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Supplementary appendix

This appendix formed part of the original submission and has been peer reviewed. We post it as supplied by the authors.

Supplement to: Motzer R, Porta C, Alekseev B, et al. Health-related quality-of-life outcomes in patients with advanced renal cell carcinoma treated with lenvatinib plus pembrolizumab or everolimus versus sunitinib (CLEAR): a randomised, phase 3 study. *Lancet Oncol* 2022; published online April 27. https://doi.org/10.1016/S1470-2045(22)00212-1.

Appendix

Supplementary Data

Table S1. HRQoL Collection Schedule

Phase	**Prerandomization**	**Randomization (21-day cycles)**				
	Baseline	**Treatment period**				
Day	Days −3 to −1	C1D1	C2D1	C3D1	C4D1 to last cycle D1	OTV
Study-drug treatment		21-day cycles of lenvatinib daily + everolimus daily *or* 21-day cycles of lenvatinib daily + pembrolizumab intravenously every 21 days *or* sunitinib daily for 4 weeks plus 2 weeks off				
Tumor assessments		Every 8 weeks from date of randomization (sooner if clinically indicated), until IRR confirmation of progressive disease				X
HRQoL	X		X	X	X	X

The off-treatment visit should occur within 30 days of the final dose of study treatment.

C#, cycle #; D#, day #; HRQoL, health-related quality of life; IRR, independent radiologic review; OTV, off-treatment visit.

Table S2. HRQoL Completion and Compliance Rates

Timepoint	LEN + PEMBRO (n = 355)		SUN (n = 357)		LEN + EVE (n = 357)	
Rate, n (%)	**Completion**	**Compliance**	**Completion**	**Compliance**	**Completion**	**Compliance**
All instruments						
Baseline	338 (95·2)	338/352 (96·0)	328 (91·9)	328/340 (96·5)	343 (96·1)	343/355 (96·6)
Cycle 4	317 (89·3)	317/332 (95·5)	264 (73·9)	264/289 (91·3)	305 (85·4)	305/326 (93·6)
Cycle 8	302 (85·1)	302/309 (97·7)	222 (62·2)	222/237 (93·7)	262 (73·4)	262/269 (97·4)
Cycle 12	277 (78·0)	277/283 (97·9)	171 (47·9)	171/176 (97·2)	206 (57·7)	206/212 (97·2)
Cycle 16	240 (67·6)	240/252 (95·2)	143 (40·1)	143/147 (97·3)	171 (47·9)	171/179 (95·5)
Cycle 20	223 (62·8)	223/234 (95·3)	114 (31·9)	114/119 (95·8)	156 (43·7)	156/160 (97·5)
Cycle 24	192 (54·1)	192/194 (99·0)	93 (26·1)	93/97 (95·9)	123 (34·5)	123/128 (96·1)
Cycle 28	156 (43·9)	156/162 (96·3)	73 (20·4)	73/78 (93·6)	100 (28·0)	100/103 (97·1)
Cycle 32	124 (34·9)	124/138 (89·9)	57 (16·0)	57/58 (98·3)	74 (20·7)	74/79 (93·7)
Cycle 36	97 (27·3)	97/103 (94·2)	47 (13·2)	47/51 (92·2)	53 (14·8)	53/60 (88·3)
Cycle 40	57 (16·1)	57/61 (93·4)	28 (7·8)	28/32 (87·5)	36 (10·1)	36/40 (90·0)
Cycle 44	30 (8·5)	30/31 (96·8)	18 (5·0)	18/18 (100)	12 (3·4)	12/13 (92·3)
Cycle 48	12 (3·4)	12/14 (85·7)	8 (2·2)	8/8 (100)	5 (1·4)	5/5 (100)
Off-treatment	142 (40·0)	142/177 (80·2)	199 (55·7)	199/237 (84·0)	160 (44·8)	160/203 (78·8)
FKSI-DRS						
Baseline	336 (94·6)	336/352 (95·5)	323 (90·5)	323/340 (95·0)	340 (95·2)	340/355 (95·8)
Cycle 4	315 (88·7)	315/332 (94·9)	260 (72·8)	260/289 (90·0)	303 (84·9)	303/326 (92·9)
Cycle 8	302 (85·1)	302/309 (97·7)	222 (62·2)	222/237 (93·7)	261 (73·1)	261/269 (97·0)
Cycle 12	276 (77·7)	276/283 (97·5)	171 (47·9)	171/176 (97·2)	204 (57·1)	204/212 (96·2)
Cycle 16	239 (67·3)	239/252 (94·8)	143 (40·1)	143/147 (97·3)	171 (47·9)	171/179 (95·5)
Cycle 20	222 (62·5)	222/234 (94·9)	114 (31·9)	114/119 (95·8)	156 (43·7)	156/160 (97·5)
Cycle 24	190 (53·5)	190/194 (97·9)	92 (25·8)	92/97 (94.8)	122 (34·2)	122/128 (95·3)
Cycle 28	156 (43·9)	156/162 (96·3)	72 (20·2)	72/78 (92.3)	100 (28·0)	100/103 (97·1)
Cycle 32	124 (34·9)	124/138 (89·9)	57 (16·0)	57/58 (98.3)	74 (20·7)	74/79 (93·7)
Cycle 36	97 (27·3)	97/103 (94·2)	47 (13·2)	47/51 (92.2)	53 (14·8)	53/60 (88·3)
Cycle 40	57 (16·1)	57/61 (93·4)	28 (7·8)	28/32 (87.5)	36 (10·1)	36/40 (90·0)
Cycle 44	30 (8·5)	30/31 (96·8)	18 (5·0)	18/18 (100)	12 (3·4)	12/13 (92·3)
Cycle 48	12 (3·4)	12/14 (85·7)	8 (2·2)	8/8 (100)	5 (1·4)	5/5 (100)
Off-treatment	141 (39·7)	141/177 (79·7)	197 (55·2)	197/237 (83·1)	159 (44·5)	159/203 (78·3)
EORTC QLQ-C30						
Baseline	336 (94·6)	336/352 (95·5)	327 (91·6)	327/340 (96·2)	341 (95·5)	341/355 (96·1)
Cycle 4	316 (89·0)	316/ 332 (95·2)	263 (73·7)	263/289 (91·0)	304 (85·2)	304/326 (93·3)
Cycle 8	302 (85·1)	302/309 (97·7)	222 (62·2)	222/237 (93·7)	262 (73·4)	262/269 (97·4)
Cycle 12	277 (78·0)	277/283 (97·9)	171 (47·9)	171/176 (97·2)	206 (57·7)	206/212 (97·2)
Cycle 16	240 (67·6)	240/252 (95·2)	143 (40·1)	143/147 (97·3)	171 (47·9)	171/179 (95·5)
Cycle 20	223 (62·8)	223/234 (95·3)	114 (31·9)	114/119 (95·8)	156 (43·7)	156/160 (97·5)
Cycle 24	191 (53·8)	191/194 (98·5)	93 (26·1)	93/97 (95·9)	123 (34·5)	123/128 (96·1)
Cycle 28	156 (43·9)	156/162 (96·3)	73 (20·4)	73/78 (93·6)	100 (28·0)	100/103 (97·1)
Cycle 32	124 (34.9)	124/138 (89·9)	57 (16·0)	57/58 (98·3)	74 (20·7)	74/79 (93·7)
Cycle 36	97 (27·3)	97/103 (94·2)	47 (13·2)	47/51 (92·2)	53 (14·8)	53/60 (88·3)
Cycle 40	57 (16·1)	57/61 (93·4)	28 (7·8)	28/32 (87·5)	36 (10·1)	36/40 (90·0)
Cycle 44	30 (8·5)	30/31 (96·8)	18 (5·0)	18/18 (100)	12 (3·4)	12/13 (92·3)
Cycle 48	12 (3·4)	12/14 (85·7)	8 (2·2)	8/8 (100)	5 (1·4)	5/5 (100)
Off-treatment	142 (40·0)	142/177 (80·2)	199 (55·7)	199/237 (84·0)	159 (44·5)	159/203 (78·3)
EQ-5D-3L						
Baseline	338 (95·2)	338/352 (96·0)	324 (90·8)	324/340 (95·3)	342 (95·8)	342/355 (96·3)
Cycle 4	316 (89·0)	316/332 (95·2)	263 (73·7)	263/289 (91·0)	304 (85·2)	304/326 (93·3)

Cycle 8	302 (85·1)	302/309 (97·7)	222 (62·2)	222/237 (93·7)	262 (73·4)	262/269 (97·4)
Cycle 12	276 (77·7)	276/283 (97·5)	171 (47·9)	171/176 (97·2)	205 (57·4)	205/212 (96·7)
Cycle 16	240 (67·6)	240/252 (95·2)	143 (40·1)	143/147 (97·3)	171 (47·9)	171/179 (95·5)
Cycle 20	223 (62·8)	223/234 (95·3)	113 (31·7)	113/119 (95·0)	156 (43·7)	156/160 (97·5)
Cycle 24	192 (54·1)	192/194 (99·0)	93 (26·1)	93/97 (95·9)	123 (34·5)	123/128 (96·1)
Cycle 28	156 (43·9)	156/162 (96·3)	73 (20·4)	73/78 (93·6)	99 (27·7)	99/103 (96·1)
Cycle 32	124 (34·9)	124/138 (89·9)	57 (16·0)	57/58 (98·3)	74 (20·7)	74/79 (93·7)
Cycle 36	97 (27·3)	97/103 (94·2)	47 (13·2)	47/51 (92·2)	53 (14·8)	53/60 (88·3)
Cycle 40	57 (16·1)	57/61 (93·4)	28 (7·8)	28/32 (87·5)	36 (10·1)	36/40 (90·0)
Cycle 44	30 (8·5)	30/31 (96·8)	18 (5·0)	18/18 (100)	12 (3·4)	12/13 (92·3)
Cycle 48	12 (3·4)	12/14 (85·7)	8 (2·2)	8/8 (100)	5 (1·4)	5/5 (100)
Off-treatment	142 (40·0)	142/177 (80·2)	198 (55·5)	198/237 (83·5)	160 (44·8)	160/203 (78·8)

Completion rates: percentage of patients who completed the instrument among all patients who were enrolled in the full analysis set at baseline and were assessed for each of the HRQoL outcomes by assessment time point and treatment arm. Compliance rates: percentage of patients who completed the instrument among all patients who were still enrolled in the study and on study treatment at a particular postbaseline time point and were, therefore, expected to complete the instrument.

EORTC QLQ-C30, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire; EQ-5D-3L, EuroQol 5 Dimensions 3 Levels; EVE, everolimus; FKSI-DRS, Functional Assessment of Cancer Therapy Kidney Symptom Index–Disease-Related Symptoms; LEN, lenvatinib; PEMBRO, pembrolizumab.

Table S3. Baseline (SD) HRQoL Scores

Mean scores[a]	LEN + PEMBRO (n = 351)	SUN (n = 340)	LEN + EVE (n = 352)
FKSI-DRS total score	31·28 (4·410)	30·89 (4·895)	30·57 (4·974)
EORTC QLQ-C30 functional scales			
GHS/QoL	71·90 (21·182)	70·49 (21·267)	69·92 (22·007)
Physical	84·17 (18·784)	82·64 (19·422)	82·78 (19·327)
Role	82·49 (25·472)	80·63 (26·504)	79·61 (27·739)
Emotional	83·20 (18·399)	82·05 (17·992)	82·29 (18·526)
Cognitive	90·43 (16·990)	89·81 (15·926)	90·13 (14·640)
Social	86·56 (22·014)	84·91 (23·317)	84·46 (24·847)
EORTC QLQ-C30 symptom scales			
Fatigue	24·71 (21·753)	24·97 (22·008)	24·64 (22·868)
Nausea/vomiting	3·43 (10·744)	4·89 (12·718)	4·26 (12·102)
Pain	16·52 (22·211)	20·64 (25·704)	19·50 (25·246)
Dyspnea	12·64 (20·864)	14·01 (24·067)	13·57 (21·744)
Insomnia	21·26 (26·669)	23·85 (27·042)	22·65 (28·283)
Appetite loss	11·94 (21·659)	12·44 (22·647)	13·67 (24·326)
Constipation	11·24 (21·183)	11·31 (22·255)	10·39 (20·559)
Diarrhea	5·27 (13·230)	7·65 (18·257)	6·18 (14·633)
Financial difficulties	13·39 (25·021)	14·72 (26·174)	13·82 (25·637)
EQ-5D-3L			
Index	0·83 (0·190)	0·81 (0·218)	0·81 (0·234)
VAS	76·32 (18·155)	75·03 (17·496)	74·03 (18·979)

[a]The FKSI-DRS instrument is measured on a scale of 0–36, with higher scores corresponding to better HRQoL. Scores on all scales of the EORTC QLQ-C30 range from 0–100, for the GHS/QoL and all functional scales, a higher scale corresponds to better HRQoL, for the symptom scales, a higher scale corresponds to worse symptoms. The EQ-5D-3L VAS is measured on a scale of 0–100, with higher scores corresponding to better HRQoL, and the EQ-5D-3L index ranges from 0–1, with higher scores representing better HRQoL.

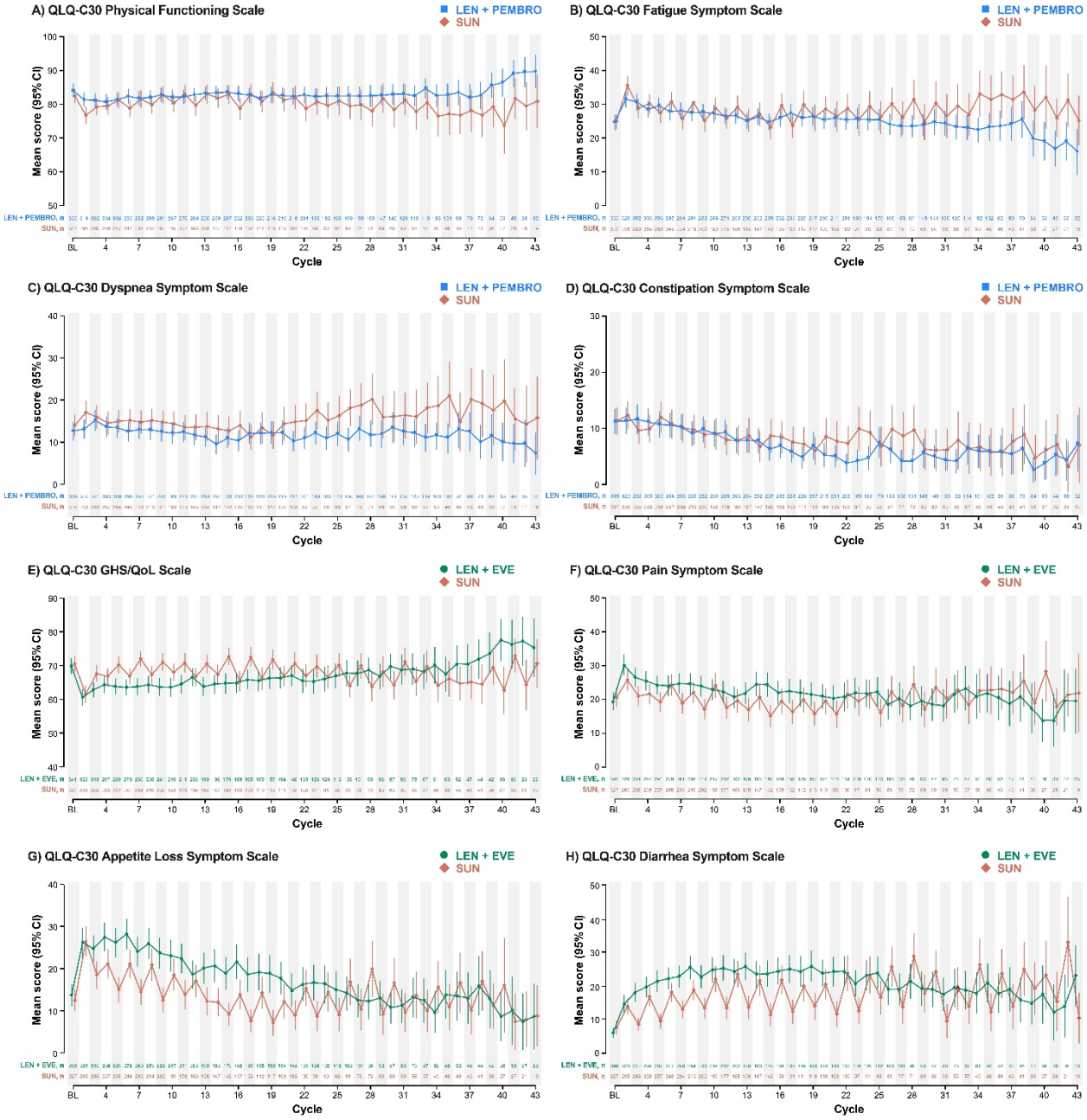
EORTC QLQ-C30, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire; EQ-5D-3L, EuroQol 5 Dimensions 3 Levels; EVE, everolimus; FKSI-DRS, Functional Assessment of Cancer Therapy Kidney Symptom Index–Disease-Related Symptoms; GHS/QoL, global health status/quality of life; HRQoL, health-related quality of life; LEN, lenvatinib; PEMBRO, pembrolizumab; SD, standard deviation; SUN, sunitinib; VAS, visual analog scale.

Table S4. Death and Deterioration Events by First and Definitive Deterioration on Selected Scales

Scale	Event, n (%)	LEN+PEMBRO	SUN	LEN+EVE
FKSI-DRS Total Score	First Deterioration: Death	2 (0·75)	2 (0·92)	4 (1·54)
	First Deterioration: Deterioration	263 (99·25)	216 (99·08)	256 (98·46)
	Definitive Deterioration: Death	5 (4·55)	3 (2·86)	9 (6·98)
	Definitive Deterioration: Deterioration	105 (95·45)	102 (97·14)	120 (93·02)
EORTC QLQ-C30 Global Health Status/QoL	First Deterioration: Death	4 (1·57)	3 (1·24)	7 (2·67)
	First Deterioration: Deterioration	251 (98·43)	239 (98·76)	255 (97·33)
	Definitive Deterioration: Death	4 (3·03)	5 (3·47)	8 (4·85)
	Definitive Deterioration: Deterioration	128 (96·97)	139 (96·53)	157 (95·15)
EORTC QLQ-C30 Physical Functioning	First Deterioration: Death	2 (0·85)	3 (1·32)	1 (0·40)
	First Deterioration: Deterioration	234 (99·15)	225 (98·68)	251 (99·60)
	Definitive Deterioration: Death	6 (5·00)	4 (2·78)	8 (5·30)
	Definitive Deterioration: Deterioration	114 (95·00)	140 (97·22)	143 (94·70)
EQ-5D Index	First Deterioration: Death	3 (1·15)	3 (1·35)	6 (2·30)
	First Deterioration: Deterioration	257 (98·85)	219 (98·65)	255 (97·70)
	Definitive Deterioration: Death	5 (3·70)	3 (2·50)	12 (8·28)
	Definitive Deterioration: Deterioration	130 (96·30)	117 (97·50)	133 (91·72)
EQ-5D VAS	First Deterioration: Death	2 (0·81)	4 (1·63)	3 (1·09)
	First Deterioration: Deterioration	244 (99·19)	242 (98·37)	272 (98·91)
	Definitive Deterioration: Death	7 (4·96)	5 (3·47)	8 (4·65)
	Definitive Deterioration: Deterioration	134 (95·04)	139 (96·53)	164 (95·35)

EORTC QLQ-C30, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire; EQ-5D-3L, EuroQol 5 Dimensions 3 Levels; EVE, everolimus; FKSI-DRS, Functional Assessment of Cancer Therapy Kidney Symptom Index–Disease-Related Symptoms; GHS/QoL, global health status/quality of life; LEN, lenvatinib; PEMBRO, pembrolizumab; SUN, sunitinib; VAS, visual analog scale.

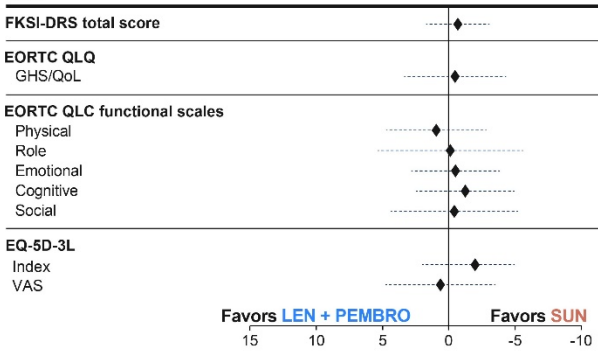
Figure S1. Observed Mean Scores Over Time of HRQoL Scales with Nominally Significant Least Squares Mean Differences for Lenvatinib + Pembrolizumab vs Sunitinib (A-D) and for Lenvatinib + Everolimus vs Sunitinib (E-H)

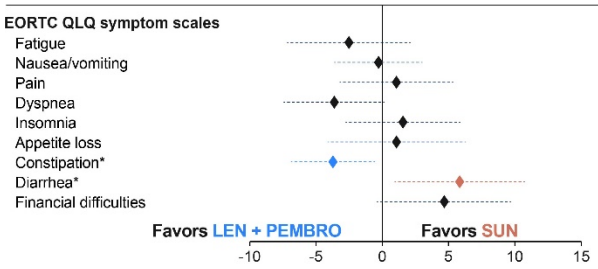


CI, confidence interval; EORTC QLQ-C-30, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire; EQ-5D-3L, EuroQol 5 Dimensions 3 Levels; EVE, everolimus; FKSI-DRS, Functional Assessment of Cancer Therapy Kidney Symptom Index–Disease-Related Symptoms; GHS/QoL, global health status/quality of life; HRQoL, health-related quality of life; LEN, lenvatinib; LS, least squares; PEMBRO, pembrolizumab; SUN, sunitinib.

Figure S2. MSKCC and IMDC Risk Group Subgroup Analyses of Least Squares Mean Change From Baseline in Lenvatinib + Pembrolizumab and Sunitinib Arms

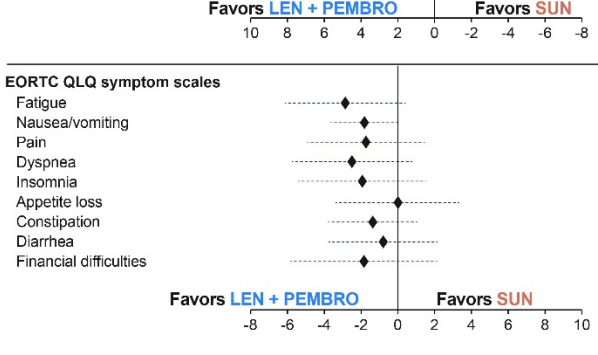
MSKCC favorable subgroup





Scale	LEN + PEMBRO	SUN	LS Mean Difference (95% CI)	*p* value
FKSI-DRS total score	-3·47 (0·842)	-2·78 (0·881)	-0·69 (-3·08, 1·72)	0·58
EORTC QLQ				
GHS/QoL	-9·09 (1·346)	-8·62 (1·409)	-0·47 (-4·31, 3·37)	0·81
EORTC QLC functional scales				
Physical	-6·99 (1·331)	-7·93 (1·393)	0·95 (-2·85, 4·74)	0·62
Role	-12·24 (1·929)	-12·13 (2·009)	-0·11 (-5·60, 5·38)	0·97
Emotional	2·23 (1·169)	2·72 (1·220)	-0·50 (-3·83, 2·84)	0·77
Cognitive	-4·61 (1·301)	-3·37 (1·356)	-1·24 (-4·94, 2·47)	0·51
Social	-8·38 (1·682)	-7·97 (1·764)	-0·42 (-5·22, 4·39)	0·86
EQ-5D-3L				
Index	-6 (1·2)	-4 (1.·3)	-2 (-5, 2)	0·36
VAS	-7·02 (1·456)	-7·65 (1·520)	0·63 (-3·52, 4·78)	0·77
EORTC QLQ symptom scales				
Fatigue	6·89 (1·638)	9·40 (1·705)	-2·51 (-7·17, 2·14)	0·29
Nausea/vomiting	4·93 (1·158)	5·22 (1·217)	-0·29 (-3·62, 3·04)	0·86
Pain	7·18 (1·497)	6·11 (1·580)	1·07 (-3·22, 5·36)	0·62
Dyspnea	1·83 (1·333)	5·46 (1·395)	-3·63 (-7·44, 0·18)	0·062
Insomnia	-0·64 (1·511)	-2·20 (1·597)	1·56 (-2·77, 5·90)	0·48
Appetite loss	10·41 (1·822)	9·32 (1·921)	1·09 (-4·13, 6·31)	0·68
Constipation*	-0·42 (1·098)	3·30 (1·171)	-3·72 (-6·88, -0·55)	0·022
Diarrhea*	12·29 (1·697)	6·45 (1·817)	5·84 (0·93, 10·75)	0·020
Financial difficulties	4·97 (1·779)	0·31 (1·854)	4·67 (-0·40, 9·73)	0·071

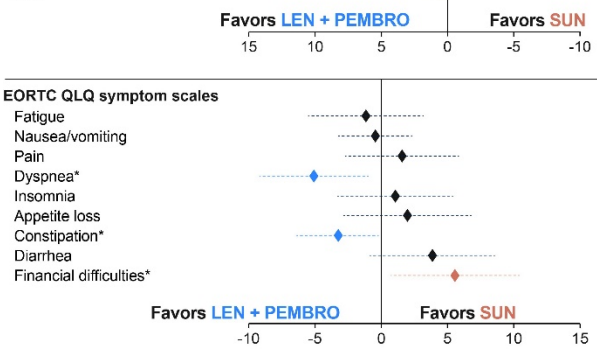
MSKCC intermediate/poor subgroup



Scale	LEN + PEMBRO	SUN	LS Mean Difference (95% CI)	*p* value
FKSI-DRS total score	-1·50 (0·669)	-2·53 (0·783)	1·03 (-1·00, 3·03)	0·32
EORTC QLQ				
GHS/QoL	-4·10 (0·906)	-5·06 (1·041)	0·96 (-1·75, 3·68)	0·49
EORTC QLC functional scales				
Physical*	-4·84 (1·065)	-8·49 (1·229)	3·66 (0·46, 6·85)	0·025
Role	-7·38 (1·352)	-11·30 (1·568)	3·92 (-0·14, 7·99)	0·059
Emotional	1·67 (0·946)	-0·70 (1·084)	2·37 (-0·46, 5·20)	0·10
Cognitive	-5·61 (0·956)	-5·45 (1·074)	-0·16 (-2·98, 2·66)	0·91
Social*	-6·41 (1·328)	-10·94 (1·513)	4·53 (0·58, 8·48)	0·025
EQ-5D-3L				
Index*	-3 (1·1)	-8 (1·3)	4 (1, 8)	0·011
VAS	-3·74 (0·934)	-5·78 (1·086)	2·03 (-0·78, 4·84)	0·16
EORTC QLQ symptom scales				
Fatigue	4·97 (1·092)	7·83 (1·270)	-2·86 (-6·15, 0·43)	0·088
Nausea/vomiting	2·90 (0·610)	4·71 (0·704)	-1·82 (-3·65, 0·01)	0·052
Pain	3·58 (1·054)	5·30 (1·241)	-1·73 (-4·93, 1·47)	0·29
Dyspnea	1·67 (1·086)	4·17 (1·259)	-2·50 (-5·77, 0·77)	0·13
Insomnia	-1·91 (1·160)	0·02 (1·338)	-1·93 (-5·41, 1·55)	0·28
Appetite loss	6·00 (1·118)	6·02 (1·293)	-0·02 (-3·38, 3·33)	0·99
Constipation	-1·41 (0·805)	-0·04 (0·930)	-1·36 (-3·78, 1·05)	0·27
Diarrhea	10·72 (0·964)	11·52 (1·156)	-0·80 (-3·76, 2·16)	0·60
Financial difficulties	2·52 (1·351)	4·39 (1·527)	-1·87 (-5·88, 2·13)	0·36

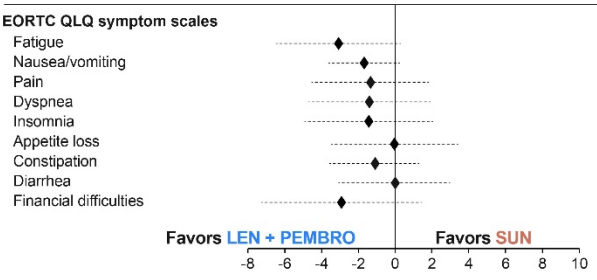
IMDC favorable subgroup

Scale	LEN + PEMBRO	SUN	LS Mean Difference (95% CI)	*p* value
FKSI-DRS total score	-4·67 (0·958)	-3·69 (0·981)	-0·97 (-3·58, 1·61)	0·45
EORTC QLQ				
GHS/QoL	-8·98 (1·386)	-8·77 (1·390)	-0·21 (-3·86, 3·43)	0·91
EORTC QLC functional scales				
Physical	-10·07 (1·501)	-10·14 (1·526)	0·06 (-4·01, 4·14)	0·98
Role	-14·92 (2·008)	-13·50 (2·028)	-1·43 (-6·78, 3·92)	0·60
Emotional	0·94 (1·269)	1·55 (1·286)	-0·61 (-4·04, 2·81)	0·72
Cognitive	-4·25 (1·346)	-3·68 (1·348)	-0·56 (-4·16, 3·03)	0·76
Social	-9·89 (1·847)	-9·60 (1·861)	-0·29 (-5·26, 4·67)	0·91
EQ-5D-3L				
Index	-8 (1·4)	-6 (1·5)	-2 (-6, 2)	0·32
VAS	-7·96 (1·522)	-8·57 (1·539)	0·61 (-3·50, 4·72)	0·77
EORTC QLQ symptom scales				
Fatigue	10·11 (1·647)	11·26 (1·655)	-1·16 (-5·52, 3·21)	0·60
Nausea/vomiting	5·07 (1·049)	5·51 (1·066)	-0·44 (-3·24, 2·35)	0·76
Pain	8·64 (1·612)	7·07 (1·636)	1·57 (-2·73, 5·87)	0·47
Dyspnea*	2·17 (1·555)	7·25 (1·561)	-5·09 (-9·20, -0·97)	0·016
Insomnia	0·89 (1·649)	-0·17 (1·660)	1·07 (-3·30, 5·44)	0·63
Appetite loss	11·82 (1·829)	9·84 (1·843)	1·98 (-2·85, 6·81)	0·42
Constipation*	0·64 (1·170)	3·93 (1·180)	-3·29 (-6·39, -0·20)	0·037
Diarrhea	12·00 (1·756)	8·14 (1·787)	3·87 (-0·86, 8·59)	0·11
Financial difficulties*	5·26 (1·781)	-0·31 (1·798)	5·56 (0·69, 10·44)	0·026



IMDC intermediate /poor subgroup

Scale	LEN + PEMBRO	SUN	LS Mean Difference (95% CI)	*p* value
FKSI-DRS total score	-0·72 (0·861)	-1·42 (0·961)	0·67 (-1·25, 2·58)	0·49
EORTC QLQ				
GHS/QoL	-6·16 (1·275)	-6·96 (1·410)	0·80 (-2·01, 3·61)	0·58
EORTC QLC functional scales				
Physical*	-3·90 (1·388)	-8·14 (1·544)	4·25 (1·01, 7·48)	0·010
Role*	-6·52 (1·885)	-11·50 (2·079)	4·98 (0·80, 9·16)	0·020
Emotional	3·68 (1·278)	1·08 (1·413)	2·60 (-0·38, 5·57)	0·087
Cognitive	-4·35 (1·266)	-3·77 (1·387)	-0·58 (-3·48, 2·32)	0·70
Social*	-5·18 (1·759)	-9·84 (1·947)	4·66 (0·60, 8·72)	0·025
EQ-5D-3L				
Index*	-3 (1·5)	-7 (1·7)	5 (1, 8)	0·011
VAS	-5·09 (1·237)	-6·89 (1·386)	1·80 (-1·09, 4·69)	0·22
EORTC QLQ symptom scales				
Fatigue	2·53 (1·521)	5·60 (1·684)	-3·07 (-6·44, 0·31)	0·075
Nausea/vomiting	4·08 (0·907)	5·77 (1·008)	-1·68 (-3·61, 0·25)	0·088
Pain	3·45 (1·410)	4·80 (1·601)	-1·35 (-4·54, 1·83)	0·40
Dyspnea	0·84 (1·466)	2·25 (1·644)	-1·40 (-4·72, 1·91)	0·41
Insomnia	-2·03 (1·595)	-0·60 (1·772)	-1·43 (-4·92, 2·06)	0·42
Appetite loss	5·98 (1·597)	6·01 (1·779)	-0·03 (-3·47, 3·41)	0·99
Constipation	-0·75 (1·138)	0·37 (1·268)	-1·12 (-3·56, 1·31)	0·36
Diarrhea	10·34 (1·320)	10·39 (1·532)	-0·04 (-3·08, 2·99)	0·98
Financial difficulties	1·80 (1·858)	4·71 (2·036)	-2·91 (-7·27, 1·46)	0·19



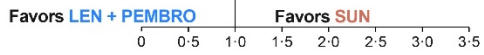
*Denotes a statistically significant log-rank difference ($P < 0·05$). For presentation, scores from the FKSI-DRS and EQ-5D-3L Index instruments were transformed to the scale of 0–100 (FKSI-DRS transformed score = (raw score/36)*100; EQ-5D-3L Index transformed score = (raw score)*100).

CI, confidence interval; EORTC QLQ, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire; EQ-5D-3L, EuroQol 5 Dimensions 3 Levels; FKSI-DRS, Functional Assessment of Cancer Therapy Kidney Symptom Index–Disease-Related Symptoms; LS, least squares; GHS/QoL, global health status/quality of life; IMDC, International Metastatic RCC Database Consortium; LEN, lenvatinib; MSKCC, Memorial Sloan Kettering Cancer Center; PEMBRO, pembrolizumab; SUN, sunitinib; VAS, visual analog scale.

Figure S3. MSKCC and IMDC Risk Group Subgroup Analyses of Time to First Deterioration in Lenvatinib + Pembrolizumab and Sunitinib Arms

MSKCC favorable subgroup

Scale	# Pts with Events/ # Pts		Median Time to Deterioration in Weeks (95% CI)		Hazard Ratio (95% CI)	Log-rank *p* value
	L + P	SUN	LEN + PEMBRO	SUN		
FKSI-DRS total score	51/91	39/91	54·57 (33·29, 103·43)	102·29 (27·14, NE)	1·12 (0·74, 1·71)	0·59
EORTC QLQ						
GHS/QoL	76/91	73/91	12·00 (6·29, 15·29)	9·29 (3·43, 18·14)	0·93 (0·67, 1·28)	0·67
EORTC QLC functional scales						
Physical	64/91	63/91	15·14 (10·57, 30·14)	18·14 (9·14, 31·00)	0·87 (0·61, 1·24)	0·45
Role	77/91	72/91	8·14 (6·14, 12·14)	7·14 (3·71, 15·14)	1·09 (0·79, 1·51)	0·61
Emotional	46/91	36/91	88·00 (42·14, NE)	NE (53·00, NE)	1·04 (0·67, 1·62)	0·86
Cognitive	62/91	50/91	18·00 (12·14, 42·29)	20·14 (15·14, 102·29)	1·18 (0·81, 1·72)	0·38
Social	68/91	63/91	15·14 (9·14, 24·14)	15·29 (9·14, 21·14)	0·98 (0·70, 1·39)	0·93
EORTC QLQ symptom scales						
Fatigue	80/91	75/91	6·14 (3·29, 11·86)	3·43 (3·29, 6·14)	0·93 (0·68, 1·28)	0·66
Nausea/vomiting	65/91	58/91	21·14 (15·29, 39·00)	20·14 (12·29, 27·57)	0·93 (0·65, 1·33)	0·73
Pain	78/91	73/91	6·29 (3·43, 9·14)	12·00 (6·14, 15·14)	1·20 (0·87, 1·65)	0·30
Dyspnea	55/91	55/91	30·71 (18·29, 57·29)	27·14 (18·14, 57·00)	0·87 (0·60, 1·27)	0·47
Insomnia	60/91	49/91	28·00 (15·43, 39·14)	33·43 (15·29, 84·29)	1·13 (0·77, 1·65)	0·53
Appetite loss	69/91	67/91	21·14 (15·14, 29·14)	8·86 (3·57, 15·14)	0·77 (0·55, 1·07)	0·13
Constipation	50/91	55/91	45·14 (18·86, 104·86)	21·29 (12·14, 48·14)	0·71 (0·48, 1·04)	0·085
Diarrhea	74/91	62/91	15·43 (12·29, 27·14)	18·00 (12·14, 30·00)	1·07 (0·76, 1·50)	0·71
Financial difficulties*	40/91	20/91	126·29 (46·00, NE)	NE (NE, NE)	1·85 (1·08, 3·17)	0·023
EQ-5D-3L						
Index	72/91	63/91	10·57 (6·29, 18·29)	18·14 (9·43, 30·14)	1·09 (0·77, 1·53)	0·62
VAS	57/91	53/90	30·14 (14·14, 72·86)	29·86 (14·86, 56·86)	0·90 (0·62, 1·32)	0·60

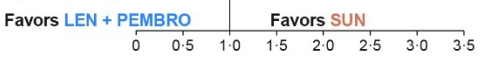


MSKCC intermediate/poor subgroup

Scale	# Pts with Events/ # Pts		Median Time to Deterioration in Weeks (95% CI)		Hazard Ratio (95% CI)	Log-rank *p* value
	L + P	SUN	LEN + PEMBRO	SUN		
FKSI-DRS total score	189/239	157/226	9·29 (6·43, 12·29)	12·14 (9·14, 15·29)	1·10 (0·89, 1·36)	0·41
EORTC QLQ						
GHS/QoL	179/239	169/229	12·14 (6·29, 15·71)	9·14 (6·29, 12·14)	0·86 (0·70, 1·06)	0·17
EORTC QLC functional scales						
Physical*	172/238	165/229	15·43 (12·14, 24·29)	9·43 (9·14, 15·14)	0·79 (0·63, 0·98)	0·046
Role	177/238	173/229	9·14 (6·29, 12·43)	9·29 (6·57, 12·43)	0·89 (0·72, 1·10)	0·15
Emotional	143/239	122/229	30·43 (22·29, 48·86)	27·14 (18·14, 44·29)	0·92 (0·72, 1·18)	0·51
Cognitive	170/239	149/229	13·29 (10·29, 21·29)	15·14 (11·86, 21·29)	0·98 (0·79, 1·23)	0·97
Social	179/239	161/229	9·57 (9·00, 15·14)	9·57 (6·43, 15·14)	0·97 (0·79, 1·20)	0·76
EORTC QLQ symptom scales						
Fatigue	199/238	190/229	6·29 (3·57, 6·86)	6·14 (4·00, 6·29)	0·91 (0·74, 1·11)	0·38
Nausea/vomiting	176/238	145/229	21·14 (18·14, 27·14)	15·43 (9·43, 21·29)	0·97 (0·78, 1·21)	0·92
Pain	193/239	167/229	9·14 (6·29, 9·43)	9·86 (9·00, 15·14)	1·05 (0·85, 1·29)	0·73
Dyspnea*	135/238	134/228	45·29 (24·71, 58·14)	18·00 (15·14, 26·29)	0·76 (0·60, 0·97)	0·027
Insomnia	157/237	135/229	20·86 (12·43, 27·29)	16·00 (12·14, 26·29)	0·96 (0·76, 1·21)	0·82
Appetite loss	182/238	166/229	18·14 (12·29, 21·29)	10·14 (7·43, 18·14)	0·84 (0·68, 1·03)	0·091
Constipation	142/238	111/229	30·14 (21·14, 48·86)	37·14 (24·57, 93·00)	1·09 (0·84, 1·40)	0·37
Diarrhea	192/238	170/229	15·43 (12·29, 20·86)	13·14 (9·43, 15·29)	0·81 (0·66, 1·00)	0·054
Financial difficulties	118/239	98/228	66·14 (48·14, 102·43)	48·86 (31·43, 120·29)	0·87 (0·66, 1·14)	0·42
EQ-5D-3L						
Index	188/239	159/224	9·14 (6·29, 9·29)	12·57 (9·29, 15·29)	1·12 (0·91, 1·39)	0·35
VAS*	175/241	172/225	9·71 (6·43, 15·14)	9·14 (6·29, 12·29)	0·81 (0·65, 1·00)	0·049

IMDC favorable subgroup

Scale	# Pts with Events/ # Pts: L + P	# Pts with Events/ # Pts: SUN	Median Time to Deterioration in Weeks (95% CI): LEN + PEMBRO	Median Time to Deterioration in Weeks (95% CI): SUN	Hazard Ratio (95% CI)	Log-rank *p* value
FKSI-DRS total score	60/104	50/110	42·29 (27·29, 90·29)	102·29 (24·14, NE)	1·13 (0·77, 1·66)	0·53
EORTC QLQ						
GHS/QoL	87/103	88/110	12·14 (6·29, 15·29)	9·14 (4·14, 13·71)	0·87 (0·64, 1·18)	0·41
EORTC QLC functional scales						
Physical	78/103	78/110	15·14 (12·00, 25·14)	18·29 (12·00, 27·57)	0·94 (0·68, 1·30)	0·73
Role	87/103	85/110	9·14 (6·14, 12·14)	9·29 (6·00, 15·29)	1·08 (0·80, 1·46)	0·65
Emotional	54/103	49/110	81·29 (39·14, 114·29)	87·57 (24·14, NE)	0·99 (0·66, 1·48)	0·97
Cognitive	70/103	67/110	18·00 (11·86, 36·29)	21·14 (15·14, 41·71)	1·07 (0·76, 1·50)	0·71
Social	76/103	77/110	15·29 (9·14, 27·29)	12·43 (8·86, 21·14)	0·87 (0·63, 1·21)	0·43
EORTC QLQ symptom scales						
Fatigue	92/103	93/110	6·14 (3·29, 9·14)	3·57 (3·29, 6·14)	0·99 (0·74, 1·33)	0·96
Nausea/vomiting	73/103	70/110	27·29 (18·14, 45·43)	18·43 (12·29, 27·86)	0·91 (0·65, 1·27)	0·60
Pain	89/103	89/110	6·29 (3·43, 9·14)	12·29 (9·29, 15·43)	1·17 (0·86, 1·60)	0·34
Dyspnea*	58/103	71/109	48·14 (21·29, 114·29)	22·00 (12·43, 42·14)	0·67 (0·47, 0·95)	0·027
Insomnia	66/103	60/110	30·57 (21·29, 42·29)	33·43 (15·29, 84·29)	1·10 (0·77, 1·57)	0·61
Appetite loss	78/103	83/110	18·29 (13·29, 27·14)	6·29 (3·71, 15·14)	0·79 (0·57, 1·08)	0·17
Constipation	61/103	67/110	27·43 (15·43, 81·29)	21·29 (13·71, 48·14)	0·81 (0·57, 1·15)	0·26
Diarrhea	83/103	77/110	18·14 (12·29, 28·29)	15·29 (12·14, 26·86)	0·96 (0·70, 1·33)	0·82
Financial difficulties*	52/103	30/110	57·29 (36·14, NE)	NE (NE, NE)	1·69 (1·06, 2·68)	0·025
EQ-5D-3L						
Index	85/103	82/110	9·14 (6·29, 15·29)	15·14 (9·43, 21·14)	1·11 (0·82, 1·52)	0·50
VAS	66/104	62/109	30·43 (15·29, 72·86)	29·86 (14·86, 63·57)	0·92 (0·64, 1·31)	0·63



IMDC intermediate/poor subgroup

Scale	# Pts with Events/ # Pts: L + P	# Pts with Events/ # Pts: SUN	Median Time to Deterioration in Weeks (95% CI): LEN + PEMBRO	Median Time to Deterioration in Weeks (95% CI): SUN	Hazard Ratio (95% CI)	Log-rank *p* value
FKSI-DRS total score	128/225	95/204	45·29 (30·14, 66·14)	45·00 (24·14, 75·14)	1·06 (0·81, 1·39)	0·70
EORTC QLQ						
GHS/QoL	167/226	151/207	9·71 (6·29, 15·71)	9·14 (6·29, 13·29)	0·88 (0·70, 1·10)	0·23
EORTC QLC functional scales						
Physical*	157/225	148/207	15·29 (12·14, 24·71)	9·29 (7·29, 15·14)	0·77 (0·61, 0·97)	0·027
Role	167/225	157/207	9·14 (6·29, 12·29)	9·14 (6·29, 12·29)	0·90 (0·72, 1·13)	0·29
Emotional	134/226	107/207	35·29 (21·29, 54·29)	27·29 (18·14, 45·29)	0·93 (0·72, 1·20)	0·55
Cognitive	161/226	130/207	13·43 (9·43, 21·29)	15·29 (9·71, 21·29)	0·99 (0·79, 1·25)	0·95
Social	171/226	145/207	9·29 (8·14, 13·14)	9·57 (7·29, 15·71)	1·01 (0·81, 1·27)	0·91
EORTC QLQ symptom scales						
Fatigue	186/225	170/207	6·29 (4·00, 7·86)	6·14 (3·86, 6·29)	0·90 (0·73, 1·11)	0·30
Nausea/vomiting	168/225	131/207	18·43 (15·29, 26·71)	15·43 (9·29, 21·86)	0·97 (0·77, 1·23)	0·84
Pain	181/226	149/207	9·14 (6·29, 9·43)	9·43 (6·43, 15·14)	1·03 (0·82, 1·28)	0·89
Dyspnea	131/225	115/207	36·14 (22·14, 51·29)	20·71 (15·29, 36·14)	0·86 (0·67, 1·11)	0·24
Insomnia	150/224	122/207	18·14 (12·14, 24·43)	15·14 (12·14, 21·86)	0·99 (0·77, 1·26)	0·92
Appetite loss	173/225	148/207	18·14 (12·57, 22·14)	12·00 (8·00, 18·29)	0·84 (0·68, 1·05)	0·15
Constipation	130/225	98/207	37·00 (22·29, 66·57)	42·14 (26·14, 93·00)	1·09 (0·83, 1·42)	0·56
Diarrhea	182/225	153/207	15·14 (12·29, 20·86)	13·57 (9·43, 15·29)	0·82 (0·66, 1·03)	0·084
Financial difficulties	106/226	86/206	83·14 (48·86, NE)	48·14 (31·43, 120·29)	0·82 (0·61, 1·10)	0·19
EQ-5D-3L						
Index	174/226	137/207	9·00 (6·29, 9·29)	14·86 (9·29, 18·14)	1·13 (0·90, 1·43)	0·32
VAS	141/227	121/203	26·71 (18·29, 48·29)	24·14 (15·29, 27·29)	0·87 (0·68, 1·12)	0·26

*Denotes a statistically significant log-rank difference ($P < 0·05$).

CI, confidence interval; EORTC QLQ, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire; EQ-5D-3L, EuroQol 5 Dimensions 3 Levels; FKSI-DRS, Functional Assessment of Cancer Therapy Kidney Symptom Index–Disease-Related Symptoms; GHS/QoL, global health status/quality of life; IMDC, International Metastatic RCC Database Consortium; L / LEN, lenvatinib; MSKCC, Memorial Sloan Kettering Cancer Center; P / PEMBRO, pembrolizumab; S / SUN, sunitinib; VAS, visual analog scale.

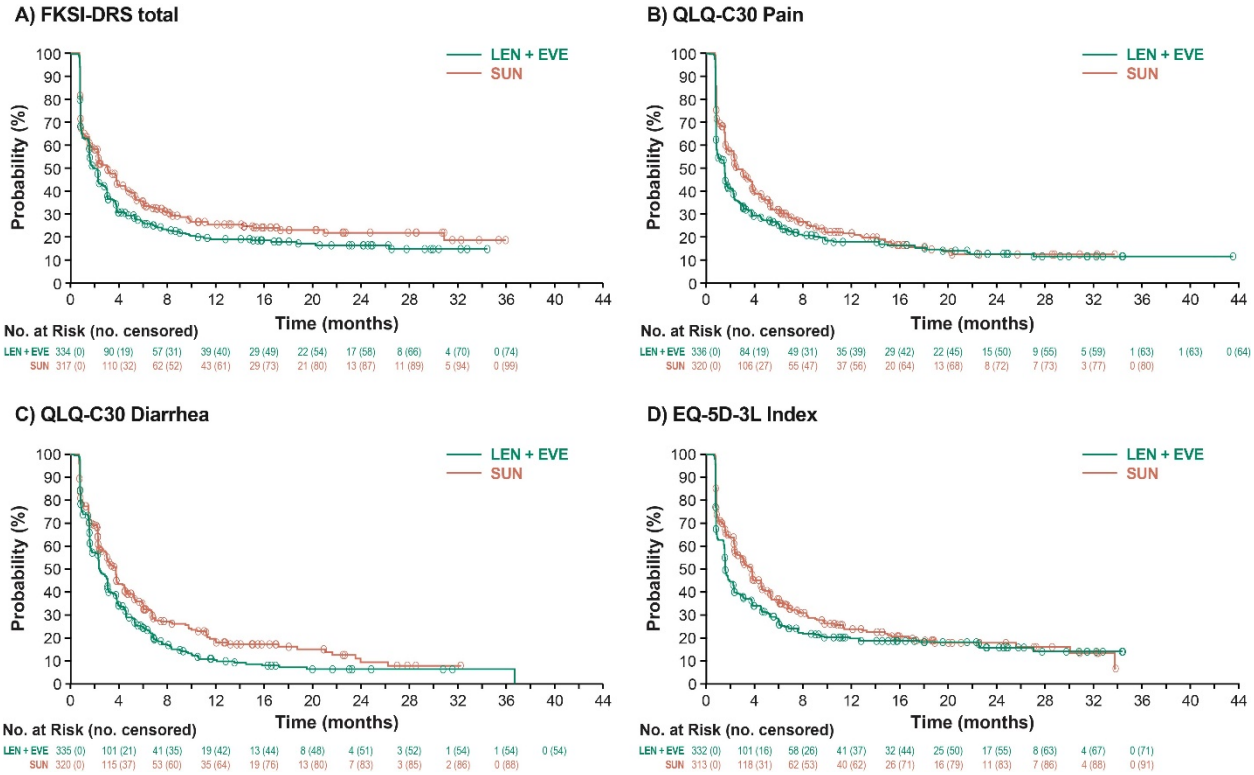
Figure S4. Time to First Deterioration: Lenvatinib + Everolimus vs Sunitinib

Scale/ Total/Comparison	# Pts with Events/ # Pts		Median Time to Deterioration in Weeks (95% CI)		Hazard Ratio (95% CI)	Log-rank *p* value
	L + E	SUN	LEN + EVE	SUN		
FKSI-DRS total score*	260/334	218/317	7·86 (6·29, 9·14)	12·14 (9·14, 15·29)	1·22 (1·01, 1·46)	0·042
EORTC QLQ-C30						
Global health status/QoL	262/336	242/320	9·00 (6·29, 11·43)	9·14 (6·29, 12·14)	1·04 (0·87, 1·24)	0·71
Physical functioning	252/336	228/320	9·43 (7·71, 12·29)	12·71 (9·29, 18·14)	1·05 (0·88, 1·26)	0·57
Role functioning	267/335	245/320	6·57 (6·29, 9·14)	9·29 (6·29, 12·29)	1·07 (0·90, 1·28)	0·40
Emotional functioning	195/336	158/320	27·14 (22·29, 35·14)	37·00 (22·43, 65·57)	1·16 (0·94, 1·43)	0·19
Cognitive functioning	235/336	199/320	15·57 (12·14, 19·43)	16·00 (13·14, 21·29)	1·16 (0·96, 1·40)	0·11
Social functioning	257/335	224/320	9·14 (6·29, 12·14)	12·29 (9·14, 15·29)	1·16 (0·97, 1·39)	0·12
Fatigue	294/335	265/320	5·71 (3·43, 6·14)	6·00 (3·57, 6·14)	1·07 (0·90, 1·26)	0·50
Nausea and vomiting	245/335	203/320	15·29 (12·29, 18·57)	16·00 (12·29, 21·14)	1·12 (0·93, 1·35)	0·24
Pain*	272/336	240/320	6·14 (4·00, 6·29)	9·86 (9·14, 14·71)	1·28 (1·08, 1·52)	0·0061
Dyspnea	215/334	189/319	18·43 (12·29, 24·14)	21·14 (15·43, 32·71)	1·06 (0·87, 1·29)	0·61
Insomnia	225/335	184/320	12·86 (12·14, 18·14)	19·14 (15·00, 30·43)	1·19 (0·98, 1·45)	0·080
Appetite loss	264/334	233/320	8·86 (6·29, 9·29)	9·14 (6·29, 15·14)	1·15 (0·97, 1·38)	0·11
Constipation	197/335	166/320	27·14 (21·57, 38·86)	32·71 (24·14, 50·86)	1·11 (0·90, 1·37)	0·29
Diarrhea*	281/335	232/320	9·57 (9·14, 12·14)	15·14 (12·14, 15·43)	1·31 (1·10, 1·56)	0·0038
Financial difficulties	155/335	118/319	59·29 (37·14, NE)	120·29 (58·57, NE)	1·21 (0·95, 1·54)	0·10
EQ-5D						
Index*	261/332	222/313	6·29 (6·14, 7·86)	15·00 (11·86, 18·14)	1·28 (1·07, 1·53)	0·0075
EQ-VAS (7 point MID)	275/334	246/315	6·43 (6·29, 8·29)	9·14 (6·29, 12·00)	1·09 (0·92, 1·30)	0·40

*Denotes a statistically significant log-rank difference ($P < 0·05$).

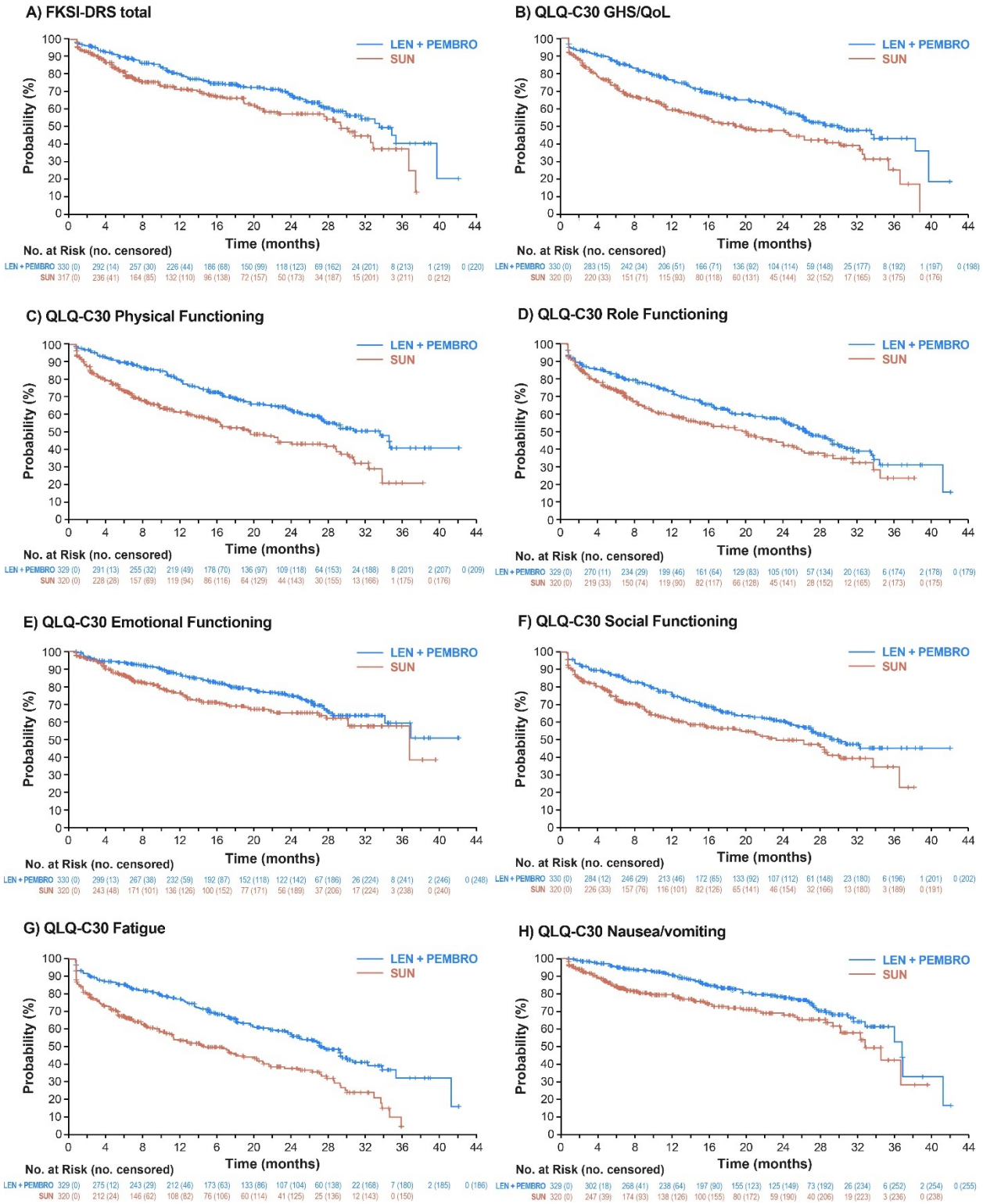
CI, confidence interval; EORTC QLQ-C30, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire; EQ-5D-3L, EuroQol 5 Dimensions 3 Levels; EQ-VAS, EuroQol visual analog scale; FKSI-DRS, Functional Assessment of Cancer Therapy Kidney Symptom Index–Disease-Related Symptoms; LEN, lenvatinib; PEMBRO, pembrolizumab.

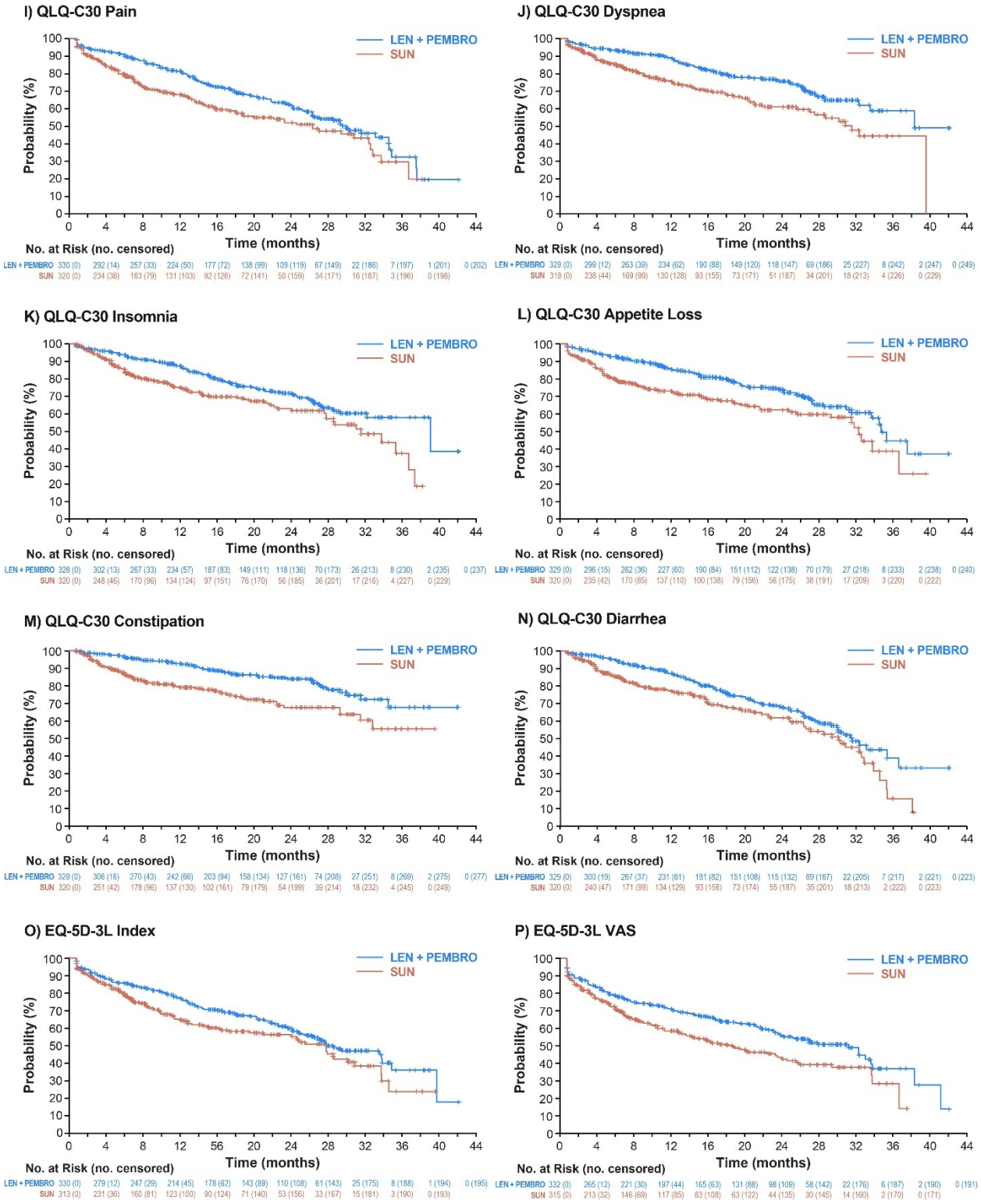
Figure S5. Kaplan-Meier Plots of Nominally Significant Scales for Time to First Deterioration: Lenvatinib + Everolimus vs Sunitinib



EQ-5D-3L, EuroQol 5 Dimensions 3 Levels; EVE, everolimus; FKSI-DRS, Functional Assessment of Cancer Therapy Kidney Symptom Index–Disease-Related Symptoms; LEN, lenvatinib; QLQ-C30, Quality of Life Questionnaire; SUN, sunitinib.

Figure S6. Kaplan-Meier Plots of Nominally Significant Scales for Time to Definitive Deterioration: Lenvatinib + Pembrolizumab vs Sunitinib



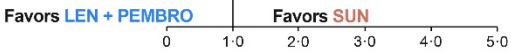


EORTC QLQ, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire; EQ-5D-3L, EuroQol 5 Dimensions 3 Levels; LEN, lenvatinib; PEMBRO, pembrolizumab; SUN, sunitinib; VAS, visual analog scale.

Figure S7. MSKCC and IMDC Risk Group Subgroup Analyses of Time to Definitive Deterioration in Lenvatinib + Pembrolizumab and Sunitinib Arms

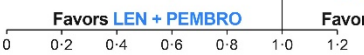
MSKCC favorable subgroup

Scale	# Pts with Events/ # Pts		Median Time to Deterioration in Weeks (95% CI)		Hazard Ratio (95% CI)	Log-rank *p* value
	L + P	SUN	LEN + PEMBRO	SUN		
FKSI-DRS total score	32/91	27/91	132·14 (113·57, NE)	120·57 (84·29, NE)	0·90 (0·53, 1·51)	0·48
EORTC QLQ						
GHS/QoL*	39/91	45/91	114·29 (90·14, NE)	69·14 (45·14, NE)	0·64 (0·42, 0·99)	0·035
EORTC QLC functional scales						
Physical*	31/91	37/91	122·71 (102·29, NE)	90·14 (65·14, NE)	0·61 (0·38, 0·99)	0·031
Role	42/91	36/91	105·00 (88·00, NE)	114·00 (75·29, NE)	0·91 (0·58, 1·43)	0·61
Emotional	20/91	17/91	NE (113·86, NE)	NE (120·57, NE)	0·87 (0·45, 1·68)	0·62
Cognitive	39/91	22/91	114·43 (95·00, 134·71)	NE (108·57, NE)	1·32 (0·78, 2·25)	0·30
Social	38/91	29/91	116·43 (97·00, NE)	NE (114·00, NE)	1·04 (0·64, 1·69)	0·97
EORTC QLQ symptom scales						
Fatigue*	40/91	50/91	117·29 (90·29,135·29)	72·29 (42·14, 93·14)	0·54 (0·36, 0·83)	0·0026
Nausea/vomiting	14/91	17/91	165·00 (NE, NE)	NE (120·57, NE)	0·60 (0·29, 1·24)	0·17
Pain	38/91	34/91	119·71 (88·00, NE)	117·57 (69·14, NE)	0·88 (0·55, 1·40)	0·54
Dyspnea*	16/91	24/91	NE (129·14, NE)	126·14 (84·14, NE)	0·47 (0·25, 0·89)	0·018
Insomnia	22/91	15/91	NE (128·71, NE)	141·14 (126·14, NE)	1·16 (0·59, 2·29)	0·63
Appetite loss	26/91	18/91	138·14 (126·14, 141·29)	NE (126·14, NE)	1·09 (0·59, 1·99)	0·65
Constipation	11/91	16/91	NE (NE, NE)	NE (126·14, NE)	0·51 (0·24, 1·10)	0·085
Diarrhea	30/91	20/91	141·29 (120·29, NE)	138·14 (114·00, NE)	1·01 (0·57, 1·80)	0·99
Financial difficulties	22/91	9/91	NE (129·14, NE)	NE (NE, NE)	2·08 (0·95, 4·53)	0·059
EQ-5D-3L						
Index	35/91	28/89	135·29 (105·00, NE)	114·14 (98·86, NE)	1·04 (0·63, 1·73)	0·98
VAS	40/91	40/90	124·86 (87·00, NE)	74·86 (51·29, NE)	0·83 (0·53, 1·29)	0·34



MSKCC intermediate/poor subgroup

Scale	# Pts with Events/ # Pts		Median Time to Deterioration in Weeks (95% CI)		Hazard Ratio (95% CI)	Log-rank *p* value
	L + P	SUN	LEN + PEMBRO	SUN		
FKSI-DRS total score*	78/239	78/226	139·43 (114·14, NE)	117·43 (83·71, 146·71)	0·64 (0·47, 0·88)	0.0062
EORTC QLQ						
GHS/QoL*	93/239	99/229	108·00 (102·14, NE)	97·00 (52·29, 120·57)	0·59 (0·44, 0·78)	0·0003
EORTC QLC functional scales						
Physical*	89/238	107/229	134·14 (108·14, NE)	74·43 (45·29, 115·00)	0·49 (0·37, 0·66)	<·0001
Role*	108/238	109/229	105·43 (83·14, 117·29)	63·00 (39·14, 84·14)	0·64 (0·49, 0·84)	0·0011
Emotional*	62/239	63/229	147·57 (136·43, NE)	147·00 (88·43, NE)	0·60 (0·42, 0·85)	0·0043
Cognitive	99/239	77/229	105·57 (85·14, 147·43)	102·29 (72·14, NE)	0·85 (0·63, 1·15)	0·29
Social*	90/239	100/229	129·14 (99·14, NE)	75·57 (48·14, 105·14)	0·54 (0·40, 0·72)	<·0001
EORTC QLQ symptom scales						
Fatigue*	103/238	120/229	108·14 (94·43, 120·29)	57·00 (39·57, 84·14)	0·53 (0·41, 0·70)	<·0001
Nausea/vomiting*	60/238	65/229	143·86 (126·29, NE)	131·29 (117·43, 146·71)	0·52 (0·36, 0·75)	0·0013
Pain*	90/239	88/229	118·14 (102·14, 138·29)	98·29 (63·29, 130·29)	0·62 (0·46, 0·83)	0·0025
Dyspnea*	64/238	66/228	153·14 (134·14, NE)	123·43 (108·14, NE)	0·59 (0·41, 0·84)	0·0036
Insomnia*	69/237	76/229	156·14 (108·57, NE)	114·29 (84·29, 146·71)	0·54 (0·39, 0·75)	0·0003
Appetite loss*	63/238	80/229	150·29 (124·00, NE)	127·29 (86·29, 135·14)	0·48 (0·34, 0·67)	<·0001
Constipation*	41/238	55/229	NE (138·14, NE)	NE (117·29, NE)	0·45 (0·30, 0·68)	0·0003
Diarrhea*	76/238	77/229	126·29 (111·00, 146·29)	105·29 (83·71, 129·14)	0·57 (0·41, 0·78)	0·0007
Financial difficulties*	58/239	58/228	153·57 (153·57, NE)	NE (105·29, NE)	0·62 (0·43, 0·90)	0·025
EQ-5D-3L						
Index*	100/239	92/224	108·14 (96·29, 139·43)	98·29 (49·00, 120·29)	0·68 (0·51, 0·91)	0·0089
VAS*	101/241	104/225	129·14 (93·14, 153·29)	72·43 (45·29, 94·00)	0·62 (0·47, 0·82)	0·0020

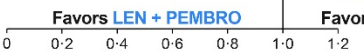


IMDC favorable subgroup

Scale	# Pts with Events/ # Pts: L + P	# Pts with Events/ # Pts: SUN	Median Time to Deterioration in Weeks (95% CI): LEN + PEMBRO	Median Time to Deterioration in Weeks (95% CI): SUN	Hazard Ratio (95% CI)	Log-rank *p* value
FKSI-DRS total score	46/104	37/110	119·57 (95·29, 141·29)	120·57 (83·71, NE)	1·08 (0·69, 1·70)	0·92
EORTC QLQ						
GHS/QoL	48/103	52/110	105·29 (82·14, NE)	79·71 (62·86, 130·29)	0·79 (0·52, 1·19)	0·22
EORTC QLC functional scales						
Physical	43/103	49/110	110·14 (72·14, NE)	90·14 (65·14, 135·14)	0·77 (0·50, 1·17)	0·15
Role	51/103	46/110	99·29 (66·43, 137·71)	114·00 (75·29, NE)	1·00 (0·66, 1·50)	0·96
Emotional	25/103	22/110	NE (NE, NE)	NE (120·57, NE)	0·99 (0·55, 1·79)	0·99
Cognitive	47/103	30/110	105·14 (95·00, 122·29)	NE (108·57, NE)	1·23 (0·77, 1·96)	0·46
Social	42/103	42/110	116·43 (90·43, NE)	120·57 (105·14, NE)	0·94 (0·61, 1·46)	0·86
EORTC QLQ symptom scales						
Fatigue*	52/103	62/110	99·43 (75·14, 122·57)	70·00 (45·14, 93·14)	0·67 (0·46, 0·98)	0·029
Nausea/vomiting	17/103	23/110	165·00 (NE, NE)	NE (NE, NE)	0·60 (0·31, 1·17)	0·11
Pain	45/103	41/110	105·57 (87·14, NE)	129·57 (75·29, 134·86)	1·01 (0·65, 1·57)	0·92
Dyspnea*	20/103	33/109	NE (129·14, NE)	123·43 (84·14, NE)	0·55 (0·31, 0·97)	0·031
Insomnia	28/103	22/110	NE (117·14, NE)	141·14 (124·00, NE)	1·22 (0·67, 2·22)	0·62
Appetite loss	30/103	27/110	138·14 (126·14, 141·29)	135·14 (126·14, NE)	1·01 (0·59, 1·75)	0·95
Constipation	16/103	22/110	NE (NE, NE)	NE (126·14, NE)	0·66 (0·34, 1·27)	0·16
Diarrhea	34/103	29/110	141·29 (120·29, NE)	130·29 (114·00, 152·29)	1·03 (0·61, 1·74)	0·97
Financial difficulties	28/103	16/110	NE (129·14, NE)	NE (NE, NE)	1·56 (0·83, 2·94)	0·19
EQ-5D-3L						
Index	48/104	38/110	105·86 (84·29, NE)	114·14 (99·14, 138·14)	1·26 (0·81, 1·97)	0·36
VAS	46/104	47/109	124·86 (87·00, NE)	102·14 (63·14, NE)	0·83 (0·55, 1·25)	0·28

IMDC intermediate/poor subgroup

Scale	# Pts with Events/ # Pts: L + P	# Pts with Events/ # Pts: SUN	Median Time to Deterioration in Weeks (95% CI): LEN + PEMBRO	Median Time to Deterioration in Weeks (95% CI): SUN	Hazard Ratio (95% CI)	Log-rank *p* value
FKSI-DRS total score*	64/225	67/204	NE (134·14, NE)	117·14 (75·43, NE)	0·55 (0·39, 0·78)	0·0016
EORTC QLQ						
GHS/QoL*	84/226	90/207	134·14 (102·14, NE)	63·14 (45·29, 105·14)	0·51 (0·38, 0·69)	<·0001
EORTC QLC functional scales						
Physical*	76/225	94/207	138·14 (115·00, NE)	65·57 (51·14, 115·00)	0·42 (0·31, 0·57)	<·0001
Role*	99/225	96/207	108·14 (93·57, 126·14)	57·57 (39·57, 87·29)	0·58 (0·43, 0·77)	0·0003
Emotional*	57/226	57/207	147·57 (136·43, NE)	147·00 (78·00, NE)	0·51 (0·35, 0·74)	0·0004
Cognitive	91/226	67/207	111·14 (91·86, 147·43)	99·14 (65·57, NE)	0·80 (0·58, 1·10)	0·19
Social*	86/226	86/207	120·14 (100·57, NE)	75·57 (48·86, 105·14)	0·51 (0·37, 0·69)	<·0001
EORTC QLQ symptom scales						
Fatigue*	90/225	107/207	117·14 (99·57, NE)	51·29 (38·86, 80·00)	0·47 (0·35, 0·63)	<·0001
Nausea/vomiting*	57/225	58/207	143·86 (126·29, 147·57)	129·29 (114·29, NE)	0·48 (0·33, 0·70)	0·0002
Pain*	83/226	79/207	120·57 (105·43, 139·43)	93·00 (57·00, 131·29)	0·55 (0·40, 0·76)	0·0004
Dyspnea*	60/225	54/207	153·14 (114·14, NE)	129·29 (110·00, NE)	0·57 (0·39, 0·84)	0·0037
Insomnia*	62/224	68/207	156·14 (156·14, NE)	96·00 (75·29, 146·71)	0·49 (0·35, 0·70)	<·0001
Appetite loss*	59/225	70/207	150·29 (150·29, NE)	127·29 (86·29, NE)	0·45 (0·32, 0·65)	<·0001
Constipation*	36/225	48/207	NE (138·14, NE)	NE (117·29, NE)	0·39 (0·25, 0·61)	<·0001
Diarrhea*	72/225	67/207	120·14 (109·14, 146·29)	105·14 (78·57, 129·14)	0·54 (0·38, 0·76)	0·0002
Financial difficulties*	52/226	49/206	153·57 (153·57, NE)	NE (102·71, NE)	0·61 (0·41, 0·91)	0·017
EQ-5D-3L						
Index*	87/225	81/200	117·57 (102·14, NE)	84·14 (45·29, 114·43)	0·58 (0·42, 0·79)	0·0006
VAS*	95/227	95/203	129·14 (91·86, NE)	57·43 (42·29, 89·86)	0·60 (0·45, 0·80)	0·0007

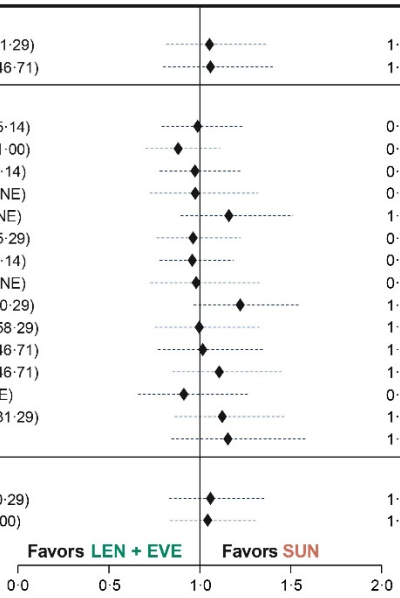


*Denotes a statistically significant log-rank difference ($P < 0·05$).

CI, confidence interval; EORTC QLQ, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire; EQ-5D-3L, EuroQol 5 Dimensions 3 Levels; FKSI-DRS, Functional Assessment of Cancer Therapy Kidney Symptom Index–Disease-Related Symptoms; GHS/QoL, global health status/quality of life; IMDC, International Metastatic RCC Database Consortium; L / LEN, lenvatinib; MSKCC, Memorial Sloan Kettering Cancer Center; P / PEMBRO, pembrolizumab; S / SUN, sunitinib; VAS, visual analog scale.

Figure S8. Time to Definitive Deterioration: Lenvatinib + Everolimus vs Sunitinib

Scale/ Total/Comparison	# Pts with Events/ # Pts		Median Time to Deterioration in Weeks (95% CI)		Hazard Ratio (95% CI)	Log-rank *p* value
	L + E	SUN	LEN + EVE	SUN		
FKSI-DRS						
Total score (3 point MID)	129/334	105/317	114·14 (90·43, NE)	117·43 (90·14, 131·29)	1·06 (0·81, 1·37)	0.68
Total score (4 point MID)	107/334	88/317	123·29 (117·14, NE)	128·29 (114·57, 146·71)	1·06 (0·80, 1·41)	0.64
EORTC QLQ-C30						
Global health status/QoL	165/336	144/320	81·86 (63·57, 98·29)	75·14 (57·29, 105·14)	0·99 (0·79, 1·24)	0.97
Physical functioning	151/336	144/320	82·29 (66·43, 118·71)	78·14 (63·14, 111·00)	0·88 (0·70, 1·11)	0.32
Role functioning	166/335	145/320	71·71 (57·14, 95·71)	78·29 (54·14, 96·14)	0·98 (0·78, 1·22)	0.90
Emotional functioning	94/336	80/320	129·00 (120·14, 174·29)	147·00 (120·57, NE)	0·98 (0·72, 1·32)	0.85
Cognitive functioning	132/336	99/320	108·14 (81·00, 123·14)	135·00 (99·14, NE)	1·16 (0·89, 1·51)	0.26
Social functioning	149/335	129/320	93·43 (81·00, 113·71)	93·14 (66·43, 115·29)	0·97 (0·76, 1·22)	0.77
Fatigue	190/335	170/320	66·00 (48·29, 77·86)	59·00 (45·14, 81·14)	0·96 (0·78, 1·19)	0.78
Nausea and vomiting	93/335	82/320	129·14 (113·86, NE)	131·29 (120·57, NE)	0·98 (0·73, 1·33)	0.87
Pain	164/336	122/320	79·29 (62·86, 99·29)	105·29 (75·29, 130·29)	1·22 (0·97, 1·55)	0.078
Dyspnea	105/334	90/319	128·14 (119·14, NE)	126·14 (108·14, 158·29)	1·00 (0·75, 1·33)	0.98
Insomnia	109/335	91/320	129·00 (97·29, NE)	126·14 (111·14, 146·71)	1·02 (0·77, 1·35)	0.79
Appetite loss	124/334	98/320	114·14 (101·29, 129·00)	129·29 (117·29, 146·71)	1·11 (0·85, 1·45)	0.42
Constipation	76/335	71/320	NE (128·86, NE)	NE (126·14, NE)	0·92 (0·66, 1·27)	0.50
Diarrhea	127/335	97/320	103·29 (92·14, 116·71)	120·43 (105·14, 131·29)	1·13 (0·86, 1·47)	0.27
Financial difficulties	91/335	67/319	NE (108·43, NE)	NE (NE, NE)	1·16 (0·84, 1·59)	0.41
EQ-5D						
Index	145/332	120/313	96·29 (78·00, 115·14)	111·14 (84·14, 120·29)	1·06 (0·83, 1·36)	0.56
EQ-VAS (7 point MID)	172/334	144/315	69·14 (60·00, 98·29)	74·86 (54·14, 96·00)	1·05 (0·84, 1·31)	0.74



CI, confidence interval; EORTC QLQ-C30, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire; EQ-5D-3L, EuroQol 5 Dimensions 3 Levels; EVE, everolimus; FKSI-DRS, Functional Assessment of Cancer Therapy Kidney Symptom Index–Disease-Related Symptoms; LEN, lenvatinib.

Table S5. Reasons for screening failure

Patient	Specific Reason
1	Insurance issues
2	Patient decided to proceed with other treatment options
3	Patient decided to proceed with other treatment options
4	Patient decided to proceed with other treatment options
5	Unable to receive IV contrast for baseline imaging
6	Scans needed to be repeated with contrast
7	Randomization expired
8	Personal travel time
9	Patient was admitted to hospice upon hospital discharge
10	Physician elected to treat subject with other treatment options
11	Unable to receive IV contrast for baseline imaging
12	Unable to receive IV contrast for baseline imaging
13	Concomitant medications being taken
14	Exceeded screening period
15	Unable to perform CT/MRI with contrast
16	Unable to perform CT/MRI with contrast
17	Bone marrow had not recovered from radiation yet
18	Patient had to undergo radiation
19	Admitted to hospice
20	Bone scan problems
21	General worsening of the patient's health condition
22	Insurance issue
23	Exceeded screening period
24	PI decision
25	Exceeded screening period
26	Medical decision due to hyperglycemia
27	Procedures could not be performed within time limit
28	Disease progression
29	Disease progression
30	Patient refusal
31	ECOG 3
32	Planned surgery
33	Patient worsening/PI withdrawing patient from the trial
34	Exceeded screening period

CT/MRI, computed tomography/magnetic resonance imaging; ECOG, Eastern Cooperative Oncology Group; PI, principal investigator.

List of all sites and investigators with patient enrollment

Country	Principal Investigator	Patients (N = 1069)
Russian Federation	Boris Ya Alekseev	39
United States of America	Robert Motzer	36
Russian Federation	Evgeny Kopyltsov	27
Korea, Republic of	Sun Young Rha	25
United States of America	Toni Choueiri	21
Spain	Maria Jose Mendez	20
Russian Federation	Vsevolod Matveev	19
Russian Federation	Vadim Kozlov	19
Korea, Republic of	Sung Hoo Hong	17
Russian Federation	Anna Alyasova	17
Canada	Anil Kapoor	14
Spain	Teresa Alonso Gordoa	14
Canada	Eric Winquist	13
Spain	Jose Pablo Maroto	13
United States of America	Jaime Merchan	13
Australia	Jeffrey Goh	13
Australia	Howard Gurney	12
Korea, Republic of	Miso Kim	12
Canada	Georg Bjarnason	11
Italy	Paolo Pedrazzoli	11
Italy	Giuseppe Procopio	11
United States of America	Vijay Patel	11
Czechia	Tomas Buchler	11
Israel	Avivit Peer	11
Japan	Toshio Takagi	11
France	Frdric Rolland	10
Italy	Ugo de Giorgi	10
Australia	Shirley Wong	10
Czechia	Bohuslav Melichar	10
Korea, Republic of	Se Hoon Park	10
Russian Federation	Sergey Tjulandin	10
Germany	Michael Staehler	9
Poland	Slawomir Mandziuk	9
Israel	David Sarid	9
Japan	Go Kimura	9
Korea, Republic of	Seong II Seo	9
France	Sylvie Zanetta	8
Ireland	Raymond McDermott	8
Spain	Emilio Esteban Gonzalez	8
Spain	Francisco Garcia del Muro Solans	8

Spain	Jesus Garcia	8
Spain	Javier Puente Vazquez	8
United States of America	Ivor Percent	8
United States of America	Manis Agrawal	8
United States of America	David Waterhouse	8
Australia	Andrew Weickhardt	8
Czechia	Jiri Tomasek	8
Korea, Republic of	Jae Lyun Lee	8
France	Sylvie Negrier	7
France	Eric Voog	7
Italy	Roberto Sabbatini	7
Spain	Jose Angel Arranza Arija	7
Spain	Juan Carles	7
United States of America	Theodore Gourdin	7
Israel	Olesya Goldman	7
Japan	Satoshi Fukasawa	7
Japan	Satoshi Tamada	7
Japan	Masatoshi Eto	7
Korea, Republic of	Jinsoo Chung	7
Austria	Manuela Schmidinger	6
United Kingdom of Great Britain and Northern Ireland	Manon Pillai	6
United Kingdom of Great Britain and Northern Ireland	Sara Rudman	6
United States of America	Saby George	6
United States of America	Elisabeth Heath	6
United States of America	Carlos Alemany	6
United States of America	Marc Matrana	6
Israel	Victoria Neiman	6
Japan	Yuji Miura	6
Japan	Mototsugu Oya	6
Japan	Yoshihisa Matsukawa	6
Japan	Satoshi Anai	6
Germany	Maria De Santis	5
Greece	Aristotelis Bamias	5
Greece	Christos Papandreou	5
Ireland	Oscar Breathnach	5
Italy	Daniele Santini	5
Italy	Francesco Carrozza	5
Netherlands	Johannes van Thienen	5
Poland	Jacek Jassem	5
Spain	Begona Mellado Gonzalez	5
United Kingdom of Great Britain and Northern Ireland	Hilary Glen	5

United States of America	Thomas Hutson	5
United States of America	Daniel Spitz	5
Japan	Yoshihiko Tomita	5
Japan	Masahiro Nozawa	5
Japan	Hideki Sakai	5
Korea, Republic of	Choung Soo Kim	5
Canada	Naveen S Basappa	4
France	Diego Tosi	4
France	Stephane Oudard	4
France	Frdric Rolland	4
Greece	Haralabos Kalofonos	4
Italy	Fabio Calabro	4
Italy	Ferdinando Riccardi	4
Netherlands	BBM Britt	4
Spain	Begona Perez Valderrama	4
United States of America	Johanna Bendell	4
United States of America	Sandy Srinivas	4
United States of America	Nafisa Burhani	4
United States of America	Stephen Richey	4
United States of America	Ralph Hauke	4
Czechia	Jana Prausova	4
Belgium	Wim Wynendaele	3
Canada	Christina Canil	3
Canada	Catherine Sperlich	3
France	Luca Campedel	3
Germany	Jens Bedke	3
Italy	Alketa Hamzaj	3
Poland	Violetta Sulzyc	3
United Kingdom of Great Britain and Northern Ireland	Thomas Powles	3
United States of America	Toni Choueiri	3
United States of America	Stephanie Graff	3
Australia	Ian Davis	3
Czechia	Jana Katolicka	3
Japan	Shingo Hatakeyama	3
Japan	Mitsuru Saito	3
Japan	Masayoshi Nagata	3
Japan	Keiichi Kondo	3
Japan	Masafumi Oyama	3
Japan	Kenichi Harada	3
Japan	Atsushi Takamoto	3
Japan	Jun Teishima	3
Japan	Takeshi Kishida	3

Korea, Republic of	Tae Gyun Kwon	3
Russian Federation	Oleg Karyakin	3
Austria	Wolfgang Loidl	2
Belgium	Daisy Luyten	2
France	Philippe Barthelemy	2
Germany	Jan Schleicher	2
Germany	Lothar Bergmann	2
Germany	Philipp Ivanyi	2
Germany	Martin Boegemann	2
Greece	Sofia Baka	2
Ireland	Richard Bambury	2
Italy	Sandro Pignata	2
Italy	Francesco Massari	2
Spain	Pablo Borrega	2
Spain	Enrique Grande Pulido	2
Spain	Ignacio Duran Martinez	2
Switzerland	Julian Schardt	2
United Kingdom of Great Britain and Northern Ireland	Jahangeer Malik	2
United Kingdom of Great Britain and Northern Ireland	Tom Geldart	2
United States of America	Luke Nordquist	2
United States of America	Subramanya Rao	2
United States of America	Mehmood Hashmi	2
United States of America	Alan Koletsky	2
United States of America	Robert Alter	2
United States of America	Donald Richards	2
United States of America	Ronald Harris	2
Australia	Ian Byard	2
Czechia	Petra Holeckova	2
Israel	Avishay Sella	2
Israel	Raanan Berger	2
Japan	Takahiro Osawa	2
Japan	Naoya Masumori	2
Japan	Takatsugu Okegawa	2
Japan	Hiroyuki Tsunemori	2
Japan	Masayuki Takahashi	2
Austria	Gerald KLINGLMAIR	1
Belgium	Dirk Schrijvers	1
Belgium	Rutten Annemie	1
Belgium	Peter Schatteman	1
Belgium	Spyridon Sideris	1
Belgium	Christine Gennigens	1
Canada	Christian Kollmannsberger	1

Germany	Stefan Siemer	1
Ireland	Paul Donnellan	1
Italy	Francesco Boccardo	1
Italy	Giovanni Lo Re	1
Italy	VINCENZO EMANUELE CHIURI	1
Italy	Mimma Rizzo	1
Netherlands	Alfonsus van den Eertwegh	1
Spain	Miguel Angel Climent Duran	1
United Kingdom of Great Britain and Northern Ireland	Loretta Sweeney	1
United Kingdom of Great Britain and Northern Ireland	Christy Ralph	1
United States of America	Ana Molina	1
United States of America	Benjamin Gartrell	1
United States of America	Mike Cusnir	1
United States of America	Cameron Blair Harkness	1
United States of America	Habib Ghaddar	1
United States of America	Sucharu Prakash	1