 [0.84; 1.36]	0.586	
IMDC Prognostic Status at Baseline									
Favorable	104	82 (78.8)	3.5 [2.1; 7.8]	110	68 (61.8)	4.9 [2.8; 7.0]	1.15 [0.82; 1.59]	0.420	0.224
Intermediate	196	146 (74.5)	3.5 [2.2; 4.3]	173	111 (64.2)	3.5 [2.8; 5.6]	1.16 [0.89; 1.49]	0.270	
Poor	29	11 (37.9)	Not reached [7.0; -]	31	13 (41.9)	7.7 [3.0; -]	0.65 [0.28; 1.54]	0.329	

a: Database Cutoff Date: 28AUG2020

b: Number of participants: full-analysis-set population, participants with data for the specific endpoint in each row recorded at baseline and at least at one post-baseline visit

c: Time to first deterioration is defined as the time from the date of randomization to the first onset of a pre-specified number of points or more decrease from baseline

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

e: Based on Cox regression model with treatment as a covariate stratified by geographic region (Region 1: Western Europe and North America, Region 2: Rest of the World) and MSKCC prognostic groups (favourable, intermediate and poor risk) 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 regression model with geographic region (Region 1: Western Europe and North America, Region 2: Rest of the World), MSKCC prognostic groups (favorable, intermediate and poor risk) in IxRS, treatment and subgroup as covariates, and treatment-by-subgroup interaction (p-value of likelihood ratio test for interaction term)

CI: Confidence Interval; IMDC: International Metastatic Renal Cell Carcinoma Database Consortium; KPS: Karnofsky Performance Status; MSKCC: Memorial Sloan Kettering Cancer Center

EQ-5D VAS (7 Punkte)

Tabelle 4G-16: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für die EQ-5D VAS (7 Punkte) aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE 581[a]	**Pembrolizumab + Lenvatinib**			**Sunitinib**			**Pembrolizumab + Lenvatinib vs. Sunitinib**		
Time to first deterioration	**N[b]**	**Participants with Event[c] n (%)**	**Median Time[d] in Months [95 %-CI]**	**N[b]**	**Participants with Event[c] n (%)**	**Median Time[d] in Months [95 %-CI]**	**Hazard Ratio[e] [95 %-CI][e]**	**p-Value[e,f]**	**p-Value for Interaction Test[g]**
Gender									
Male	236	179 (75.8)	2.2 [2.0; 3.5]	242	187 (77.3)	2.1 [1.4; 2.8]	0.84 [0.68; 1.04]	0.103	0.801
Female	96	67 (69.8)	1.9 [1.4; 3.1]	73	59 (80.8)	1.7 [1.4; 2.8]	0.83 [0.58; 1.18]	0.298	
IMDC Group Prognostic Status at Baseline									
Favorable	104	82 (78.8)	2.0 [1.4; 2.9]	109	87 (79.8)	1.4 [0.8; 2.6]	0.86 [0.63; 1.17]	0.334	0.970
Intermediate or Poor	227	164 (72.2)	2.2 [1.7; 3.5]	203	156 (76.8)	2.1 [1.7; 2.9]	0.84 [0.67; 1.06]	0.135	
IMDC Prognostic Status at Baseline									
Favorable	104	82 (78.8)	2.0 [1.4; 2.9]	109	87 (79.8)	1.4 [0.8; 2.6]	0.86 [0.63; 1.17]	0.334	0.738
Intermediate	198	144 (72.7)	2.2 [1.4; 3.4]	172	134 (77.9)	2.1 [1.7; 2.9]	0.90 [0.71; 1.15]	0.401	
Poor	29	20 (69.0)	4.9 [1.4; 13.2]	31	22 (71.0)	2.2 [0.8; 5.6]	0.60 [0.30; 1.20]	0.149	

a: Database Cutoff Date: 28AUG2020

b: Number of participants: full-analysis-set population, participants with data for the specific endpoint in each row recorded at baseline and at least at one post-baseline visit

c: Time to first deterioration is defined as the time from the date of randomization to the first onset of a pre-specified number of points or more decrease from baseline

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

e: Based on Cox regression model with treatment as a covariate stratified by geographic region (Region 1: Western Europe and North America, Region 2: Rest of the World) and MSKCC prognostic groups (favourable, intermediate and poor risk) 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 regression model with geographic region (Region 1: Western Europe and North America, Region 2: Rest of the World), MSKCC prognostic groups (favorable, intermediate and poor risk) in IxRS, treatment and subgroup as covariates, and treatment-by-subgroup interaction (p-value of likelihood ratio test for interaction term)

CI: Confidence Interval; IMDC: International Metastatic Renal Cell Carcinoma Database Consortium; MSKCC: Memorial Sloan Kettering Cancer Center

EQ-5D VAS (10 Punkte)

Tabelle 4G-17: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für die EQ-5D VAS (10 Punkte) aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE 581[a]	**Pembrolizumab + Lenvatinib**			**Sunitinib**			**Pembrolizumab + Lenvatinib vs. Sunitinib**		
Time to first deterioration	**N[b]**	**Participants with Event[c] n (%)**	**Median Time[d] in Months [95 %-CI]**	**N[b]**	**Participants with Event[c] n (%)**	**Median Time[d] in Months [95 %-CI]**	**Hazard Ratio[e] [95 %-CI][e]**	**p-Value[e,f]**	**p-Value for Interaction Test[g]**
Gender									
Male	236	175 (74.2)	2.7 [2.1; 3.5]	242	179 (74.0)	2.1 [1.5; 3.1]	0.86 [0.70; 1.06]	0.168	0.921
Female	96	67 (69.8)	2.1 [1.4; 2.8]	73	58 (79.5)	2.1 [1.4; 3.5]	0.87 [0.61; 1.25]	0.450	
IMDC Group Prognostic Status at Baseline									
Favorable	104	80 (76.9)	2.0 [1.4; 2.9]	109	84 (77.1)	2.1 [1.4; 2.8]	0.89 [0.65; 1.21]	0.453	0.972
Intermediate or Poor	227	162 (71.4)	2.7 [2.1; 3.5]	203	150 (73.9)	2.8 [1.7; 3.5]	0.88 [0.70; 1.11]	0.271	
IMDC Prognostic Status at Baseline									
Favorable	104	80 (76.9)	2.0 [1.4; 2.9]	109	84 (77.1)	2.1 [1.4; 2.8]	0.89 [0.65; 1.21]	0.453	0.661
Intermediate	198	142 (71.7)	2.2 [1.8; 3.5]	172	128 (74.4)	2.8 [1.7; 3.5]	0.94 [0.74; 1.21]	0.650	
Poor	29	20 (69.0)	4.9 [1.4; 18.7]	31	22 (71.0)	3.1 [0.8; 5.6]	0.59 [0.29; 1.20]	0.145	

a: Database Cutoff Date: 28AUG2020

b: Number of participants: full-analysis-set population, participants with data for the specific endpoint in each row recorded at baseline and at least at one post-baseline visit

c: Time to first deterioration is defined as the time from the date of randomization to the first onset of a pre-specified number of points or more decrease from baseline

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

e: Based on Cox regression model with treatment as a covariate stratified by geographic region (Region 1: Western Europe and North America, Region 2: Rest of the World) and MSKCC prognostic groups (favourable, intermediate and poor risk) 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 regression model with geographic region (Region 1: Western Europe and North America, Region 2: Rest of the World), MSKCC prognostic groups (favorable, intermediate and poor risk) in IxRS, treatment and subgroup as covariates, and treatment-by-subgroup interaction (p-value of likelihood ratio test for interaction term)

CI: Confidence Interval; IMDC: International Metastatic Renal Cell Carcinoma Database Consortium; MSKCC: Memorial Sloan Kettering Cancer Center

Gesundheitsbezogene Lebensqualität

EORTC QLQ-C30: Globaler Gesundheitsstatus

Tabelle 4G-18: Subgruppenanalysen mit nicht signifikantem Interaktionstest ($p \geq 0,05$) für den globalen Gesundheitsstatus aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE 581[a]	**Pembrolizumab + Lenvatinib**			**Sunitinib**			**Pembrolizumab + Lenvatinib vs. Sunitinib**		
Time to first deterioration	**N[b]**	**Participants with Event[c] n (%)**	**Median Time[d] in Months [95 %-CI]**	**N[b]**	**Participants with Event[c] n (%)**	**Median Time[d] in Months [95 %-CI]**	**Hazard Ratio[e] [95 %-CI][e]**	**p-Value[e,f]**	**p-Value for Interaction Test[g]**
Age category									
<65	184	138 (75.0)	2.8 [2.1; 4.4]	201	147 (73.1)	2.8 [2.1; 4.2]	0.91 [0.72; 1.15]	0.429	0.562
≥65	146	117 (80.1)	2.1 [1.4; 3.5]	119	95 (79.8)	1.4 [0.8; 2.1]	0.80 [0.61; 1.06]	0.117	
Gender									
Male	234	189 (80.8)	2.8 [1.7; 3.5]	245	185 (75.5)	2.1 [1.4; 2.8]	0.90 [0.73; 1.10]	0.310	0.750
Female	96	66 (68.8)	2.1 [1.4; 4.2]	75	57 (76.0)	2.0 [1.4; 2.8]	0.82 [0.57; 1.19]	0.298	
Region									
Western Europe and North America	176	132 (75.0)	2.8 [2.1; 3.6]	174	135 (77.6)	2.2 [1.5; 2.8]	0.81 [0.64; 1.04]	0.095	0.470
Rest of the World	154	123 (79.9)	2.1 [1.4; 3.5]	146	107 (73.3)	2.1 [0.8; 3.4]	0.97 [0.75; 1.26]	0.810	
IMDC Group Prognostic Status at Baseline									
Favorable	103	87 (84.5)	2.8 [1.4; 3.5]	110	88 (80.0)	2.1 [1.0; 3.2]	0.87 [0.64; 1.19]	0.386	0.650
Intermediate or Poor	226	167 (73.9)	2.2 [1.4; 3.6]	207	151 (72.9)	2.1 [1.4; 3.1]	0.88 [0.70; 1.10]	0.246	

a: Database Cutoff Date: 28AUG2020

b: Number of participants: full-analysis-set population, participants with data for the specific endpoint in each row recorded at baseline and at least at one post-baseline visit

c: Time to first deterioration is defined as the time from the date of randomization to the first onset of a pre-specified number of points or more decrease from baseline

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

e: Based on Cox regression model with treatment as a covariate stratified by geographic region (Region 1: Western Europe and North America, Region 2: Rest of the World) and MSKCC prognostic groups (favourable, intermediate and poor risk) 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 regression model with geographic region (Region 1: Western Europe and North America, Region 2: Rest of the World), MSKCC prognostic groups (favorable, intermediate and poor risk) in IxRS, treatment and subgroup as covariates, and treatment-by-subgroup interaction (p-value of likelihood ratio test for interaction term)

CI: Confidence Interval; IMDC: International Metastatic Renal Cell Carcinoma Database Consortium; MSKCC: Memorial Sloan Kettering Cancer Center

EORTC QLQ-C30: Emotionale Funktion

Tabelle 4G-19: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für die Funktionsskala Emotionale Funktion aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE 581[a]	**Pembrolizumab + Lenvatinib**			**Sunitinib**			**Pembrolizumab + Lenvatinib vs. Sunitinib**		**p-Value for Interaction Test[g]**
Time to first deterioration	**N[b]**	**Participants with Event[c] n (%)**	**Median Time[d] in Months [95 %-CI]**	**N[b]**	**Participants with Event[c] n (%)**	**Median Time[d] in Months [95 %-CI]**	**Hazard Ratio[e] [95 %-CI][e]**	**p-Value[e,f]**	
Age category									
<65	184	99 (53.8)	15.2 [8.3; 22.9]	201	94 (46.8)	11.8 [6.3; 23.4]	0.90 [0.67; 1.20]	0.471	0.836
≥65	146	90 (61.6)	6.9 [4.0; 10.4]	119	64 (53.8)	4.9 [3.4; 12.6]	1.00 [0.72; 1.38]	0.991	
Gender									
Male	234	135 (57.7)	11.1 [7.6; 18.7]	245	119 (48.6)	9.0 [4.9; 15.5]	0.90 [0.70; 1.16]	0.405	0.607
Female	96	54 (56.3)	6.3 [2.8; 20.2]	75	39 (52.0)	6.3 [3.5; 16.6]	1.11 [0.73; 1.68]	0.633	
Baseline KPS Score									
100-90	280	156 (55.7)	11.2 [7.6; 20.2]	268	128 (47.8)	11.2 [6.2; 20.1]	0.96 [0.76; 1.22]	0.763	0.574
80-70	50	33 (66.0)	4.2 [2.8; 9.7]	52	30 (57.7)	3.6 [2.1; 6.9]	0.82 [0.49; 1.35]	0.431	
Region									
Western Europe and North America	176	98 (55.7)	12.7 [7.6; 20.8]	174	86 (49.4)	6.9 [4.2; 20.1]	0.84 [0.62; 1.12]	0.238	0.272
Rest of the World	154	91 (59.1)	7.8 [4.9; 11.8]	146	72 (49.3)	11.2 [5.0; 15.9]	1.07 [0.78; 1.46]	0.686	
IMDC Group Prognostic Status at Baseline									
Favorable	103	54 (52.4)	18.7 [9.0; 26.3]	110	49 (44.5)	20.1 [5.6; -]	0.99 [0.66; 1.48]	0.963	0.685
Intermediate or Poor	226	134 (59.3)	8.1 [4.9; 12.5]	207	107 (51.7)	6.3 [4.2; 10.4]	0.93 [0.72; 1.20]	0.560	
IMDC Prognostic Status at Baseline									
Favorable	103	54 (52.4)	18.7 [9.0; 26.3]	110	49 (44.5)	20.1 [5.6; -]	0.99 [0.66; 1.48]	0.963	0.585
Intermediate	197	119 (60.4)	6.4 [4.9; 11.8]	175	91 (52.0)	6.9 [4.1; 11.8]	0.98 [0.74; 1.29]	0.861	
Poor	29	15 (51.7)	10.4 [2.8; -]	32	16 (50.0)	4.9 [2.1; 8.3]	0.85 [0.39; 1.86]	0.686	

a: Database Cutoff Date: 28AUG2020

b: Number of participants: full-analysis-set population, participants with data for the specific endpoint in each row recorded at baseline and at least at one post-baseline visit

c: Time to first deterioration is defined as the time from the date of randomization to the first onset of a pre-specified number of points or more decrease from baseline

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

e: Based on Cox regression model with treatment as a covariate stratified by geographic region (Region 1: Western Europe and North America, Region 2: Rest of the World) and MSKCC prognostic groups (favourable, intermediate and poor risk) using Wald confidence interval

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

Study: KEYNOTE 581[a]	Pembrolizumab + Lenvatinib			Sunitinib			Pembrolizumab + Lenvatinib vs. Sunitinib		p-Value for Interaction Test[g]
Time to first deterioration	N[b]	Participants with Event[c] n (%)	Median Time[d] in Months [95 %-CI]	N[b]	Participants with Event[c] n (%)	Median Time[d] in Months [95 %-CI]	Hazard Ratio[e] [95 %-CI][e]	p-Value[e,f]	
g: Based on Cox regression model with geographic region (Region 1: Western Europe and North America, Region 2: Rest of the World), MSKCC prognostic groups (favorable, intermediate and poor risk) in IxRS, treatment and subgroup as covariates, and treatment-by-subgroup interaction (p-value of likelihood ratio test for interaction term)									
CI: Confidence Interval; IMDC: International Metastatic Renal Cell Carcinoma Database Consortium; KPS: Karnofsky Performance Status; MSKCC: Memorial Sloan Kettering Cancer Center									

EORTC QLQ-C30: Kognitive Funktion

Tabelle 4G-20: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für die Funktionsskala Kognitive Funktion aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE 581[a]	Pembrolizumab + Lenvatinib			Sunitinib			Pembrolizumab + Lenvatinib vs. Sunitinib		p-Value for Interaction Test[g]
Time to first deterioration	N[b]	Participants with Event[c] n (%)	Median Time[d] in Months [95 %-CI]	N[b]	Participants with Event[c] n (%)	Median Time[d] in Months [95 %-CI]	Hazard Ratio[e] [95 %-CI][e]	p-Value[e,f]	
Age category									
<65	184	125 (67.9)	4.2 [2.8; 7.8]	201	110 (54.7)	6.2 [4.0; 12.4]	1.15 [0.88; 1.49]	0.301	0.076
≥65	146	107 (73.3)	2.8 [2.1; 4.1]	119	89 (74.8)	2.8 [1.7; 3.5]	0.83 [0.63; 1.11]	0.216	
Gender									
Male	234	165 (70.5)	3.7 [2.8; 6.3]	245	152 (62.0)	4.2 [3.5; 6.2]	1.00 [0.80; 1.25]	0.988	0.608
Female	96	67 (69.8)	2.8 [2.1; 4.2]	75	47 (62.7)	2.9 [2.1; 4.9]	1.06 [0.72; 1.55]	0.766	
Baseline KPS Score									
100-90	280	197 (70.4)	3.5 [2.7; 4.9]	268	163 (60.8)	3.7 [3.0; 5.5]	1.10 [0.89; 1.36]	0.364	0.230
80-70	50	35 (70.0)	4.1 [2.7; 8.3]	52	36 (69.2)	4.2 [1.7; 4.9]	0.85 [0.52; 1.38]	0.504	
IMDC Group Prognostic Status at Baseline									
Favorable	103	70 (68.0)	4.1 [2.7; 8.3]	110	67 (60.9)	4.9 [3.5; 9.6]	1.07 [0.76; 1.50]	0.707	0.627
Intermediate or Poor	226	161 (71.2)	3.1 [2.2; 4.9]	207	130 (62.8)	3.5 [2.2; 4.9]	0.99 [0.79; 1.25]	0.952	
IMDC Prognostic Status at Baseline									
Favorable	103	70 (68.0)	4.1 [2.7; 8.3]	110	67 (60.9)	4.9 [3.5; 9.6]	1.07 [0.76; 1.50]	0.707	0.812
Intermediate	197	139 (70.6)	3.5 [2.7; 5.6]	175	111 (63.4)	3.5 [2.1; 5.5]	0.97 [0.75; 1.25]	0.832	
Poor	29	22 (75.9)	2.7 [1.4; 3.1]	32	19 (59.4)	3.0 [1.7; 7.2]	1.05 [0.54; 2.02]	0.895	

Study: KEYNOTE 581[a]	Pembrolizumab + Lenvatinib			Sunitinib			Pembrolizumab + Lenvatinib vs. Sunitinib		p-Value for Interaction Test[g]
Time to first deterioration	N[b]	Participants with Event[c] n (%)	Median Time[d] in Months [95 %-CI]	N[b]	Participants with Event[c] n (%)	Median Time[d] in Months [95 %-CI]	Hazard Ratio[e] [95 %-CI][e]	p-Value[e,f]	
a: Database Cutoff Date: 28AUG2020									
b: Number of participants: full-analysis-set population, participants with data for the specific endpoint in each row recorded at baseline and at least at one post-baseline visit									
c: Time to first deterioration is defined as the time from the date of randomization to the first onset of a pre-specified number of points or more decrease from baseline									
d: From product-limit (Kaplan-Meier) method for censored data									
e: Based on Cox regression model with treatment as a covariate stratified by geographic region (Region 1: Western Europe and North America, Region 2: Rest of the World) and MSKCC prognostic groups (favourable, intermediate and poor risk) 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 regression model with geographic region (Region 1: Western Europe and North America, Region 2: Rest of the World), MSKCC prognostic groups (favorable, intermediate and poor risk) in IxRS, treatment and subgroup as covariates, and treatment-by-subgroup interaction (p-value of likelihood ratio test for interaction term)									
CI: Confidence Interval; IMDC: International Metastatic Renal Cell Carcinoma Database Consortium; KPS: Karnofsky Performance Status; MSKCC: Memorial Sloan Kettering Cancer Center									

EORTC QLQ-C30: Körperliche Funktion

Tabelle 4G-21: Subgruppenanalysen mit nicht signifikantem Interaktionstest ($p \geq 0{,}05$) für die Funktionsskala Körperliche Funktion aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE 581[a]	Pembrolizumab + Lenvatinib			Sunitinib			Pembrolizumab + Lenvatinib vs. Sunitinib		p-Value for Interaction Test[g]
Time to first deterioration	N[b]	Participants with Event[c] n (%)	Median Time[d] in Months [95 %-CI]	N[b]	Participants with Event[c] n (%)	Median Time[d] in Months [95 %-CI]	Hazard Ratio[e] [95 %-CI][e]	p-Value[e,f]	
Age category									
<65	183	129 (70.5)	4.3 [3.2; 6.9]	201	135 (67.2)	3.5 [2.1; 4.8]	0.84 [0.66; 1.08]	0.178	0.497
≥65	146	107 (73.3)	2.9 [2.1; 4.2]	119	93 (78.2)	2.1 [1.3; 3.1]	0.77 [0.58; 1.03]	0.078	
Gender									
Male	234	170 (72.6)	4.2 [3.2; 6.2]	245	167 (68.2)	3.5 [2.2; 4.8]	0.88 [0.70; 1.09]	0.234	0.078
Female	95	66 (69.5)	2.8 [2.1; 4.9]	75	61 (81.3)	1.4 [0.8; 2.1]	0.67 [0.46; 0.96]	0.028	
Baseline KPS Score									
100-90	279	199 (71.3)	3.5 [2.8; 5.6]	268	191 (71.3)	2.9 [2.1; 4.2]	0.82 [0.67; 1.00]	0.051	0.747
80-70	50	37 (74.0)	3.5 [2.1; 7.0]	52	37 (71.2)	2.1 [1.4; 4.9]	0.90 [0.56; 1.45]	0.660	
IMDC Group Prognostic Status at Baseline									
Favorable	103	78 (75.7)	3.5 [2.8; 5.8]	110	78 (70.9)	4.2 [2.8; 6.3]	0.94 [0.68; 1.30]	0.711	0.220
Intermediate or Poor	225	157	3.5	207	148	2.1	0.77	0.027	

Study: KEYNOTE 581[a]	Pembrolizumab + Lenvatinib			Sunitinib			Pembrolizumab + Lenvatinib vs. Sunitinib		p-Value for Interaction Test[g]
Time to first deterioration	N[b]	Participants with Event[c] n (%)	Median Time[d] in Months [95 %-CI]	N[b]	Participants with Event[c] n (%)	Median Time[d] in Months [95 %-CI]	Hazard Ratio[e] [95 %-CI][e]	p-Value[e,f]	
		(69.8)	[2.8; 5.7]		(71.5)	[1.7; 3.5]	[0.61; 0.97]		
IMDC Prognostic Status at Baseline									
Favorable	103	78 (75.7)	3.5 [2.8; 5.8]	110	78 (70.9)	4.2 [2.8; 6.3]	0.94 [0.68; 1.30]	0.711	0.312
Intermediate	196	139 (70.9)	3.5 [2.1; 4.9]	175	126 (72.0)	2.1 [1.5; 3.5]	0.80 [0.62; 1.03]	0.081	
Poor	29	18 (62.1)	7.0 [2.8; 21.5]	32	22 (68.8)	3.0 [0.8; 5.7]	0.53 [0.27; 1.04]	0.065	

a: Database Cutoff Date: 28AUG2020

b: Number of participants: full-analysis-set population, participants with data for the specific endpoint in each row recorded at baseline and at least at one post-baseline visit

c: Time to first deterioration is defined as the time from the date of randomization to the first onset of a pre-specified number of points or more decrease from baseline

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

e: Based on Cox regression model with treatment as a covariate stratified by geographic region (Region 1: Western Europe and North America, Region 2: Rest of the World) and MSKCC prognostic groups (favourable, intermediate and poor risk) 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 regression model with geographic region (Region 1: Western Europe and North America, Region 2: Rest of the World), MSKCC prognostic groups (favorable, intermediate and poor risk) in IxRS, treatment and subgroup as covariates, and treatment-by-subgroup interaction (p-value of likelihood ratio test for interaction term)

CI: Confidence Interval; IMDC: International Metastatic Renal Cell Carcinoma Database Consortium; KPS: Karnofsky Performance Status; MSKCC: Memorial Sloan Kettering Cancer Center

EORTC QLQ-C30: Rollenfunktion

Tabelle 4G-22: Subgruppenanalysen mit nicht signifikantem Interaktionstest ($p \geq 0,05$) für die Funktionsskala Rollenfunktion aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE 581[a]	Pembrolizumab + Lenvatinib			Sunitinib			Pembrolizumab + Lenvatinib vs. Sunitinib		p-Value for Interaction Test[g]
Time to first deterioration	N[b]	Participants with Event[c] n (%)	Median Time[d] in Months [95 %-CI]	N[b]	Participants with Event[c] n (%)	Median Time[d] in Months [95 %-CI]	Hazard Ratio[e] [95 %-CI][e]	p-Value[e,f]	
Age category									
<65	183	137 (74.9)	2.8 [1.4; 2.9]	201	143 (71.1)	2.8 [2.1; 3.5]	1.02 [0.80; 1.29]	0.899	0.258
≥65	146	117 (80.1)	1.5 [1.4; 2.8]	119	102 (85.7)	1.4 [1.2; 1.7]	0.83 [0.64; 1.09]	0.186	
Gender									
Male	234	186 (79.5)	2.4 [1.4; 2.9]	245	186 (75.9)	2.1 [1.7; 3.2]	0.96 [0.78; 1.18]	0.686	0.543
Female	95	68 (71.6)	1.4 [0.8; 2.6]	75	59 (78.7)	1.4 [1.0; 2.6]	0.89 [0.62; 1.27]	0.515	
Baseline KPS Score									
100-90	280	225 (80.4)	2.1 [1.4; 2.8]	268	211 (78.7)	2.1 [1.4; 2.8]	0.97 [0.80; 1.18]	0.776	0.237

Study: KEYNOTE 581[a]	Pembrolizumab + Lenvatinib			Sunitinib			Pembrolizumab + Lenvatinib vs. Sunitinib		p-Value for Interaction Test[g]
Time to first deterioration	N[b]	Participants with Event[c] n (%)	Median Time[d] in Months [95 %-CI]	N[b]	Participants with Event[c] n (%)	Median Time[d] in Months [95 %-CI]	Hazard Ratio[e] [95 %-CI][e]	p-Value[e,f]	
80-70	49	29 (59.2)	4.9 [1.4; -]	52	34 (65.4)	2.2 [1.4; 4.9]	0.90 [0.53; 1.51]	0.681	
Region									
Western Europe and North America	175	127 (72.6)	2.4 [1.4; 3.5]	174	130 (74.7)	2.6 [1.7; 3.5]	0.91 [0.71; 1.17]	0.471	0.678
Rest of the World	154	127 (82.5)	1.4 [1.4; 2.8]	146	115 (78.8)	1.5 [1.2; 2.6]	0.97 [0.75; 1.25]	0.792	
IMDC Group Prognostic Status at Baseline									
Favorable	103	87 (84.5)	2.1 [1.4; 2.8]	110	85 (77.3)	2.1 [1.4; 3.5]	1.08 [0.80; 1.46]	0.626	0.309
Intermediate or Poor	225	167 (74.2)	2.1 [1.4; 2.8]	207	157 (75.8)	2.1 [1.4; 2.8]	0.90 [0.72; 1.13]	0.359	
IMDC Prognostic Status at Baseline									
Favorable	103	87 (84.5)	2.1 [1.4; 2.8]	110	85 (77.3)	2.1 [1.4; 3.5]	1.08 [0.80; 1.46]	0.626	0.550
Intermediate	197	150 (76.1)	2.1 [1.4; 2.8]	175	139 (79.4)	2.1 [1.4; 2.8]	0.92 [0.72; 1.16]	0.473	
Poor	28	17 (60.7)	6.3 [0.9; 24.9]	32	18 (56.3)	3.1 [1.4; 11.8]	0.69 [0.33; 1.44]	0.322	

a: Database Cutoff Date: 28AUG2020

b: Number of participants: full-analysis-set population, participants with data for the specific endpoint in each row recorded at baseline and at least at one post-baseline visit

c: Time to first deterioration is defined as the time from the date of randomization to the first onset of a pre-specified number of points or more decrease from baseline

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

e: Based on Cox regression model with treatment as a covariate stratified by geographic region (Region 1: Western Europe and North America, Region 2: Rest of the World) and MSKCC prognostic groups (favourable, intermediate and poor risk) 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 regression model with geographic region (Region 1: Western Europe and North America, Region 2: Rest of the World), MSKCC prognostic groups (favorable, intermediate and poor risk) in IxRS, treatment and subgroup as covariates, and treatment-by-subgroup interaction (p-value of likelihood ratio test for interaction term)

CI: Confidence Interval; IMDC: International Metastatic Renal Cell Carcinoma Database Consortium; KPS: Karnofsky Performance Status; MSKCC: Memorial Sloan Kettering Cancer Center

EORTC QLQ-C30: Soziale Funktion

Tabelle 4G-23: Subgruppenanalysen mit nicht signifikantem Interaktionstest ($p \geq 0,05$) für die Funktionsskala Soziale Funktion aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE 581[a]	Pembrolizumab + Lenvatinib			Sunitinib			Pembrolizumab + Lenvatinib vs. Sunitinib		p-Value for Interaction Test[g]
Time to first deterioration	N[b]	Participants with Event[c] n (%)	Median Time[d] in Months [95 %-CI]	N[b]	Participants with Event[c] n (%)	Median Time[d] in Months [95 %-CI]	Hazard Ratio[e] [95 %-CI][e]	p-Value[e,f]	
Age category									
<65	184	137	3.2	201	139	3.5	0.99	0.965	0.728

Study: KEYNOTE 581[a]	Pembrolizumab + Lenvatinib			Sunitinib			Pembrolizumab + Lenvatinib vs. Sunitinib		p-Value for Interaction Test[g]
Time to first deterioration	N[b]	Participants with Event[c] n (%)	Median Time[d] in Months [95 %-CI]	N[b]	Participants with Event[c] n (%)	Median Time[d] in Months [95 %-CI]	Hazard Ratio[e] [95 %-CI][e]	p-Value[e,f]	
		(74.5)	[2.1; 4.2]		(69.2)	[2.1; 4.2]	[0.78; 1.26]		
≥65	146	110 (75.3)	2.2 [1.5; 3.2]	119	85 (71.4)	2.1 [1.5; 3.5]	0.94 [0.71; 1.26]	0.699	
Gender									
Male	234	179 (76.5)	3.0 [2.2; 3.8]	245	173 (70.6)	2.8 [2.0; 3.8]	0.93 [0.75; 1.15]	0.488	0.390
Female	96	68 (70.8)	1.5 [1.4; 3.2]	75	51 (68.0)	2.6 [1.5; 5.0]	1.17 [0.80; 1.69]	0.424	
Baseline KPS Score									
100-90	280	216 (77.1)	2.4 [2.1; 3.5]	268	190 (70.9)	2.8 [2.1; 3.7]	1.03 [0.85; 1.26]	0.757	0.109
80-70	50	31 (62.0)	4.1 [2.1; 11.8]	52	34 (65.4)	2.6 [1.5; 6.2]	0.76 [0.46; 1.28]	0.307	
Region									
Western Europe and North America	176	131 (74.4)	2.7 [2.1; 3.5]	174	122 (70.1)	3.5 [2.1; 4.2]	0.97 [0.76; 1.25]	0.819	0.994
Rest of the World	154	116 (75.3)	2.8 [1.5; 4.0]	146	102 (69.9)	2.1 [1.4; 3.7]	0.97 [0.74; 1.26]	0.809	
IMDC Group Prognostic Status at Baseline									
Favorable	103	76 (73.8)	3.5 [2.1; 6.3]	110	77 (70.0)	2.9 [2.0; 4.9]	0.87 [0.63; 1.21]	0.419	0.663
Intermediate or Poor	226	171 (75.7)	2.1 [1.9; 3.0]	207	145 (70.0)	2.2 [1.7; 3.6]	1.01 [0.81; 1.27]	0.900	
IMDC Prognostic Status at Baseline									
Favorable	103	76 (73.8)	3.5 [2.1; 6.3]	110	77 (70.0)	2.9 [2.0; 4.9]	0.87 [0.63; 1.21]	0.419	0.700
Intermediate	197	152 (77.2)	2.1 [1.5; 2.8]	175	125 (71.4)	2.2 [1.7; 3.7]	1.04 [0.82; 1.32]	0.762	
Poor	29	19 (65.5)	3.4 [1.4; 11.8]	32	20 (62.5)	1.7 [0.8; 8.3]	0.86 [0.44; 1.71]	0.675	

a: Database Cutoff Date: 28AUG2020

b: Number of participants: full-analysis-set population, participants with data for the specific endpoint in each row recorded at baseline and at least at one post-baseline visit

c: Time to first deterioration is defined as the time from the date of randomization to the first onset of a pre-specified number of points or more decrease from baseline

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

e: Based on Cox regression model with treatment as a covariate stratified by geographic region (Region 1: Western Europe and North America, Region 2: Rest of the World) and MSKCC prognostic groups (favourable, intermediate and poor risk) 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 regression model with geographic region (Region 1: Western Europe and North America, Region 2: Rest of the World), MSKCC prognostic groups (favorable, intermediate and poor risk) in IxRS, treatment and subgroup as covariates, and treatment-by-subgroup interaction (p-value of likelihood ratio test for interaction term)

CI: Confidence Interval; IMDC: International Metastatic Renal Cell Carcinoma Database Consortium; KPS: Karnofsky Performance Status; MSKCC: Memorial Sloan Kettering Cancer Center

Nebenwirkungen

Unerwünschte Ereignisse

Unerwünschte Ereignisse gesamt

Tabelle 4G-24: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für den Endpunkt Unerwünschte Ereignisse gesamt aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE 581[a]	Pembrolizumab + Lenvatinib			Sunitinib			Pembrolizumab + Lenvatinib vs. Sunitinib		
Adverse Events	N[b]	Participants with Event n (%)	Median Time[c] in weeks [95 %-CI]	N[b]	Participants with Event n (%)	Median Time[c] in weeks [95 %-CI]	Hazard Ratio [95 %-CI][d]	p-Value[d,e]	p-Value for Interaction Test[f]
Age category									
<65	193	193 (100.0)	1.1 [1.0; 1.3]	215	211 (98.1)	1.3 [1.1; 1.4]	1.13 [0.93; 1.38]	0.206	0.453
≥65	159	158 (99.4)	1.1 [0.7; 1.3]	125	124 (99.2)	1.1 [0.9; 1.3]	1.01 [0.80; 1.28]	0.915	
Region									
Western Europe and North America	197	196 (99.5)	1.0 [0.7; 1.1]	189	186 (98.4)	1.1 [1.0; 1.3]	1.13 [0.92; 1.38]	0.249	0.799
Rest of the World	155	155 (100.0)	1.3 [1.1; 1.6]	151	149 (98.7)	1.3 [1.1; 1.6]	1.08 [0.86; 1.36]	0.484	
Gender									
Male	252	251 (99.6)	1.1 [1.0; 1.3]	260	255 (98.1)	1.3 [1.1; 1.4]	1.16 [0.97; 1.38]	0.098	0.139
Female	100	100 (100.0)	1.1 [0.7; 1.4]	80	80 (100.0)	1.1 [0.7; 1.3]	0.89 [0.66; 1.20]	0.439	
Baseline KPS Score									
100-90	292	292 (100.0)	1.1 [1.0; 1.3]	282	280 (99.3)	1.1 [1.1; 1.3]	1.11 [0.94; 1.30]	0.231	0.813
80-70	60	59 (98.3)	1.3 [1.1; 1.9]	58	55 (94.8)	1.6 [0.9; 2.3]	1.05 [0.72; 1.52]	0.800	
IMDC Prognostic Status at Baseline									
Favorable	109	109 (100.0)	1.3 [1.0; 1.6]	117	114 (97.4)	1.3 [1.1; 1.6]	1.12 [0.86; 1.46]	0.406	0.391
Intermediate	208	207 (99.5)	1.1 [1.0; 1.3]	185	184 (99.5)	1.1 [1.0; 1.3]	1.01 [0.83; 1.24]	0.897	
Poor	33	33 (100.0)	1.0 [0.4; 1.3]	35	34 (97.1)	1.9 [1.1; 2.1]	1.46 [0.89; 2.39]	0.130	
IMDC Group Prognostic Status at Baseline									
Favorable	109	109 (100.0)	1.3 [1.0; 1.6]	117	114 (97.4)	1.3 [1.1; 1.6]	1.12 [0.86; 1.46]	0.406	0.791
Intermediate or Poor	241	240 (99.6)	1.1 [1.0; 1.3]	220	218 (99.1)	1.1 [1.0; 1.4]	1.07 [0.89; 1.29]	0.464	

a: Database Cutoff Date: 28AUG2020
b: Number of participants: all-participants-as-treated population
c: From product-limit (Kaplan-Meier) method for censored data
d: Based on Cox regression model with treatment as a covariate using Wald confidence interval
e: Two-sided p-value using Wald test (Score test in case of zero event in one treatment group)

Study: KEYNOTE 581[a]	Pembrolizumab + Lenvatinib			Sunitinib			Pembrolizumab + Lenvatinib vs. Sunitinib		
Adverse Events	N[b]	Participants with Event n (%)	Median Time[c] in weeks [95 %-CI]	N[b]	Participants with Event n (%)	Median Time[c] in weeks [95 %-CI]	Hazard Ratio [95 %-CI][d]	p-Value[d,e]	p-Value for Interaction Test[f]
f: Based on Cox model with treatment and subgroup as covariates, and treatment-by-subgroup interaction (p-value of likelihood ratio test for interaction term)									
CI: Confidence Interval; IMDC: International Metastatic Renal Cell Carcinoma Database Consortium; KPS: Karnofsky Performance Status									

Schwerwiegende unerwünschte Ereignisse

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

Study: KEYNOTE 581[a]	Pembrolizumab + Lenvatinib			Sunitinib			Pembrolizumab + Lenvatinib vs. Sunitinib		
Serious Adverse Events	N[b]	Participants with Event n (%)	Median Time[c] in weeks [95 %-CI]	N[b]	Participants with Event n (%)	Median Time[c] in weeks [95 %-CI]	Hazard Ratio [95 %-CI][d]	p-Value[d,e]	p-Value for Interaction Test[f]
Age category									
<65	193	89 (46.1)	114.6 [82.7; 134.0]	215	64 (29.8)	Not reached [-; -]	1.37 [0.99; 1.89]	0.058	0.831
≥65	159	89 (56.0)	51.1 [34.0; 103.0]	125	49 (39.2)	Not reached [85.1; -]	1.34 [0.95; 1.90]	0.097	
Region									
Western Europe and North America	197	106 (53.8)	82.1 [50.1; 116.7]	189	65 (34.4)	Not reached [92.7; -]	1.38 [1.01; 1.88]	0.042	0.937
Rest of the World	155	72 (46.5)	103.0 [64.6; -]	151	48 (31.8)	Not reached [-; -]	1.41 [0.98; 2.04]	0.063	
Gender									
Male	252	123 (48.8)	99.1 [70.9; 121.3]	260	78 (30.0)	Not reached [-; -]	1.43 [1.07; 1.89]	0.015	0.544
Female	100	55 (55.0)	38.6 [21.0; -]	80	35 (43.8)	Not reached [44.6; -]	1.27 [0.83; 1.95]	0.265	
Baseline KPS Score									
100-90	292	139 (47.6)	101.0 [71.9; 134.0]	282	89 (31.6)	Not reached [-; -]	1.39 [1.06; 1.81]	0.016	0.983
80-70	60	39 (65.0)	35.1 [17.0; 82.7]	58	24 (41.4)	Not reached [16.7; -]	1.41 [0.85; 2.35]	0.185	

Study: KEYNOTE 581[a]	Pembrolizumab + Lenvatinib			Sunitinib			Pembrolizumab + Lenvatinib vs. Sunitinib		
Serious Adverse Events	N[b]	Participants with Event n (%)	Median Time[c] in weeks [95 %-CI]	N[b]	Participants with Event n (%)	Median Time[c] in weeks [95 %-CI]	Hazard Ratio [95 %-CI][d]	p-Value[d,e]	p-Value for Interaction Test[f]
IMDC Prognostic Status at Baseline									
Favorable	109	51 (46.8)	114.6 [57.1; -]	117	32 (27.4)	Not reached [-; -]	1.66 [1.07; 2.59]	0.024	0.456
Intermediate	208	107 (51.4)	82.1 [48.9; 121.3]	185	65 (35.1)	Not reached [92.9; -]	1.32 [0.97; 1.80]	0.076	
Poor	33	19 (57.6)	82.7 [14.6; -]	35	14 (40.0)	Not reached [16.7; -]	1.13 [0.56; 2.29]	0.736	
IMDC Group Prognostic Status at Baseline									
Favorable	109	51 (46.8)	114.6 [57.1; -]	117	32 (27.4)	Not reached [-; -]	1.66 [1.07; 2.59]	0.024	0.286
Intermediate or Poor	241	126 (52.3)	82.1 [48.9; 113.9]	220	79 (35.9)	Not reached [92.9; -]	1.28 [0.97; 1.70]	0.086	

a: Database Cutoff Date: 28AUG2020
b: Number of participants: all-participants-as-treated population
c: From product-limit (Kaplan-Meier) method for censored data
d: Based on Cox regression model with treatment as a covariate using Wald confidence interval
e: Two-sided p-value using Wald test (Score test in case of zero event in one treatment group)
f: Based on Cox model with treatment and subgroup as covariates, and treatment-by-subgroup interaction (p-value of likelihood ratio test for interaction term)
CI: Confidence Interval; IMDC: International Metastatic Renal Cell Carcinoma Database Consortium; KPS: Karnofsky Performance Status

Schwere unerwünschte Ereignisse (CTCAE-Grad 3-5)

Tabelle 4G-26: Subgruppenanalysen mit nicht signifikantem Interaktionstest ($p \geq 0,05$) für den Endpunkt Schwere unerwünschte Ereignisse (CTCAE-Grad 3-5) aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE 581[a]	Pembrolizumab + Lenvatinib			Sunitinib			Pembrolizumab + Lenvatinib vs. Sunitinib		
Severe Adverse Events (CTCAE-Grade 3-5)	N[b]	Participants with Event n (%)	Median Time[c] in weeks [95 %-CI]	N[b]	Participants with Event n (%)	Median Time[c] in weeks [95 %-CI]	Hazard Ratio [95 %-CI][d]	p-Value[d,e]	p-Value for Interaction Test[f]
Age category									
<65	193	149 (77.2)	18.1 [12.1; 26.0]	215	150 (69.8)	15.1 [12.1; 19.3]	0.97 [0.77; 1.22]	0.782	0.405
≥65	159	141 (88.7)	5.3 [3.7; 8.7]	125	94 (75.2)	4.6 [3.1; 8.4]	1.13 [0.87; 1.47]	0.352	
Region									
Western Europe and North America	197	162 (82.2)	9.0 [6.0; 12.6]	189	134 (70.9)	12.1 [9.0; 16.3]	1.09 [0.87; 1.38]	0.446	0.937
Rest of the World	155	128 (82.6)	14.1 [7.9; 18.3]	151	110 (72.8)	10.0 [6.3; 15.6]	1.07 [0.83; 1.38]	0.599	

Study: KEYNOTE 581[a]	Pembrolizumab + Lenvatinib			Sunitinib			Pembrolizumab + Lenvatinib vs. Sunitinib		
Severe Adverse Events (CTCAE-Grade 3-5)	N[b]	Participants with Event n (%)	Median Time[c] in weeks [95 %-CI]	N[b]	Participants with Event n (%)	Median Time[c] in weeks [95 %-CI]	Hazard Ratio [95 %-CI][d]	p-Value[d,e]	p-Value for Interaction Test[f]
Gender									
Male	252	203 (80.6)	12.6 [10.1; 19.4]	260	175 (67.3)	14.0 [9.4; 18.1]	1.10 [0.90; 1.35]	0.348	0.495
Female	100	87 (87.0)	5.9 [3.1; 8.0]	80	69 (86.3)	7.9 [3.1; 12.3]	0.97 [0.71; 1.34]	0.862	
Baseline KPS Score									
100-90	292	238 (81.5)	10.3 [7.1; 14.1]	282	200 (70.9)	13.9 [9.0; 16.3]	1.10 [0.91; 1.33]	0.307	0.534
80-70	60	52 (86.7)	11.9 [5.3; 16.9]	58	44 (75.9)	9.4 [5.1; 11.7]	0.91 [0.61; 1.37]	0.665	
IMDC Prognostic Status at Baseline									
Favorable	109	87 (79.8)	12.0 [5.9; 24.3]	117	84 (71.8)	14.9 [9.9; 27.0]	1.12 [0.83; 1.51]	0.457	0.808
Intermediate	208	174 (83.7)	10.1 [7.1; 15.6]	185	131 (70.8)	9.7 [6.1; 15.1]	1.07 [0.85; 1.35]	0.549	
Poor	33	27 (81.8)	11.4 [3.1; 31.1]	35	26 (74.3)	9.4 [6.1; 15.0]	0.87 [0.50; 1.51]	0.622	
IMDC Group Prognostic Status at Baseline									
Favorable	109	87 (79.8)	12.0 [5.9; 24.3]	117	84 (71.8)	14.9 [9.9; 27.0]	1.12 [0.83; 1.51]	0.457	0.686
Intermediate or Poor	241	201 (83.4)	10.3 [7.1; 15.1]	220	157 (71.4)	9.7 [6.1; 14.1]	1.04 [0.85; 1.28]	0.701	

a: Database Cutoff Date: 28AUG2020

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

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

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

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

f: Based on Cox 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; IMDC: International Metastatic Renal Cell Carcinoma Database Consortium; KPS: Karnofsky Performance Status

Therapieabbruch wegen unerwünschter Ereignisse

Tabelle 4G-27: Subgruppenanalysen mit nicht signifikantem Interaktionstest ($p \geq 0,05$) für den Endpunkt Therapieabbruch wegen unerwünschter Ereignisse aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE 581[a]	**Pembrolizumab + Lenvatinib**			**Sunitinib**			**Pembrolizumab + Lenvatinib vs. Sunitinib**		
Adverse Events Leading to Treatment Discontinuation	**N[b]**	**Participants with Event n (%)**	**Median Time[c] in weeks [95 %-CI]**	**N[b]**	**Participants with Event n (%)**	**Median Time[c] in weeks [95 %-CI]**	**Hazard Ratio [95 %-CI][d]**	**p-Value[d,e]**	**p-Value for Interaction Test[f]**
Age category									
<65	193	57 (29.5)	Not reached [126.7; -]	215	24 (11.2)	Not reached [-; -]	1.96 [1.21; 3.17]	0.006	0.987
≥65	159	74 (46.5)	105.7 [63.3; -]	125	25 (20.0)	Not reached [-; -]	2.08 [1.32; 3.28]	0.002	
Region									
Western Europe and North America	197	79 (40.1)	126.7 [86.0; -]	189	30 (15.9)	Not reached [-; -]	2.06 [1.35; 3.15]	< 0.001	0.795
Rest of the World	155	52 (33.5)	Not reached [108.4; -]	151	19 (12.6)	Not reached [-; -]	2.21 [1.31; 3.75]	0.003	
Gender									
Male	252	92 (36.5)	156.0 [108.4; -]	260	37 (14.2)	Not reached [-; -]	2.01 [1.37; 2.95]	< 0.001	0.790
Female	100	39 (39.0)	Not reached [72.1; -]	80	12 (15.0)	Not reached [-; -]	2.38 [1.25; 4.56]	0.009	
IMDC Prognostic Status at Baseline									
Favorable	109	44 (40.4)	126.7 [99.1; -]	117	20 (17.1)	Not reached [-; -]	2.21 [1.30; 3.75]	0.003	0.110
Intermediate	208	78 (37.5)	156.0 [105.1; -]	185	22 (11.9)	Not reached [-; -]	2.44 [1.52; 3.93]	< 0.001	
Poor	33	9 (27.3)	Not reached [78.9; -]	35	7 (20.0)	Not reached [32.3; -]	0.76 [0.27; 2.14]	0.597	
IMDC Group Prognostic Status at Baseline									
Favorable	109	44 (40.4)	126.7 [99.1; -]	117	20 (17.1)	Not reached [-; -]	2.21 [1.30; 3.75]	0.003	0.763
Intermediate or Poor	241	87 (36.1)	156.0 [105.3; -]	220	29 (13.2)	Not reached [-; -]	2.03 [1.33; 3.10]	0.001	

a: Database Cutoff Date: 28AUG2020

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

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

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

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

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

CI: Confidence Interval; IMDC: International Metastatic Renal Cell Carcinoma Database Consortium; KPS: Karnofsky Performance Status

Unerwünschte Ereignisse (gegliedert nach SOC und PT)

Unerwünschte Ereignisse gesamt (SOC und PT)

Tabelle 4G-28:Subgruppenanalysen mit nicht signifikantem Interaktionstest ($p \geq 0,05$) für den Endpunkt Unerwünschte Ereignisse gesamt (SOC) aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE 581[a]	**Pembrolizumab + Lenvatinib**			**Sunitinib**			**Pembrolizumab + Lenvatinib vs. Sunitinib**		
Adverse Events	**N[b]**	**Participants with Event n (%)**	**Median Time[c] in weeks [95 %-CI]**	**N[b]**	**Participants with Event n (%)**	**Median Time[c] in weeks [95 %-CI]**	**Hazard Ratio [95 %-CI][d]**	**p-Value[d,e]**	**p-Value for Interaction Test[f]**
SOC[g]: Blood and lymphatic system disorders									
Age category									
<65	193	35 (18.1)	Not reached [-; -]	215	77 (35.8)	Not reached [84.3; -]	0.36 [0.24; 0.54]	< 0.001	0.914
≥65	159	34 (21.4)	Not reached [-; -]	125	53 (42.4)	48.1 [24.9; -]	0.37 [0.24; 0.57]	< 0.001	
Region									
Western Europe and North America	197	43 (21.8)	Not reached [-; -]	189	68 (36.0)	Not reached [54.3; -]	0.44 [0.30; 0.65]	< 0.001	0.188
Rest of the World	155	26 (16.8)	Not reached [-; -]	151	62 (41.1)	Not reached [34.9; -]	0.30 [0.19; 0.47]	< 0.001	
Gender									
Male	252	42 (16.7)	Not reached [-; -]	260	98 (37.7)	Not reached [54.3; -]	0.31 [0.21; 0.45]	< 0.001	0.110
Female	100	27 (27.0)	Not reached [109.6; -]	80	32 (40.0)	Not reached [30.0; -]	0.53 [0.32; 0.89]	0.016	
Baseline KPS Score									
100-90	292	55 (18.8)	Not reached [-; -]	282	104 (36.9)	Not reached [84.3; -]	0.38 [0.28; 0.53]	< 0.001	0.712
80-70	60	14 (23.3)	Not reached [98.3; -]	58	26 (44.8)	48.1 [9.1; -]	0.30 [0.15; 0.60]	< 0.001	
IMDC Prognostic Status at Baseline									
Favorable	109	13 (11.9)	Not reached [-; -]	117	40 (34.2)	Not reached [84.3; -]	0.27 [0.14; 0.50]	< 0.001	0.382
Intermediate	208	49 (23.6)	Not reached [-; -]	185	74 (40.0)	94.9 [34.9; -]	0.43 [0.30; 0.62]	< 0.001	
Poor	33	7 (21.2)	Not reached [98.3; -]	35	15 (42.9)	21.0 [12.1; -]	0.23 [0.09; 0.62]	0.004	
IMDC Group Prognostic Status at Baseline									
Favorable	109	13 (11.9)	Not reached [-; -]	117	40 (34.2)	Not reached [84.3; -]	0.27 [0.14; 0.50]	< 0.001	0.277
Intermediate or Poor	241	56 (23.2)	Not reached [-; -]	220	89 (40.5)	94.9 [33.6; -]	0.40 [0.28; 0.56]	< 0.001	
SOC[g]: Endocrine disorders									
Age category									
<65	193	106 (54.9)	38.6 [27.1; 57.3]	215	63 (29.3)	128.9 [62.9; -]	1.92 [1.41; 2.63]	< 0.001	0.427
≥65	159	74	51.1	125	37	Not reached	1.58	0.024	

Study: KEYNOTE 581[a]	Pembrolizumab + Lenvatinib			Sunitinib			Pembrolizumab + Lenvatinib vs. Sunitinib		
Adverse Events	N[b]	Participants with Event n (%)	Median Time[c] in weeks [95 %-CI]	N[b]	Participants with Event n (%)	Median Time[c] in weeks [95 %-CI]	Hazard Ratio [95 %-CI][d]	p-Value[d,e]	p-Value for Interaction Test[f]
		(46.5)	[24.3; -]		(29.6)	[72.1; -]	[1.06; 2.34]		
Region									
Western Europe and North America	197	98 (49.7)	50.9 [27.1; 99.3]	189	50 (26.5)	Not reached [72.1; -]	1.94 [1.38; 2.73]	< 0.001	0.553
Rest of the World	155	82 (52.9)	38.6 [23.6; 93.1]	151	50 (33.1)	80.9 [62.9; -]	1.65 [1.16; 2.34]	0.005	
Gender									
Male	252	134 (53.2)	39.0 [27.1; 57.1]	260	74 (28.5)	128.9 [69.3; -]	1.90 [1.43; 2.52]	< 0.001	0.395
Female	100	46 (46.0)	62.1 [23.9; -]	80	26 (32.5)	Not reached [42.1; -]	1.47 [0.91; 2.37]	0.119	
Baseline KPS Score									
100-90	292	147 (50.3)	49.0 [27.9; 99.3]	282	81 (28.7)	128.9 [80.1; -]	1.83 [1.40; 2.40]	< 0.001	0.601
80-70	60	33 (55.0)	26.9 [15.6; 53.1]	58	19 (32.8)	45.0 [29.1; -]	1.55 [0.88; 2.74]	0.127	
IMDC Prognostic Status at Baseline									
Favorable	109	53 (48.6)	49.0 [26.1; -]	117	32 (27.4)	Not reached [105.3; -]	2.06 [1.32; 3.19]	0.001	0.626
Intermediate	208	110 (52.9)	35.3 [23.9; 57.3]	185	61 (33.0)	69.1 [51.1; -]	1.59 [1.16; 2.18]	0.004	
Poor	33	15 (45.5)	62.1 [19.9; -]	35	7 (20.0)	Not reached [33.1; -]	1.48 [0.59; 3.73]	0.406	
IMDC Group Prognostic Status at Baseline									
Favorable	109	53 (48.6)	49.0 [26.1; -]	117	32 (27.4)	Not reached [105.3; -]	2.06 [1.32; 3.19]	0.001	0.324
Intermediate or Poor	241	125 (51.9)	43.9 [27.1; 58.3]	220	68 (30.9)	69.1 [57.1; -]	1.58 [1.17; 2.13]	0.003	
SOC[g]: Eye disorders									
Age category									
<65	193	20 (10.4)	Not reached [-; -]	215	25 (11.6)	Not reached [-; -]	0.66 [0.37; 1.21]	0.179	0.275
≥65	159	15 (9.4)	Not reached [-; -]	125	22 (17.6)	Not reached [112.3; -]	0.40 [0.20; 0.77]	0.006	
Region									
Western Europe and North America	197	21 (10.7)	Not reached [-; -]	189	29 (15.3)	Not reached [-; -]	0.51 [0.29; 0.89]	0.019	0.686
Rest of the World	155	14 (9.0)	Not reached [-; -]	151	18 (11.9)	Not reached [-; -]	0.58 [0.29; 1.18]	0.132	
Gender									
Male	252	17 (6.7)	Not reached [-; -]	260	32 (12.3)	Not reached [-; -]	0.39 [0.22; 0.71]	0.002	0.197
Female	100	18 (18.0)	Not reached [-; -]	80	15 (18.8)	Not reached [-; -]	0.76 [0.38; 1.53]	0.444	

Study: KEYNOTE 581[a]	Pembrolizumab + Lenvatinib			Sunitinib			Pembrolizumab + Lenvatinib vs. Sunitinib		
Adverse Events	N[b]	Participants with Event n (%)	Median Time[c] in weeks [95 %-CI]	N[b]	Participants with Event n (%)	Median Time[c] in weeks [95 %-CI]	Hazard Ratio [95 %-CI][d]	p-Value[d,e]	p-Value for Interaction Test[f]
Baseline KPS Score									
100-90	292	31 (10.6)	Not reached [-; -]	282	44 (15.6)	Not reached [-; -]	0.51 [0.32; 0.82]	0.005	0.454
80-70	60	4 (6.7)	Not reached [-; -]	58	3 (5.2)	Not reached [-; -]	0.98 [0.21; 4.56]	0.975	
IMDC Prognostic Status at Baseline									
Favorable	109	9 (8.3)	Not reached [-; -]	117	16 (13.7)	Not reached [-; -]	0.49 [0.22; 1.12]	0.090	0.570
Intermediate	208	21 (10.1)	Not reached [-; -]	185	28 (15.1)	Not reached [-; -]	0.49 [0.27; 0.87]	0.014	
Poor	33	5 (15.2)	Not reached [-; -]	35	3 (8.6)	Not reached [33.7; -]	1.00 [0.23; 4.43]	> 0.999	
IMDC Group Prognostic Status at Baseline									
Favorable	109	9 (8.3)	Not reached [-; -]	117	16 (13.7)	Not reached [-; -]	0.49 [0.22; 1.12]	0.090	0.903
Intermediate or Poor	241	26 (10.8)	Not reached [-; -]	220	31 (14.1)	Not reached [-; -]	0.54 [0.32; 0.92]	0.023	
SOC[g]: Gastrointestinal disorders									
Age category									
<65	193	166 (86.0)	5.9 [4.3; 9.0]	215	175 (81.4)	2.3 [2.1; 3.1]	0.88 [0.71; 1.08]	0.222	0.302
≥65	159	139 (87.4)	5.7 [4.0; 10.1]	125	111 (88.8)	2.6 [2.1; 3.3]	0.70 [0.54; 0.90]	0.006	
Region									
Western Europe and North America	197	180 (91.4)	4.0 [3.0; 5.3]	189	167 (88.4)	2.1 [2.1; 2.4]	0.82 [0.66; 1.01]	0.058	0.956
Rest of the World	155	125 (80.6)	11.9 [6.6; 18.1]	151	119 (78.8)	7.9 [2.4; 9.4]	0.82 [0.64; 1.05]	0.122	
Gender									
Male	252	223 (88.5)	6.1 [4.9; 9.3]	260	216 (83.1)	2.9 [2.3; 3.4]	0.89 [0.74; 1.08]	0.241	0.053
Female	100	82 (82.0)	5.0 [2.7; 7.1]	80	70 (87.5)	2.1 [1.4; 2.4]	0.64 [0.46; 0.88]	0.006	
Baseline KPS Score									
100-90	292	257 (88.0)	5.1 [4.0; 6.7]	282	244 (86.5)	2.1 [2.1; 2.6]	0.79 [0.67; 0.95]	0.010	0.352
80-70	60	48 (80.0)	10.0 [4.9; 17.3]	58	42 (72.4)	9.4 [3.1; 11.7]	0.93 [0.61; 1.41]	0.730	
IMDC Prognostic Status at Baseline									
Favorable	109	95 (87.2)	5.0 [3.0; 8.3]	117	97 (82.9)	2.4 [2.0; 4.1]	0.90 [0.68; 1.19]	0.460	0.829
Intermediate	208	182 (87.5)	6.1 [5.1; 9.6]	185	158 (85.4)	2.4 [2.1; 3.1]	0.79 [0.64; 0.98]	0.035	
Poor	33	27	4.9	35	29	2.7	0.79	0.400	

Study: KEYNOTE 581[a]	Pembrolizumab + Lenvatinib			Sunitinib			Pembrolizumab + Lenvatinib vs. Sunitinib		
Adverse Events	N[b]	Participants with Event n (%)	Median Time[c] in weeks [95 %-CI]	N[b]	Participants with Event n (%)	Median Time[c] in weeks [95 %-CI]	Hazard Ratio [95 %-CI][d]	p-Value[d,e]	p-Value for Interaction Test[f]
		(81.8)	[2.0; 10.0]		(82.9)	[2.1; 9.4]	[0.46; 1.36]		
IMDC Group Prognostic Status at Baseline									
Favorable	109	95 (87.2)	5.0 [3.0; 8.3]	117	97 (82.9)	2.4 [2.0; 4.1]	0.90 [0.68; 1.19]	0.460	0.531
Intermediate or Poor	241	209 (86.7)	5.9 [4.9; 9.3]	220	187 (85.0)	2.5 [2.1; 3.1]	0.79 [0.65; 0.96]	0.019	
SOC[g]: Musculoskeletal and connective tissue disorders									
Age category									
<65	193	124 (64.2)	25.1 [15.0; 41.6]	215	100 (46.5)	60.3 [40.1; 80.4]	1.42 [1.09; 1.85]	0.009	0.620
≥65	159	104 (65.4)	30.4 [19.9; 42.6]	125	56 (44.8)	58.6 [46.9; 91.4]	1.54 [1.11; 2.13]	0.009	
Region									
Western Europe and North America	197	138 (70.1)	17.6 [8.9; 32.3]	189	95 (50.3)	46.9 [23.9; 59.7]	1.44 [1.11; 1.88]	0.006	0.802
Rest of the World	155	90 (58.1)	41.6 [29.6; 59.7]	151	61 (40.4)	91.4 [58.6; 125.1]	1.50 [1.09; 2.08]	0.014	
Gender									
Male	252	172 (68.3)	27.0 [14.6; 38.7]	260	123 (47.3)	59.3 [44.9; 75.3]	1.50 [1.19; 1.89]	< 0.001	0.812
Female	100	56 (56.0)	38.4 [18.1; 59.7]	80	33 (41.3)	78.3 [40.1; -]	1.41 [0.92; 2.17]	0.119	
Baseline KPS Score									
100-90	292	192 (65.8)	27.7 [17.6; 38.7]	282	131 (46.5)	60.3 [46.9; 82.3]	1.53 [1.22; 1.91]	< 0.001	0.348
80-70	60	36 (60.0)	39.1 [12.1; 60.1]	58	25 (43.1)	49.0 [21.1; -]	1.15 [0.69; 1.92]	0.600	
IMDC Prognostic Status at Baseline									
Favorable	109	69 (63.3)	34.3 [10.1; 48.9]	117	55 (47.0)	60.3 [46.9; 125.1]	1.57 [1.10; 2.23]	0.013	0.753
Intermediate	208	134 (64.4)	30.7 [20.0; 40.1]	185	86 (46.5)	51.0 [32.9; 80.4]	1.33 [1.02; 1.75]	0.038	
Poor	33	24 (72.7)	9.1 [2.6; 38.4]	35	15 (42.9)	18.1 [12.3; -]	1.71 [0.89; 3.31]	0.108	
IMDC Group Prognostic Status at Baseline									
Favorable	109	69 (63.3)	34.3 [10.1; 48.9]	117	55 (47.0)	60.3 [46.9; 125.1]	1.57 [1.10; 2.23]	0.013	0.555
Intermediate or Poor	241	158 (65.6)	27.6 [17.6; 39.1]	220	101 (45.9)	51.0 [32.6; 80.4]	1.37 [1.06; 1.76]	0.015	
SOC[g]: Nervous system disorders									
Age category									
<65	193	89 (46.1)	107.4 [59.0; -]	215	113 (52.6)	32.4 [8.7; 68.6]	0.65 [0.49; 0.86]	0.003	0.581
≥65	159	81	53.1	125	72	21.1	0.70	0.027	

Study: KEYNOTE 581[a]	Pembrolizumab + Lenvatinib			Sunitinib			Pembrolizumab + Lenvatinib vs. Sunitinib		
Adverse Events	N[b]	Participants with Event n (%)	Median Time[c] in weeks [95 %-CI]	N[b]	Participants with Event n (%)	Median Time[c] in weeks [95 %-CI]	Hazard Ratio [95 %-CI][d]	p-Value[d,e]	p-Value for Interaction Test[f]
		(50.9)	[36.4; 101.4]		(57.6)	[9.1; 51.1]	[0.51; 0.96]		
Region									
Western Europe and North America	197	107 (54.3)	48.4 [24.1; 78.3]	189	120 (63.5)	12.1 [6.1; 20.3]	0.65 [0.50; 0.84]	0.001	0.610
Rest of the World	155	63 (40.6)	Not reached [79.4; -]	151	65 (43.0)	Not reached [38.1; -]	0.72 [0.51; 1.02]	0.062	
Gender									
Male	252	122 (48.4)	79.1 [49.1; 129.0]	260	138 (53.1)	26.0 [12.1; 56.1]	0.69 [0.54; 0.88]	0.003	0.583
Female	100	48 (48.0)	61.1 [42.0; -]	80	47 (58.8)	16.7 [5.3; 68.3]	0.61 [0.40; 0.91]	0.016	
Baseline KPS Score									
100-90	292	138 (47.3)	93.4 [54.7; -]	282	160 (56.7)	21.4 [8.7; 40.9]	0.62 [0.49; 0.78]	< 0.001	0.065
80-70	60	32 (53.3)	30.0 [18.1; -]	58	25 (43.1)	79.7 [15.0; -]	1.04 [0.61; 1.76]	0.884	
IMDC Prognostic Status at Baseline									
Favorable	109	55 (50.5)	72.1 [36.6; -]	117	65 (55.6)	26.0 [6.0; 87.6]	0.72 [0.50; 1.03]	0.071	0.755
Intermediate	208	96 (46.2)	79.4 [50.7; -]	185	102 (55.1)	21.4 [9.1; 68.3]	0.64 [0.48; 0.85]	0.002	
Poor	33	19 (57.6)	42.4 [20.4; 93.4]	35	17 (48.6)	17.9 [5.3; -]	0.67 [0.34; 1.32]	0.242	
IMDC Group Prognostic Status at Baseline									
Favorable	109	55 (50.5)	72.1 [36.6; -]	117	65 (55.6)	26.0 [6.0; 87.6]	0.72 [0.50; 1.03]	0.071	0.747
Intermediate or Poor	241	115 (47.7)	78.3 [48.4; -]	220	119 (54.1)	21.4 [10.4; 56.1]	0.65 [0.50; 0.84]	0.001	
SOC[g]: Renal and urinary disorders									
Age category									
<65	193	79 (40.9)	116.7 [85.0; -]	215	43 (20.0)	Not reached [-; -]	1.78 [1.23; 2.59]	0.002	0.378
≥65	159	74 (46.5)	62.4 [36.1; -]	125	40 (32.0)	Not reached [-; -]	1.44 [0.98; 2.11]	0.064	
Gender									
Male	252	113 (44.8)	105.0 [60.9; -]	260	65 (25.0)	Not reached [-; -]	1.64 [1.21; 2.23]	0.002	0.781
Female	100	40 (40.0)	113.9 [57.0; -]	80	18 (22.5)	Not reached [75.1; -]	1.76 [1.01; 3.09]	0.046	

Study: KEYNOTE 581[a]	Pembrolizumab + Lenvatinib			Sunitinib			Pembrolizumab + Lenvatinib vs. Sunitinib		
Adverse Events	N[b]	Participants with Event n (%)	Median Time[c] in weeks [95 %-CI]	N[b]	Participants with Event n (%)	Median Time[c] in weeks [95 %-CI]	Hazard Ratio [95 %-CI][d]	p-Value[d,e]	p-Value for Interaction Test[f]
IMDC Prognostic Status at Baseline									
Favorable	109	45 (41.3)	116.7 [73.4; -]	117	23 (19.7)	Not reached [-; -]	2.13 [1.29; 3.53]	0.003	0.175
Intermediate	208	95 (45.7)	84.3 [60.0; -]	185	49 (26.5)	Not reached [101.7; -]	1.55 [1.10; 2.19]	0.013	
Poor	33	12 (36.4)	Not reached [46.1; -]	35	11 (31.4)	Not reached [15.1; -]	0.86 [0.37; 2.00]	0.725	
IMDC Group Prognostic Status at Baseline									
Favorable	109	45 (41.3)	116.7 [73.4; -]	117	23 (19.7)	Not reached [-; -]	2.13 [1.29; 3.53]	0.003	0.185
Intermediate or Poor	241	107 (44.4)	96.1 [60.3; -]	220	60 (27.3)	Not reached [101.7; -]	1.42 [1.03; 1.96]	0.030	
SOC[g]: Respiratory, thoracic and mediastinal disorders									
Age category									
<65	193	113 (58.5)	31.9 [15.7; 68.4]	215	85 (39.5)	94.1 [56.1; -]	1.59 [1.20; 2.11]	0.001	0.584
≥65	159	101 (63.5)	17.6 [9.1; 34.0]	125	48 (38.4)	Not reached [33.3; -]	1.81 [1.28; 2.56]	< 0.001	
Region									
Western Europe and North America	197	134 (68.0)	15.7 [9.1; 27.1]	189	80 (42.3)	63.4 [33.1; -]	1.84 [1.39; 2.43]	< 0.001	0.389
Rest of the World	155	80 (51.6)	49.9 [19.4; -]	151	53 (35.1)	Not reached [77.1; -]	1.54 [1.09; 2.18]	0.015	
Baseline KPS Score									
100-90	292	179 (61.3)	22.9 [13.6; 41.7]	282	112 (39.7)	Not reached [57.1; -]	1.73 [1.36; 2.19]	< 0.001	0.870
80-70	60	35 (58.3)	31.1 [14.6; 71.6]	58	21 (36.2)	94.1 [30.1; -]	1.62 [0.94; 2.80]	0.081	
IMDC Prognostic Status at Baseline									
Favorable	109	63 (57.8)	41.7 [13.9; 72.4]	117	49 (41.9)	94.1 [56.1; -]	1.52 [1.05; 2.21]	0.028	0.649
Intermediate	208	129 (62.0)	22.7 [14.3; 40.4]	185	71 (38.4)	125.1 [51.4; -]	1.78 [1.33; 2.38]	< 0.001	
Poor	33	21 (63.6)	13.0 [4.0; 79.4]	35	11 (31.4)	Not reached [15.0; -]	2.25 [1.08; 4.70]	0.031	
IMDC Group Prognostic Status at Baseline									
Favorable	109	63 (57.8)	41.7 [13.9; 72.4]	117	49 (41.9)	94.1 [56.1; -]	1.52 [1.05; 2.21]	0.028	0.442
Intermediate or Poor	241	150 (62.2)	21.1 [11.4; 31.9]	220	82 (37.3)	125.1 [51.4; -]	1.83 [1.40; 2.39]	< 0.001	
SOC[g]: Vascular disorders									

Study: KEYNOTE 581[a]	Pembrolizumab + Lenvatinib			Sunitinib			Pembrolizumab + Lenvatinib vs. Sunitinib		
Adverse Events	N[b]	Participants with Event n (%)	Median Time[c] in weeks [95 %-CI]	N[b]	Participants with Event n (%)	Median Time[c] in weeks [95 %-CI]	Hazard Ratio [95 %-CI][d]	p-Value[d,e]	p-Value for Interaction Test[f]
Age category									
<65	193	116 (60.1)	26.3 [13.7; 65.0]	215	91 (42.3)	92.9 [45.3; -]	1.36 [1.03; 1.79]	0.030	0.490
≥65	159	98 (61.6)	11.1 [5.3; 33.1]	125	65 (52.0)	27.1 [8.9; 105.1]	1.18 [0.86; 1.61]	0.308	
Region									
Western Europe and North America	197	137 (69.5)	9.0 [5.9; 14.0]	189	94 (49.7)	33.1 [15.7; 72.1]	1.37 [1.05; 1.78]	0.020	0.471
Rest of the World	155	77 (49.7)	57.1 [26.0; -]	151	62 (41.1)	105.1 [48.4; -]	1.18 [0.85; 1.66]	0.321	
Gender									
Male	252	157 (62.3)	19.0 [11.1; 42.1]	260	124 (47.7)	56.7 [27.1; 105.1]	1.27 [1.00; 1.60]	0.051	0.682
Female	100	57 (57.0)	14.0 [5.9; 55.3]	80	32 (40.0)	Not reached [19.0; -]	1.45 [0.94; 2.23]	0.096	
Baseline KPS Score									
100-90	292	180 (61.6)	18.0 [9.1; 35.3]	282	134 (47.5)	57.0 [27.1; -]	1.28 [1.02; 1.60]	0.030	0.756
80-70	60	34 (56.7)	19.0 [8.0; 126.9]	58	22 (37.9)	Not reached [26.6; -]	1.38 [0.80; 2.37]	0.248	
IMDC Prognostic Status at Baseline									
Favorable	109	66 (60.6)	18.6 [9.0; 49.7]	117	56 (47.9)	57.0 [9.6; -]	1.24 [0.87; 1.77]	0.242	0.423
Intermediate	208	125 (60.1)	15.1 [8.1; 57.1]	185	88 (47.6)	48.4 [19.0; -]	1.25 [0.95; 1.64]	0.110	
Poor	33	21 (63.6)	26.3 [5.1; 76.4]	35	10 (28.6)	Not reached [26.6; -]	1.87 [0.87; 4.05]	0.110	
IMDC Group Prognostic Status at Baseline									
Favorable	109	66 (60.6)	18.6 [9.0; 49.7]	117	56 (47.9)	57.0 [9.6; -]	1.24 [0.87; 1.77]	0.242	0.716
Intermediate or Poor	241	146 (60.6)	16.4 [9.0; 42.1]	220	98 (44.5)	64.0 [26.6; -]	1.32 [1.02; 1.71]	0.033	

a: Database Cutoff Date: 28AUG2020

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

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

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

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

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

g: 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; IMDC: International Metastatic Renal Cell Carcinoma Database Consortium; KPS: Karnofsky Performance Status; SOC: System Organ Class

Tabelle 4G-29: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für den Endpunkt Unerwünschte Ereignisse gesamt (PT) aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE 581[a]	Pembrolizumab + Lenvatinib			Sunitinib			Pembrolizumab + Lenvatinib vs. Sunitinib		
Adverse Events	N[b]	Participants with Event n (%)	Median Time[c] in weeks [95 %-CI]	N[b]	Participants with Event n (%)	Median Time[c] in weeks [95 %-CI]	Hazard Ratio [95 %-CI][d]	p-Value[d,e]	p-Value for Interaction Test[f]
SOC: Blood and lymphatic system disorders, PT[g]: Anaemia									
Age category									
<65	193	21 (10.9)	Not reached [-; -]	215	35 (16.3)	Not reached [-; -]	0.49 [0.28; 0.85]	0.011	0.683
≥65	159	22 (13.8)	Not reached [-; -]	125	31 (24.8)	Not reached [-; -]	0.45 [0.26; 0.78]	0.004	
Region									
Western Europe and North America	197	26 (13.2)	Not reached [-; -]	189	34 (18.0)	Not reached [-; -]	0.56 [0.34; 0.94]	0.030	0.465
Rest of the World	155	17 (11.0)	Not reached [-; -]	151	32 (21.2)	Not reached [-; -]	0.41 [0.23; 0.75]	0.003	
Gender									
Male	252	27 (10.7)	Not reached [-; -]	260	53 (20.4)	Not reached [-; -]	0.40 [0.25; 0.63]	< 0.001	0.081
Female	100	16 (16.0)	Not reached [-; -]	80	13 (16.3)	Not reached [-; -]	0.84 [0.40; 1.76]	0.642	
Baseline KPS Score									
100-90	292	34 (11.6)	Not reached [-; -]	282	46 (16.3)	Not reached [-; -]	0.58 [0.37; 0.90]	0.015	0.083
80-70	60	9 (15.0)	Not reached [-; -]	58	20 (34.5)	72.1 [48.1; -]	0.26 [0.12; 0.59]	0.001	
IMDC Prognostic Status at Baseline									
Favorable	109	8 (7.3)	Not reached [-; -]	117	13 (11.1)	Not reached [-; -]	0.54 [0.22; 1.30]	0.166	0.495
Intermediate	208	29 (13.9)	Not reached [-; -]	185	40 (21.6)	Not reached [-; -]	0.49 [0.30; 0.80]	0.004	
Poor	33	6 (18.2)	Not reached [-; -]	35	12 (34.3)	Not reached [12.3; -]	0.30 [0.11; 0.86]	0.025	
IMDC Group Prognostic Status at Baseline									
Favorable	109	8 (7.3)	Not reached [-; -]	117	13 (11.1)	Not reached [-; -]	0.54 [0.22; 1.30]	0.166	0.584
Intermediate or Poor	241	35 (14.5)	Not reached [-; -]	220	52 (23.6)	Not reached [-; -]	0.45 [0.29; 0.70]	< 0.001	
SOC: Blood and lymphatic system disorders, PT[g]: Leukopenia									
Age category									
<65	193	3 (1.6)	Not reached [-; -]	215	10 (4.7)	Not reached [-; -]	0.27 [0.07; 1.00]	0.051	0.283
≥65	159	2 (1.3)	Not reached [-; -]	125	14 (11.2)	Not reached [-; -]	0.10 [0.02; 0.42]	0.002	

Study: KEYNOTE 581[a]	Pembrolizumab + Lenvatinib			Sunitinib			Pembrolizumab + Lenvatinib vs. Sunitinib		
Adverse Events	N[b]	Participants with Event n (%)	Median Time[c] in weeks [95 %-CI]	N[b]	Participants with Event n (%)	Median Time[c] in weeks [95 %-CI]	Hazard Ratio [95 %-CI][d]	p-Value[d,e]	p-Value for Interaction Test[f]
Region									
Western Europe and North America	197	2 (1.0)	Not reached [-; -]	189	10 (5.3)	Not reached [-; -]	0.17 [0.04; 0.77]	0.022	0.935
Rest of the World	155	3 (1.9)	Not reached [-; -]	151	14 (9.3)	Not reached [-; -]	0.17 [0.05; 0.61]	0.006	
Gender									
Male	252	2 (0.8)	Not reached [-; -]	260	17 (6.5)	Not reached [-; -]	0.10 [0.02; 0.45]	0.002	0.288
Female	100	3 (3.0)	Not reached [-; -]	80	7 (8.8)	Not reached [-; -]	0.29 [0.08; 1.14]	0.077	
Baseline KPS Score									
100-90	292	3 (1.0)	Not reached [-; -]	282	16 (5.7)	Not reached [-; -]	0.16 [0.05; 0.56]	0.004	0.831
80-70	60	2 (3.3)	Not reached [-; -]	58	8 (13.8)	Not reached [78.4; -]	0.15 [0.03; 0.73]	0.019	
IMDC Prognostic Status at Baseline									
Favorable	109	1 (0.9)	Not reached [-; -]	117	6 (5.1)	Not reached [-; -]	0.17 [0.02; 1.39]	0.099	0.299
Intermediate	208	4 (1.9)	Not reached [-; -]	185	13 (7.0)	Not reached [-; -]	0.22 [0.07; 0.68]	0.008	
Poor	33	0 (0.0)	Not reached [-; -]	35	5 (14.3)	Not reached [-; -]	n.a. [n.a.; n.a.]	0.012	
IMDC Group Prognostic Status at Baseline									
Favorable	109	1 (0.9)	Not reached [-; -]	117	6 (5.1)	Not reached [-; -]	0.17 [0.02; 1.39]	0.099	0.991
Intermediate or Poor	241	4 (1.7)	Not reached [-; -]	220	18 (8.2)	Not reached [-; -]	0.16 [0.05; 0.47]	< 0.001	
SOC: Blood and lymphatic system disorders, PTs[g]: Neutropenia									
Age category									
<65	193	5 (2.6)	Not reached [-; -]	215	27 (12.6)	Not reached [-; -]	0.17 [0.07; 0.45]	< 0.001	0.780
≥65	159	4 (2.5)	Not reached [-; -]	125	19 (15.2)	Not reached [-; -]	0.13 [0.04; 0.38]	< 0.001	
Region									
Western Europe and North America	197	3 (1.5)	Not reached [-; -]	189	18 (9.5)	Not reached [-; -]	0.13 [0.04; 0.44]	0.001	0.752
Rest of the World	155	6 (3.9)	Not reached [-; -]	151	28 (18.5)	Not reached [-; -]	0.17 [0.07; 0.41]	< 0.001	
Gender									
Male	252	4 (1.6)	Not reached [-; -]	260	34 (13.1)	Not reached [-; -]	0.09 [0.03; 0.27]	< 0.001	0.149
Female	100	5 (5.0)	Not reached [-; -]	80	12 (15.0)	Not reached [-; -]	0.29 [0.10; 0.83]	0.021	

Study: KEYNOTE 581[a]	Pembrolizumab + Lenvatinib			Sunitinib			Pembrolizumab + Lenvatinib vs. Sunitinib		
Adverse Events	N[b]	Participants with Event n (%)	Median Time[c] in weeks [95 %-CI]	N[b]	Participants with Event n (%)	Median Time[c] in weeks [95 %-CI]	Hazard Ratio [95 %-CI][d]	p-Value[d,e]	p-Value for Interaction Test[f]
Baseline KPS Score									
100-90	292	7 (2.4)	Not reached [-; -]	282	37 (13.1)	Not reached [-; -]	0.15 [0.07; 0.34]	< 0.001	0.960
80-70	60	2 (3.3)	Not reached [-; -]	58	9 (15.5)	Not reached [-; -]	0.14 [0.03; 0.67]	0.014	
IMDC Prognostic Status at Baseline									
Favorable	109	3 (2.8)	Not reached [-; -]	117	17 (14.5)	Not reached [-; -]	0.17 [0.05; 0.57]	0.004	0.536
Intermediate	208	6 (2.9)	Not reached [-; -]	185	25 (13.5)	Not reached [-; -]	0.16 [0.07; 0.40]	< 0.001	
Poor	33	0 (0.0)	Not reached [-; -]	35	3 (8.6)	Not reached [-; -]	n.a. [n.a.; n.a.]	0.090	
IMDC Group Prognostic Status at Baseline									
Favorable	109	3 (2.8)	Not reached [-; -]	117	17 (14.5)	Not reached [-; -]	0.17 [0.05; 0.57]	0.004	0.899
Intermediate or Poor	241	6 (2.5)	Not reached [-; -]	220	28 (12.7)	Not reached [-; -]	0.15 [0.06; 0.36]	< 0.001	
SOC: Blood and lymphatic system disorders, PT[g]: Thrombocytopenia									
Age category									
<65	193	6 (3.1)	Not reached [-; -]	215	33 (15.3)	Not reached [-; -]	0.17 [0.07; 0.40]	< 0.001	0.305
≥65	159	9 (5.7)	Not reached [-; -]	125	20 (16.0)	Not reached [-; -]	0.31 [0.14; 0.69]	0.004	
Region									
Western Europe and North America	197	8 (4.1)	Not reached [-; -]	189	34 (18.0)	Not reached [-; -]	0.19 [0.09; 0.40]	< 0.001	0.378
Rest of the World	155	7 (4.5)	Not reached [-; -]	151	19 (12.6)	Not reached [-; -]	0.32 [0.13; 0.76]	0.010	
Gender									
Male	252	9 (3.6)	Not reached [-; -]	260	38 (14.6)	Not reached [-; -]	0.20 [0.10; 0.42]	< 0.001	0.621
Female	100	6 (6.0)	Not reached [-; -]	80	15 (18.8)	Not reached [-; -]	0.29 [0.11; 0.74]	0.010	
Baseline KPS Score									
100-90	292	11 (3.8)	Not reached [-; -]	282	41 (14.5)	Not reached [-; -]	0.22 [0.12; 0.44]	< 0.001	0.783
80-70	60	4 (6.7)	Not reached [-; -]	58	12 (20.7)	Not reached [-; -]	0.24 [0.08; 0.76]	0.016	

Study: KEYNOTE 581[a]	Pembrolizumab + Lenvatinib			Sunitinib			Pembrolizumab + Lenvatinib vs. Sunitinib		
Adverse Events	N[b]	Participants with Event n (%)	Median Time[c] in weeks [95 %-CI]	N[b]	Participants with Event n (%)	Median Time[c] in weeks [95 %-CI]	Hazard Ratio [95 %-CI][d]	p-Value[d,e]	p-Value for Interaction Test[f]
IMDC Prognostic Status at Baseline									
Favorable	109	3 (2.8)	Not reached [-; -]	117	21 (17.9)	Not reached [-; -]	0.13 [0.04; 0.45]	0.001	0.141
Intermediate	208	12 (5.8)	Not reached [-; -]	185	27 (14.6)	Not reached [-; -]	0.34 [0.17; 0.67]	0.002	
Poor	33	0 (0.0)	Not reached [-; -]	35	4 (11.4)	Not reached [-; -]	n.a. [n.a.; n.a.]	0.030	
IMDC Group Prognostic Status at Baseline									
Favorable	109	3 (2.8)	Not reached [-; -]	117	21 (17.9)	Not reached [-; -]	0.13 [0.04; 0.45]	0.001	0.234
Intermediate or Poor	241	12 (5.0)	Not reached [-; -]	220	31 (14.1)	Not reached [-; -]	0.30 [0.15; 0.58]	< 0.001	
SOC: Endocrine disorders, PT[g]: Adrenal insufficiency									
Age category									
<65	193	12 (6.2)	Not reached [-; -]	215	0 (0.0)	Not reached [-; -]	n.a. [n.a.; n.a.]	0.002	0.998
≥65	159	5 (3.1)	Not reached [-; -]	125	0 (0.0)	Not reached [-; -]	n.a. [n.a.; n.a.]	0.105	
Region									
Western Europe and North America	197	10 (5.1)	Not reached [-; -]	189	0 (0.0)	Not reached [-; -]	n.a. [n.a.; n.a.]	0.017	0.998
Rest of the World	155	7 (4.5)	Not reached [-; -]	151	0 (0.0)	Not reached [-; -]	n.a. [n.a.; n.a.]	0.018	
Gender									
Male	252	15 (6.0)	Not reached [-; -]	260	0 (0.0)	Not reached [-; -]	n.a. [n.a.; n.a.]	0.001	0.998
Female	100	2 (2.0)	Not reached [-; -]	80	0 (0.0)	Not reached [-; -]	n.a. [n.a.; n.a.]	0.280	
Baseline KPS Score									
100-90	292	13 (4.5)	Not reached [-; -]	282	0 (0.0)	Not reached [-; -]	n.a. [n.a.; n.a.]	0.002	0.998
80-70	60	4 (6.7)	Not reached [-; -]	58	0 (0.0)	Not reached [-; -]	n.a. [n.a.; n.a.]	0.163	
IMDC Prognostic Status at Baseline									
Favorable	109	6 (5.5)	n.c.	117	0 (0.0)	n.c.	n.c.	n.c.	n.c.
Intermediate	208	9 (4.3)	n.c.	185	0 (0.0)	n.c.	n.c.	n.c.	
Poor	33	2 (6.1)	n.c.	35	0 (0.0)	n.c.	n.c.	n.c.	

Study: KEYNOTE 581[a]	Pembrolizumab + Lenvatinib			Sunitinib			Pembrolizumab + Lenvatinib vs. Sunitinib		
Adverse Events	N[b]	Participants with Event n (%)	Median Time[c] in weeks [95 %-CI]	N[b]	Participants with Event n (%)	Median Time[c] in weeks [95 %-CI]	Hazard Ratio [95 %-CI][d]	p-Value[d,e]	p-Value for Interaction Test[f]
IMDC Group Prognostic Status at Baseline									
Favorable	109	6 (5.5)	Not reached [-; -]	117	0 (0.0)	Not reached [-; -]	n.a. [n.a.; n.a.]	0.020	0.998
Intermediate or Poor	241	11 (4.6)	Not reached [-; -]	220	0 (0.0)	Not reached [-; -]	n.a. [n.a.; n.a.]	0.012	
SOC: Endocrine disorders, PT[g]: Hypothyroidism									
Age category									
<65	193	99 (51.3)	50.9 [31.6; -]	215	56 (26.0)	Not reached [80.9; -]	1.94 [1.40; 2.69]	< 0.001	0.378
≥65	159	67 (42.1)	Not reached [34.0; -]	125	34 (27.2)	Not reached [80.1; -]	1.55 [1.03; 2.35]	0.037	
Region									
Western Europe and North America	197	92 (46.7)	57.3 [32.9; -]	189	43 (22.8)	Not reached [128.9; -]	2.11 [1.47; 3.03]	< 0.001	0.230
Rest of the World	155	74 (47.7)	54.1 [32.9; -]	151	47 (31.1)	105.3 [69.0; -]	1.51 [1.05; 2.17]	0.028	
Gender									
Male	252	122 (48.4)	53.6 [33.9; -]	260	68 (26.2)	Not reached [80.9; -]	1.82 [1.35; 2.45]	< 0.001	0.767
Female	100	44 (44.0)	67.1 [26.9; -]	80	22 (27.5)	Not reached [54.3; -]	1.66 [0.99; 2.77]	0.052	
Baseline KPS Score									
100-90	292	135 (46.2)	77.1 [36.0; -]	282	71 (25.2)	Not reached [128.9; -]	1.89 [1.42; 2.52]	< 0.001	0.323
80-70	60	31 (51.7)	41.0 [16.3; 62.1]	58	19 (32.8)	45.0 [29.1; -]	1.35 [0.76; 2.40]	0.306	
IMDC Prognostic Status at Baseline									
Favorable	109	48 (44.0)	Not reached [27.9; -]	117	29 (24.8)	Not reached [128.9; -]	2.05 [1.29; 3.25]	0.002	0.664
Intermediate	208	102 (49.0)	51.1 [31.6; -]	185	55 (29.7)	80.9 [57.1; -]	1.57 [1.13; 2.18]	0.007	
Poor	33	14 (42.4)	93.1 [19.9; -]	35	6 (17.1)	Not reached [33.1; -]	1.61 [0.60; 4.27]	0.342	
IMDC Group Prognostic Status at Baseline									
Favorable	109	48 (44.0)	Not reached [27.9; -]	117	29 (24.8)	Not reached [128.9; -]	2.05 [1.29; 3.25]	0.002	0.364
Intermediate or Poor	241	116 (48.1)	53.6 [33.9; -]	220	61 (27.7)	Not reached [64.6; -]	1.57 [1.15; 2.15]	0.004	
SOC: Eye disorders, PT[g]: Eyelid oedema									

Study: KEYNOTE 581[a]	Pembrolizumab + Lenvatinib			Sunitinib			Pembrolizumab + Lenvatinib vs. Sunitinib		
Adverse Events	N[b]	Participants with Event n (%)	Median Time[c] in weeks [95 %-CI]	N[b]	Participants with Event n (%)	Median Time[c] in weeks [95 %-CI]	Hazard Ratio [95 %-CI][d]	p-Value[d,e]	p-Value for Interaction Test[f]
Age category									
<65	193	1 (0.5)	n.c.	215	7 (3.3)	n.c.	n.c.	n.c.	n.c.
≥65	159	0 (0.0)	n.c.	125	3 (2.4)	n.c.	n.c.	n.c.	
Region									
Western Europe and North America	197	1 (0.5)	n.c.	189	5 (2.6)	n.c.	n.c.	n.c.	n.c.
Rest of the World	155	0 (0.0)	n.c.	151	5 (3.3)	n.c.	n.c.	n.c.	
Gender									
Male	252	1 (0.4)	n.c.	260	6 (2.3)	n.c.	n.c.	n.c.	n.c.
Female	100	0 (0.0)	n.c.	80	4 (5.0)	n.c.	n.c.	n.c.	
IMDC Prognostic Status at Baseline									
Favorable	109	0 (0.0)	n.c.	117	3 (2.6)	n.c.	n.c.	n.c.	n.c.
Intermediate	208	1 (0.5)	n.c.	185	7 (3.8)	n.c.	n.c.	n.c.	
Poor	33	0 (0.0)	n.c.	35	0 (0.0)	n.c.	n.c.	n.c.	
IMDC Group Prognostic Status at Baseline									
Favorable	109	0 (0.0)	n.c.	117	3 (2.6)	n.c.	n.c.	n.c.	n.c.
Intermediate or Poor	241	1 (0.4)	n.c.	220	7 (3.2)	n.c.	n.c.	n.c.	
SOC: Gastrointestinal disorders, PT[g]: Abdominal pain									
Age category									
<65	193	41 (21.2)	Not reached [-; -]	215	17 (7.9)	Not reached [-; -]	2.27 [1.29; 4.00]	0.005	0.868
≥65	159	33 (20.8)	Not reached [-; -]	125	11 (8.8)	Not reached [-; -]	2.13 [1.07; 4.21]	0.030	
Region									
Western Europe and North America	197	48 (24.4)	Not reached [-; -]	189	16 (8.5)	Not reached [-; -]	2.55 [1.44; 4.49]	0.001	0.488
Rest of the World	155	26 (16.8)	Not reached [-; -]	151	12 (7.9)	Not reached [-; -]	1.82 [0.92; 3.62]	0.086	
Gender									
Male	252	55 (21.8)	Not reached [-; -]	260	19 (7.3)	Not reached [-; -]	2.62 [1.55; 4.42]	< 0.001	0.250
Female	100	19 (19.0)	Not reached [-; -]	80	9 (11.3)	Not reached [-; -]	1.47 [0.66; 3.26]	0.341	

Study: KEYNOTE 581[a]	Pembrolizumab + Lenvatinib			Sunitinib			Pembrolizumab + Lenvatinib vs. Sunitinib		
Adverse Events	N[b]	Participants with Event n (%)	Median Time[c] in weeks [95 %-CI]	N[b]	Participants with Event n (%)	Median Time[c] in weeks [95 %-CI]	Hazard Ratio [95 %-CI][d]	p-Value[d,e]	p-Value for Interaction Test[f]
Baseline KPS Score									
100-90	292	65 (22.3)	Not reached [-; -]	282	23 (8.2)	Not reached [-; -]	2.42 [1.50; 3.90]	< 0.001	0.368
80-70	60	9 (15.0)	Not reached [-; -]	58	5 (8.6)	Not reached [-; -]	1.43 [0.48; 4.31]	0.523	
IMDC Prognostic Status at Baseline									
Favorable	109	22 (20.2)	Not reached [-; -]	117	9 (7.7)	Not reached [-; -]	2.42 [1.11; 5.26]	0.026	0.856
Intermediate	208	41 (19.7)	Not reached [-; -]	185	14 (7.6)	Not reached [-; -]	2.29 [1.24; 4.21]	0.008	
Poor	33	11 (33.3)	Not reached [48.4; -]	35	5 (14.3)	Not reached [-; -]	1.62 [0.55; 4.78]	0.380	
IMDC Group Prognostic Status at Baseline									
Favorable	109	22 (20.2)	Not reached [-; -]	117	9 (7.7)	Not reached [-; -]	2.42 [1.11; 5.26]	0.026	0.732
Intermediate or Poor	241	52 (21.6)	Not reached [-; -]	220	19 (8.6)	Not reached [-; -]	2.12 [1.25; 3.60]	0.005	
SOC: Gastrointestinal disorders, PT[g]: Dry mouth									
Age category									
<65	193	22 (11.4)	Not reached [-; -]	215	7 (3.3)	Not reached [-; -]	3.08 [1.31; 7.22]	0.010	0.773
≥65	159	14 (8.8)	Not reached [-; -]	125	4 (3.2)	Not reached [-; -]	2.46 [0.81; 7.50]	0.113	
Region									
Western Europe and North America	197	28 (14.2)	Not reached [-; -]	189	8 (4.2)	Not reached [-; -]	2.93 [1.33; 6.44]	0.008	0.750
Rest of the World	155	8 (5.2)	Not reached [-; -]	151	3 (2.0)	Not reached [-; -]	2.39 [0.63; 9.01]	0.200	
Gender									
Male	252	27 (10.7)	Not reached [-; -]	260	7 (2.7)	Not reached [-; -]	3.38 [1.47; 7.77]	0.004	0.317
Female	100	9 (9.0)	Not reached [-; -]	80	4 (5.0)	Not reached [-; -]	1.71 [0.53; 5.56]	0.373	
Baseline KPS Score									
100-90	292	28 (9.6)	Not reached [-; -]	282	8 (2.8)	Not reached [-; -]	3.01 [1.37; 6.62]	0.006	0.698
80-70	60	8 (13.3)	Not reached [-; -]	58	3 (5.2)	129.1 [129.1; -]	2.24 [0.59; 8.49]	0.235	

Study: KEYNOTE 581[a]	Pembrolizumab + Lenvatinib			Sunitinib			Pembrolizumab + Lenvatinib vs. Sunitinib		
Adverse Events	N[b]	Participants with Event n (%)	Median Time[c] in weeks [95 %-CI]	N[b]	Participants with Event n (%)	Median Time[c] in weeks [95 %-CI]	Hazard Ratio [95 %-CI][d]	p-Value[d,e]	p-Value for Interaction Test[f]
IMDC Prognostic Status at Baseline									
Favorable	109	13 (11.9)	Not reached [-; -]	117	3 (2.6)	Not reached [-; -]	4.49 [1.28; 15.78]	0.019	0.527
Intermediate	208	18 (8.7)	Not reached [-; -]	185	7 (3.8)	Not reached [129.1; -]	1.92 [0.80; 4.61]	0.145	
Poor	33	4 (12.1)	Not reached [-; -]	35	1 (2.9)	Not reached [-; -]	3.62 [0.40; 32.53]	0.251	
IMDC Group Prognostic Status at Baseline									
Favorable	109	13 (11.9)	Not reached [-; -]	117	3 (2.6)	Not reached [-; -]	4.49 [1.28; 15.78]	0.019	0.290
Intermediate or Poor	241	22 (9.1)	Not reached [-; -]	220	8 (3.6)	Not reached [-; -]	2.10 [0.93; 4.74]	0.074	
SOC: Gastrointestinal disorders, PT[g]: Dyspepsia									
Age category									
<65	193	23 (11.9)	Not reached [-; -]	215	32 (14.9)	Not reached [141.1; -]	0.64 [0.38; 1.11]	0.111	0.304
≥65	159	16 (10.1)	Not reached [-; -]	125	23 (18.4)	Not reached [-; -]	0.43 [0.23; 0.82]	0.011	
Region									
Western Europe and North America	197	28 (14.2)	Not reached [-; -]	189	35 (18.5)	Not reached [-; -]	0.59 [0.35; 0.97]	0.037	0.537
Rest of the World	155	11 (7.1)	Not reached [-; -]	151	20 (13.2)	141.1 [141.1; -]	0.48 [0.23; 1.02]	0.056	
Gender									
Male	252	29 (11.5)	Not reached [-; -]	260	44 (16.9)	Not reached [141.1; -]	0.53 [0.33; 0.85]	0.009	0.765
Female	100	10 (10.0)	Not reached [-; -]	80	11 (13.8)	Not reached [-; -]	0.61 [0.26; 1.45]	0.265	
Baseline KPS Score									
100-90	292	37 (12.7)	Not reached [-; -]	282	50 (17.7)	Not reached [141.1; -]	0.58 [0.38; 0.90]	0.014	0.408
80-70	60	2 (3.3)	Not reached [-; -]	58	5 (8.6)	Not reached [-; -]	0.28 [0.05; 1.49]	0.136	
SOC: Gastrointestinal disorders, PT[g]: Gastrooesophageal reflux disease									
Age category									
<65	193	9 (4.7)	Not reached [-; -]	215	20 (9.3)	Not reached [-; -]	0.41 [0.19; 0.92]	0.030	0.795
≥65	159	7 (4.4)	Not reached [-; -]	125	10 (8.0)	Not reached [-; -]	0.46 [0.17; 1.22]	0.118	

Study: KEYNOTE 581[a]	Pembrolizumab + Lenvatinib			Sunitinib			Pembrolizumab + Lenvatinib vs. Sunitinib		
Adverse Events	N[b]	Participants with Event n (%)	Median Time[c] in weeks [95 %-CI]	N[b]	Participants with Event n (%)	Median Time[c] in weeks [95 %-CI]	Hazard Ratio [95 %-CI][d]	p-Value[d,e]	p-Value for Interaction Test[f]
Region									
Western Europe and North America	197	15 (7.6)	Not reached [-; -]	189	24 (12.7)	Not reached [-; -]	0.47 [0.25; 0.90]	0.024	0.212
Rest of the World	155	1 (0.6)	Not reached [-; -]	151	6 (4.0)	Not reached [-; -]	0.16 [0.02; 1.30]	0.086	
Gender									
Male	252	11 (4.4)	Not reached [-; -]	260	20 (7.7)	Not reached [-; -]	0.46 [0.22; 0.97]	0.043	0.653
Female	100	5 (5.0)	Not reached [-; -]	80	10 (12.5)	Not reached [-; -]	0.35 [0.12; 1.03]	0.057	
Baseline KPS Score									
100-90	292	12 (4.1)	Not reached [-; -]	282	26 (9.2)	Not reached [-; -]	0.38 [0.19; 0.76]	0.006	0.339
80-70	60	4 (6.7)	Not reached [-; -]	58	4 (6.9)	Not reached [-; -]	0.63 [0.15; 2.58]	0.522	
IMDC Prognostic Status at Baseline									
Favorable	109	4 (3.7)	Not reached [-; -]	117	14 (12.0)	Not reached [-; -]	0.27 [0.09; 0.83]	0.022	0.339
Intermediate	208	9 (4.3)	Not reached [-; -]	185	13 (7.0)	Not reached [-; -]	0.51 [0.22; 1.20]	0.121	
Poor	33	3 (9.1)	Not reached [-; -]	35	2 (5.7)	Not reached [-; -]	0.89 [0.14; 5.80]	0.907	
IMDC Group Prognostic Status at Baseline									
Favorable	109	4 (3.7)	Not reached [-; -]	117	14 (12.0)	Not reached [-; -]	0.27 [0.09; 0.83]	0.022	0.227
Intermediate or Poor	241	12 (5.0)	Not reached [-; -]	220	15 (6.8)	Not reached [-; -]	0.57 [0.27; 1.23]	0.155	
SOC: Gastrointestinal disorders, PT[g]: Stomatitis									
Age category									
<65	193	69 (35.8)	Not reached [125.9; -]	215	80 (37.2)	Not reached [104.6; -]	0.77 [0.56; 1.06]	0.111	0.522
≥65	159	53 (33.3)	Not reached [-; -]	125	51 (40.8)	136.7 [15.9; -]	0.69 [0.47; 1.02]	0.063	
Region									
Western Europe and North America	197	84 (42.6)	Not reached [54.1; -]	189	89 (47.1)	104.6 [15.6; -]	0.72 [0.53; 0.98]	0.034	0.962
Rest of the World	155	38 (24.5)	Not reached [125.9; -]	151	42 (27.8)	Not reached [-; -]	0.75 [0.48; 1.17]	0.205	
Gender									
Male	252	85 (33.7)	Not reached [-; -]	260	93 (35.8)	Not reached [112.1; -]	0.80 [0.59; 1.07]	0.129	0.303
Female	100	37 (37.0)	125.9 [48.3; -]	80	38 (47.5)	136.7 [4.1; -]	0.59 [0.37; 0.93]	0.024	

Study: KEYNOTE 581[a]	Pembrolizumab + Lenvatinib			Sunitinib			Pembrolizumab + Lenvatinib vs. Sunitinib		
Adverse Events	N[b]	Participants with Event n (%)	Median Time[c] in weeks [95 %-CI]	N[b]	Participants with Event n (%)	Median Time[c] in weeks [95 %-CI]	Hazard Ratio [95 %-CI][d]	p-Value[d,e]	p-Value for Interaction Test[f]
Baseline KPS Score									
100-90	292	105 (36.0)	Not reached [125.9; -]	282	110 (39.0)	136.7 [112.1; -]	0.77 [0.59; 1.01]	0.057	0.534
80-70	60	17 (28.3)	Not reached [-; -]	58	21 (36.2)	Not reached [15.1; -]	0.57 [0.30; 1.10]	0.093	
IMDC Prognostic Status at Baseline									
Favorable	109	40 (36.7)	Not reached [104.9; -]	117	52 (44.4)	112.1 [18.1; -]	0.67 [0.44; 1.01]	0.055	0.684
Intermediate	208	70 (33.7)	Not reached [-; -]	185	66 (35.7)	136.7 [136.7; -]	0.79 [0.56; 1.11]	0.169	
Poor	33	12 (36.4)	Not reached [26.9; -]	35	11 (31.4)	Not reached [15.1; -]	0.98 [0.43; 2.25]	0.971	
IMDC Group Prognostic Status at Baseline									
Favorable	109	40 (36.7)	Not reached [104.9; -]	117	52 (44.4)	112.1 [18.1; -]	0.67 [0.44; 1.01]	0.055	0.455
Intermediate or Poor	241	82 (34.0)	Not reached [-; -]	220	77 (35.0)	136.7 [136.7; -]	0.81 [0.59; 1.11]	0.192	
SOC: General disorders and administration site conditions, PT[g]: Face oedema									
Age category									
<65	193	3 (1.6)	Not reached [-; -]	215	9 (4.2)	Not reached [-; -]	0.32 [0.09; 1.19]	0.089	0.810
≥65	159	1 (0.6)	Not reached [-; -]	125	3 (2.4)	Not reached [-; -]	0.22 [0.02; 2.13]	0.191	
Region									
Western Europe and North America	197	1 (0.5)	n.c.	189	7 (3.7)	n.c.	n.c.	n.c.	n.c.
Rest of the World	155	3 (1.9)	n.c.	151	5 (3.3)	n.c.	n.c.	n.c.	
Gender									
Male	252	3 (1.2)	Not reached [-; -]	260	9 (3.5)	Not reached [-; -]	0.29 [0.08; 1.06]	0.061	0.888
Female	100	1 (1.0)	Not reached [-; -]	80	3 (3.8)	Not reached [-; -]	0.25 [0.03; 2.37]	0.225	
Baseline KPS Score									
100-90	292	3 (1.0)	Not reached [-; -]	282	11 (3.9)	Not reached [-; -]	0.24 [0.07; 0.85]	0.028	0.448
80-70	60	1 (1.7)	Not reached [-; -]	58	1 (1.7)	Not reached [-; -]	0.54 [0.03; 8.98]	0.671	

Study: KEYNOTE 581[a]	Pembrolizumab + Lenvatinib			Sunitinib			Pembrolizumab + Lenvatinib vs. Sunitinib		
Adverse Events	N[b]	Participants with Event n (%)	Median Time[c] in weeks [95 %-CI]	N[b]	Participants with Event n (%)	Median Time[c] in weeks [95 %-CI]	Hazard Ratio [95 %-CI][d]	p-Value[d,e]	p-Value for Interaction Test[f]
IMDC Prognostic Status at Baseline									
Favorable	109	1 (0.9)	n.c.	117	6 (5.1)	n.c.	n.c.	n.c.	n.c.
Intermediate	208	2 (1.0)	n.c.	185	5 (2.7)	n.c.	n.c.	n.c.	
Poor	33	1 (3.0)	n.c.	35	1 (2.9)	n.c.	n.c.	n.c.	
IMDC Group Prognostic Status at Baseline									
Favorable	109	1 (0.9)	n.c.	117	6 (5.1)	n.c.	n.c.	n.c.	n.c.
Intermediate or Poor	241	3 (1.2)	n.c.	220	6 (2.7)	n.c.	n.c.	n.c.	
SOC: Hepatobiliary disorders, PTg: Jaundice									
Age category									
<65	193	0 (0.0)	n.c.	215	4 (1.9)	n.c.	n.c.	n.c.	n.c.
≥65	159	0 (0.0)	n.c.	125	7 (5.6)	n.c.	n.c.	n.c.	
Region									
Western Europe and North America	197	0 (0.0)	n.c.	189	7 (3.7)	n.c.	n.c.	n.c.	n.c.
Rest of the World	155	0 (0.0)	n.c.	151	4 (2.6)	n.c.	n.c.	n.c.	
Gender									
Male	252	0 (0.0)	n.c.	260	8 (3.1)	n.c.	n.c.	n.c.	n.c.
Female	100	0 (0.0)	n.c.	80	3 (3.8)	n.c.	n.c.	n.c.	
Baseline KPS Score									
100-90	292	0 (0.0)	n.c.	282	8 (2.8)	n.c.	n.c.	n.c.	n.c.
80-70	60	0 (0.0)	n.c.	58	3 (5.2)	n.c.	n.c.	n.c.	
IMDC Prognostic Status at Baseline									
Favorable	109	0 (0.0)	n.c.	117	2 (1.7)	n.c.	n.c.	n.c.	n.c.
Intermediate	208	0 (0.0)	n.c.	185	9 (4.9)	n.c.	n.c.	n.c.	
Poor	33	0 (0.0)	n.c.	35	0 (0.0)	n.c.	n.c.	n.c.	

Study: KEYNOTE 581[a]	Pembrolizumab + Lenvatinib			Sunitinib			Pembrolizumab + Lenvatinib vs. Sunitinib		
Adverse Events	N[b]	Participants with Event n (%)	Median Time[c] in weeks [95 %-CI]	N[b]	Participants with Event n (%)	Median Time[c] in weeks [95 %-CI]	Hazard Ratio [95 %-CI][d]	p-Value[d,e]	p-Value for Interaction Test[f]
IMDC Group Prognostic Status at Baseline									
Favorable	109	0 (0.0)	n.c.	117	2 (1.7)	n.c.	n.c.	n.c.	n.c.
Intermediate or Poor	241	0 (0.0)	n.c.	220	9 (4.1)	n.c.	n.c.	n.c.	
SOC: Investigations, PT[g]: Amylase increased									
Age category									
<65	193	35 (18.1)	Not reached [-; -]	215	16 (7.4)	Not reached [-; -]	2.05 [1.13; 3.71]	0.018	0.618
≥65	159	28 (17.6)	Not reached [-; -]	125	12 (9.6)	Not reached [-; -]	1.69 [0.86; 3.32]	0.131	
Region									
Western Europe and North America	197	41 (20.8)	Not reached [-; -]	189	18 (9.5)	Not reached [-; -]	1.93 [1.10; 3.37]	0.021	0.995
Rest of the World	155	22 (14.2)	Not reached [-; -]	151	10 (6.6)	Not reached [-; -]	1.85 [0.88; 3.93]	0.106	
Gender									
Male	252	48 (19.0)	Not reached [-; -]	260	23 (8.8)	Not reached [-; -]	1.87 [1.14; 3.08]	0.014	0.796
Female	100	15 (15.0)	Not reached [-; -]	80	5 (6.3)	Not reached [-; -]	2.13 [0.77; 5.91]	0.145	
Baseline KPS Score									
100-90	292	52 (17.8)	Not reached [-; -]	282	23 (8.2)	Not reached [-; -]	1.96 [1.20; 3.20]	0.008	0.836
80-70	60	11 (18.3)	Not reached [106.1; -]	58	5 (8.6)	Not reached [-; -]	1.66 [0.57; 4.86]	0.352	
IMDC Prognostic Status at Baseline									
Favorable	109	20 (18.3)	Not reached [-; -]	117	10 (8.5)	Not reached [-; -]	2.04 [0.96; 4.37]	0.065	0.147
Intermediate	208	33 (15.9)	Not reached [-; -]	185	17 (9.2)	Not reached [-; -]	1.47 [0.82; 2.66]	0.196	
Poor	33	10 (30.3)	Not reached [102.0; -]	35	1 (2.9)	Not reached [-; -]	7.29 [0.90; 58.92]	0.062	
IMDC Group Prognostic Status at Baseline									
Favorable	109	20 (18.3)	Not reached [-; -]	117	10 (8.5)	Not reached [-; -]	2.04 [0.96; 4.37]	0.065	0.808
Intermediate or Poor	241	43 (17.8)	Not reached [-; -]	220	18 (8.2)	Not reached [-; -]	1.82 [1.04; 3.16]	0.035	
SOC: Investigations, PT[g]: Neutrophil count decreased									

Study: KEYNOTE 581[a]	Pembrolizumab + Lenvatinib			Sunitinib			Pembrolizumab + Lenvatinib vs. Sunitinib		
Adverse Events	N[b]	Participants with Event n (%)	Median Time[c] in weeks [95 %-CI]	N[b]	Participants with Event n (%)	Median Time[c] in weeks [95 %-CI]	Hazard Ratio [95 %-CI][d]	p-Value[d,e]	p-Value for Interaction Test[f]
Age category									
<65	193	4 (2.1)	Not reached [-; -]	215	23 (10.7)	Not reached [-; -]	0.15 [0.05; 0.44]	< 0.001	0.959
≥65	159	4 (2.5)	Not reached [-; -]	125	17 (13.6)	Not reached [-; -]	0.15 [0.05; 0.44]	< 0.001	
Region									
Western Europe and North America	197	6 (3.0)	Not reached [-; -]	189	20 (10.6)	Not reached [-; -]	0.22 [0.09; 0.56]	0.001	0.191
Rest of the World	155	2 (1.3)	Not reached [-; -]	151	20 (13.2)	Not reached [-; -]	0.08 [0.02; 0.35]	< 0.001	
Gender									
Male	252	4 (1.6)	Not reached [-; -]	260	30 (11.5)	Not reached [-; -]	0.11 [0.04; 0.30]	< 0.001	0.258
Female	100	4 (4.0)	Not reached [-; -]	80	10 (12.5)	Not reached [-; -]	0.27 [0.08; 0.86]	0.028	
IMDC Prognostic Status at Baseline									
Favorable	109	3 (2.8)	Not reached [-; -]	117	19 (16.2)	Not reached [-; -]	0.15 [0.04; 0.49]	0.002	0.982
Intermediate	208	5 (2.4)	Not reached [-; -]	185	21 (11.4)	Not reached [-; -]	0.17 [0.06; 0.45]	< 0.001	
Poor	33	0 (0.0)	Not reached [-; -]	35	0 (0.0)	Not reached [-; -]	n.a. [n.a.; n.a.]	n.a.	
IMDC Group Prognostic Status at Baseline									
Favorable	109	3 (2.8)	Not reached [-; -]	117	19 (16.2)	Not reached [-; -]	0.15 [0.04; 0.49]	0.002	0.844
Intermediate or Poor	241	5 (2.1)	Not reached [-; -]	220	21 (9.5)	Not reached [-; -]	0.17 [0.06; 0.45]	< 0.001	
SOC: Investigations, PT[g]: Platelet count decreased									
Age category									
<65	193	5 (2.6)	Not reached [-; -]	215	28 (13.0)	Not reached [-; -]	0.18 [0.07; 0.48]	< 0.001	0.196
≥65	159	17 (10.7)	Not reached [-; -]	125	33 (26.4)	134.3 [-; -]	0.34 [0.19; 0.61]	< 0.001	
Region									
Western Europe and North America	197	9 (4.6)	Not reached [-; -]	189	26 (13.8)	Not reached [134.3; -]	0.27 [0.12; 0.57]	< 0.001	0.943
Rest of the World	155	13 (8.4)	Not reached [-; -]	151	35 (23.2)	Not reached [-; -]	0.33 [0.18; 0.63]	< 0.001	
Gender									
Male	252	14 (5.6)	Not reached [-; -]	260	43 (16.5)	Not reached [-; -]	0.29 [0.16; 0.53]	< 0.001	0.887
Female	100	8 (8.0)	Not reached [-; -]	80	18 (22.5)	134.3 [-; -]	0.32 [0.14; 0.74]	0.008	

Study: KEYNOTE 581[a]	Pembrolizumab + Lenvatinib			Sunitinib			Pembrolizumab + Lenvatinib vs. Sunitinib		
Adverse Events	N[b]	Participants with Event n (%)	Median Time[c] in weeks [95 %-CI]	N[b]	Participants with Event n (%)	Median Time[c] in weeks [95 %-CI]	Hazard Ratio [95 %-CI][d]	p-Value[d,e]	p-Value for Interaction Test[f]
Baseline KPS Score									
100-90	292	18 (6.2)	Not reached [-; -]	282	52 (18.4)	Not reached [134.3; -]	0.30 [0.18; 0.52]	< 0.001	0.683
80-70	60	4 (6.7)	Not reached [-; -]	58	9 (15.5)	Not reached [-; -]	0.28 [0.08; 0.93]	0.037	
IMDC Prognostic Status at Baseline									
Favorable	109	8 (7.3)	Not reached [-; -]	117	25 (21.4)	Not reached [-; -]	0.31 [0.14; 0.69]	0.004	> 0.999
Intermediate	208	14 (6.7)	Not reached [-; -]	185	36 (19.5)	Not reached [134.3; -]	0.29 [0.16; 0.55]	< 0.001	
Poor	33	0 (0.0)	Not reached [-; -]	35	0 (0.0)	Not reached [-; -]	n.a. [n.a.; n.a.]	n.a.	
IMDC Group Prognostic Status at Baseline									
Favorable	109	8 (7.3)	Not reached [-; -]	117	25 (21.4)	Not reached [-; -]	0.31 [0.14; 0.69]	0.004	0.961
Intermediate or Poor	241	14 (5.8)	Not reached [-; -]	220	36 (16.4)	Not reached [134.3; -]	0.30 [0.16; 0.56]	< 0.001	
SOC: Investigations, PT[g]: Weight decreased									
Age category									
<65	193	56 (29.0)	Not reached [-; -]	215	20 (9.3)	Not reached [-; -]	2.78 [1.67; 4.64]	< 0.001	0.681
≥65	159	49 (30.8)	Not reached [114.1; -]	125	11 (8.8)	Not reached [-; -]	3.34 [1.73; 6.42]	< 0.001	
Region									
Western Europe and North America	197	66 (33.5)	Not reached [-; -]	189	24 (12.7)	Not reached [-; -]	2.39 [1.50; 3.81]	< 0.001	0.102
Rest of the World	155	39 (25.2)	Not reached [-; -]	151	7 (4.6)	Not reached [-; -]	5.09 [2.28; 11.39]	< 0.001	
Gender									
Male	252	83 (32.9)	Not reached [-; -]	260	21 (8.1)	Not reached [-; -]	3.75 [2.32; 6.05]	< 0.001	0.069
Female	100	22 (22.0)	Not reached [-; -]	80	10 (12.5)	Not reached [-; -]	1.64 [0.78; 3.47]	0.196	
Baseline KPS Score									
100-90	292	85 (29.1)	Not reached [-; -]	282	22 (7.8)	Not reached [-; -]	3.53 [2.21; 5.64]	< 0.001	0.149
80-70	60	20 (33.3)	Not reached [67.0; -]	58	9 (15.5)	Not reached [-; -]	1.70 [0.77; 3.75]	0.190	

Study: KEYNOTE 581[a]	Pembrolizumab + Lenvatinib			Sunitinib			Pembrolizumab + Lenvatinib vs. Sunitinib		
Adverse Events	N[b]	Participants with Event n (%)	Median Time[c] in weeks [95 %-CI]	N[b]	Participants with Event n (%)	Median Time[c] in weeks [95 %-CI]	Hazard Ratio [95 %-CI][d]	p-Value[d,e]	p-Value for Interaction Test[f]
IMDC Prognostic Status at Baseline									
Favorable	109	38 (34.9)	Not reached [114.1; -]	117	11 (9.4)	Not reached [-; -]	3.93 [2.01; 7.70]	< 0.001	0.265
Intermediate	208	58 (27.9)	Not reached [-; -]	185	15 (8.1)	Not reached [-; -]	3.06 [1.73; 5.40]	< 0.001	
Poor	33	9 (27.3)	Not reached [67.0; -]	35	5 (14.3)	Not reached [-; -]	1.13 [0.36; 3.53]	0.830	
IMDC Group Prognostic Status at Baseline									
Favorable	109	38 (34.9)	Not reached [114.1; -]	117	11 (9.4)	Not reached [-; -]	3.93 [2.01; 7.70]	< 0.001	0.324
Intermediate or Poor	241	67 (27.8)	Not reached [-; -]	220	20 (9.1)	Not reached [-; -]	2.61 [1.58; 4.31]	< 0.001	
SOC: Investigations, PT[g]: White blood cell count decreased									
Age category									
<65	193	2 (1.0)	Not reached [-; -]	215	14 (6.5)	Not reached [-; -]	0.13 [0.03; 0.57]	0.007	0.361
≥65	159	8 (5.0)	Not reached [132.3; -]	125	19 (15.2)	Not reached [-; -]	0.24 [0.10; 0.55]	< 0.001	
Gender									
Male	252	7 (2.8)	Not reached [-; -]	260	24 (9.2)	Not reached [-; -]	0.23 [0.10; 0.53]	< 0.001	0.915
Female	100	3 (3.0)	Not reached [-; -]	80	9 (11.3)	Not reached [-; -]	0.20 [0.05; 0.76]	0.018	
Baseline KPS Score									
100-90	292	8 (2.7)	Not reached [-; -]	282	26 (9.2)	Not reached [-; -]	0.23 [0.10; 0.51]	< 0.001	0.831
80-70	60	2 (3.3)	Not reached [-; -]	58	7 (12.1)	Not reached [-; -]	0.17 [0.03; 0.84]	0.030	
IMDC Prognostic Status at Baseline									
Favorable	109	3 (2.8)	Not reached [-; -]	117	14 (12.0)	Not reached [-; -]	0.19 [0.05; 0.67]	0.009	0.960
Intermediate	208	7 (3.4)	Not reached [-; -]	185	19 (10.3)	Not reached [-; -]	0.25 [0.10; 0.60]	0.002	
Poor	33	0 (0.0)	Not reached [-; -]	35	0 (0.0)	Not reached [-; -]	n.a. [n.a.; n.a.]	n.a.	
IMDC Group Prognostic Status at Baseline									
Favorable	109	3 (2.8)	Not reached [-; -]	117	14 (12.0)	Not reached [-; -]	0.19 [0.05; 0.67]	0.009	0.782
Intermediate or Poor	241	7 (2.9)	Not reached [-; -]	220	19 (8.6)	Not reached [-; -]	0.25 [0.10; 0.60]	0.002	
SOC: Metabolism and nutrition disorders, PT[g]: Hypercholesterolaemia									

Study: KEYNOTE 581[a]	Pembrolizumab + Lenvatinib			Sunitinib			Pembrolizumab + Lenvatinib vs. Sunitinib		
Adverse Events	N[b]	Participants with Event n (%)	Median Time[c] in weeks [95 %-CI]	N[b]	Participants with Event n (%)	Median Time[c] in weeks [95 %-CI]	Hazard Ratio [95 %-CI][d]	p-Value[d,e]	p-Value for Interaction Test[f]
Age category									
<65	193	19 (9.8)	Not reached [-; -]	215	4 (1.9)	Not reached [-; -]	4.29 [1.45; 12.64]	0.008	0.585
≥65	159	12 (7.5)	Not reached [-; -]	125	3 (2.4)	Not reached [-; -]	2.57 [0.72; 9.15]	0.145	
Region									
Western Europe and North America	197	13 (6.6)	Not reached [-; -]	189	3 (1.6)	Not reached [-; -]	3.63 [1.03; 12.80]	0.045	0.865
Rest of the World	155	18 (11.6)	Not reached [-; -]	151	4 (2.6)	Not reached [-; -]	3.59 [1.21; 10.63]	0.021	
Gender									
Male	252	19 (7.5)	Not reached [-; -]	260	6 (2.3)	Not reached [-; -]	2.61 [1.04; 6.56]	0.042	0.252
Female	100	12 (12.0)	Not reached [-; -]	80	1 (1.3)	Not reached [-; -]	8.38 [1.09; 64.49]	0.041	
Baseline KPS Score									
100-90	292	26 (8.9)	Not reached [-; -]	282	5 (1.8)	Not reached [-; -]	4.19 [1.60; 10.93]	0.003	0.365
80-70	60	5 (8.3)	Not reached [-; -]	58	2 (3.4)	Not reached [72.0; -]	1.68 [0.32; 8.70]	0.539	
IMDC Prognostic Status at Baseline									
Favorable	109	7 (6.4)	Not reached [-; -]	117	2 (1.7)	Not reached [-; -]	3.47 [0.72; 16.73]	0.121	0.357
Intermediate	208	19 (9.1)	Not reached [-; -]	185	5 (2.7)	Not reached [-; -]	2.53 [0.94; 6.81]	0.067	
Poor	33	5 (15.2)	Not reached [-; -]	35	0 (0.0)	Not reached [-; -]	n.a. [n.a.; n.a.]	0.037	
IMDC Group Prognostic Status at Baseline									
Favorable	109	7 (6.4)	Not reached [-; -]	117	2 (1.7)	Not reached [-; -]	3.47 [0.72; 16.73]	0.121	0.976
Intermediate or Poor	241	24 (10.0)	Not reached [-; -]	220	5 (2.3)	Not reached [-; -]	3.29 [1.25; 8.68]	0.016	
SOC: Musculoskeletal and connective tissue disorders, PT[g]: Arthralgia									
Age category									
<65	193	61 (31.6)	Not reached [-; -]	215	34 (15.8)	Not reached [-; -]	1.63 [1.07; 2.50]	0.023	0.730
≥65	159	38 (23.9)	Not reached [-; -]	125	18 (14.4)	Not reached [-; -]	1.53 [0.87; 2.68]	0.139	
Region									
Western Europe and North America	197	76 (38.6)	Not reached [81.4; -]	189	36 (19.0)	Not reached [-; -]	1.75 [1.18; 2.62]	0.006	0.290
Rest of the World	155	23 (14.8)	Not reached [-; -]	151	16 (10.6)	Not reached [-; -]	1.20 [0.63; 2.27]	0.580	

Study: KEYNOTE 581[a]	Pembrolizumab + Lenvatinib			Sunitinib			Pembrolizumab + Lenvatinib vs. Sunitinib		
Adverse Events	N[b]	Participants with Event n (%)	Median Time[c] in weeks [95 %-CI]	N[b]	Participants with Event n (%)	Median Time[c] in weeks [95 %-CI]	Hazard Ratio [95 %-CI][d]	p-Value[d,e]	p-Value for Interaction Test[f]
Gender									
Male	252	75 (29.8)	Not reached [-; -]	260	38 (14.6)	Not reached [-; -]	1.76 [1.19; 2.61]	0.005	0.325
Female	100	24 (24.0)	Not reached [-; -]	80	14 (17.5)	Not reached [-; -]	1.15 [0.59; 2.24]	0.672	
Baseline KPS Score									
100-90	292	85 (29.1)	Not reached [-; -]	282	42 (14.9)	Not reached [-; -]	1.70 [1.17; 2.47]	0.005	0.305
80-70	60	14 (23.3)	Not reached [-; -]	58	10 (17.2)	Not reached [49.0; -]	1.10 [0.49; 2.51]	0.813	
IMDC Prognostic Status at Baseline									
Favorable	109	31 (28.4)	Not reached [-; -]	117	18 (15.4)	Not reached [-; -]	1.87 [1.05; 3.34]	0.035	0.694
Intermediate	208	55 (26.4)	Not reached [-; -]	185	29 (15.7)	Not reached [-; -]	1.30 [0.83; 2.05]	0.254	
Poor	33	12 (36.4)	Not reached [81.4; -]	35	5 (14.3)	Not reached [24.0; -]	2.08 [0.70; 6.14]	0.186	
IMDC Group Prognostic Status at Baseline									
Favorable	109	31 (28.4)	Not reached [-; -]	117	18 (15.4)	Not reached [-; -]	1.87 [1.05; 3.34]	0.035	0.467
Intermediate or Poor	241	67 (27.8)	Not reached [-; -]	220	34 (15.5)	Not reached [-; -]	1.38 [0.91; 2.09]	0.132	
SOC: Musculoskeletal and connective tissue disorders, PT[g]: Musculoskeletal pain									
Age category									
<65	193	30 (15.5)	Not reached [-; -]	215	10 (4.7)	Not reached [-; -]	3.05 [1.49; 6.24]	0.002	0.072
≥65	159	18 (11.3)	Not reached [-; -]	125	11 (8.8)	Not reached [-; -]	1.07 [0.50; 2.27]	0.870	
Region									
Western Europe and North America	197	35 (17.8)	Not reached [-; -]	189	13 (6.9)	Not reached [-; -]	2.27 [1.20; 4.31]	0.012	0.389
Rest of the World	155	13 (8.4)	Not reached [-; -]	151	8 (5.3)	Not reached [-; -]	1.35 [0.56; 3.27]	0.505	
Gender									
Male	252	38 (15.1)	Not reached [-; -]	260	16 (6.2)	Not reached [-; -]	2.13 [1.18; 3.82]	0.012	0.536
Female	100	10 (10.0)	Not reached [-; -]	80	5 (6.3)	Not reached [-; -]	1.45 [0.49; 4.26]	0.498	
Baseline KPS Score									
100-90	292	43 (14.7)	Not reached [-; -]	282	19 (6.7)	Not reached [-; -]	1.93 [1.12; 3.32]	0.018	> 0.999
80-70	60	5 (8.3)	Not reached [-; -]	58	2 (3.4)	Not reached [-; -]	2.13 [0.41; 11.10]	0.370	

Study: KEYNOTE 581[a]	Pembrolizumab + Lenvatinib			Sunitinib			Pembrolizumab + Lenvatinib vs. Sunitinib		
Adverse Events	N[b]	Participants with Event n (%)	Median Time[c] in weeks [95 %-CI]	N[b]	Participants with Event n (%)	Median Time[c] in weeks [95 %-CI]	Hazard Ratio [95 %-CI][d]	p-Value[d,e]	p-Value for Interaction Test[f]
IMDC Prognostic Status at Baseline									
Favorable	109	13 (11.9)	Not reached [-; -]	117	10 (8.5)	Not reached [-; -]	1.28 [0.56; 2.93]	0.556	0.389
Intermediate	208	29 (13.9)	Not reached [-; -]	185	10 (5.4)	Not reached [-; -]	2.19 [1.07; 4.52]	0.033	
Poor	33	6 (18.2)	Not reached [-; -]	35	1 (2.9)	Not reached [-; -]	6.33 [0.76; 52.65]	0.088	
IMDC Group Prognostic Status at Baseline									
Favorable	109	13 (11.9)	Not reached [-; -]	117	10 (8.5)	Not reached [-; -]	1.28 [0.56; 2.93]	0.556	0.245
Intermediate or Poor	241	35 (14.5)	Not reached [-; -]	220	11 (5.0)	Not reached [-; -]	2.49 [1.26; 4.92]	0.009	
SOC: Musculoskeletal and connective tissue disorders, PT[g]: Myalgia									
Age category									
<65	193	33 (17.1)	Not reached [-; -]	215	6 (2.8)	Not reached [-; -]	5.54 [2.32; 13.26]	< 0.001	0.273
≥65	159	23 (14.5)	Not reached [-; -]	125	6 (4.8)	Not reached [-; -]	2.62 [1.07; 6.45]	0.036	
Region									
Western Europe and North America	197	35 (17.8)	Not reached [-; -]	189	9 (4.8)	Not reached [-; -]	3.18 [1.52; 6.64]	0.002	0.354
Rest of the World	155	21 (13.5)	Not reached [-; -]	151	3 (2.0)	Not reached [-; -]	6.36 [1.89; 21.34]	0.003	
Gender									
Male	252	42 (16.7)	Not reached [-; -]	260	8 (3.1)	Not reached [-; -]	4.83 [2.26; 10.30]	< 0.001	0.349
Female	100	14 (14.0)	Not reached [-; -]	80	4 (5.0)	Not reached [-; -]	2.49 [0.82; 7.57]	0.109	
Baseline KPS Score									
100-90	292	51 (17.5)	Not reached [-; -]	282	9 (3.2)	Not reached [-; -]	4.98 [2.45; 10.13]	< 0.001	0.122
80-70	60	5 (8.3)	Not reached [-; -]	58	3 (5.2)	Not reached [80.7; -]	1.34 [0.32; 5.70]	0.689	
IMDC Prognostic Status at Baseline									
Favorable	109	21 (19.3)	Not reached [-; -]	117	6 (5.1)	Not reached [-; -]	3.61 [1.46; 8.96]	0.006	0.793
Intermediate	208	31 (14.9)	Not reached [-; -]	185	5 (2.7)	Not reached [-; -]	5.05 [1.96; 13.00]	< 0.001	
Poor	33	3 (9.1)	Not reached [-; -]	35	1 (2.9)	Not reached [-; -]	1.27 [0.11; 13.99]	0.847	

Study: KEYNOTE 581[a]	Pembrolizumab + Lenvatinib			Sunitinib			Pembrolizumab + Lenvatinib vs. Sunitinib		
Adverse Events	N[b]	Participants with Event n (%)	Median Time[c] in weeks [95 %-CI]	N[b]	Participants with Event n (%)	Median Time[c] in weeks [95 %-CI]	Hazard Ratio [95 %-CI][d]	p-Value[d,e]	p-Value for Interaction Test[f]
IMDC Group Prognostic Status at Baseline									
Favorable	109	21 (19.3)	Not reached [-; -]	117	6 (5.1)	Not reached [-; -]	3.61 [1.46; 8.96]	0.006	0.779
Intermediate or Poor	241	34 (14.1)	Not reached [-; -]	220	6 (2.7)	Not reached [-; -]	4.46 [1.87; 10.67]	< 0.001	
SOC: Nervous system disorders, PT[g]: Ageusia									
Age category									
<65	193	3 (1.6)	Not reached [-; -]	215	10 (4.7)	Not reached [-; -]	0.30 [0.08; 1.08]	0.066	0.446
≥65	159	1 (0.6)	Not reached [-; -]	125	6 (4.8)	Not reached [-; -]	0.12 [0.01; 1.01]	0.051	
Region									
Western Europe and North America	197	2 (1.0)	Not reached [-; -]	189	13 (6.9)	Not reached [-; -]	0.13 [0.03; 0.57]	0.007	0.204
Rest of the World	155	2 (1.3)	Not reached [-; -]	151	3 (2.0)	Not reached [-; -]	0.63 [0.10; 3.76]	0.611	
Gender									
Male	252	4 (1.6)	Not reached [-; -]	260	12 (4.6)	Not reached [-; -]	0.32 [0.10; 0.99]	0.049	0.121
Female	100	0 (0.0)	Not reached [-; -]	80	4 (5.0)	Not reached [-; -]	n.a. [n.a.; n.a.]	0.013	
Baseline KPS Score									
100-90	292	4 (1.4)	Not reached [-; -]	282	15 (5.3)	Not reached [-; -]	0.23 [0.08; 0.71]	0.010	0.494
80-70	60	0 (0.0)	Not reached [-; -]	58	1 (1.7)	Not reached [-; -]	n.a. [n.a.; n.a.]	0.313	
IMDC Prognostic Status at Baseline									
Favorable	109	1 (0.9)	n.c.	117	5 (4.3)	n.c.	n.c.	n.c.	n.c.
Intermediate	208	1 (0.5)	n.c.	185	8 (4.3)	n.c.	n.c.	n.c.	
Poor	33	2 (6.1)	n.c.	35	3 (8.6)	n.c.	n.c.	n.c.	
IMDC Group Prognostic Status at Baseline									
Favorable	109	1 (0.9)	Not reached [-; -]	117	5 (4.3)	Not reached [-; -]	0.21 [0.02; 1.81]	0.156	0.954
Intermediate or Poor	241	3 (1.2)	Not reached [-; -]	220	11 (5.0)	Not reached [-; -]	0.21 [0.06; 0.76]	0.017	
SOC: Nervous system disorders, PT[g]: Dysgeusia									
Age category									
<65	193	22 (11.4)	Not reached [-; -]	215	66 (30.7)	Not reached [-; -]	0.28 [0.17; 0.46]	< 0.001	0.153
≥65	159	21	Not reached	125	29	Not reached	0.49	0.012	

Study: KEYNOTE 581[a]	Pembrolizumab + Lenvatinib			Sunitinib			Pembrolizumab + Lenvatinib vs. Sunitinib		
Adverse Events	N[b]	Participants with Event n (%)	Median Time[c] in weeks [95 %-CI]	N[b]	Participants with Event n (%)	Median Time[c] in weeks [95 %-CI]	Hazard Ratio [95 %-CI][d]	p-Value[d,e]	p-Value for Interaction Test[f]
		(13.2)	[-; -]		(23.2)	[-; -]	[0.28; 0.86]		
Region									
Western Europe and North America	197	31 (15.7)	Not reached [-; -]	189	64 (33.9)	Not reached [-; -]	0.35 [0.23; 0.54]	< 0.001	0.694
Rest of the World	155	12 (7.7)	Not reached [-; -]	151	31 (20.5)	Not reached [-; -]	0.32 [0.16; 0.63]	< 0.001	
Gender									
Male	252	33 (13.1)	Not reached [-; -]	260	74 (28.5)	Not reached [-; -]	0.36 [0.24; 0.54]	< 0.001	0.687
Female	100	10 (10.0)	Not reached [-; -]	80	21 (26.3)	Not reached [-; -]	0.33 [0.16; 0.71]	0.004	
Baseline KPS Score									
100-90	292	40 (13.7)	Not reached [-; -]	282	86 (30.5)	Not reached [-; -]	0.36 [0.24; 0.52]	< 0.001	0.693
80-70	60	3 (5.0)	Not reached [-; -]	58	9 (15.5)	Not reached [-; -]	0.26 [0.07; 0.99]	0.048	
IMDC Prognostic Status at Baseline									
Favorable	109	18 (16.5)	Not reached [-; -]	117	38 (32.5)	Not reached [-; -]	0.41 [0.23; 0.72]	0.002	0.709
Intermediate	208	22 (10.6)	Not reached [-; -]	185	50 (27.0)	Not reached [-; -]	0.32 [0.19; 0.52]	< 0.001	
Poor	33	3 (9.1)	Not reached [-; -]	35	6 (17.1)	Not reached [-; -]	0.48 [0.12; 1.93]	0.303	
IMDC Group Prognostic Status at Baseline									
Favorable	109	18 (16.5)	Not reached [-; -]	117	38 (32.5)	Not reached [-; -]	0.41 [0.23; 0.72]	0.002	0.473
Intermediate or Poor	241	25 (10.4)	Not reached [-; -]	220	56 (25.5)	Not reached [-; -]	0.33 [0.21; 0.53]	< 0.001	
SOC: Renal and urinary disorders, PTs: Proteinuria									
Age category									
<65	193	51 (26.4)	Not reached [-; -]	215	21 (9.8)	Not reached [-; -]	2.35 [1.41; 3.91]	0.001	0.507
≥65	159	53 (33.3)	Not reached [-; -]	125	22 (17.6)	Not reached [-; -]	1.93 [1.17; 3.18]	0.010	
Gender									
Male	252	77 (30.6)	Not reached [-; -]	260	37 (14.2)	Not reached [-; -]	1.96 [1.32; 2.90]	< 0.001	0.188
Female	100	27 (27.0)	Not reached [113.9; -]	80	6 (7.5)	Not reached [-; -]	3.66 [1.51; 8.89]	0.004	

Study: KEYNOTE 581[a]	Pembrolizumab + Lenvatinib			Sunitinib			Pembrolizumab + Lenvatinib vs. Sunitinib		
Adverse Events	N[b]	Participants with Event n (%)	Median Time[c] in weeks [95 %-CI]	N[b]	Participants with Event n (%)	Median Time[c] in weeks [95 %-CI]	Hazard Ratio [95 %-CI][d]	p-Value[d,e]	p-Value for Interaction Test[f]
Baseline KPS Score									
100-90	292	94 (32.2)	Not reached [-; -]	282	36 (12.8)	Not reached [-; -]	2.43 [1.65; 3.57]	< 0.001	0.183
80-70	60	10 (16.7)	Not reached [-; -]	58	7 (12.1)	Not reached [-; -]	1.16 [0.44; 3.09]	0.759	
IMDC Prognostic Status at Baseline									
Favorable	109	29 (26.6)	Not reached [-; -]	117	16 (13.7)	Not reached [-; -]	1.97 [1.07; 3.62]	0.030	0.801
Intermediate	208	66 (31.7)	Not reached [125.1; -]	185	23 (12.4)	Not reached [-; -]	2.33 [1.45; 3.76]	< 0.001	
Poor	33	8 (24.2)	Not reached [69.4; -]	35	4 (11.4)	Not reached [-; -]	1.54 [0.45; 5.26]	0.495	
IMDC Group Prognostic Status at Baseline									
Favorable	109	29 (26.6)	Not reached [-; -]	117	16 (13.7)	Not reached [-; -]	1.97 [1.07; 3.62]	0.030	0.700
Intermediate or Poor	241	74 (30.7)	Not reached [125.1; -]	220	27 (12.3)	Not reached [-; -]	2.22 [1.42; 3.46]	< 0.001	
SOC: Respiratory, thoracic and mediastinal disorders, PT[g]: Dysphonia									
Age category									
<65	193	50 (25.9)	Not reached [-; -]	215	8 (3.7)	Not reached [-; -]	7.51 [3.56; 15.84]	< 0.001	0.925
≥65	159	55 (34.6)	129.3 [129.3; -]	125	6 (4.8)	Not reached [-; -]	7.77 [3.34; 18.06]	< 0.001	
Region									
Western Europe and North America	197	62 (31.5)	Not reached [127.7; -]	189	8 (4.2)	Not reached [-; -]	8.28 [3.96; 17.30]	< 0.001	0.847
Rest of the World	155	43 (27.7)	Not reached [-; -]	151	6 (4.0)	Not reached [-; -]	7.37 [3.14; 17.33]	< 0.001	
Baseline KPS Score									
100-90	292	94 (32.2)	Not reached [129.3; -]	282	14 (5.0)	Not reached [-; -]	7.17 [4.09; 12.58]	< 0.001	0.104
80-70	60	11 (18.3)	Not reached [-; -]	58	0 (0.0)	Not reached [-; -]	n.a. [n.a.; n.a.]	0.002	
IMDC Prognostic Status at Baseline									
Favorable	109	36 (33.0)	Not reached [-; -]	117	5 (4.3)	Not reached [-; -]	8.92 [3.50; 22.73]	< 0.001	0.592
Intermediate	208	61 (29.3)	Not reached [129.3; -]	185	7 (3.8)	Not reached [-; -]	8.26 [3.78; 18.07]	< 0.001	
Poor	33	7 (21.2)	Not reached [-; -]	35	2 (5.7)	Not reached [-; -]	3.36 [0.69; 16.34]	0.134	

Study: KEYNOTE 581[a]	Pembrolizumab + Lenvatinib			Sunitinib			Pembrolizumab + Lenvatinib vs. Sunitinib		
Adverse Events	N[b]	Participants with Event n (%)	Median Time[c] in weeks [95 %-CI]	N[b]	Participants with Event n (%)	Median Time[c] in weeks [95 %-CI]	Hazard Ratio [95 %-CI][d]	p-Value[d,e]	p-Value for Interaction Test[f]
IMDC Group Prognostic Status at Baseline									
Favorable	109	36 (33.0)	Not reached [-; -]	117	5 (4.3)	Not reached [-; -]	8.92 [3.50; 22.73]	< 0.001	0.713
Intermediate or Poor	241	68 (28.2)	Not reached [129.3; -]	220	9 (4.1)	Not reached [-; -]	7.20 [3.59; 14.45]	< 0.001	
SOC: Respiratory, thoracic and mediastinal disorders, PT[g]: Epistaxis									
Age category									
<65	193	17 (8.8)	Not reached [-; -]	215	23 (10.7)	Not reached [-; -]	0.70 [0.37; 1.31]	0.261	0.248
≥65	159	8 (5.0)	Not reached [-; -]	125	14 (11.2)	Not reached [-; -]	0.40 [0.17; 0.96]	0.041	
Region									
Western Europe and North America	197	19 (9.6)	Not reached [-; -]	189	26 (13.8)	Not reached [-; -]	0.58 [0.32; 1.06]	0.076	0.653
Rest of the World	155	6 (3.9)	Not reached [-; -]	151	11 (7.3)	Not reached [-; -]	0.50 [0.18; 1.35]	0.172	
Gender									
Male	252	21 (8.3)	Not reached [-; -]	260	26 (10.0)	Not reached [-; -]	0.73 [0.41; 1.30]	0.286	0.092
Female	100	4 (4.0)	Not reached [-; -]	80	11 (13.8)	Not reached [-; -]	0.24 [0.08; 0.77]	0.017	
Baseline KPS Score									
100-90	292	23 (7.9)	Not reached [-; -]	282	31 (11.0)	Not reached [-; -]	0.64 [0.37; 1.09]	0.102	0.270
80-70	60	2 (3.3)	Not reached [-; -]	58	6 (10.3)	Not reached [-; -]	0.25 [0.05; 1.25]	0.092	
IMDC Prognostic Status at Baseline									
Favorable	109	10 (9.2)	Not reached [-; -]	117	14 (12.0)	Not reached [-; -]	0.72 [0.32; 1.62]	0.426	0.591
Intermediate	208	11 (5.3)	Not reached [-; -]	185	19 (10.3)	Not reached [-; -]	0.42 [0.20; 0.90]	0.025	
Poor	33	3 (9.1)	Not reached [-; -]	35	3 (8.6)	Not reached [-; -]	0.70 [0.13; 3.82]	0.683	
IMDC Group Prognostic Status at Baseline									
Favorable	109	10 (9.2)	Not reached [-; -]	117	14 (12.0)	Not reached [-; -]	0.72 [0.32; 1.62]	0.426	0.463
Intermediate or Poor	241	14 (5.8)	Not reached [-; -]	220	22 (10.0)	Not reached [-; -]	0.47 [0.24; 0.93]	0.029	
SOC: Respiratory, thoracic and mediastinal disorders, PT[g]: Pneumonitis									

Study: KEYNOTE 581[a]	Pembrolizumab + Lenvatinib			Sunitinib			Pembrolizumab + Lenvatinib vs. Sunitinib		
Adverse Events	N[b]	Participants with Event n (%)	Median Time[c] in weeks [95 %-CI]	N[b]	Participants with Event n (%)	Median Time[c] in weeks [95 %-CI]	Hazard Ratio [95 %-CI][d]	p-Value[d,e]	p-Value for Interaction Test[f]
Age category									
<65	193	8 (4.1)	Not reached [-; -]	215	0 (0.0)	Not reached [-; -]	n.a. [n.a.; n.a.]	0.009	0.998
≥65	159	10 (6.3)	Not reached [-; -]	125	0 (0.0)	Not reached [-; -]	n.a. [n.a.; n.a.]	0.010	
Region									
Western Europe and North America	197	9 (4.6)	n.c.	189	0 (0.0)	n.c.	n.c.	n.c.	n.c.
Rest of the World	155	9 (5.8)	n.c.	151	0 (0.0)	n.c.	n.c.	n.c.	
Gender									
Male	252	11 (4.4)	Not reached [-; -]	260	0 (0.0)	Not reached [-; -]	n.a. [n.a.; n.a.]	0.003	0.998
Female	100	7 (7.0)	Not reached [-; -]	80	0 (0.0)	Not reached [-; -]	n.a. [n.a.; n.a.]	0.026	
Baseline KPS Score									
100-90	292	12 (4.1)	Not reached [-; -]	282	0 (0.0)	Not reached [-; -]	n.a. [n.a.; n.a.]	0.002	0.998
80-70	60	6 (10.0)	Not reached [-; -]	58	0 (0.0)	Not reached [-; -]	n.a. [n.a.; n.a.]	0.050	
IMDC Prognostic Status at Baseline									
Favorable	109	6 (5.5)	Not reached [-; -]	117	0 (0.0)	Not reached [-; -]	n.a. [n.a.; n.a.]	0.014	> 0.999
Intermediate	208	11 (5.3)	Not reached [-; -]	185	0 (0.0)	Not reached [-; -]	n.a. [n.a.; n.a.]	0.007	
Poor	33	1 (3.0)	Not reached [-; -]	35	0 (0.0)	Not reached [-; -]	n.a. [n.a.; n.a.]	0.375	
IMDC Group Prognostic Status at Baseline									
Favorable	109	6 (5.5)	Not reached [-; -]	117	0 (0.0)	Not reached [-; -]	n.a. [n.a.; n.a.]	0.014	0.998
Intermediate or Poor	241	12 (5.0)	Not reached [-; -]	220	0 (0.0)	Not reached [-; -]	n.a. [n.a.; n.a.]	0.005	
SOC: Skin and subcutaneous tissue disorders, PT[g]: Palmar-plantar erythrodysaesthesia syndrome									
Age category									
<65	193	59 (30.6)	Not reached [-; -]	215	82 (38.1)	141.1 [57.3; -]	0.65 [0.46; 0.91]	0.012	0.762
≥65	159	42 (26.4)	Not reached [-; -]	125	45 (36.0)	Not reached [28.7; -]	0.60 [0.39; 0.92]	0.018	
Gender									
Male	252	75 (29.8)	Not reached [-; -]	260	98 (37.7)	141.1 [57.3; -]	0.64 [0.47; 0.86]	0.004	0.794
Female	100	26 (26.0)	Not reached [-; -]	80	29 (36.3)	Not reached [27.4; -]	0.58 [0.34; 0.99]	0.047	

Study: KEYNOTE 581[a]	Pembrolizumab + Lenvatinib			Sunitinib			Pembrolizumab + Lenvatinib vs. Sunitinib		
Adverse Events	N[b]	Participants with Event n (%)	Median Time[c] in weeks [95 %-CI]	N[b]	Participants with Event n (%)	Median Time[c] in weeks [95 %-CI]	Hazard Ratio [95 %-CI][d]	p-Value[d,e]	p-Value for Interaction Test[f]
Baseline KPS Score									
100-90	292	91 (31.2)	Not reached [-; -]	282	120 (42.6)	120.1 [28.7; -]	0.60 [0.46; 0.79]	< 0.001	0.185
80-70	60	10 (16.7)	Not reached [-; -]	58	7 (12.1)	141.1 [-; -]	1.00 [0.38; 2.65]	0.999	
IMDC Prognostic Status at Baseline									
Favorable	109	35 (32.1)	Not reached [-; -]	117	56 (47.9)	38.6 [18.6; -]	0.55 [0.36; 0.83]	0.005	0.557
Intermediate	208	61 (29.3)	Not reached [-; -]	185	66 (35.7)	120.1 [60.4; -]	0.67 [0.47; 0.96]	0.027	
Poor	33	5 (15.2)	Not reached [-; -]	35	4 (11.4)	Not reached [-; -]	0.99 [0.26; 3.74]	0.989	
IMDC Group Prognostic Status at Baseline									
Favorable	109	35 (32.1)	Not reached [-; -]	117	56 (47.9)	38.6 [18.6; -]	0.55 [0.36; 0.83]	0.005	0.355
Intermediate or Poor	241	66 (27.4)	Not reached [-; -]	220	70 (31.8)	141.1 [120.1; -]	0.70 [0.50; 0.98]	0.038	
SOC: Skin and subcutaneous tissue disorders, PT[g]: Pruritus									
Age category									
<65	193	26 (13.5)	Not reached [-; -]	215	18 (8.4)	Not reached [-; -]	1.38 [0.75; 2.52]	0.301	0.107
≥65	159	32 (20.1)	Not reached [-; -]	125	8 (6.4)	Not reached [-; -]	2.94 [1.35; 6.38]	0.007	
Region									
Western Europe and North America	197	38 (19.3)	Not reached [-; -]	189	16 (8.5)	Not reached [-; -]	1.97 [1.09; 3.54]	0.024	0.807
Rest of the World	155	20 (12.9)	Not reached [-; -]	151	10 (6.6)	Not reached [-; -]	1.75 [0.82; 3.76]	0.147	
Gender									
Male	252	45 (17.9)	Not reached [-; -]	260	24 (9.2)	Not reached [-; -]	1.69 [1.03; 2.78]	0.038	0.162
Female	100	13 (13.0)	Not reached [-; -]	80	2 (2.5)	Not reached [-; -]	4.70 [1.06; 20.96]	0.042	
Baseline KPS Score									
100-90	292	50 (17.1)	Not reached [-; -]	282	24 (8.5)	Not reached [-; -]	1.82 [1.12; 2.97]	0.016	0.489
80-70	60	8 (13.3)	Not reached [-; -]	58	2 (3.4)	Not reached [-; -]	2.99 [0.62; 14.33]	0.171	

Study: KEYNOTE 581[a]	Pembrolizumab + Lenvatinib			Sunitinib			Pembrolizumab + Lenvatinib vs. Sunitinib		
Adverse Events	N[b]	Participants with Event n (%)	Median Time[c] in weeks [95 %-CI]	N[b]	Participants with Event n (%)	Median Time[c] in weeks [95 %-CI]	Hazard Ratio [95 %-CI][d]	p-Value[d,e]	p-Value for Interaction Test[f]
IMDC Prognostic Status at Baseline									
Favorable	109	15 (13.8)	Not reached [-; -]	117	10 (8.5)	Not reached [-; -]	1.56 [0.70; 3.47]	0.276	0.684
Intermediate	208	35 (16.8)	Not reached [-; -]	185	14 (7.6)	Not reached [-; -]	1.90 [1.02; 3.54]	0.044	
Poor	33	8 (24.2)	Not reached [97.1; -]	35	2 (5.7)	Not reached [-; -]	3.22 [0.66; 15.66]	0.147	
IMDC Group Prognostic Status at Baseline									
Favorable	109	15 (13.8)	Not reached [-; -]	117	10 (8.5)	Not reached [-; -]	1.56 [0.70; 3.47]	0.276	0.526
Intermediate or Poor	241	43 (17.8)	Not reached [-; -]	220	16 (7.3)	Not reached [-; -]	2.05 [1.15; 3.65]	0.015	
SOC: Skin and subcutaneous tissue disorders, PT[g]: Rash									
Age category									
<65	193	55 (28.5)	Not reached [-; -]	215	34 (15.8)	Not reached [-; -]	1.51 [0.98; 2.32]	0.060	0.287
≥65	159	41 (25.8)	Not reached [-; -]	125	13 (10.4)	Not reached [-; -]	2.32 [1.24; 4.34]	0.008	
Region									
Western Europe and North America	197	54 (27.4)	Not reached [-; -]	189	24 (12.7)	Not reached [-; -]	1.90 [1.17; 3.09]	0.009	0.562
Rest of the World	155	42 (27.1)	Not reached [-; -]	151	23 (15.2)	Not reached [-; -]	1.57 [0.94; 2.61]	0.084	
Baseline KPS Score									
100-90	292	80 (27.4)	Not reached [-; -]	282	43 (15.2)	Not reached [-; -]	1.60 [1.10; 2.33]	0.013	0.197
80-70	60	16 (26.7)	127.4 [106.3; -]	58	4 (6.9)	Not reached [-; -]	3.07 [1.02; 9.27]	0.047	
IMDC Prognostic Status at Baseline									
Favorable	109	24 (22.0)	Not reached [-; -]	117	14 (12.0)	Not reached [-; -]	1.73 [0.89; 3.35]	0.103	0.184
Intermediate	208	63 (30.3)	Not reached [127.4; -]	185	32 (17.3)	Not reached [-; -]	1.47 [0.95; 2.25]	0.081	
Poor	33	9 (27.3)	Not reached [36.1; -]	35	1 (2.9)	Not reached [-; -]	8.96 [1.13; 71.06]	0.038	
IMDC Group Prognostic Status at Baseline									
Favorable	109	24 (22.0)	Not reached [-; -]	117	14 (12.0)	Not reached [-; -]	1.73 [0.89; 3.35]	0.103	0.938
Intermediate or Poor	241	72 (29.9)	Not reached [127.4; -]	220	33 (15.0)	Not reached [-; -]	1.67 [1.10; 2.53]	0.016	

Study: KEYNOTE 581[a]	Pembrolizumab + Lenvatinib			Sunitinib			Pembrolizumab + Lenvatinib vs. Sunitinib		
Adverse Events	N[b]	Participants with Event n (%)	Median Time[c] in weeks [95 %-CI]	N[b]	Participants with Event n (%)	Median Time[c] in weeks [95 %-CI]	Hazard Ratio [95 %-CI][d]	p-Value[d,e]	p-Value for Interaction Test[f]
SOC: Skin and subcutaneous tissue disorders, PT[g]: Rash maculo-papular									
Region									
Western Europe and North America	197	21 (10.7)	Not reached [-; -]	189	3 (1.6)	Not reached [-; -]	5.40 [1.60; 18.19]	0.006	0.158
Rest of the World	155	8 (5.2)	Not reached [-; -]	151	4 (2.6)	Not reached [-; -]	1.74 [0.52; 5.78]	0.368	
Gender									
Male	252	25 (9.9)	Not reached [-; -]	260	6 (2.3)	Not reached [-; -]	3.52 [1.44; 8.62]	0.006	0.829
Female	100	4 (4.0)	Not reached [-; -]	80	1 (1.3)	Not reached [-; -]	2.90 [0.32; 26.03]	0.341	
Baseline KPS Score									
100-90	292	22 (7.5)	Not reached [-; -]	282	6 (2.1)	Not reached [-; -]	3.10 [1.25; 7.67]	0.014	0.618
80-70	60	7 (11.7)	Not reached [113.9; -]	58	1 (1.7)	Not reached [-; -]	3.97 [0.48; 33.01]	0.202	
IMDC Prognostic Status at Baseline									
Favorable	109	8 (7.3)	Not reached [-; -]	117	2 (1.7)	Not reached [-; -]	3.79 [0.80; 17.90]	0.093	0.962
Intermediate	208	17 (8.2)	Not reached [-; -]	185	4 (2.2)	Not reached [-; -]	3.06 [1.03; 9.14]	0.045	
Poor	33	4 (12.1)	Not reached [-; -]	35	1 (2.9)	Not reached [39.3; -]	3.38 [0.37; 30.94]	0.281	
IMDC Group Prognostic Status at Baseline									
Favorable	109	8 (7.3)	Not reached [-; -]	117	2 (1.7)	Not reached [-; -]	3.79 [0.80; 17.90]	0.093	0.790
Intermediate or Poor	241	21 (8.7)	Not reached [-; -]	220	5 (2.3)	Not reached [-; -]	3.08 [1.15; 8.21]	0.025	
SOC: Skin and subcutaneous tissue disorders, PT[g]: Skin discolouration									
Age category									
<65	193	1 (0.5)	n.c.	215	5 (2.3)	n.c.	n.c.	n.c.	n.c.
≥65	159	0 (0.0)	n.c.	125	5 (4.0)	n.c.	n.c.	n.c.	
Region									
Western Europe and North America	197	1 (0.5)	n.c.	189	3 (1.6)	n.c.	n.c.	n.c.	n.c.
Rest of the World	155	0 (0.0)	n.c.	151	7 (4.6)	n.c.	n.c.	n.c.	

Study: KEYNOTE 581[a]	Pembrolizumab + Lenvatinib			Sunitinib			Pembrolizumab + Lenvatinib vs. Sunitinib		
Adverse Events	N[b]	Participants with Event n (%)	Median Time[c] in weeks [95 %-CI]	N[b]	Participants with Event n (%)	Median Time[c] in weeks [95 %-CI]	Hazard Ratio [95 %-CI][d]	p-Value[d,e]	p-Value for Interaction Test[f]
Gender									
Male	252	1 (0.4)	n.c.	260	8 (3.1)	n.c.	n.c.	n.c.	n.c.
Female	100	0 (0.0)	n.c.	80	2 (2.5)	n.c.	n.c.	n.c.	
IMDC Prognostic Status at Baseline									
Favorable	109	0 (0.0)	n.c.	117	2 (1.7)	n.c.	n.c.	n.c.	n.c.
Intermediate	208	1 (0.5)	n.c.	185	8 (4.3)	n.c.	n.c.	n.c.	
Poor	33	0 (0.0)	n.c.	35	0 (0.0)	n.c.	n.c.	n.c.	
IMDC Group Prognostic Status at Baseline									
Favorable	109	0 (0.0)	n.c.	117	2 (1.7)	n.c.	n.c.	n.c.	n.c.
Intermediate or Poor	241	1 (0.4)	n.c.	220	8 (3.6)	n.c.	n.c.	n.c.	
SOC: Skin and subcutaneous tissue disorders, PT[g]: Yellow skin									
Age category									
<65	193	0 (0.0)	Not reached [-; -]	215	21 (9.8)	Not reached [-; -]	n.a. [n.a.; n.a.]	< 0.001	0.997
≥65	159	0 (0.0)	Not reached [-; -]	125	11 (8.8)	Not reached [-; -]	n.a. [n.a.; n.a.]	< 0.001	
Region									
Western Europe and North America	197	0 (0.0)	Not reached [-; -]	189	24 (12.7)	Not reached [-; -]	n.a. [n.a.; n.a.]	< 0.001	0.997
Rest of the World	155	0 (0.0)	Not reached [-; -]	151	8 (5.3)	Not reached [-; -]	n.a. [n.a.; n.a.]	0.004	
Gender									
Male	252	0 (0.0)	Not reached [-; -]	260	25 (9.6)	Not reached [-; -]	n.a. [n.a.; n.a.]	< 0.001	0.997
Female	100	0 (0.0)	Not reached [-; -]	80	7 (8.8)	Not reached [-; -]	n.a. [n.a.; n.a.]	0.003	
Baseline KPS Score									
100-90	292	0 (0.0)	Not reached [-; -]	282	30 (10.6)	Not reached [-; -]	n.a. [n.a.; n.a.]	< 0.001	0.997
80-70	60	0 (0.0)	Not reached [-; -]	58	2 (3.4)	Not reached [-; -]	n.a. [n.a.; n.a.]	0.149	

Study: KEYNOTE 581[a]	Pembrolizumab + Lenvatinib			Sunitinib			Pembrolizumab + Lenvatinib vs. Sunitinib		
Adverse Events	N[b]	Participants with Event n (%)	Median Time[c] in weeks [95 %-CI]	N[b]	Participants with Event n (%)	Median Time[c] in weeks [95 %-CI]	Hazard Ratio [95 %-CI][d]	p-Value[d,e]	p-Value for Interaction Test[f]
IMDC Prognostic Status at Baseline									
Favorable	109	0 (0.0)	Not reached [-; -]	117	13 (11.1)	Not reached [-; -]	n.a. [n.a.; n.a.]	< 0.001	> 0.999
Intermediate	208	0 (0.0)	Not reached [-; -]	185	18 (9.7)	Not reached [-; -]	n.a. [n.a.; n.a.]	< 0.001	
Poor	33	0 (0.0)	Not reached [-; -]	35	1 (2.9)	Not reached [-; -]	n.a. [n.a.; n.a.]	0.332	
IMDC Group Prognostic Status at Baseline									
Favorable	109	0 (0.0)	Not reached [-; -]	117	13 (11.1)	Not reached [-; -]	n.a. [n.a.; n.a.]	< 0.001	0.997
Intermediate or Poor	241	0 (0.0)	Not reached [-; -]	220	19 (8.6)	Not reached [-; -]	n.a. [n.a.; n.a.]	< 0.001	
SOC: Vascular disorders, PT[g]: Hypertension									
Age category									
<65	193	106 (54.9)	58.3 [16.4; 91.6]	215	83 (38.6)	Not reached [64.0; -]	1.37 [1.03; 1.83]	0.031	0.502
≥65	159	89 (56.0)	15.0 [5.9; 63.0]	125	58 (46.4)	34.1 [20.6; -]	1.19 [0.86; 1.66]	0.298	
Region									
Western Europe and North America	197	125 (63.5)	11.7 [6.1; 24.0]	189	86 (45.5)	57.0 [27.1; -]	1.36 [1.03; 1.79]	0.029	0.591
Rest of the World	155	70 (45.2)	117.4 [35.3; -]	151	55 (36.4)	Not reached [105.1; -]	1.23 [0.86; 1.75]	0.252	
Gender									
Male	252	143 (56.7)	38.1 [13.7; 76.4]	260	109 (41.9)	105.1 [45.3; -]	1.32 [1.03; 1.69]	0.030	0.859
Female	100	52 (52.0)	18.3 [6.3; -]	80	32 (40.0)	Not reached [19.0; -]	1.31 [0.85; 2.04]	0.225	
Baseline KPS Score									
100-90	292	166 (56.8)	21.1 [11.9; 63.1]	282	120 (42.6)	105.1 [45.3; -]	1.33 [1.05; 1.69]	0.017	0.793
80-70	60	29 (48.3)	91.1 [9.0; -]	58	21 (36.2)	Not reached [26.6; -]	1.17 [0.66; 2.08]	0.586	
IMDC Prognostic Status at Baseline									
Favorable	109	60 (55.0)	24.0 [9.3; 126.9]	117	53 (45.3)	Not reached [21.1; -]	1.18 [0.82; 1.71]	0.373	0.235
Intermediate	208	115 (55.3)	26.0 [9.7; 77.4]	185	79 (42.7)	105.1 [28.0; -]	1.29 [0.97; 1.72]	0.080	
Poor	33	18 (54.5)	38.1 [5.9; -]	35	7 (20.0)	Not reached [54.1; -]	2.21 [0.90; 5.41]	0.082	

Study: KEYNOTE 581[a]	Pembrolizumab + Lenvatinib			Sunitinib			Pembrolizumab + Lenvatinib vs. Sunitinib		
Adverse Events	N[b]	Participants with Event n (%)	Median Time[c] in weeks [95 %-CI]	N[b]	Participants with Event n (%)	Median Time[c] in weeks [95 %-CI]	Hazard Ratio [95 %-CI][d]	p-Value[d,e]	p-Value for Interaction Test[f]
IMDC Group Prognostic Status at Baseline									
Favorable	109	60 (55.0)	24.0 [9.3; 126.9]	117	53 (45.3)	Not reached [21.1; -]	1.18 [0.82; 1.71]	0.373	0.430
Intermediate or Poor	241	133 (55.2)	38.1 [12.1; 75.4]	220	86 (39.1)	105.1 [38.7; -]	1.38 [1.05; 1.81]	0.020	

a: Database Cutoff Date: 28AUG2020
b: Number of participants: all-participants-as-treated population
c: From product-limit (Kaplan-Meier) method for censored data
d: Based on Cox regression model with treatment as a covariate using Wald confidence interval
e: Two-sided p-value using Wald test (Score test in case of zero event in one treatment group)
f: Based on Cox model with treatment and subgroup as covariates, and treatment-by-subgroup interaction (p-value of likelihood ratio test for interaction term)
g: 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; IMDC: International Metastatic Renal Cell Carcinoma Database Consortium; KPS: Karnofsky Performance Status; n.a.: not applicable (when estimation not possible); n.c.: not calculated. At least 10 subjects per subgroup and at least 10 events in one of the subgroups necessary; PT: Preferred Term; SOC: System Organ Class

Schwerwiegende unerwünschte Ereignisse (SOC und PT)

Tabelle 4G-30: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für den Endpunkt Schwerwiegende unerwünschte Ereignisse (SOC) aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE 581[a]	Pembrolizumab + Lenvatinib			Sunitinib			Pembrolizumab + Lenvatinib vs. Sunitinib		
Serious Adverse Events	N[b]	Participants with Event n (%)	Median Time[c] in weeks [95 %-CI]	N[b]	Participants with Event n (%)	Median Time[c] in weeks [95 %-CI]	Hazard Ratio [95 %-CI][d]	p-Value[d,e]	p-Value for Interaction Test[f]
SOC[g]: Blood and lymphatic system disorders									
Age category									
<65	193	1 (0.5)	n.c.	215	4 (1.9)	n.c.	n.c.	n.c.	n.c.
≥65	159	2 (1.3)	n.c.	125	6 (4.8)	n.c.	n.c.	n.c.	
Region									
Western Europe and North America	197	2 (1.0)	Not reached [-; -]	189	8 (4.2)	Not reached [-; -]	0.20 [0.04; 0.97]	0.046	0.616
Rest of the World	155	1 (0.6)	Not reached [-; -]	151	2 (1.3)	Not reached [-; -]	0.45 [0.04; 4.98]	0.515	
Gender									
Male	252	2 (0.8)	Not reached [-; -]	260	8 (3.1)	Not reached [-; -]	0.23 [0.05; 1.08]	0.062	0.736
Female	100	1 (1.0)	Not reached [-; -]	80	2 (2.5)	Not reached [-; -]	0.36 [0.03; 4.01]	0.407	

Study: KEYNOTE 581[a]	Pembrolizumab + Lenvatinib			Sunitinib			Pembrolizumab + Lenvatinib vs. Sunitinib		
Serious Adverse Events	N[b]	Participants with Event n (%)	Median Time[c] in weeks [95 %-CI]	N[b]	Participants with Event n (%)	Median Time[c] in weeks [95 %-CI]	Hazard Ratio [95 %-CI][d]	p-Value[d,e]	p-Value for Interaction Test[f]
Baseline KPS Score									
100-90	292	3 (1.0)	n.c.	282	6 (2.1)	n.c.	n.c.	n.c.	n.c.
80-70	60	0 (0.0)	n.c.	58	4 (6.9)	n.c.	n.c.	n.c.	
IMDC Prognostic Status at Baseline									
Favorable	109	0 (0.0)	n.c.	117	2 (1.7)	n.c.	n.c.	n.c.	n.c.
Intermediate	208	3 (1.4)	n.c.	185	5 (2.7)	n.c.	n.c.	n.c.	
Poor	33	0 (0.0)	n.c.	35	2 (5.7)	n.c.	n.c.	n.c.	
IMDC Group Prognostic Status at Baseline									
Favorable	109	0 (0.0)	Not reached [-; -]	117	2 (1.7)	Not reached [-; -]	n.a. [n.a.; n.a.]	0.146	0.311
Intermediate or Poor	241	3 (1.2)	Not reached [-; -]	220	7 (3.2)	Not reached [-; -]	0.34 [0.09; 1.32]	0.118	
SOC[g]: Cardiac disorders									
Age category									
<65	193	12 (6.2)	Not reached [-; -]	215	1 (0.5)	Not reached [-; -]	8.96 [1.16; 69.33]	0.036	0.202
≥65	159	11 (6.9)	Not reached [156.0; -]	125	3 (2.4)	Not reached [-; -]	2.20 [0.61; 7.94]	0.228	
Region									
Western Europe and North America	197	14 (7.1)	Not reached [156.0; -]	189	3 (1.6)	Not reached [-; -]	3.05 [0.87; 10.72]	0.082	0.478
Rest of the World	155	9 (5.8)	Not reached [-; -]	151	1 (0.7)	Not reached [-; -]	6.82 [0.86; 54.01]	0.069	
Gender									
Male	252	19 (7.5)	Not reached [156.0; -]	260	3 (1.2)	Not reached [-; -]	4.36 [1.28; 14.79]	0.018	0.599
Female	100	4 (4.0)	Not reached [-; -]	80	1 (1.3)	Not reached [-; -]	3.07 [0.34; 27.46]	0.316	
Baseline KPS Score									
100-90	292	20 (6.8)	Not reached [156.0; -]	282	3 (1.1)	Not reached [-; -]	4.82 [1.43; 16.29]	0.011	0.461
80-70	60	3 (5.0)	Not reached [-; -]	58	1 (1.7)	Not reached [-; -]	1.61 [0.16; 15.93]	0.682	

Study: KEYNOTE 581[a]	Pembrolizumab + Lenvatinib			Sunitinib			Pembrolizumab + Lenvatinib vs. Sunitinib		
Serious Adverse Events	N[b]	Participants with Event n (%)	Median Time[c] in weeks [95 %-CI]	N[b]	Participants with Event n (%)	Median Time[c] in weeks [95 %-CI]	Hazard Ratio [95 %-CI][d]	p-Value[d,e]	p-Value for Interaction Test[f]
IMDC Prognostic Status at Baseline									
Favorable	109	8 (7.3)	Not reached [-; -]	117	0 (0.0)	Not reached [-; -]	n.a. [n.a.; n.a.]	0.009	0.061
Intermediate	208	12 (5.8)	Not reached [156.0; -]	185	4 (2.2)	Not reached [-; -]	1.75 [0.55; 5.54]	0.344	
Poor	33	3 (9.1)	Not reached [-; -]	35	0 (0.0)	Not reached [-; -]	n.a. [n.a.; n.a.]	0.257	
SOC[g]: Endocrine disorders									
Age category									
<65	193	4 (2.1)	n.c.	215	0 (0.0)	n.c.	n.c.	n.c.	n.c.
≥65	159	7 (4.4)	n.c.	125	1 (0.8)	n.c.	n.c.	n.c.	
Region									
Western Europe and North America	197	4 (2.0)	n.c.	189	1 (0.5)	n.c.	n.c.	n.c.	n.c.
Rest of the World	155	7 (4.5)	n.c.	151	0 (0.0)	n.c.	n.c.	n.c.	
Gender									
Male	252	9 (3.6)	Not reached [-; -]	260	1 (0.4)	Not reached [-; -]	8.01 [1.01; 63.35]	0.049	0.573
Female	100	2 (2.0)	Not reached [-; -]	80	0 (0.0)	Not reached [-; -]	n.a. [n.a.; n.a.]	0.233	
Baseline KPS Score									
100-90	292	8 (2.7)	n.c.	282	1 (0.4)	n.c.	n.c.	n.c.	n.c.
80-70	60	3 (5.0)	n.c.	58	0 (0.0)	n.c.	n.c.	n.c.	
IMDC Prognostic Status at Baseline									
Favorable	109	5 (4.6)	n.c.	117	0 (0.0)	n.c.	n.c.	n.c.	n.c.
Intermediate	208	5 (2.4)	n.c.	185	1 (0.5)	n.c.	n.c.	n.c.	
Poor	33	0 (0.0)	n.c.	35	0 (0.0)	n.c.	n.c.	n.c.	
IMDC Group Prognostic Status at Baseline									
Favorable	109	5 (4.6)	n.c.	117	0 (0.0)	n.c.	n.c.	n.c.	n.c.
Intermediate or Poor	241	5 (2.1)	n.c.	220	1 (0.5)	n.c.	n.c.	n.c.	

Study: KEYNOTE 581[a]	Pembrolizumab + Lenvatinib			Sunitinib			Pembrolizumab + Lenvatinib vs. Sunitinib		
Serious Adverse Events	N[b]	Participants with Event n (%)	Median Time[c] in weeks [95 %-CI]	N[b]	Participants with Event n (%)	Median Time[c] in weeks [95 %-CI]	Hazard Ratio [95 %-CI][d]	p-Value[d,e]	p-Value for Interaction Test[f]

a: Database Cutoff Date: 28AUG2020

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

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

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

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

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

g: 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; IMDC: International Metastatic Renal Cell Carcinoma Database Consortium; KPS: Karnofsky Performance Status; n.a.: not applicable (when estimation not possible); n.c.: not calculated. At least 10 subjects per subgroup and at least 10 events in one of the subgroups necessary; SOC: System Organ Class

Tabelle 4G-31: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für den Endpunkt Schwere unerwünschte Ereignisse (CTCAE-Grad 3-5) (SOC) aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE 581[a]	Pembrolizumab + Lenvatinib			Sunitinib			Pembrolizumab + Lenvatinib vs. Sunitinib		
Severe Adverse Events (CTCAE-Grade 3-5)	N[b]	Participants with Event n (%)	Median Time[c] in weeks [95 %-CI]	N[b]	Participants with Event n (%)	Median Time[c] in weeks [95 %-CI]	Hazard Ratio [95 %-CI][d]	p-Value[d,e]	p-Value for Interaction Test[f]
SOC[g]: Blood and lymphatic system disorders									
Age category									
<65	193	6 (3.1)	Not reached [-; -]	215	31 (14.4)	Not reached [-; -]	0.17 [0.07; 0.41]	< 0.001	0.725
≥65	159	8 (5.0)	Not reached [-; -]	125	24 (19.2)	Not reached [-; -]	0.20 [0.09; 0.45]	< 0.001	
Region									
Western Europe and North America	197	7 (3.6)	Not reached [-; -]	189	28 (14.8)	Not reached [-; -]	0.18 [0.08; 0.41]	< 0.001	0.863
Rest of the World	155	7 (4.5)	Not reached [-; -]	151	27 (17.9)	Not reached [-; -]	0.21 [0.09; 0.47]	< 0.001	
Gender									
Male	252	8 (3.2)	Not reached [-; -]	260	38 (14.6)	Not reached [-; -]	0.16 [0.08; 0.35]	< 0.001	0.592
Female	100	6 (6.0)	Not reached [-; -]	80	17 (21.3)	Not reached [-; -]	0.23 [0.09; 0.59]	0.002	
Baseline KPS Score									
100-90	292	12 (4.1)	Not reached [-; -]	282	41 (14.5)	Not reached [-; -]	0.22 [0.12; 0.43]	< 0.001	0.235
80-70	60	2 (3.3)	Not reached [-; -]	58	14 (24.1)	Not reached [33.1; -]	0.09 [0.02; 0.39]	0.001	

Study: KEYNOTE 581[a]	Pembrolizumab + Lenvatinib			Sunitinib			Pembrolizumab + Lenvatinib vs. Sunitinib		
Severe Adverse Events (CTCAE-Grade 3-5)	N[b]	Participants with Event n (%)	Median Time[c] in weeks [95 %-CI]	N[b]	Participants with Event n (%)	Median Time[c] in weeks [95 %-CI]	Hazard Ratio [95 %-CI][d]	p-Value[d,e]	p-Value for Interaction Test[f]
IMDC Group Prognostic Status at Baseline									
Favorable	109	1 (0.9)	Not reached [-; -]	117	19 (16.2)	Not reached [-; -]	0.05 [0.01; 0.35]	0.003	0.062
Intermediate or Poor	241	13 (5.4)	Not reached [-; -]	220	35 (15.9)	Not reached [-; -]	0.25 [0.13; 0.48]	< 0.001	
SOC[g]: Cardiac disorders									
Age category									
<65	193	12 (6.2)	Not reached [-; -]	215	3 (1.4)	Not reached [-; -]	2.93 [0.82; 10.51]	0.098	0.792
≥65	159	13 (8.2)	156.0 [-; -]	125	2 (1.6)	Not reached [-; -]	4.05 [0.91; 18.04]	0.067	
Region									
Western Europe and North America	197	16 (8.1)	Not reached [156.0; -]	189	3 (1.6)	Not reached [-; -]	3.34 [0.97; 11.57]	0.057	0.989
Rest of the World	155	9 (5.8)	Not reached [-; -]	151	2 (1.3)	Not reached [-; -]	3.35 [0.72; 15.60]	0.124	
Gender									
Male	252	18 (7.1)	Not reached [156.0; -]	260	3 (1.2)	Not reached [-; -]	4.03 [1.18; 13.73]	0.026	0.444
Female	100	7 (7.0)	Not reached [-; -]	80	2 (2.5)	Not reached [-; -]	2.41 [0.50; 11.65]	0.275	
Baseline KPS Score									
100-90	292	21 (7.2)	Not reached [156.0; -]	282	4 (1.4)	Not reached [-; -]	3.68 [1.26; 10.77]	0.017	0.725
80-70	60	4 (6.7)	Not reached [-; -]	58	1 (1.7)	Not reached [-; -]	2.18 [0.23; 20.36]	0.495	
IMDC Prognostic Status at Baseline									
Favorable	109	8 (7.3)	Not reached [-; -]	117	1 (0.9)	Not reached [-; -]	6.69 [0.83; 53.66]	0.074	0.347
Intermediate	208	14 (6.7)	Not reached [156.0; -]	185	4 (2.2)	Not reached [-; -]	2.06 [0.66; 6.39]	0.211	
Poor	33	3 (9.1)	Not reached [-; -]	35	0 (0.0)	Not reached [-; -]	n.a. [n.a.; n.a.]	0.338	
IMDC Group Prognostic Status at Baseline									
Favorable	109	8 (7.3)	Not reached [-; -]	117	1 (0.9)	Not reached [-; -]	6.69 [0.83; 53.66]	0.074	0.323
Intermediate or Poor	241	17 (7.1)	Not reached [156.0; -]	220	4 (1.8)	Not reached [-; -]	2.39 [0.79; 7.23]	0.124	
SOC[g]: Endocrine disorders									
Age category									
<65	193	4 (2.1)	n.c.	215	0 (0.0)	n.c.	n.c.	n.c.	n.c.
≥65	159	6 (3.8)	n.c.	125	0 (0.0)	n.c.	n.c.	n.c.	

Study: KEYNOTE 581[a]	Pembrolizumab + Lenvatinib			Sunitinib			Pembrolizumab + Lenvatinib vs. Sunitinib		
Severe Adverse Events (CTCAE-Grade 3-5)	N[b]	Participants with Event n (%)	Median Time[c] in weeks [95 %-CI]	N[b]	Participants with Event n (%)	Median Time[c] in weeks [95 %-CI]	Hazard Ratio [95 %-CI][d]	p-Value[d,e]	p-Value for Interaction Test[f]
Region									
Western Europe and North America	197	5 (2.5)	n.c.	189	0 (0.0)	n.c.	n.c.	n.c.	n.c.
Rest of the World	155	5 (3.2)	n.c.	151	0 (0.0)	n.c.	n.c.	n.c.	
Gender									
Male	252	7 (2.8)	n.c.	260	0 (0.0)	n.c.	n.c.	n.c.	n.c.
Female	100	3 (3.0)	n.c.	80	0 (0.0)	n.c.	n.c.	n.c.	
Baseline KPS Score									
100-90	292	8 (2.7)	n.c.	282	0 (0.0)	n.c.	n.c.	n.c.	n.c.
80-70	60	2 (3.3)	n.c.	58	0 (0.0)	n.c.	n.c.	n.c.	
IMDC Prognostic Status at Baseline									
Favorable	109	5 (4.6)	n.c.	117	0 (0.0)	n.c.	n.c.	n.c.	n.c.
Intermediate	208	4 (1.9)	n.c.	185	0 (0.0)	n.c.	n.c.	n.c.	
Poor	33	0 (0.0)	n.c.	35	0 (0.0)	n.c.	n.c.	n.c.	
IMDC Group Prognostic Status at Baseline									
Favorable	109	5 (4.6)	n.c.	117	0 (0.0)	n.c.	n.c.	n.c.	n.c.
Intermediate or Poor	241	4 (1.7)	n.c.	220	0 (0.0)	n.c.	n.c.	n.c.	
SOC[g]: Renal and urinary disorders									
Age category									
<65	193	20 (10.4)	Not reached [-; -]	215	11 (5.1)	Not reached [-; -]	1.51 [0.72; 3.16]	0.280	0.874
≥65	159	26 (16.4)	Not reached [-; -]	125	10 (8.0)	Not reached [-; -]	1.75 [0.84; 3.64]	0.135	
Region									
Western Europe and North America	197	22 (11.2)	Not reached [-; -]	189	13 (6.9)	Not reached [-; -]	1.21 [0.60; 2.42]	0.597	0.166
Rest of the World	155	24 (15.5)	Not reached [-; -]	151	8 (5.3)	Not reached [-; -]	2.57 [1.15; 5.73]	0.021	
Gender									
Male	252	31 (12.3)	Not reached [-; -]	260	15 (5.8)	Not reached [-; -]	1.68 [0.90; 3.13]	0.101	> 0.999
Female	100	15 (15.0)	Not reached [-; -]	80	6 (7.5)	Not reached [-; -]	1.71 [0.66; 4.44]	0.270	

Study: KEYNOTE 581[a]	Pembrolizumab + Lenvatinib			Sunitinib			Pembrolizumab + Lenvatinib vs. Sunitinib		
Severe Adverse Events (CTCAE-Grade 3-5)	N[b]	Participants with Event n (%)	Median Time[c] in weeks [95 %-CI]	N[b]	Participants with Event n (%)	Median Time[c] in weeks [95 %-CI]	Hazard Ratio [95 %-CI][d]	p-Value[d,e]	p-Value for Interaction Test[f]
Baseline KPS Score									
100-90	292	39 (13.4)	Not reached [-; -]	282	15 (5.3)	Not reached [-; -]	2.07 [1.14; 3.77]	0.017	0.133
80-70	60	7 (11.7)	Not reached [121.3; -]	58	6 (10.3)	Not reached [-; -]	0.81 [0.27; 2.46]	0.708	
SOC[g]: Skin and subcutaneous tissue disorders									
Region									
Western Europe and North America	197	22 (11.2)	Not reached [-; -]	189	12 (6.3)	Not reached [-; -]	1.43 [0.70; 2.91]	0.321	0.348
Rest of the World	155	18 (11.6)	Not reached [-; -]	151	6 (4.0)	Not reached [-; -]	2.52 [1.00; 6.37]	0.050	
Gender									
Male	252	27 (10.7)	Not reached [-; -]	260	15 (5.8)	Not reached [-; -]	1.48 [0.78; 2.79]	0.228	0.283
Female	100	13 (13.0)	Not reached [-; -]	80	3 (3.8)	Not reached [-; -]	3.33 [0.95; 11.73]	0.061	
Baseline KPS Score									
100-90	292	33 (11.3)	Not reached [-; -]	282	17 (6.0)	Not reached [-; -]	1.60 [0.89; 2.89]	0.116	0.226
80-70	60	7 (11.7)	Not reached [-; -]	58	1 (1.7)	Not reached [-; -]	4.85 [0.59; 39.92]	0.142	
IMDC Prognostic Status at Baseline									
Favorable	109	11 (10.1)	Not reached [-; -]	117	10 (8.5)	Not reached [-; -]	1.07 [0.45; 2.51]	0.883	0.232
Intermediate	208	28 (13.5)	Not reached [-; -]	185	8 (4.3)	Not reached [-; -]	2.59 [1.17; 5.70]	0.018	
Poor	33	1 (3.0)	Not reached [-; -]	35	0 (0.0)	Not reached [-; -]	n.a. [n.a.; n.a.]	0.303	
IMDC Group Prognostic Status at Baseline									
Favorable	109	11 (10.1)	Not reached [-; -]	117	10 (8.5)	Not reached [-; -]	1.07 [0.45; 2.51]	0.883	0.120
Intermediate or Poor	241	29 (12.0)	Not reached [-; -]	220	8 (3.6)	Not reached [-; -]	2.66 [1.21; 5.86]	0.015	

a: Database Cutoff Date: 28AUG2020

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

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

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

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

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

g: 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; CTCAE: Common Terminology Criteria for Adverse Events; IMDC: International Metastatic Renal Cell Carcinoma Database Consortium; KPS: Karnofsky Performance Status; n.a.: not applicable (when estimation not possible); n.c.: not calculated. At least 10 subjects per subgroup and at least 10 events in one of the subgroups necessary; SOC: System Organ Class

Tabelle 4G-32: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für den Endpunkt Schwere unerwünschte Ereignisse (CTCAE-Grad 3-5) (PT) aus RCT mit dem zu bewertenden Arzneimittel

Study: KEYNOTE 581[a]	**Pembrolizumab + Lenvatinib**			**Sunitinib**			**Pembrolizumab + Lenvatinib vs. Sunitinib**		
Severe Adverse Events (CTCAE-Grade 3-5)	**N[b]**	**Participants with Event n (%)**	**Median Time[c] in weeks [95 %-CI]**	**N[b]**	**Participants with Event n (%)**	**Median Time[c] in weeks [95 %-CI]**	**Hazard Ratio [95 %-CI][d]**	**p-Value[d,e]**	**p-Value for Interaction Test[f]**
SOC: Blood and lymphatic system disorders, PT[g]: Anaemia									
Age category									
<65	193	3 (1.6)	Not reached [-; -]	215	7 (3.3)	Not reached [-; -]	0.35 [0.09; 1.36]	0.130	0.603
≥65	159	4 (2.5)	Not reached [-; -]	125	11 (8.8)	Not reached [-; -]	0.23 [0.07; 0.71]	0.011	
Region									
Western Europe and North America	197	4 (2.0)	Not reached [-; -]	189	10 (5.3)	Not reached [-; -]	0.28 [0.09; 0.91]	0.034	0.962
Rest of the World	155	3 (1.9)	Not reached [-; -]	151	8 (5.3)	Not reached [-; -]	0.29 [0.08; 1.09]	0.066	
Gender									
Male	252	4 (1.6)	Not reached [-; -]	260	13 (5.0)	Not reached [-; -]	0.24 [0.08; 0.76]	0.014	0.589
Female	100	3 (3.0)	Not reached [-; -]	80	5 (6.3)	Not reached [-; -]	0.37 [0.09; 1.55]	0.174	
Baseline KPS Score									
100-90	292	5 (1.7)	Not reached [-; -]	282	12 (4.3)	Not reached [-; -]	0.30 [0.10; 0.85]	0.024	0.658
80-70	60	2 (3.3)	Not reached [-; -]	58	6 (10.3)	Not reached [-; -]	0.23 [0.05; 1.18]	0.079	
IMDC Prognostic Status at Baseline									
Favorable	109	1 (0.9)	Not reached [-; -]	117	3 (2.6)	Not reached [-; -]	0.29 [0.03; 2.79]	0.285	0.088
Intermediate	208	6 (2.9)	Not reached [-; -]	185	9 (4.9)	Not reached [-; -]	0.44 [0.16; 1.25]	0.125	
Poor	33	0 (0.0)	Not reached [-; -]	35	5 (14.3)	Not reached [36.3; -]	n.a. [n.a.; n.a.]	0.004	
IMDC Group Prognostic Status at Baseline									
Favorable	109	1 (0.9)	Not reached [-; -]	117	3 (2.6)	Not reached [-; -]	0.29 [0.03; 2.79]	0.285	0.908
Intermediate or Poor	241	6 (2.5)	Not reached [-; -]	220	14 (6.4)	Not reached [-; -]	0.28 [0.11; 0.73]	0.009	
SOC: Blood and lymphatic system disorders, PT[g]: Neutropenia									
Age category									
<65	193	2 (1.0)	Not reached [-; -]	215	14 (6.5)	Not reached [-; -]	0.13 [0.03; 0.59]	0.008	0.191
≥65	159	0 (0.0)	Not reached [-; -]	125	6 (4.8)	Not reached [-; -]	n.a. [n.a.; n.a.]	0.002	

Study: KEYNOTE 581[a]	Pembrolizumab + Lenvatinib			Sunitinib			Pembrolizumab + Lenvatinib vs. Sunitinib		
Severe Adverse Events (CTCAE-Grade 3-5)	N[b]	Participants with Event n (%)	Median Time[c] in weeks [95 %-CI]	N[b]	Participants with Event n (%)	Median Time[c] in weeks [95 %-CI]	Hazard Ratio [95 %-CI][d]	p-Value[d,e]	p-Value for Interaction Test[f]
Region									
Western Europe and North America	197	0 (0.0)	Not reached [-; -]	189	6 (3.2)	Not reached [-; -]	n.a. [n.a.; n.a.]	0.010	0.240
Rest of the World	155	2 (1.3)	Not reached [-; -]	151	14 (9.3)	Not reached [-; -]	0.11 [0.03; 0.50]	0.004	
Gender									
Male	252	1 (0.4)	Not reached [-; -]	260	15 (5.8)	Not reached [-; -]	0.05 [0.01; 0.41]	0.005	0.551
Female	100	1 (1.0)	Not reached [-; -]	80	5 (6.3)	Not reached [-; -]	0.15 [0.02; 1.27]	0.082	
Baseline KPS Score									
100-90	292	2 (0.7)	Not reached [-; -]	282	16 (5.7)	Not reached [-; -]	0.10 [0.02; 0.44]	0.002	0.335
80-70	60	0 (0.0)	Not reached [-; -]	58	4 (6.9)	Not reached [-; -]	n.a. [n.a.; n.a.]	0.017	
IMDC Prognostic Status at Baseline									
Favorable	109	0 (0.0)	Not reached [-; -]	117	10 (8.5)	Not reached [-; -]	n.a. [n.a.; n.a.]	0.001	0.344
Intermediate	208	2 (1.0)	Not reached [-; -]	185	10 (5.4)	Not reached [-; -]	0.14 [0.03; 0.66]	0.013	
Poor	33	0 (0.0)	Not reached [-; -]	35	0 (0.0)	Not reached [-; -]	n.a. [n.a.; n.a.]	n.a.	
IMDC Group Prognostic Status at Baseline									
Favorable	109	0 (0.0)	Not reached [-; -]	117	10 (8.5)	Not reached [-; -]	n.a. [n.a.; n.a.]	0.001	0.145
Intermediate or Poor	241	2 (0.8)	Not reached [-; -]	220	10 (4.5)	Not reached [-; -]	0.14 [0.03; 0.65]	0.012	
SOC: Blood and lymphatic system disorders, PT[g]: Thrombocytopenia									
Age category									
<65	193	1 (0.5)	Not reached [-; -]	215	10 (4.7)	Not reached [-; -]	0.09 [0.01; 0.72]	0.023	0.880
≥65	159	1 (0.6)	Not reached [-; -]	125	9 (7.2)	Not reached [-; -]	0.08 [0.01; 0.61]	0.015	
Region									
Western Europe and North America	197	1 (0.5)	Not reached [-; -]	189	15 (7.9)	Not reached [-; -]	0.05 [0.01; 0.40]	0.004	0.375
Rest of the World	155	1 (0.6)	Not reached [-; -]	151	4 (2.6)	Not reached [-; -]	0.22 [0.02; 1.95]	0.173	
Gender									
Male	252	2 (0.8)	Not reached [-; -]	260	12 (4.6)	Not reached [-; -]	0.14 [0.03; 0.65]	0.012	0.157
Female	100	0 (0.0)	Not reached [-; -]	80	7 (8.8)	Not reached [-; -]	n.a. [n.a.; n.a.]	0.002	

Study: KEYNOTE 581[a]	Pembrolizumab + Lenvatinib			Sunitinib			Pembrolizumab + Lenvatinib vs. Sunitinib		
Severe Adverse Events (CTCAE-Grade 3-5)	N[b]	Participants with Event n (%)	Median Time[c] in weeks [95 %-CI]	N[b]	Participants with Event n (%)	Median Time[c] in weeks [95 %-CI]	Hazard Ratio [95 %-CI][d]	p-Value[d,e]	p-Value for Interaction Test[f]
Baseline KPS Score									
100-90	292	2 (0.7)	Not reached [-; -]	282	14 (5.0)	Not reached [-; -]	0.12 [0.03; 0.53]	0.005	0.271
80-70	60	0 (0.0)	Not reached [-; -]	58	5 (8.6)	Not reached [-; -]	n.a. [n.a.; n.a.]	0.008	
IMDC Prognostic Status at Baseline									
Favorable	109	0 (0.0)	Not reached [-; -]	117	6 (5.1)	Not reached [-; -]	n.a. [n.a.; n.a.]	0.014	0.426
Intermediate	208	2 (1.0)	Not reached [-; -]	185	11 (5.9)	Not reached [-; -]	0.13 [0.03; 0.61]	0.010	
Poor	33	0 (0.0)	Not reached [-; -]	35	2 (5.7)	Not reached [-; -]	n.a. [n.a.; n.a.]	0.091	
IMDC Group Prognostic Status at Baseline									
Favorable	109	0 (0.0)	Not reached [-; -]	117	6 (5.1)	Not reached [-; -]	n.a. [n.a.; n.a.]	0.014	0.288
Intermediate or Poor	241	2 (0.8)	Not reached [-; -]	220	13 (5.9)	Not reached [-; -]	0.11 [0.03; 0.50]	0.004	
SOC: Investigations, PT[g]: Amylase increased									
Age category									
<65	193	20 (10.4)	Not reached [-; -]	215	7 (3.3)	Not reached [-; -]	2.67 [1.12; 6.34]	0.026	0.955
≥65	159	12 (7.5)	Not reached [-; -]	125	3 (2.4)	Not reached [-; -]	3.11 [0.88; 11.05]	0.079	
Region									
Western Europe and North America	197	23 (11.7)	Not reached [-; -]	189	6 (3.2)	Not reached [-; -]	3.47 [1.41; 8.55]	0.007	0.489
Rest of the World	155	9 (5.8)	Not reached [-; -]	151	4 (2.6)	Not reached [-; -]	1.85 [0.57; 6.04]	0.307	
Gender									
Male	252	26 (10.3)	Not reached [-; -]	260	9 (3.5)	Not reached [-; -]	2.59 [1.21; 5.55]	0.014	0.620
Female	100	6 (6.0)	Not reached [-; -]	80	1 (1.3)	Not reached [-; -]	4.82 [0.58; 40.05]	0.146	
Baseline KPS Score									
100-90	292	29 (9.9)	Not reached [-; -]	282	9 (3.2)	Not reached [-; -]	2.84 [1.34; 6.02]	0.006	0.930
80-70	60	3 (5.0)	Not reached [-; -]	58	1 (1.7)	Not reached [-; -]	2.42 [0.25; 23.66]	0.448	

Study: KEYNOTE 581[a]	Pembrolizumab + Lenvatinib			Sunitinib			Pembrolizumab + Lenvatinib vs. Sunitinib		
Severe Adverse Events (CTCAE-Grade 3-5)	N[b]	Participants with Event n (%)	Median Time[c] in weeks [95 %-CI]	N[b]	Participants with Event n (%)	Median Time[c] in weeks [95 %-CI]	Hazard Ratio [95 %-CI][d]	p-Value[d,e]	p-Value for Interaction Test[f]
IMDC Prognostic Status at Baseline									
Favorable	109	12 (11.0)	Not reached [-; -]	117	3 (2.6)	Not reached [-; -]	4.17 [1.18; 14.79]	0.027	0.113
Intermediate	208	15 (7.2)	Not reached [-; -]	185	7 (3.8)	Not reached [-; -]	1.63 [0.66; 4.02]	0.292	
Poor	33	5 (15.2)	Not reached [-; -]	35	0 (0.0)	Not reached [-; -]	n.a. [n.a.; n.a.]	0.028	
IMDC Group Prognostic Status at Baseline									
Favorable	109	12 (11.0)	Not reached [-; -]	117	3 (2.6)	Not reached [-; -]	4.17 [1.18; 14.79]	0.027	0.408
Intermediate or Poor	241	20 (8.3)	Not reached [-; -]	220	7 (3.2)	Not reached [-; -]	2.25 [0.95; 5.35]	0.067	
SOC: Investigations, PT[g]: Neutrophil count decreased									
Age category									
<65	193	3 (1.6)	Not reached [-; -]	215	10 (4.7)	Not reached [-; -]	0.28 [0.08; 1.03]	0.056	0.802
≥65	159	3 (1.9)	Not reached [-; -]	125	9 (7.2)	137.7 [137.7; -]	0.19 [0.05; 0.72]	0.014	
Gender									
Male	252	3 (1.2)	Not reached [-; -]	260	13 (5.0)	Not reached [-; -]	0.20 [0.06; 0.69]	0.011	0.554
Female	100	3 (3.0)	Not reached [-; -]	80	6 (7.5)	Not reached [-; -]	0.31 [0.08; 1.26]	0.102	
Baseline KPS Score									
100-90	292	6 (2.1)	Not reached [-; -]	282	17 (6.0)	Not reached [137.7; -]	0.28 [0.11; 0.72]	0.008	0.280
80-70	60	0 (0.0)	Not reached [-; -]	58	2 (3.4)	Not reached [-; -]	n.a. [n.a.; n.a.]	0.080	
IMDC Prognostic Status at Baseline									
Favorable	109	2 (1.8)	Not reached [-; -]	117	12 (10.3)	Not reached [137.7; -]	0.15 [0.03; 0.68]	0.014	0.602
Intermediate	208	4 (1.9)	Not reached [-; -]	185	7 (3.8)	Not reached [-; -]	0.45 [0.13; 1.56]	0.210	
Poor	33	0 (0.0)	Not reached [-; -]	35	0 (0.0)	Not reached [-; -]	n.a. [n.a.; n.a.]	n.a.	
IMDC Group Prognostic Status at Baseline									
Favorable	109	2 (1.8)	Not reached [-; -]	117	12 (10.3)	Not reached [137.7; -]	0.15 [0.03; 0.68]	0.014	0.319
Intermediate or Poor	241	4 (1.7)	Not reached [-; -]	220	7 (3.2)	Not reached [-; -]	0.46 [0.13; 1.57]	0.214	

Study: KEYNOTE 581[a]	Pembrolizumab + Lenvatinib			Sunitinib			Pembrolizumab + Lenvatinib vs. Sunitinib		
Severe Adverse Events (CTCAE-Grade 3-5)	N[b]	Participants with Event n (%)	Median Time[c] in weeks [95 %-CI]	N[b]	Participants with Event n (%)	Median Time[c] in weeks [95 %-CI]	Hazard Ratio [95 %-CI][d]	p-Value[d,e]	p-Value for Interaction Test[f]
SOC: Investigations, PT[g]: Platelet count decreased									
Age category									
<65	193	3 (1.6)	Not reached [-; -]	215	9 (4.2)	Not reached [-; -]	0.34 [0.09; 1.25]	0.104	0.130
≥65	159	1 (0.6)	Not reached [-; -]	125	12 (9.6)	Not reached [-; -]	0.06 [0.01; 0.48]	0.008	
Region									
Western Europe and North America	197	2 (1.0)	Not reached [-; -]	189	4 (2.1)	Not reached [-; -]	0.49 [0.09; 2.65]	0.404	0.200
Rest of the World	155	2 (1.3)	Not reached [-; -]	151	17 (11.3)	Not reached [-; -]	0.10 [0.02; 0.45]	0.002	
Gender									
Male	252	2 (0.8)	Not reached [-; -]	260	14 (5.4)	Not reached [-; -]	0.14 [0.03; 0.60]	0.009	0.683
Female	100	2 (2.0)	Not reached [-; -]	80	7 (8.8)	Not reached [-; -]	0.22 [0.04; 1.04]	0.056	
Baseline KPS Score									
100-90	292	4 (1.4)	Not reached [-; -]	282	21 (7.4)	Not reached [-; -]	0.17 [0.06; 0.50]	0.001	0.997
80-70	60	0 (0.0)	Not reached [-; -]	58	0 (0.0)	Not reached [-; -]	n.a. [n.a.; n.a.]	n.a.	
IMDC Prognostic Status at Baseline									
Favorable	109	1 (0.9)	Not reached [-; -]	117	10 (8.5)	Not reached [-; -]	0.10 [0.01; 0.78]	0.028	0.793
Intermediate	208	3 (1.4)	Not reached [-; -]	185	11 (5.9)	Not reached [-; -]	0.23 [0.07; 0.84]	0.026	
Poor	33	0 (0.0)	Not reached [-; -]	35	0 (0.0)	Not reached [-; -]	n.a. [n.a.; n.a.]	n.a.	
IMDC Group Prognostic Status at Baseline									
Favorable	109	1 (0.9)	Not reached [-; -]	117	10 (8.5)	Not reached [-; -]	0.10 [0.01; 0.78]	0.028	0.486
Intermediate or Poor	241	3 (1.2)	Not reached [-; -]	220	11 (5.0)	Not reached [-; -]	0.24 [0.07; 0.86]	0.029	
SOC: Investigations, PT[g]: Weight decreased									
Age category									
<65	193	14 (7.3)	Not reached [-; -]	215	1 (0.5)	Not reached [-; -]	9.73 [1.28; 74.16]	0.028	0.287
≥65	159	14 (8.8)	Not reached [-; -]	125	0 (0.0)	Not reached [-; -]	n.a. [n.a.; n.a.]	0.006	
Region									
Western Europe and North America	197	18 (9.1)	Not reached [-; -]	189	1 (0.5)	Not reached [-; -]	9.96 [1.33; 74.75]	0.025	0.317
Rest of the World	155	10 (6.5)	Not reached [-; -]	151	0 (0.0)	Not reached [-; -]	n.a. [n.a.; n.a.]	0.007	

Study: KEYNOTE 581[a]	**Pembrolizumab + Lenvatinib**			**Sunitinib**			**Pembrolizumab + Lenvatinib vs. Sunitinib**		
Severe Adverse Events (CTCAE-Grade 3-5)	**N[b]**	**Participants with Event n (%)**	**Median Time[c] in weeks [95 %-CI]**	**N[b]**	**Participants with Event n (%)**	**Median Time[c] in weeks [95 %-CI]**	**Hazard Ratio [95 %-CI][d]**	**p-Value[d,e]**	**p-Value for Interaction Test[f]**
Gender									
Male	252	22 (8.7)	Not reached [-; -]	260	1 (0.4)	Not reached [-; -]	14.29 [1.92; 106.06]	0.009	0.528
Female	100	6 (6.0)	Not reached [-; -]	80	0 (0.0)	Not reached [-; -]	n.a. [n.a.; n.a.]	0.062	
IMDC Group Prognostic Status at Baseline									
Favorable	109	11 (10.1)	Not reached [-; -]	117	0 (0.0)	Not reached [-; -]	n.a. [n.a.; n.a.]	0.002	0.214
Intermediate or Poor	241	17 (7.1)	Not reached [-; -]	220	1 (0.5)	Not reached [-; -]	8.12 [1.08; 61.20]	0.042	
SOC: Renal and urinary disorders, PT[g]: Proteinuria									
Age category									
<65	193	11 (5.7)	Not reached [-; -]	215	6 (2.8)	Not reached [-; -]	1.67 [0.61; 4.55]	0.314	0.498
≥65	159	16 (10.1)	Not reached [-; -]	125	4 (3.2)	Not reached [-; -]	2.72 [0.91; 8.17]	0.075	
Region									
Western Europe and North America	197	10 (5.1)	Not reached [-; -]	189	6 (3.2)	Not reached [-; -]	1.27 [0.46; 3.55]	0.642	0.159
Rest of the World	155	17 (11.0)	Not reached [-; -]	151	4 (2.6)	Not reached [-; -]	3.70 [1.24; 11.03]	0.019	
Gender									
Male	252	19 (7.5)	Not reached [-; -]	260	8 (3.1)	Not reached [-; -]	1.99 [0.87; 4.57]	0.104	0.717
Female	100	8 (8.0)	Not reached [-; -]	80	2 (2.5)	Not reached [-; -]	2.96 [0.63; 14.00]	0.170	
Baseline KPS Score									
100-90	292	25 (8.6)	Not reached [-; -]	282	9 (3.2)	Not reached [-; -]	2.30 [1.07; 4.95]	0.033	0.737
80-70	60	2 (3.3)	Not reached [-; -]	58	1 (1.7)	Not reached [-; -]	1.51 [0.13; 17.32]	0.743	
IMDC Prognostic Status at Baseline									
Favorable	109	9 (8.3)	Not reached [-; -]	117	1 (0.9)	Not reached [-; -]	8.44 [1.07; 66.75]	0.043	0.158
Intermediate	208	15 (7.2)	Not reached [-; -]	185	7 (3.8)	Not reached [-; -]	1.61 [0.65; 3.97]	0.301	
Poor	33	3 (9.1)	Not reached [-; -]	35	2 (5.7)	Not reached [-; -]	1.43 [0.24; 8.64]	0.697	
IMDC Group Prognostic Status at Baseline									
Favorable	109	9 (8.3)	Not reached [-; -]	117	1 (0.9)	Not reached [-; -]	8.44 [1.07; 66.75]	0.043	0.060
Intermediate or Poor	241	18 (7.5)	Not reached [-; -]	220	9 (4.1)	Not reached [-; -]	1.54 [0.69; 3.44]	0.297	

Study: KEYNOTE 581[a]	Pembrolizumab + Lenvatinib			Sunitinib			Pembrolizumab + Lenvatinib vs. Sunitinib		
Severe Adverse Events (CTCAE-Grade 3-5)	N[b]	Participants with Event n (%)	Median Time[c] in weeks [95 %-CI]	N[b]	Participants with Event n (%)	Median Time[c] in weeks [95 %-CI]	Hazard Ratio [95 %-CI][d]	p-Value[d,e]	p-Value for Interaction Test[f]
SOC: Skin and subcutaneous tissue disorders, PT[g]: Rash									
Age category									
<65	193	4 (2.1)	n.c.	215	2 (0.9)	n.c.	n.c.	n.c.	n.c.
≥65	159	9 (5.7)	n.c.	125	0 (0.0)	n.c.	n.c.	n.c.	
Region									
Western Europe and North America	197	8 (4.1)	Not reached [-; -]	189	2 (1.1)	Not reached [-; -]	3.83 [0.81; 18.07]	0.089	0.183
Rest of the World	155	5 (3.2)	Not reached [-; -]	151	0 (0.0)	Not reached [-; -]	n.a. [n.a.; n.a.]	0.037	
Gender									
Male	252	5 (2.0)	n.c.	260	2 (0.8)	n.c.	n.c.	n.c.	n.c.
Female	100	8 (8.0)	n.c.	80	0 (0.0)	n.c.	n.c.	n.c.	
Baseline KPS Score									
100-90	292	11 (3.8)	Not reached [-; -]	282	2 (0.7)	Not reached [-; -]	5.25 [1.16; 23.71]	0.031	0.444
80-70	60	2 (3.3)	Not reached [-; -]	58	0 (0.0)	Not reached [-; -]	n.a. [n.a.; n.a.]	0.274	
IMDC Prognostic Status at Baseline									
Favorable	109	3 (2.8)	n.c.	117	2 (1.7)	n.c.	n.c.	n.c.	n.c.
Intermediate	208	9 (4.3)	n.c.	185	0 (0.0)	n.c.	n.c.	n.c.	
Poor	33	1 (3.0)	n.c.	35	0 (0.0)	n.c.	n.c.	n.c.	

a: Database Cutoff Date: 28AUG2020

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

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

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

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

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

g: 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; IMDC: International Metastatic Renal Cell Carcinoma Database Consortium; KPS: Karnofsky Performance Status; n.a.: not applicable (when estimation not possible); n.c.: not calculated. At least 10 subjects per subgroup and at least 10 events in one of the subgroups necessary; SOC: System Organ Class

Anhang 4-G4: Definition der Immunvermittelten unerwünschten Ereignisse (AEOSI) anhand der zugeordneten PT

Tabelle 4G-33: Definition der Immunvermittelten unerwünschten Ereignisse (AEOSI) anhand der zugeordneten PT in der Studie KEYNOTE 581/CLEAR

AEOSI	Preferred Terms	Immune-mediated (yes/no)
Pneumonitis	Acute interstitial pneumonitis, Autoimmune lung disease, Interstitial lung disease, Pneumonitis, Idiopathic pneumonia syndrome, Organising pneumonia, Immune-mediated pneumonitis	Yes
Colitis	Colitis, Colitis microscopic, Enterocolitis, Enterocolitis haemorrhagic, Necrotising colitis, Colitis erosive, Autoimmune colitis, Immune-mediated enterocolitis	Yes
Hepatitis	Hepatitis, Immune-mediated hepatitis, Autoimmune hepatitis, Hepatitis acute, Hepatitisfulminant, 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	Yes
Hypophysitis	Hypophysitis, Hypopituitarism, Lymphocytic 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	Dermatitis bullous, Dermatitis exfoliative, Dermatitis exfoliative generalised, Epidermal	Yes

Including Stevens-Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN): or **Severe Skin (continued): If grade 3 or higher**:	necrosis, Erythema multiforme, Exfoliative rash, Pemphigoid, Pemphigus, Skin necrosis, Stevens-Johnson syndrome, Toxic epidermal necrolysis, Toxic skin eruption, SJS-TEN overlap Rash, Rash erythematous, Rash maculo-papular, Rash pruritic, Rash pustular, Pruritus, Pruritus genital, Lichen planus, Oral lichen planus	Yes
Uveitis	Iritis, Uveitis, Cyclitis, Autoimmune uveitis, Iridocyclitis, Vogt-Koyanagi-Harada disease, Chorioretinitis, Choroiditis, Immune-mediated uveitis	Yes
Pancreatitis	Pancreatitis, Autoimmune pancreatitis, Pancreatitis acute, Pancreatitis haemorrhagic, Pancreatitis necrotising, Immune-mediated pancreatitis	Yes
Myositis	Myositis, Necrotising myositis, Polymyositis, Immune-mediated myositis, Rhabdomyolysis, Myopathy, Dermatomyositis, Autoimmune myositis	Yes
Guillain-Barre Syndrome	Demyelinating polyneuropathy, Guillain-Barre syndrome, Axonal neuropathy, Multifocal motor neuropathy, Polyneuropathy idiopathic progressive, Miller Fisher syndrome, Subacute inflammatory demyelinating polyneuropathy	Yes
Myocarditis	Myocarditis, Autoimmune myocarditis, Hypersensitivity myocarditis, Immune-mediated myocarditis	Yes

Encephalitis	Encephalitis, Encephalitis autoimmune, Limbic encephalitis, Noninfective encephalitis, Immune-mediated encephalitis	Yes
Sarcoidosis	Sarcoidosis, Cutaneous sarcoidosis, Ocular sarcoidosis, Pulmonary sarcoidosis	Yes
Infusion Reactions	Hypersensitivity, Drug hypersensitivity, Anaphylactic reaction, Anaphylactoid reaction, Cytokine release syndrome, Serum sickness, Serum sickness-like reaction, Infusion related reaction, Infusion related hypersensitivity reaction	No
Myasthenic Syndrome	Myasthenic syndrome, Myasthenia gravis, Myasthenia gravis crisis, Ocular myasthenia	Yes
Myelitis	Myelitis, Myelitis transverse	Yes

Anhang 4-G5: Definition der klinisch signifikanten Ereignisse (CSE) anhand der zugeordneten PT

Tabelle 4G-34: Definition der klinisch signifikanten Ereignisse (CSE) anhand der zugeordneten PT in der Studie KEYNOTE 581/CLEAR

CSE	Preferred Terms
Arterial Thromboembolic Events	Acute aortic syndrome, Acute myocardial infarction, Amaurosis, Amaurosis fugax, Angioplasty, Aortic bypass, Aortic embolus, Aortic surgery, Aortic thrombosis, Aortogram abnormal, Arterectomy, Arterectomy with graft replacement, Arterial angioplasty, Arterial bypass occlusion, Arterial bypass operation, Arterial bypass thrombosis, Arterial graft, Arterial occlusive disease, Arterial stent insertion, Arterial therapeutic procedure, Arterial thrombosis, Arteriogram abnormal, Arteriogram carotid abnormal, Arteriotomy, Artificial blood vessel occlusion, Atherectomy, Atherosclerotic plaque rupture, Atrial appendage closure, Atrial appendage resection, Basal ganglia infarction, Basilar artery occlusion, Basilar artery thrombosis, Blindness transient, Brachiocephalic artery occlusion, Capsular warning syndrome, Cardiac ventricular thrombosis, Carotid angioplasty, Carotid arterial embolus, Carotid artery bypass, Carotid artery occlusion, Carotid artery stent insertion, Carotid artery thrombosis, Carotid endarterectomy, Catheter site thrombosis, Cerebellar artery occlusion, Cerebellar artery thrombosis, Cerebral artery embolism, Cerebral artery occlusion, Cerebral artery stent insertion, Cerebral artery thrombosis, Cerebral hypoperfusion, Cerebral infarction, Cerebral ischaemia, Cerebral microembolism, Cerebrovascular accident, Cerebrovascular insufficiency, Cerebrovascular stenosis, Coeliac artery occlusion, Coronary angioplasty, Coronary arterial stent insertion, Coronary artery bypass, Coronary artery embolism, Coronary artery occlusion, Coronary artery reocclusion, Coronary artery surgery, Coronary artery thrombosis, Coronary endarterectomy, Coronary revascularisation, Coronary vascular graft occlusion, Device related thrombosis, Diplegia, Embolia cutis medicamentosa, Embolism arterial, Endarterectomy, Femoral artery embolism, Hemiparesis, Hemiplegia, Hepatic artery embolism, Hepatic artery occlusion, Hepatic artery thrombosis, Hypothenar hammer syndrome, Iliac artery embolism, Iliac artery occlusion, Internal capsule infarction, Intra-aortic balloon placement, Intracardiac thrombus, Intraoperative cerebral artery occlusion, Ischaemic cerebral infarction, Ischaemic stroke, Lacunar infarction, Leriche syndrome, Mesenteric arterial occlusion, Mesenteric arteriosclerosis, Mesenteric artery embolism, Mesenteric artery stenosis, Mesenteric artery stent insertion, Mesenteric artery thrombosis, Monoparesis, Monoplegia, Myocardial infarction, Myocardial necrosis, Ophthalmic artery thrombosis, Papillary muscle infarction, Paraneoplastic thrombosis, Paraparesis,

	Paraplegia, Paresis, Penile artery occlusion, Percutaneous coronary intervention, Peripheral arterial occlusive disease, Peripheral arterial reocclusion, Peripheral artery angioplasty, Peripheral artery bypass, Peripheral artery occlusion, Peripheral artery stent insertion, Peripheral artery surgery, Peripheral artery thrombosis, Peripheral embolism, Peripheral endarterectomy, Popliteal artery entrapment syndrome, Post procedural myocardial infarction, Postinfarction angina, Precerebral artery occlusion, Precerebral artery thrombosis, Profundaplasty, Pulmonary artery occlusion, Pulmonary artery therapeutic procedure, Pulmonary artery thrombosis, Pulmonary endarterectomy, Pulmonary tumour thrombotic microangiopathy, Renal artery angioplasty, Renal artery occlusion, Renal artery thrombosis, Renal embolism, Retinal artery embolism, Retinal artery occlusion, Retinal artery thrombosis, Silent myocardial infarction, Spinal artery embolism, Spinal artery thrombosis, Splenic artery thrombosis, Splenic embolism, Splenic infarction, Stroke in evolution, Subclavian artery embolism, Subclavian artery occlusion, Subclavian artery thrombosis, Thromboembolectomy, Thrombotic cerebral infarction, Thrombotic microangiopathy, Transient ischaemic attack, Truncus coeliacus thrombosis, Vascular pseudoaneurysm thrombosis, Vertebral artery occlusion, Vertebral artery thrombosis, Visual acuity reduced transiently

Cardiac Dysfunction	Visual acuity reduced transiently, Acute left ventricular failure, Acute pulmonary oedema, Acute right ventricular failure, Atrial septal defect acquired, Biopsy heart abnormal, Cardiac amyloidosis, Cardiac asthma, Cardiac failure, Cardiac failure acute, Cardiac failure chronic, Cardiac failure congestive, Cardiac failure high output, Cardiac hypertrophy, Cardiac iron overload, Cardiac sarcoidosis, Cardiac septal hypertrophy, Cardiogenic shock, Cardiohepatic syndrome, Cardiomyopathy, Cardiomyopathy acute, Cardiomyopathy alcoholic, Cardiomyopathy neonatal, Cardiopulmonary failure, Cardiorenal syndrome, Cardiotoxicity, Chagas' cardiomyopathy, Chronic left ventricular failure, Chronic right ventricular failure, Congestive cardiomyopathy, Congestive hepatopathy, Cor pulmonale, Cor pulmonale acute, Cor pulmonale chronic, Diabetic cardiomyopathy, Echocardiogram abnormal, Ejection fraction abnormal, Ejection fraction decreased, Eosinophilic myocarditis, Giant cell myocarditis, Hepatojugular reflux, HIV cardiomyopathy, Hypertrophic cardiomyopathy, Ischaemic cardiomyopathy, Left ventricular dysfunction, Left ventricular failure, Low cardiac output syndrome, Metabolic cardiomyopathy, Myocardial calcification, Myocardial fibrosis, Neonatal cardiac failure, Non-obstructive cardiomyopathy, Obesity cardiomyopathy, Obstructive shock, Peripartum cardiomyopathy, Pulmonary arterial wedge pressure increased, Pulmonary congestion, Pulmonary oedema, Pulmonary oedema neonatal, Radiation associated cardiac failure, Restrictive cardiomyopathy, Right ventricular dysfunction, Right ventricular ejection fraction decreased, Right ventricular failure, Stress cardiomyopathy, Tachycardia induced cardiomyopathy, Thyrotoxic cardiomyopathy, Toxic cardiomyopathy, Ventricular dysfunction, Ventricular failure, Ventricular hypokinesia, Ventricular septal defect acquired, Viral cardiomyopathy

Fistula Formation	Acquired tracheo-oesophageal fistula, Anal fistula, Anal fistula infection, Anal fistula repair, Anastomotic fistula, Anovulvar fistula, Aorto-bronchial fistula, Aortoenteric fistula, Aorto-oesophageal fistula, Arterioenteric fistula, Arteriovenous fistula, Arteriovenous fistula aneurysm, Arteriovenous fistula maturation failure, Arteriovenous fistula occlusion, Arteriovenous fistula operation, Arteriovenous fistula site complication, Arteriovenous fistula site infection, Arteriovenous fistula thrombosis, Atrio-oesophageal fistula, Biliary fistula, Biliary fistula repair, Biliary-bronchial fistula, Biliary-vascular fistula, Bladder fistula repair, Bone fistula, Bronchial fistula, Bronchial fistula repair, Bronchopleural fistula, Cerebrospinal fistula, Colon fistula repair, Colonic fistula, Congenital arteriovenous fistula, Congenital aural fistula, Congenital lip fistula, Dental fistula, Diverticular fistula, Dural arteriovenous fistula, Enterocolonic fistula, Enterocutaneous fistula, Enterovesical fistula, Female genital tract fistula, Fistula, Fistula discharge, Fistula inflammation, Fistula of small intestine, Fistula repair, Gallbladder fistula, Gallbladder fistula repair, Gastric fistula, Gastric fistula repair, Gastrointestinal fistula, Gastrointestinal fistula repair, Gastropleural fistula, Gastrosplenic fistula, Infected fistula, Intestinal fistula, Intestinal fistula infection, Intestinal fistula repair, Intrahepatic portal hepatic venous fistula, Jaw fistula, Labyrinthine fistula, Lacrimal fistula, Laryngeal fistula, Laryngeal fistula repair, Lymphatic fistula, Male genital tract fistula, Mammary fistula, Mammary fistula repair, Neovaginal fistula, Ocular fistula, Oesophageal fistula, Oesophageal fistula repair, Oesophageal-pulmonary fistula, Oesophagobronchial fistula, Oesophagomediastinal fistula, Oesophagopleural fistula, Oral cavity fistula, Oroantral fistula, Pancreatic fistula, Pancreatic fistula repair, Perineal fistula, Peritoneocutaneous fistula, Pharyngeal fistula, Pharyngeal fistula repair, Pleural fistula, Pleurocutaneous fistula, Post procedural fistula, Postauricular fistula, Pulmonary arteriovenous fistula, Pulmonary fistula, Rectal fistula repair, Rectoprostatic fistula, Rectourethral fistula, Renal pelvis fistula, Salivary gland fistula, Thyroglossal fistula, Thyroglossal fistula excision, Tracheal fistula, Tracheal fistula repair, Tracheo-oesophageal fistula, Ureteric fistula, Urethral fistula, Urethroperineal fistula, Urinary fistula, Urogenital fistula, Urogenital fistula repair, Uterine fistula, Vaginal fistula, Vaginal fistula repair, Vesical fistula, Vesicocutaneous fistula

GI Perforation	Abdominal abscess, Abdominal hernia perforation, Abdominal wall abscess, Abscess intestinal, Anal abscess, Anastomotic ulcer perforation, Appendiceal abscess, Appendicitis perforated, Chemical peritonitis, Colonic abscess, Diverticular perforation, Douglas' abscess, Duodenal perforation, Duodenal ulcer perforation, Duodenal ulcer perforation, obstructive, Duodenal ulcer repair, Gastric perforation, Gastric ulcer perforation, Gastric ulcer perforation, obstructive, Gastrointestinal anastomotic leak, Gastrointestinal perforation, Gastrointestinal ulcer perforation, Ileal perforation, Ileal ulcer perforation, Inguinal hernia perforation, Intestinal perforation, Intestinal ulcer perforation, Jejunal perforation, Jejunal ulcer perforation, Large intestinal ulcer perforation, Large intestine perforation, Lower gastrointestinal perforation, Mesenteric abscess, Neonatal intestinal perforation, Oesophageal abscess, Oesophageal perforation, Oesophageal rupture, Oesophageal ulcer perforation, Peptic ulcer perforation, Peptic ulcer perforation, obstructive, Perforated peptic ulcer oversewing, Perforated ulcer, Perineal abscess, Perirectal abscess, Peritoneal abscess, Peritonitis, Peritonitis bacterial, Pneumoperitoneum, Pneumoretroperitoneum, Procedural intestinal perforation, Rectal abscess, Rectal perforation, Retroperitoneal abscess, Small intestinal perforation, Small intestinal ulcer perforation, Umbilical hernia perforation, Upper gastrointestinal perforation

Hemorrhage	Abdominal wall haematoma, Abdominal wall haemorrhage, Abnormal withdrawal bleeding, Achenbach syndrome, Acute haemorrhagic leukoencephalitis, Acute haemorrhagic ulcerative colitis, Administration site bruise, Administration site haematoma, Administration site haemorrhage, Adrenal haematoma, Adrenal haemorrhage, Anal fissure haemorrhage, Anal haemorrhage, Anal ulcer haemorrhage, Anastomotic haemorrhage, Anastomotic ulcer haemorrhage, Aneurysm ruptured, Angina bullosa haemorrhagica, Anorectal varices haemorrhage, Anticoagulant-related nephropathy, Aortic aneurysm rupture, Aortic dissection rupture, Aortic intramural haematoma, Aortic perforation, Aortic rupture, Aponeurosis contusion, Application site bruise, Application site haematoma, Application site haemorrhage, Application site purpura, Arterial haemorrhage, Arterial intramural haematoma, Arterial perforation, Arterial rupture, Arteriovenous fistula site haematoma, Arteriovenous fistula site haemorrhage, Arteriovenous graft site haematoma, Arteriovenous graft site haemorrhage, Astringent therapy, Atrial rupture, Auricular haematoma, Basal ganglia haematoma, Basal ganglia haemorrhage, Basilar artery perforation, Bladder tamponade, Bleeding varicose vein, Blood blister, Blood loss anaemia, Blood urine, Blood urine present, Bloody discharge, Bloody peritoneal effluent, Bone contusion, Bone marrow haemorrhage, Brain contusion, Brain stem haematoma, Brain stem haemorrhage, Brain stem microhaemorrhage, Breast haematoma, Breast haemorrhage, Broad ligament haematoma, Bronchial haemorrhage, Bronchial varices haemorrhage, Bullous haemorrhagic dermatosis, Bursal haematoma, Cardiac contusion, Carotid aneurysm rupture, Carotid artery perforation, Catheter site bruise, Catheter site haematoma, Catheter site haemorrhage, Central nervous system haemorrhage, Cephalhaematoma, Cerebellar haematoma, Cerebellar haemorrhage, Cerebellar microhaemorrhage, Cerebral aneurysm perforation, Cerebral aneurysm ruptured syphilitic, Cerebral arteriovenous malformation haemorrhagic, Cerebral artery perforation, Cerebral cyst haemorrhage, Cerebral haematoma, Cerebral haemorrhage, Cerebral haemorrhage foetal, Cerebral haemorrhage neonatal, Cerebral microhaemorrhage, Cervix haematoma uterine, Cervix haemorrhage uterine, Chest wall haematoma, Choroidal haematoma, Choroidal haemorrhage, Chronic gastrointestinal bleeding, Chronic pigmented purpura, Ciliary body haemorrhage, Coital bleeding, Colonic haematoma, Conjunctival haemorrhage, Contusion, Corneal bleeding, Cullen's sign, Cystitis haemorrhagic, Deep dissecting haematoma, Diarrhoea haemorrhagic, Disseminated intravascular coagulation, Diverticulitis intestinal haemorrhagic, Diverticulum intestinal haemorrhagic, Duodenal ulcer haemorrhage,

	Duodenitis haemorrhagic, Dysfunctional uterine bleeding, Ear haemorrhage, Ecchymosis, Encephalitis haemorrhagic, Enterocolitis haemorrhagic, Epidural haemorrhage, Epistaxis, Exsanguination, Extra-axial haemorrhage, Extradural haematoma, Extradural haematoma evacuation, Extravasation blood, Eye contusion, Eye haematoma, Eye haemorrhage, Eyelid bleeding, Eyelid contusion, Eyelid haematoma, Femoral artery perforation, Femoral vein perforation, Foetal-maternal haemorrhage, Fothergill sign positive, Gastric haemorrhage, Gastric ulcer haemorrhage, Gastric ulcer haemorrhage, obstructive, Gastric varices haemorrhage, Gastritis alcoholic haemorrhagic, Gastritis haemorrhagic, Gastroduodenal haemorrhage, Gastrointestinal haemorrhage, Gastrointestinal polyp haemorrhage, Gastrointestinal ulcer haemorrhage, Gastrointestinal vascular malformation haemorrhagic, Genital contusion, Genital haemorrhage, Gingival bleeding, Graft haemorrhage, Grey Turner's sign, Haemangioma rupture, Haemarthrosis, Haematemesis, Haematochezia, Haematocoele, Haematoma, Haematoma evacuation, Haematoma infection, Haematoma muscle, Haematosalpinx, Haematospermia, Haematotympanum, Haematuria, Haematuria traumatic, Haemobilia, Haemoperitoneum, Haemophilic arthropathy, Haemophilic pseudotumour, Haemoptysis, Haemorrhage, Haemorrhage coronary artery, Haemorrhage foetal, Haemorrhage in pregnancy, Haemorrhage intracranial, Haemorrhage neonatal, Haemorrhage subcutaneous, Haemorrhage subepidermal, Haemorrhage urinary tract, Haemorrhagic adrenal infarction, Haemorrhagic arteriovenous malformation, Haemorrhagic ascites, Haemorrhagic breast cyst, Haemorrhagic cerebral infarction, Haemorrhagic cyst, Haemorrhagic diathesis, Haemorrhagic disease of newborn, Haemorrhagic disorder, Haemorrhagic erosive gastritis, Haemorrhagic hepatic cyst, Haemorrhagic infarction, Haemorrhagic necrotic pancreatitis, Haemorrhagic ovarian cyst, Haemorrhagic stroke, Haemorrhagic thyroid cyst, Haemorrhagic transformation stroke, Haemorrhagic tumour necrosis, Haemorrhagic urticaria, Haemorrhagic vasculitis, Haemorrhoidal haemorrhage, Haemostasis, Haemothorax, Henoch-Schonlein purpura, Hepatic haematoma, Hepatic haemorrhage, Hereditary haemorrhagic telangiectasia, Hyperfibrinolysis, Hyphaema, Iliac artery perforation, Iliac artery rupture, Iliac vein perforation, Immune thrombocytopenia, Implant site bruising, Implant site haematoma, Implant site haemorrhage, Incision site haematoma, Incision site haemorrhage, Increased tendency to bruise, Induced abortion haemorrhage, Inferior vena cava perforation, Infusion site bruising, Infusion site haematoma, Infusion site haemorrhage, Injection site bruising, Injection site haematoma, Injection site haemorrhage, Instillation site bruise, Instillation site

	haematoma, Instillation site haemorrhage, Internal haemorrhage, Intestinal haematoma, Intestinal haemorrhage, Intestinal varices haemorrhage, Intra-abdominal haematoma, Intra-abdominal haemorrhage, Intracerebral haematoma evacuation, Intracranial haematoma, Intracranial tumour haemorrhage, Intraocular haematoma, Intrapartum haemorrhage, Intraventricular haemorrhage, Intraventricular haemorrhage neonatal, Iris haemorrhage, Joint microhaemorrhage, Kidney contusion, Lacrimal haemorrhage, Large intestinal haemorrhage, Large intestinal ulcer haemorrhage, Laryngeal haematoma, Laryngeal haemorrhage, Lip haematoma, Lip haemorrhage, Liver contusion, Lower gastrointestinal haemorrhage, Lower limb artery perforation, Lymph node haemorrhage, Mallory-Weiss syndrome, Mediastinal haematoma, Mediastinal haemorrhage, Medical device site bruise, Medical device site haematoma, Medical device site haemorrhage, Melaena, Melaena neonatal, Meningorrhagia, Menometrorrhagia, Menorrhagia, Mesenteric haematoma, Mesenteric haemorrhage, Metrorrhagia, Mouth haemorrhage, Mucocutaneous haemorrhage, Mucosal haemorrhage, Muscle contusion, Muscle haemorrhage, Myocardial haemorrhage, Myocardial rupture, Naevus haemorrhage, Nail bed bleeding, Nasal septum haematoma, Neonatal gastrointestinal haemorrhage, Nephritis haemorrhagic, Nipple exudate bloody, Ocular retrobulbar haemorrhage, Oesophageal haemorrhage, Oesophageal intramural haematoma, Oesophageal ulcer haemorrhage, Oesophageal varices haemorrhage, Oesophagitis haemorrhagic, Optic disc haemorrhage, Optic nerve sheath haemorrhage, Oral blood blister, Oral contusion, Oral mucosa haematoma, Oral purpura, Orbital haematoma, Orbital haemorrhage, Osteorrhagia, Ovarian haematoma, Ovarian haemorrhage, Palpable purpura, Pancreatic haemorrhage, Pancreatic pseudocyst haemorrhage, Pancreatitis haemorrhagic, Papillary muscle haemorrhage, Paranasal sinus haematoma, Paranasal sinus haemorrhage, Parathyroid haemorrhage, Parotid gland haemorrhage, Pelvic haematoma, Pelvic haematoma obstetric, Pelvic haemorrhage, Penile contusion, Penile haematoma, Penile haemorrhage, Peptic ulcer haemorrhage, Pericardial haemorrhage, Perineal haematoma, Periorbital haematoma, Periorbital haemorrhage, Periosteal haematoma, Peripartum haemorrhage, Peripheral artery aneurysm rupture, Peripheral artery haematoma, Peritoneal haematoma, Periventricular haemorrhage neonatal, Petechiae, Pharyngeal contusion, Pharyngeal haematoma, Pharyngeal haemorrhage, Pituitary apoplexy, Pituitary haemorrhage, Placenta praevia haemorrhage, Polymenorrhagia, Post abortion haemorrhage, Post procedural contusion, Post procedural haematoma, Post procedural haematuria, Post procedural haemorrhage, Post

	transfusion purpura, Postmenopausal haemorrhage, Postpartum haemorrhage, Post-traumatic punctate intraepidermal haemorrhage, Premature separation of placenta, Procedural haemorrhage, Proctitis haemorrhagic, Prostatic haemorrhage, Pulmonary alveolar haemorrhage, Pulmonary contusion, Pulmonary haematoma, Pulmonary haemorrhage, Pulmonary haemorrhage neonatal, Puncture site bruise, Puncture site haematoma, Puncture site haemorrhage, Purpura, Purpura fulminans, Purpura neonatal, Purpura non-thrombocytopenic, Purpura senile, Putamen haemorrhage, Radiation associated haemorrhage, Rectal haemorrhage, Rectal ulcer haemorrhage, Renal artery perforation, Renal cyst haemorrhage, Renal haematoma, Renal haemorrhage, Respiratory tract haemorrhage, Respiratory tract haemorrhage neonatal, Retinal aneurysm rupture, Retinal haemorrhage, Retinopathy haemorrhagic, Retroperitoneal haematoma, Retroperitoneal haemorrhage, Retroplacental haematoma, Ruptured cerebral aneurysm, Scleral haemorrhage, Scrotal haematocoele, Scrotal haematoma, Scrotal haemorrhage, Shock haemorrhagic, Skin haemorrhage, Skin neoplasm bleeding, Skin ulcer haemorrhage, Small intestinal haemorrhage, Small intestinal ulcer haemorrhage, Soft tissue haemorrhage, Spermatic cord haemorrhage, Spinal cord haematoma, Spinal cord haemorrhage, Spinal epidural haematoma, Spinal epidural haemorrhage, Spinal subarachnoid haemorrhage, Spinal subdural haematoma, Spinal subdural haemorrhage, Spleen contusion, Splenic artery perforation, Splenic haematoma, Splenic haemorrhage, Splenic varices haemorrhage, Splinter haemorrhages, Spontaneous haematoma, Spontaneous haemorrhage, Stoma site haemorrhage, Stomatitis haemorrhagic, Subarachnoid haematoma, Subarachnoid haemorrhage, Subarachnoid haemorrhage neonatal, Subcapsular hepatic haematoma, Subcapsular renal haematoma, Subcapsular splenic haematoma, Subchorionic haematoma, Subchorionic haemorrhage, Subclavian artery perforation, Subclavian vein perforation, Subcutaneous haematoma, Subdural haematoma, Subdural haematoma evacuation, Subdural haemorrhage, Subdural haemorrhage neonatal, Subendocardial haemorrhage, Subgaleal haematoma, Subgaleal haemorrhage, Subretinal haematoma, Superior vena cava perforation, Testicular haemorrhage, Thalamus haemorrhage, Third stage postpartum haemorrhage, Thoracic haemorrhage, Thrombocytopenic purpura, Thrombotic thrombocytopenic purpura, Thyroid haemorrhage, Tongue haematoma, Tongue haemorrhage, Tonsillar haemorrhage, Tooth pulp haemorrhage, Tooth socket haemorrhage, Tracheal haemorrhage, Traumatic haematoma, Traumatic haemorrhage, Traumatic haemothorax, Traumatic intracranial haematoma, Traumatic intracranial haemorrhage, Tumour haemorrhage,

	Ulcer haemorrhage, Umbilical cord haemorrhage, Umbilical haematoma, Umbilical haemorrhage, Upper gastrointestinal haemorrhage, Ureteric haemorrhage, Urethral haemorrhage, Urinary bladder haematoma, Urinary bladder haemorrhage, Urogenital haemorrhage, Uterine haematoma, Uterine haemorrhage, Vaccination site bruising, Vaccination site haematoma, Vaccination site haemorrhage, Vaginal haematoma, Vaginal haemorrhage, Varicose vein ruptured, Vascular access site bruising, Vascular access site haematoma, Vascular access site haemorrhage, Vascular access site rupture, Vascular anastomotic haemorrhage, Vascular graft haemorrhage, Vascular pseudoaneurysm ruptured, Vascular purpura, Vascular rupture, Vein rupture, Venous haemorrhage, Venous perforation, Ventricle rupture, Vertebral artery perforation, Vessel puncture site bruise, Vessel puncture site haematoma, Vessel puncture site haemorrhage, Vitreous haematoma, Vitreous haemorrhage, Vulval haematoma, Vulval haematoma evacuation, Vulval haemorrhage, Withdrawal bleed, Wound haematoma, Wound haemorrhage

Hepatotoxicity	Acquired antithrombin III deficiency, Acquired factor IX deficiency, Acquired factor VIII deficiency, Acquired factor XI deficiency, Acquired hepatocerebral degeneration, Acquired protein S deficiency, Acute graft versus host disease in liver, Acute hepatic failure, Acute on chronic liver failure, Acute yellow liver atrophy, Alanine aminotransferase abnormal, Alanine aminotransferase increased, Allergic hepatitis, Alloimmune hepatitis, Ammonia abnormal, Ammonia increased, Anti factor X activity abnormal, Anti factor X activity decreased, Anti factor X activity increased, Antithrombin III decreased, Ascites, Aspartate aminotransferase abnormal, Aspartate aminotransferase increased, AST/ALT ratio abnormal, Asterixis, Autoimmune hepatitis, Bacterascites, Benign hepatic neoplasm, Benign hepatobiliary neoplasm, Bile output abnormal, Bile output decreased, Biliary ascites, Biliary cirrhosis, Biliary fibrosis, Bilirubin conjugated abnormal, Bilirubin conjugated increased, Bilirubin excretion disorder, Bilirubin urine present, Biopsy liver abnormal, Blood bilirubin abnormal, Blood bilirubin increased, Blood bilirubin unconjugated increased, Blood fibrinogen abnormal, Blood fibrinogen decreased, Blood thrombin abnormal, Blood thrombin decreased, Blood thromboplastin abnormal, Blood thromboplastin decreased, Bromosulphthalein test abnormal, Child-Pugh-Turcotte score abnormal, Child-Pugh-Turcotte score increased, Cholaemia, Cholangiosarcoma, Cholestasis, Cholestatic liver injury, Cholestatic pruritus, Chronic graft versus host disease in liver, Chronic hepatic failure, Chronic hepatitis, Coagulation factor decreased, Coagulation factor IX level abnormal, Coagulation factor IX level decreased, Coagulation factor V level abnormal, Coagulation factor V level decreased, Coagulation factor VII level abnormal, Coagulation factor VII level decreased, Coagulation factor X level abnormal, Coagulation factor X level decreased, Coma hepatic, Computerised tomogram liver abnormal, Cryptogenic cirrhosis, Diabetic hepatopathy, Drug-induced liver injury, Duodenal varices, Encephalopathy, Focal nodular hyperplasia, Foetor hepaticus, Galactose elimination capacity test abnormal, Galactose elimination capacity test decreased, Gallbladder varices, Gamma-glutamyltransferase abnormal, Gamma-glutamyltransferase increased, Gastric variceal injection, Gastric variceal ligation, Gastric varices, Gastrooesophageal variceal haemorrhage prophylaxis, Graft versus host disease in liver, Guanase increased, Haemangioma of liver, Hepaplastin abnormal, Hepaplastin decreased, Hepatectomy, Hepatic adenoma, Hepatic angiosarcoma, Hepatic artery flow decreased, Hepatic atrophy, Hepatic calcification, Hepatic cancer, Hepatic cancer metastatic, Hepatic cancer recurrent, Hepatic cancer stage I, Hepatic cancer stage II, Hepatic cancer stage III, Hepatic cancer stage IV, Hepatic cirrhosis, Hepatic cyst, Hepatic cyst ruptured,

	Hepatic encephalopathy, Hepatic encephalopathy prophylaxis, Hepatic enzyme abnormal, Hepatic enzyme decreased, Hepatic enzyme increased, Hepatic failure, Hepatic fibrosis, Hepatic function abnormal, Hepatic haemangioma rupture, Hepatic hamartoma, Hepatic hydrothorax, Hepatic hypertrophy, Hepatic infiltration eosinophilic, Hepatic lesion, Hepatic mass, Hepatic necrosis, Hepatic neoplasm, Hepatic pain, Hepatic sequestration, Hepatic steato-fibrosis, Hepatic steatosis, Hepatic vascular resistance increased, Hepatic venous pressure gradient abnormal, Hepatic venous pressure gradient increased, Hepatitis, Hepatitis acute, Hepatitis cholestatic, Hepatitis chronic active, Hepatitis chronic persistent, Hepatitis fulminant, Hepatitis toxic, Hepatobiliary cancer, Hepatobiliary cancer in situ, Hepatobiliary cyst, Hepatobiliary disease, Hepatobiliary neoplasm, Hepatobiliary scan abnormal, Hepatoblastoma, Hepatoblastoma recurrent, Hepatocellular carcinoma, Hepatocellular foamy cell syndrome, Hepatocellular injury, Hepatomegaly, Hepatopulmonary syndrome, Hepatorenal failure, Hepatorenal syndrome, Hepatosplenomegaly, Hepatotoxicity, Hyperammonaemia, Hyperbilirubinaemia, Hypercholia, Hypertransaminasaemia, Hypocoagulable state, Hypofibrinogenaemia, Hypoprothrombinaemia, Hypothrombinaemia, Hypothromboplastinaemia, Icterus index increased, Immune-mediated cholangitis, Immune-mediated hepatic disorder, Immune-mediated hepatitis, International normalised ratio abnormal, International normalised ratio increased, Intestinal varices, Ischaemic hepatitis, Jaundice, Jaundice cholestatic, Jaundice hepatocellular, Kayser-Fleischer ring, Liver carcinoma ruptured, Liver dialysis, Liver disorder, Liver function test abnormal, Liver function test decreased, Liver function test increased, Liver induration, Liver injury, Liver operation, Liver palpable, Liver scan abnormal, Liver tenderness, Liver transplant, Lupoid hepatic cirrhosis, Lupus hepatitis, Magnetic resonance imaging liver abnormal, Magnetic resonance proton density fat fraction measurement, Metabolic encephalopathy, Minimal hepatic encephalopathy, Mitochondrial aspartate aminotransferase increased, Mixed hepatocellular cholangiocarcinoma, Mixed liver injury, Molar ratio of total branched-chain amino acid to tyrosine, Nodular regenerative hyperplasia, Nonalcoholic fatty liver disease, Non-alcoholic steatohepatitis, Non-cirrhotic portal hypertension, Ocular icterus, Oedema due to hepatic disease, Parenteral nutrition associated liver disease, Perihepatic discomfort, Peripancreatic varices, Portal fibrosis, Portal hypertension, Portal hypertensive colopathy, Portal hypertensive enteropathy, Portal hypertensive gastropathy, Portal vein cavernous transformation, Portal vein dilatation, Portopulmonary hypertension, Primary biliary cholangitis, Protein C decreased, Protein S abnormal,

	Protein S decreased, Prothrombin level abnormal, Prothrombin level decreased, Prothrombin time abnormal, Prothrombin time prolonged, Prothrombin time ratio abnormal, Prothrombin time ratio increased, Radiation hepatitis, Regenerative siderotic hepatic nodule, Renal and liver transplant, Retrograde portal vein flow, Reye's syndrome, Reynold's syndrome, Splenic varices, Steatohepatitis, Subacute hepatic failure, Sugiura procedure, Thrombin time abnormal, Thrombin time prolonged, Total bile acids increased, Transaminases abnormal, Transaminases increased, Ultrasound liver abnormal, Urine bilirubin increased, Varices oesophageal, Varicose veins of abdominal wall, White nipple sign, X-ray hepatobiliary abnormal

Hypertension	Accelerated hypertension, Blood pressure ambulatory increased, Blood pressure diastolic increased, Blood pressure inadequately controlled, Blood pressure increased, Blood pressure management, Blood pressure orthostatic increased, Blood pressure systolic increased, Catecholamine crisis, Dialysis induced hypertension, Diastolic hypertension, Eclampsia, Endocrine hypertension, Essential hypertension, Gestational hypertension, HELLP syndrome, Hyperaldosteronism, Hypertension, Hypertension neonatal, Hypertensive angiopathy, Hypertensive cardiomegaly, Hypertensive cardiomyopathy, Hypertensive cerebrovascular disease, Hypertensive crisis, Hypertensive emergency, Hypertensive encephalopathy, Hypertensive end-organ damage, Hypertensive heart disease, Hypertensive nephropathy, Hypertensive urgency, Labile hypertension, Malignant hypertension, Malignant hypertensive heart disease, Malignant renal hypertension, Maternal hypertension affecting foetus, Mean arterial pressure increased, Metabolic syndrome, Neurogenic hypertension, Orthostatic hypertension, Page kidney, Postoperative hypertension, Pre-eclampsia, Prehypertension, Procedural hypertension, Renal hypertension, Renal sympathetic nerve ablation, Renovascular hypertension, Retinopathy hypertensive, Secondary aldosteronism, Secondary hypertension, Supine hypertension, Systolic hypertension, Withdrawal hypertension
Hypocalcemia	Blood calcium decreased, Calcium deficiency, Hypocalcaemia, Hypocalcaemic seizure
Hypothyroidism	Autoimmune hypothyroidism, Blood thyroid stimulating hormone abnormal, Blood thyroid stimulating hormone increased, Congenital hypothyroidism, Generalised resistance to thyroid hormone, Hypothyroidic goitre, Hypothyroidism, Immune-mediated hypothyroidism, Myxoedema, Myxoedema coma, Post procedural hypothyroidism, Primary hypothyroidism, Secondary hypothyroidism, Tertiary hypothyroidism, Thyroid atrophy, Thyroid stimulating hormone deficiency, Transient hypothyroxinaemia of prematurity
Palmar-plantar Erythrodysesthesia Syndrome	Palmar erythema, Palmar-plantar erythrodysaesthesia syndrome, Plantar erythema, Rash erythematous, Skin reaction
Posterior Reversible Encephalopathy Syndrome	Posterior reversible encephalopathy syndrome, Vascular encephalopathy

Proteinuria	Albumin globulin ratio increased, Albumin urine present, Albuminuria, Bence Jones protein urine present, Bence Jones proteinuria, Beta 2 microglobulin urine increased, Globulinuria, Microalbuminuria, Myoglobinuria, Nephrotic syndrome, Orthostatic proteinuria, Protein urine, Protein urine present, Proteinuria, Urine albumin/creatinine ratio increased, Urine protein/creatinine ratio abnormal, Urine protein/creatinine ratio increased
QT Prolongation	Electrocardiogram QT interval abnormal, Electrocardiogram QT prolonged, Long QT syndrome, Long QT syndrome congenital, Torsade de pointes, Ventricular tachycardia
Renal Events	Acute kidney injury, Acute phosphate nephropathy, Anuria, Azotaemia, Blood creatinine abnormal, Blood creatinine increased, Blood urea abnormal, Blood urea increased, Blood urea nitrogen/creatinine ratio increased, Continuous haemodiafiltration, Creatinine renal clearance abnormal, Creatinine renal clearance decreased, Creatinine urine abnormal, Creatinine urine decreased, Crystal nephropathy, Dialysis, Foetal renal impairment, Fractional excretion of sodium, Glomerular filtration rate abnormal, Glomerular filtration rate decreased, Glomerular vascular disorder, Haemodialysis, Haemofiltration, Hypercreatininaemia, Hyponatriuria, Intradialytic parenteral nutrition, Ischaemic nephropathy, Kidney injury molecule-1, Neonatal anuria, Nephritis, Nephroangiosclerosis, Nephropathy toxic, Neutrophil gelatinase-associated lipocalin increased, Oedema due to renal disease, Oliguria, Peritoneal dialysis, Prerenal failure, Renal aneurysm, Renal arteriosclerosis, Renal arteritis, Renal artery arteriosclerosis, Renal artery dissection, Renal artery fibromuscular dysplasia, Renal artery hyperplasia, Renal artery restenosis, Renal artery stenosis, Renal failure, Renal failure neonatal, Renal function test abnormal, Renal impairment, Renal impairment neonatal, Renal infarct, Renal ischaemia, Renal pseudoaneurysm, Renal transplant, Renal tubular disorder, Renal tubular dysfunction, Renal tubular injury, Renal tubular necrosis, Renal vascular thrombosis, Renal vasculitis, Renal vein compression, Renal vein embolism, Renal vein occlusion, Renal vein stenosis, Renal vein thrombosis, Renal vein varices, Renal vessel disorder, Subacute kidney injury, Tubulointerstitial nephritis, Urea renal clearance decreased, Urine output decreased