Newly approved front line regimens for metastatic RCC

Thomas Powles

Director of Barts Cancer Center.
Professor of Urology Cancer, Barts Cancer Institute.

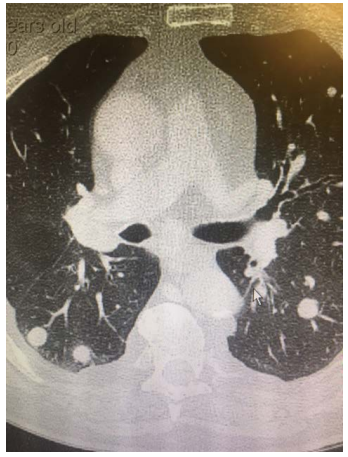
Case 1

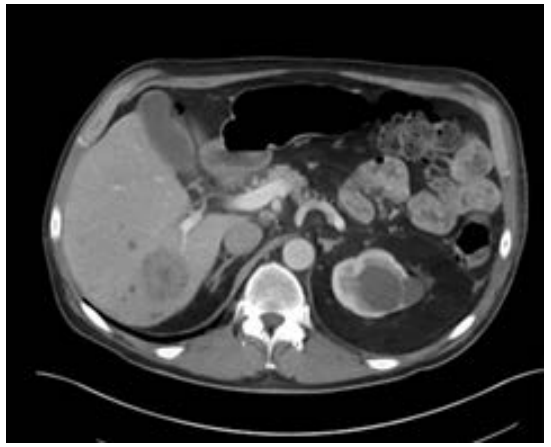
Patient characteristics

69 year old male
Performance status 1
Past medical history of heavy smoking and airways disease.

Tumor characteristics

Liver and lung mets.
Renal Mass
Biopsy from lung mets: mainly sarcomatoid features suspected renal origin view of imaging.
IMDC: poor risk disease.





Cabozantinib and nivolumab.

Data on sarcomatoid RCC with cabozantinib/nivolumab from ASCO GU 2021

	With sRCC		Without sRCC	
	NIVO+CABO n = 34	SUN n = 41	NIVO+CABO n = 279	SUN n = 278
PFS HR (95% CI)	0.39 (0.22–0.70)		0.54 (0.43–0.69)	
Median PFS, months	10.9	4.2	17.7	9.4
OS HR (95% CI)	0.36 (0.16–0.82)		0.68 (0.48–0.95)	
Median OS, months	NR	19.7	NR	NR
ORR, % (95% CI)	55.9 (37.9–72.8)	22.0 (10.6–37.6)	56.6 (50.6–62.5)	28.4 (23.2–34.1)

The other combinations have good data in sarcomatoid RCC too.

ASCO GU FEB 21 - abstract 308 - NCT03141177

Case 1 continued

Patient characteristics	69 year old male Performance status 1 Past medical history of heavy smoking and airways disease.
Tumor characteristics	Liver and lung mets. Renal Mass Biopsy from lung mets: mainly sarcomatoid features suspected renal origin view of imaging.
	Week 4: Due C2 D1 (4 weekly nivolumab) G2 Palmar Plantar Erythema G1 diarrhea G2 fatigue

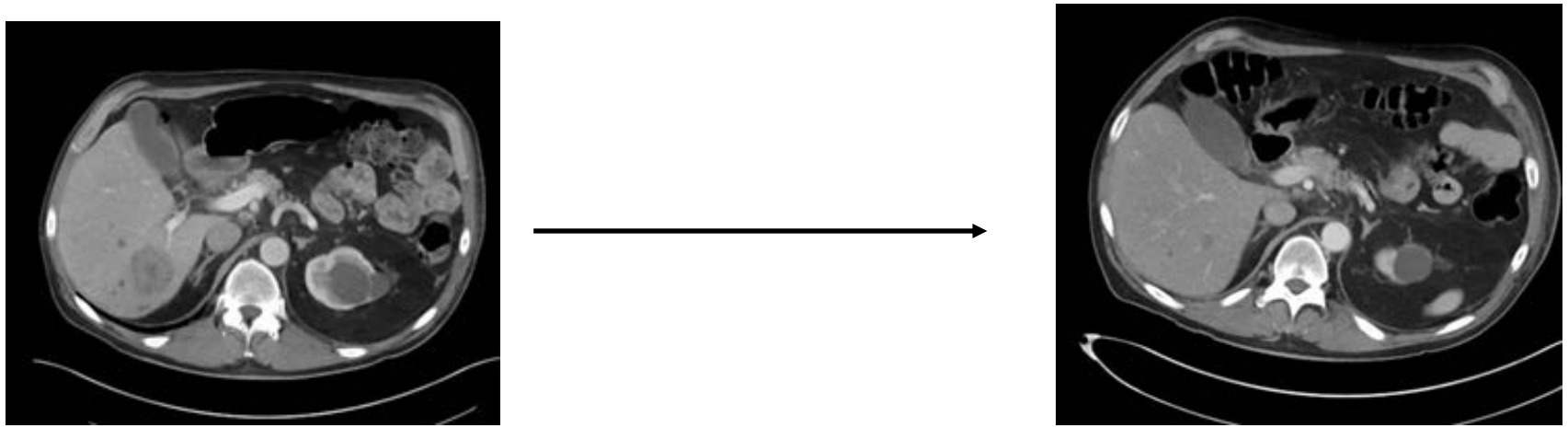
Case 1 continued

Patient characteristics	69 year old male Performance status 1 Past medical history of heavy smoking and airways disease.
Tumor characteristics	Liver and lung mets. Renal Mass Biopsy from lung mets: mainly sarcomatoid features suspected renal origin view of imaging.

Week 8: Due C3 D1:Improved adverse events.
G2 Palmar Plantar Erythema
G1 diarrhea
G2 fatigue
Dose reduce to 20mg

Case 1 continued

Patient characteristics	69 year old male Performance status 1 Past medical history of heavy smoking and airways disease.
Tumor characteristics	Liver and lung mets. Renal Mass Biopsy from lung mets: mainly sarcomatoid features suspected renal origin view of imaging.



Case 1 continued

Patient characteristics	69 year old male Performance status 1 Past medical history of heavy smoking and airways disease.
Tumor characteristics	Liver and lung mets. Renal Mass Biopsy from lung mets: mainly sarcomatoid features suspected renal origin view of imaging.

Is there ever a time to remove the kidney?

What is the best treatment option at progression?

Nivolumab plus cabozantinib versus sunitinib in first-line treatment for advanced renal cell carcinoma: first results from the randomized phase 3 CheckMate 9ER trial

Toni K. Choueiri,[1] Thomas Powles,[2] Mauricio Burotto,[3] Maria T. Bourlon,[4] Bogdan Zurawski,[5] Víctor Manuel Oyervides Juárez,[6] James J. Hsieh,[7] Umberto Basso,[8] Amishi Y. Shah,[9] Cristina Suarez,[10] Alketa Hamzaj,[11] Carlos Barrios,[12] Martin Richardet,[13] David Pook,[14] Yoshihiko Tomita,[15] Bernard Escudier,[16] Joshua Zhang,[17] Burcin Simsek,[17] Andrea B. Apolo,[18] Robert J. Motzer[19]

- [1]Dana-Farber Cancer Institute, The Lank Center for Genitourinary Oncology, Boston, MA, USA; [2]Barts Cancer Institute, Cancer Research UK Experimental Cancer Medicine Centre, Queen Mary University of London, Royal Free National Health Service Trust, London, UK; [3]Bradford Hill Clinical Research Center, Santiago, Chile; [4]Urologic Oncology Clinic, Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, Mexico City, Mexico; [5]Professor Franciszek Lukaszczyk Oncology Centre, Bydgoszcz, Poland; [6]Centro Universitario contra el Cáncer Hospital Universitario "Dr. José Eleuterio González" Universidad Autónoma de Nuevo León, Nuevo León, Mexico; [7]Siteman Cancer Center, Washington University School of Medicine, St. Louis, MO, USA; [8]Istituto Oncologico Veneto IOV IRCCS, Padova, Italy; [9]MD Anderson Cancer Center, Houston, TX, USA; [10]Vall d'Hebron Institute of Oncology, Hospital Universitari Vall d'Hebron, Vall d'Hebron Barcelona Hospital Campus, Barcelona, Spain; [11]Ospedale San Donato, Istituto Toscano Tumori, Arezzo, Italy; [12]Oncology Research Center, Hospital São Lucas, PUCRS, Porto Alegre, Brazil; [13]Fundacion Richardet Longo, Instituto Oncologico de Cordoba, Cordoba, Argentina; [14]Cabrini Monash University Department of Medical Oncology, Cabrini Health, Malvern, VIC, Australia; [15]Niigata University Graduate School of Medical and Dental Sciences, Niigata, Japan; [16]Gustave Roussy, Villejuif, France; [17]Bristol-Myers Squibb Company, Princeton, NJ, USA; [18]Center for Cancer Research, National Cancer Institute, National Institutes of Health, Bethesda, MD, USA; [19]Memorial Sloan Kettering Cancer Center, New York, NY, USA

Presentation Number 696O

CheckMate 9ER: Study design

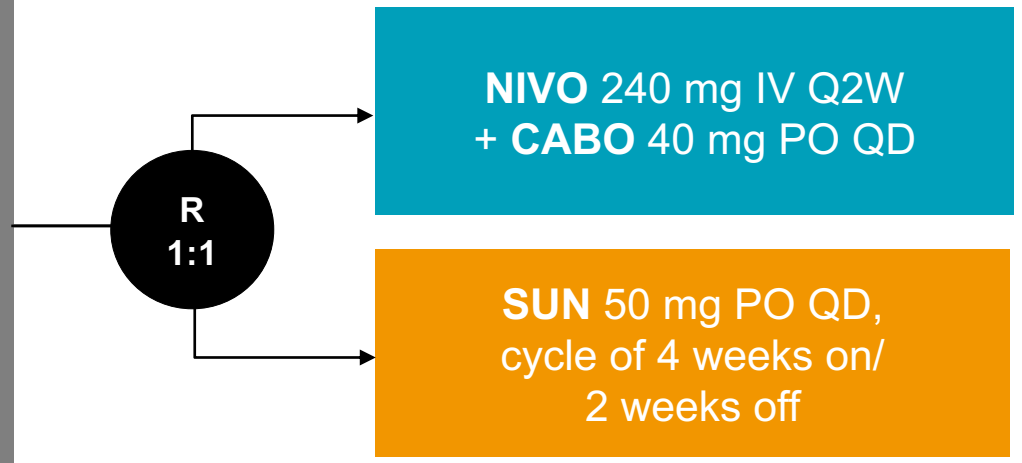
Stratification factors:

- IMDC risk score
- Tumor PD-L1 expression[a]
- Geographic region

N = 651

Key inclusion criteria[1,2]

- Previously untreated advanced or metastatic RCC with a clear cell component
- Any IMDC risk group
- No prior systemic therapy



Treat until RECIST v1.1–defined progression or unacceptable toxicity[b]

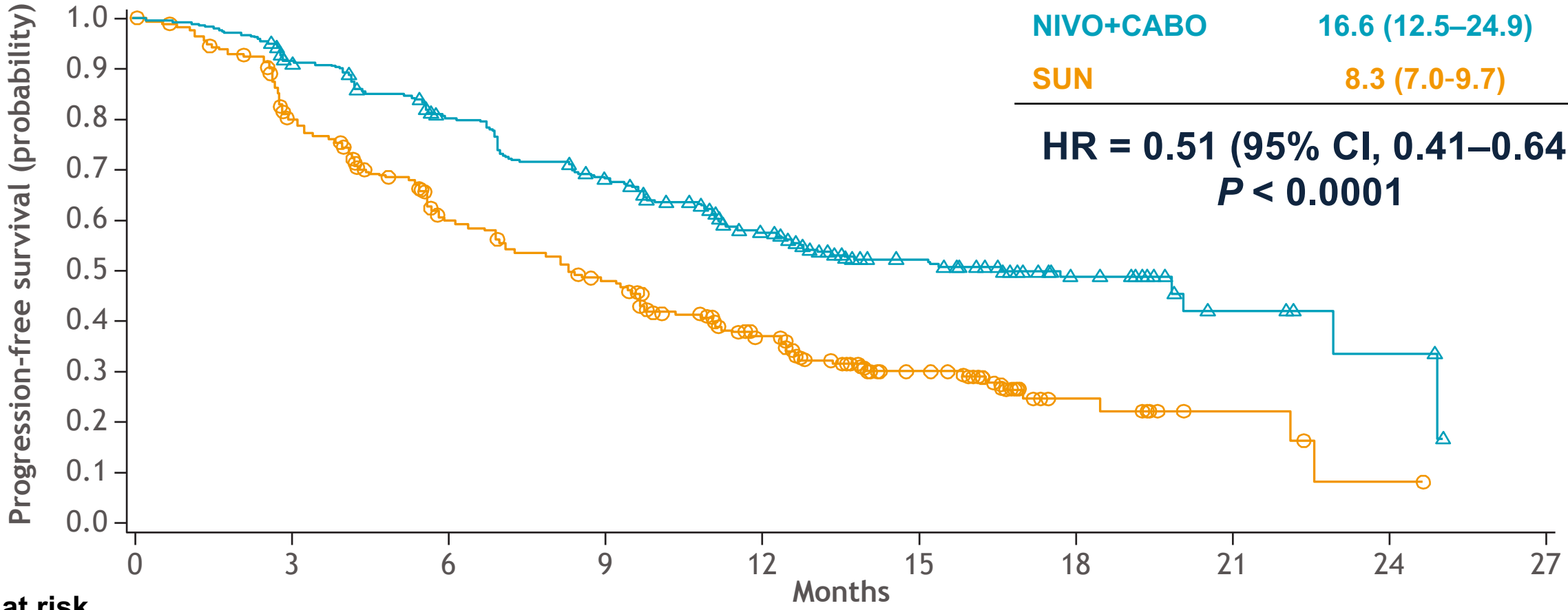
Median study follow-up, 18.1 months (range, 10.6–30.6 months)

[a]Defined as the percent of positive tumor cell membrane staining in a minimum of 100 evaluable tumor cells per validated Dako PD-L1 immunohistochemistry assay.
[b]NIVO dosing may not exceed a total of 2 years (from cycle 1); CABO and SUN treatment may continue beyond 2 years in the absence of progression or unacceptable toxicity. Patients may be treated beyond progression.
IMDC, International Metastatic Renal Cell Carcinoma Database Consortium; IV, intravenously; PD-L1, programmed death ligand 1; PO, orally; Q2W, every 2 weeks; QD, once daily; RECIST, Response Evaluation Criteria in Solid Tumors.
1. clinicaltrials.gov/ct2/show/NCT03141177. Accessed June 8, 2020; 2. Choueiri et al. Poster presented at the American Society of Clinical Oncology Annual Meeting 2018. TPS4598.

Progression-free survival per BICR

Median PFS, months (95% CI)	
NIVO+CABO	16.6 (12.5–24.9)
SUN	8.3 (7.0-9.7)

HR = 0.51 (95% CI, 0.41–0.64)
***P* < 0.0001**

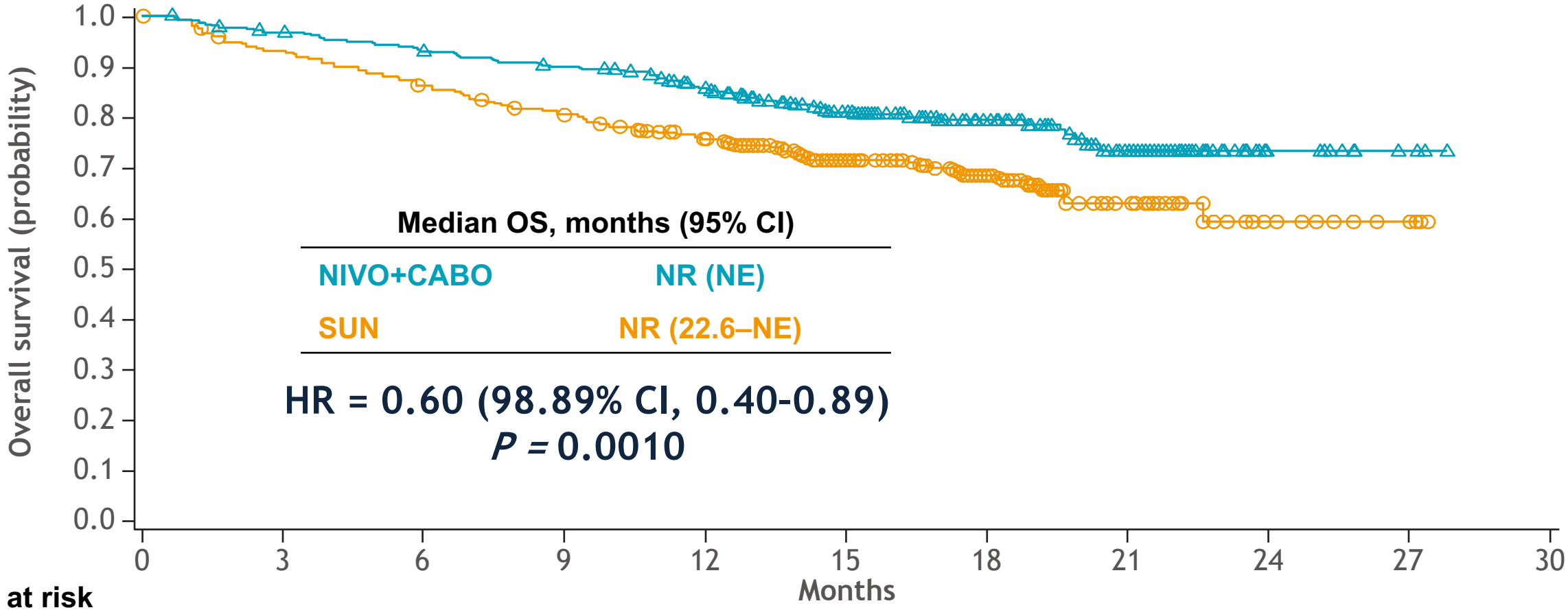


No. at risk

NIVO+CABO	323	279	234	196	144	77	35	11	4	0
SUN	328	228	159	122	79	31	10	4	1	0

Minimum study follow-up, 10.6 months.

Overall survival

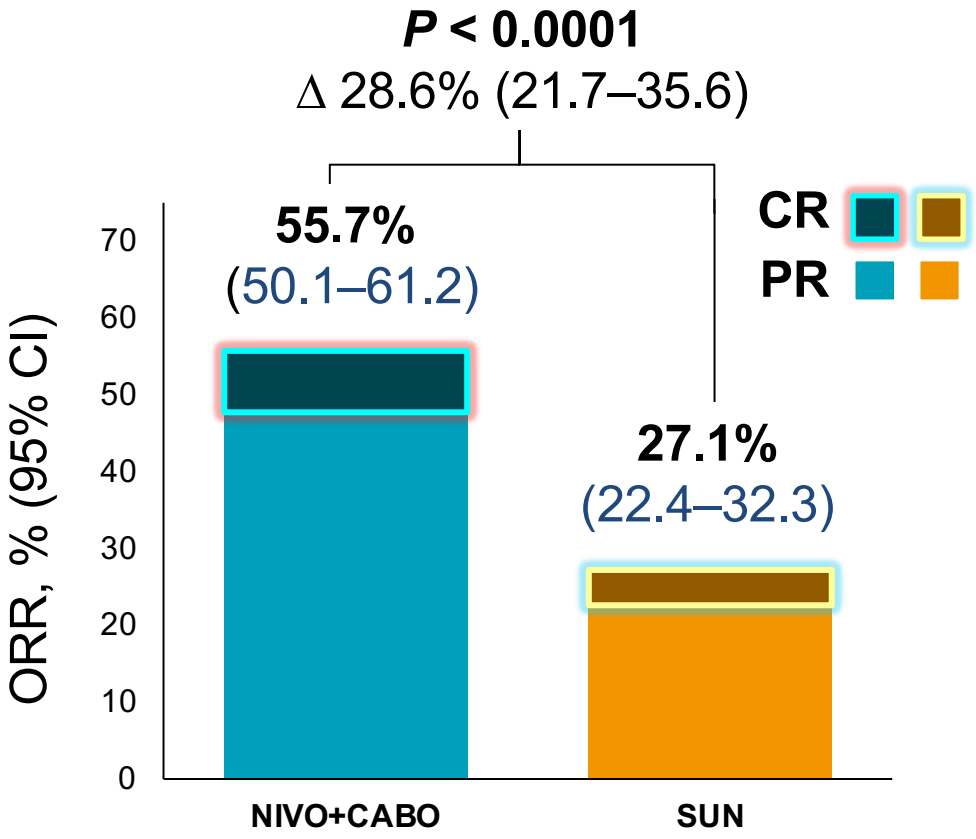


Minimum study follow-up, 10.6 months.
NE, not estimable; NR, not reached.

Overall survival in subgroups

Subgroup	NIVO+CABO	SUN	HR for death (95% CI)
	Events/no. of patients		
Overall	67/323	99/328	0.60 (0.44-0.82)
Region			
US/Europe	26/158	45/161	0.48 (0.30-0.79)
Rest of world	41/165	54/167	0.71 (0.48-1.07)
IMDC prognostic risk			
Favorable	10/74	11/72	0.84 (0.35-1.97)
Intermediate	40/188	51/188	0.70 (0.46-1.07)
Poor	17/61	37/68	0.37 (0.21-0.66)
PD-L1 expression			
≥ 1%	28/83	30/83	0.80 (0.48-1.34)
< 1% or indeterminate	39/240	69/245	0.51 (0.34-0.75)
Age			
< 65 years	31/191	66/210	0.44 (0.29-0.67)
≥ 65 years	36/132	33/118	0.90 (0.56-1.44)
Sex			
Male	47/249	66/232	0.59 (0.40-0.85)
Female	20/74	33/96	0.68 (0.39-1.18)
Karnofsky performance status			
90-100	45/257	56/241	0.69 (0.47-1.03)
≤ 80	22/66	43/85	0.52 (0.31-0.86)
Bone metastases			
Yes	24/78	33/72	0.54 (0.32-0.92)
No	43/245	66/256	0.61 (0.41-0.89)
Previous nephrectomy			
Yes	36/222	66/233	0.49 (0.33-0.74)
No	31/101	33/95	0.79 (0.48-1.29)

Objective response and best overall response per BICR



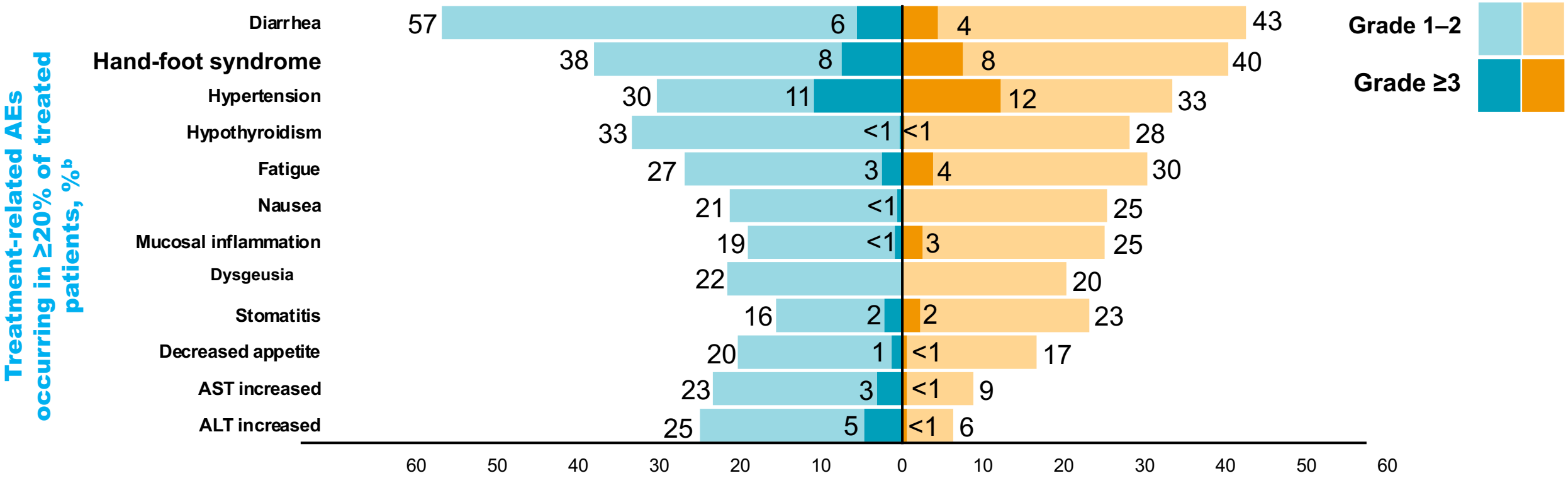
Outcome, %	NIVO+CABO (N = 323)	SUN (N = 328)
Complete response	8.0	4.6
Partial response	47.7	22.6
Stable disease	32.2	42.1
Progressive disease	5.6	13.7
Not evaluable/not assessed[a]	6.5	17.1
Median time to response (range), months[b]	2.8 (1.0–19.4)	4.2 (1.7–12.3)
Median duration of response (95% CI), months[b]	20.2 (17.3–NE)	11.5 (8.3–18.4)

- ORR favored NIVO+CABO over SUN across subgroups including by IMDC risk status, tumor PD-L1 expression (≥ 1% vs < 1%), and bone metastases

BICR-assessed ORR and BOR by RECIST v1.1.
[a]Includes patients who were never treated, those who discontinued/died before disease assessment, those without measurable disease at baseline per BICR, or other reason not reported/specified; [b]Median time to and duration of response were calculated for patients who had a complete or partial response (n = 180 with NIVO+CABO, n = 89 patients with SUN).

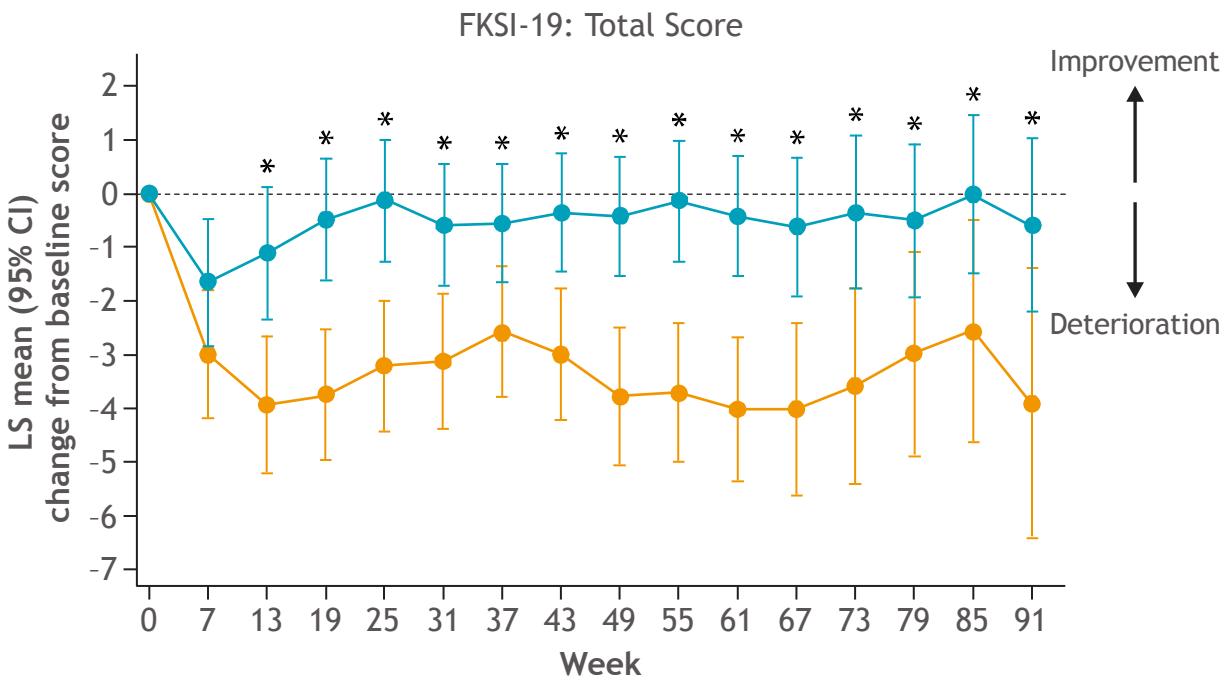
Safety summary

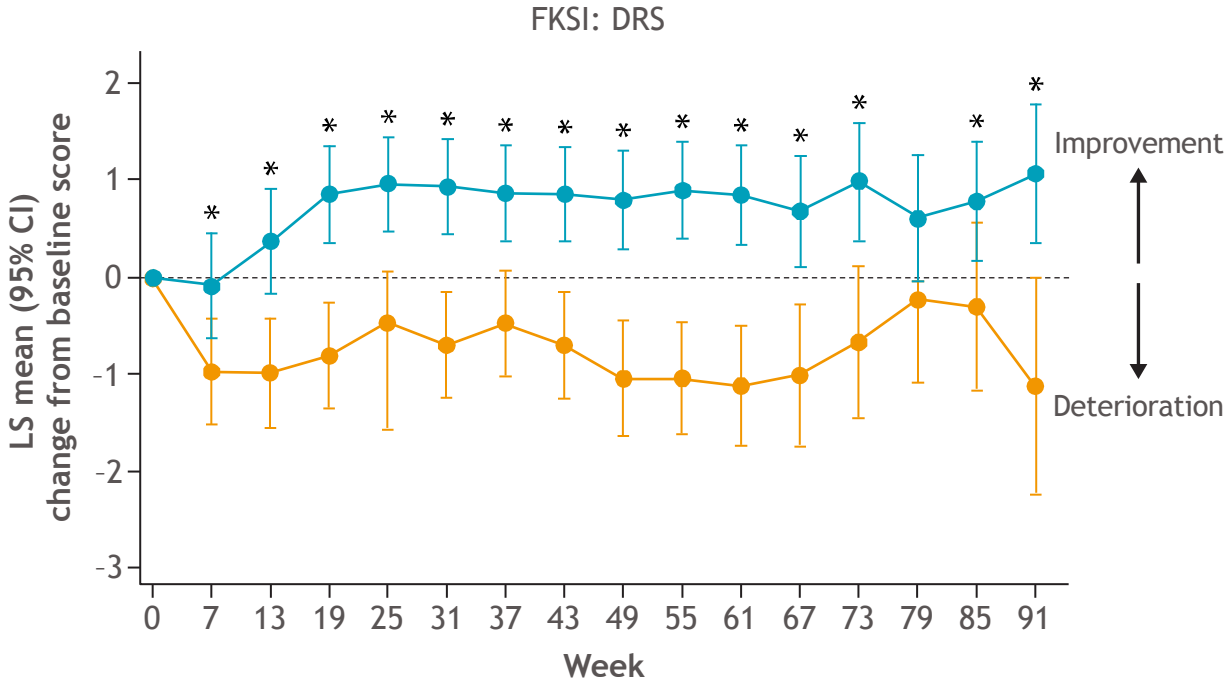
Events, %[a]	NIVO+CABO, N = 320		SUN, N = 320	
	Any grade	Grade ≥ 3	Any grade	Grade ≥ 3
All-cause AEs	100	75	99	71
Treatment-related AEs	97	61	93	51



[a]Includes events that occurred on therapy or within 30 days after the end of the treatment period of all treated patients. Treatment-related deaths per investigator: NIVO+CABO n = 1 (small intestine perforation), SUN n = 2 (pneumonia, respiratory distress); [b]Total bar represents treatment-related AEs of any grade ≥ 20% in either treatment arm; of these events, none were grade 5.

Health-related quality of life





No. at risk

NIVO+CABO	299	261	246	242	228	217	199	191	173	153	147	124	90	67	53	42
SUN	310	262	226	201	179	163	152	142	116	110	87	67	49	34	25	16

No. at risk

NIVO+CABO	299	260	246	242	228	217	199	191	173	153	147	124	90	67	53	42
SUN	310	262	226	201	178	163	152	142	116	110	87	67	49	34	25	16

*Between-arm difference was statistically significant at this timepoint ($P < 0.05$).
Change from baseline was assessed using descriptive statistics and a mixed-model repeated measures analysis, which controlled for treatment arm, time point, baseline patient-reported outcomes score, IMDC prognostic score, PD-L1 tumor expression, and region. No. at risk denotes intention-to-treat patients with baseline plus at least 1 post-baseline HRQoL assessment with non-missing patient-reported outcome data. Time 0 indicates baseline.
FKSI-19, Functional Assessment of Cancer Therapy Kidney Symptom Index-19; FKSI-DRS, FKSI disease-related symptom subscale; LS, least square.

Phase 3 trial of lenvatinib plus pembrolizumab or everolimus versus sunitinib monotherapy as a first-line treatment for patients with advanced renal cell carcinoma (CLEAR study)

Robert Motzer[1], Camillo Porta[2], Masatoshi Eto[3], Thomas Powles[4], Viktor Grünwald[5], Thomas E. Hutson[6], Boris Alekseev[7], Sun Young Rha[8], Evgeny Kopyltsov[9], María José Méndez-Vidal[10], Sung-Hoo Hong[11], Anil Kapoor[12], Teresa Alonso Gordoa[13], Jeffrey C. Goh[14], Jaime R. Merchan[15], Alan D. Smith[16], Kalgi Mody[17], Rodolfo F. Perini[18], Dongyuan Xing[17], and Toni K. Choueiri[19]

[1]Memorial Sloan Kettering Cancer Center; New York, NY, USA; [2]San Matteo University Hospital Foundation, Pavia, Italy; [3]Kyushu University, Fukuoka, Japan; [4]The Royal Free NHS Trust, London, England, UK; [5]University Hospital Essen, Essen, Germany; [6]Texas Oncology, Dallas, TX, USA; [7]P.A. Hertsen Moscow Cancer Research Institute, Moscow, Russia; [8]Yonsei Cancer Center, Yonsei University Health System, Seoul, South Korea; [9]State Institution of Healthcare "Regional Clinical Oncology Dispensary", Omsk, Russia; [10]Maimonides Institute for Biomedical research of Cordoba (IMIBIC) Hospital Universitario Reina Sofía, Medical Oncology Department, Córdoba, Spain; [11]Seoul St. Mary's Hospital, The Catholic University of Korea, Seoul, South Korea; [12]McMaster University Hamilton, Ontario, Canada; [13]Hospital Universitario Ramón y Cajal, Madrid, Spain; [14]ICON Research, South Brisbane & University of Queensland, St Lucia, Queensland, Australia; [15]University of Miami Sylvester Comprehensive Cancer Center, Miami, FL, USA; [16]Eisai Ltd., Hatfield, UK; [17]Eisai Inc., Woodcliff Lake, NJ, USA; [18]Merck & Co., Inc., Kenilworth, NJ, USA; [19]Dana-Farber Cancer Institute, Boston, MA, USA.

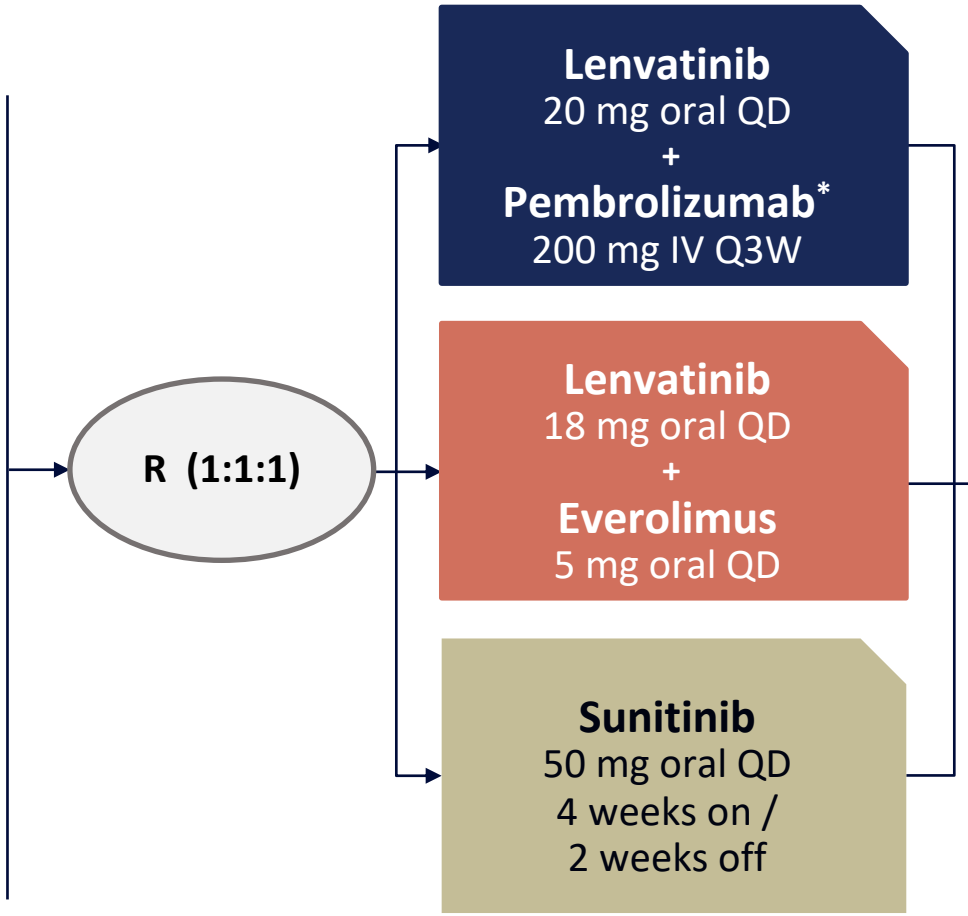
CLEAR TRIAL: Study Design

Key eligibility criteria

- Advanced clear-cell RCC
- Treatment-naïve
- Karnofsky performance status ≥70
- Measurable disease
- Adequate organ function

Stratification factors

- **Geographic region:** Western Europe and North America vs Rest of the World
- **MSKCC risk category:** Favorable, Intermediate, or Poor



Primary endpoint

- PFS by IRC per RECIST v1.1

Secondary endpoints

- OS
- ORR by IRC per RECIST v1.1
- Safety
- HRQoL

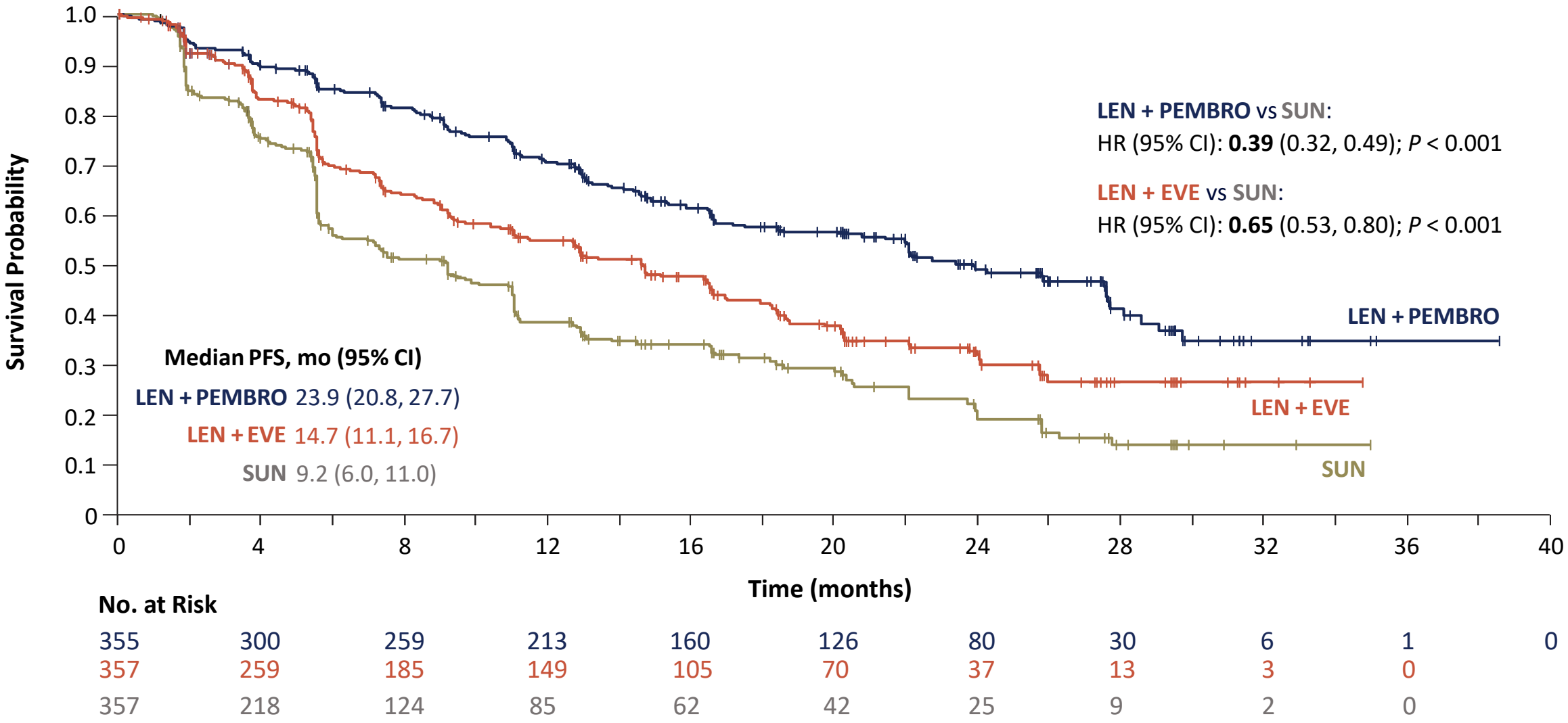
Key exploratory endpoints

- DOR
- Biomarkers

*Patients could receive a maximum of 35 pembrolizumab treatments.

DOR, duration of response; HRQoL, Health-related quality of life; IRC, Independent Review Committee; MKSCC, Memorial Sloan Kettering Cancer Center; ORR, objective response rate; OS, overall survival; R, randomization.

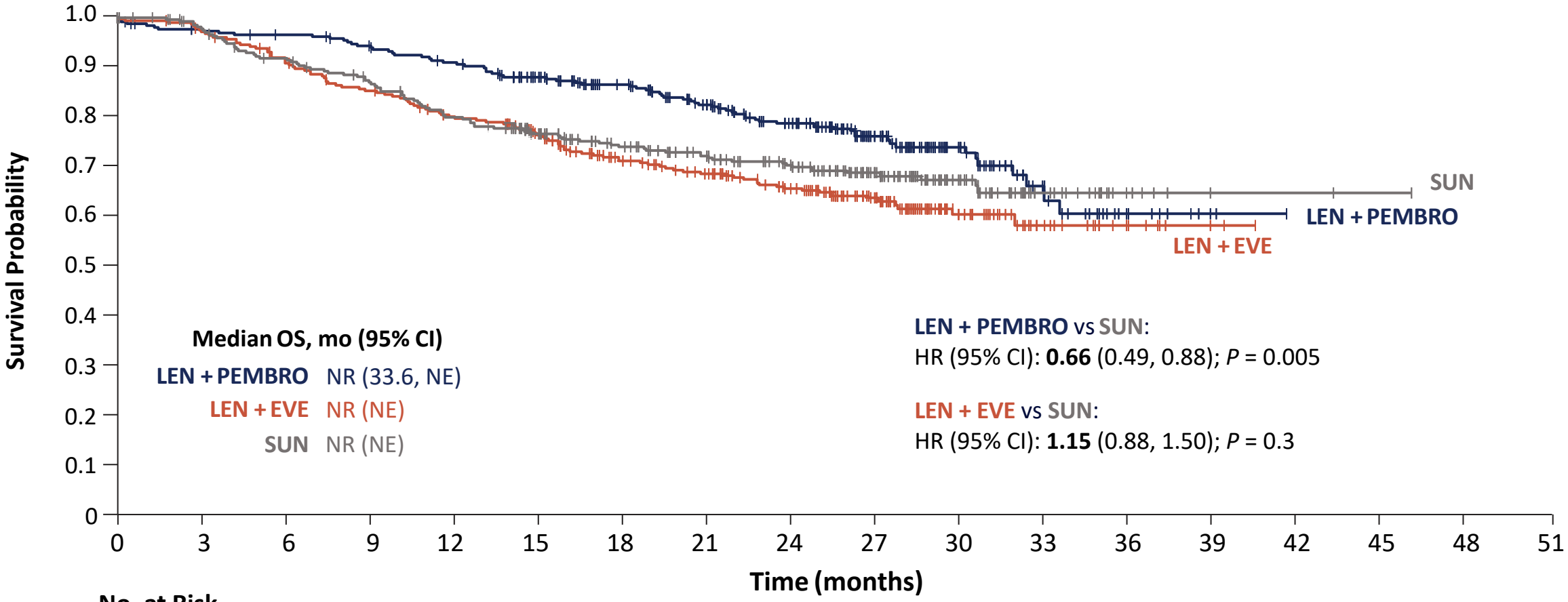
Progression-free Survival*



*By Independent Review Committee per RECIST v1.1.

PRESENTED BY: Dr. Robert Motzer

Overall Survival



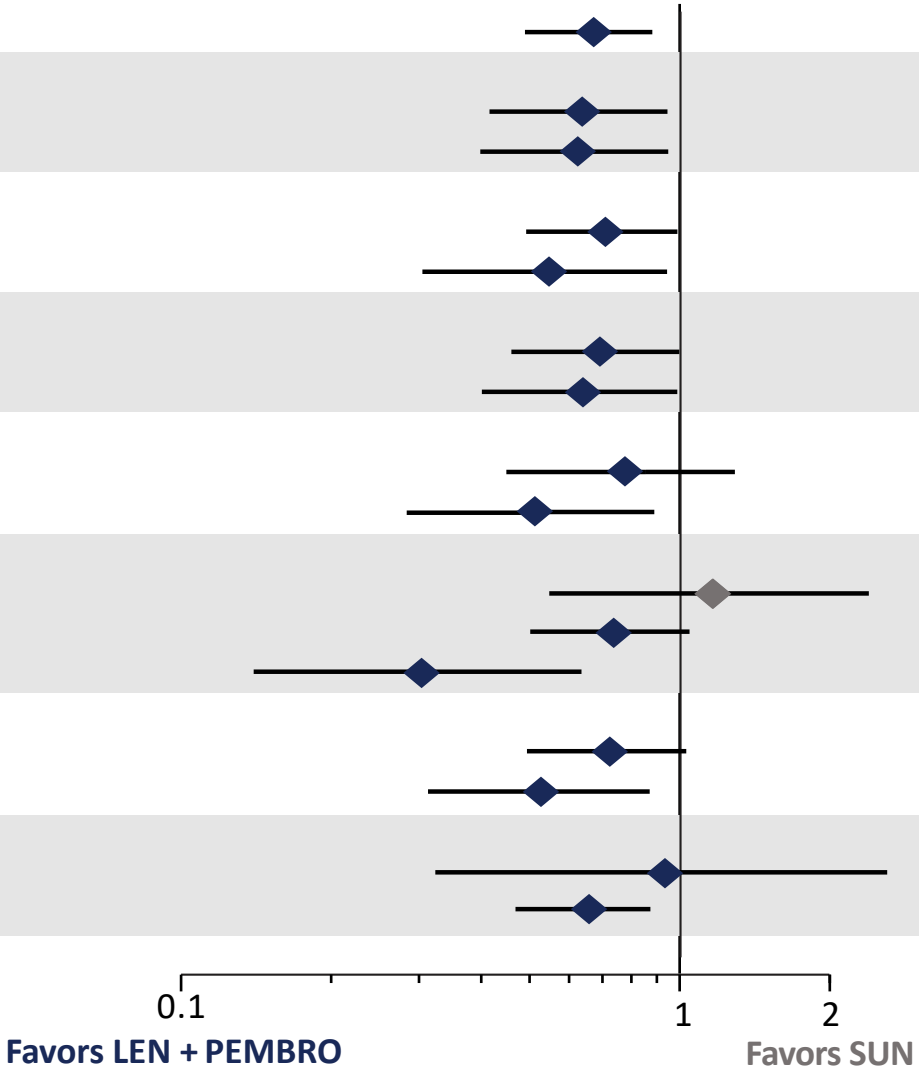
No. at Risk

355	342	338	327	313	280	253	222	188	129	66	26	10	2	0	
357	346	321	299	277	246	205	183	154	109	46	22	8	2	0	
357	332	307	289	264	236	207	186	160	112	60	25	7	2	2	1	0

NE, not estimable; NR, not reached.

Overall Survival With Lenvatinib Plus Pembrolizumab in Key Subgroups

Subgroup	LEN + PEMBRO *Events / no. of patients*	SUN *Events / no. of patients*	HR (95% CI)
Overall	80/355	101/357	0.66 (0.49–0.88)
Age			
< 65 years	41/194	57/225	0.63 (0.41–0.95)
≥ 65 years	39/161	44/132	0.61 (0.40–0.95)
Sex			
Male	59/255	71/275	0.70 (0.49–0.99)
Female	21/100	30/82	0.54 (0.30–0.94)
Geographic region			
Western Europe and NA	46/198	57/199	0.68 (0.46–1.00)
Rest of the World	34/157	44/158	0.63 (0.40–0.99)
PD-L1 expression			
≥ 1	28/107	36/119	0.76 (0.46–1.27)
< 1	21/112	31/103	0.50 (0.28–0.89)
IMDC risk group			
Favorable	14/110	15/124	1.15 (0.55–2.40)
Intermediate	56/210	60/192	0.72 (0.50–1.05)
Poor	10/33	25/37	0.30 (0.14–0.64)
Prior nephrectomy			
Yes	50/262	66/275	0.71 (0.49–1.03)
No	30/93	35/82	0.52 (0.31–0.86)
Sarcomatoid features			
Yes	9/28	7/21	0.91 (0.32–2.58)
No	71/327	94/336	0.64 (0.47–0.87)

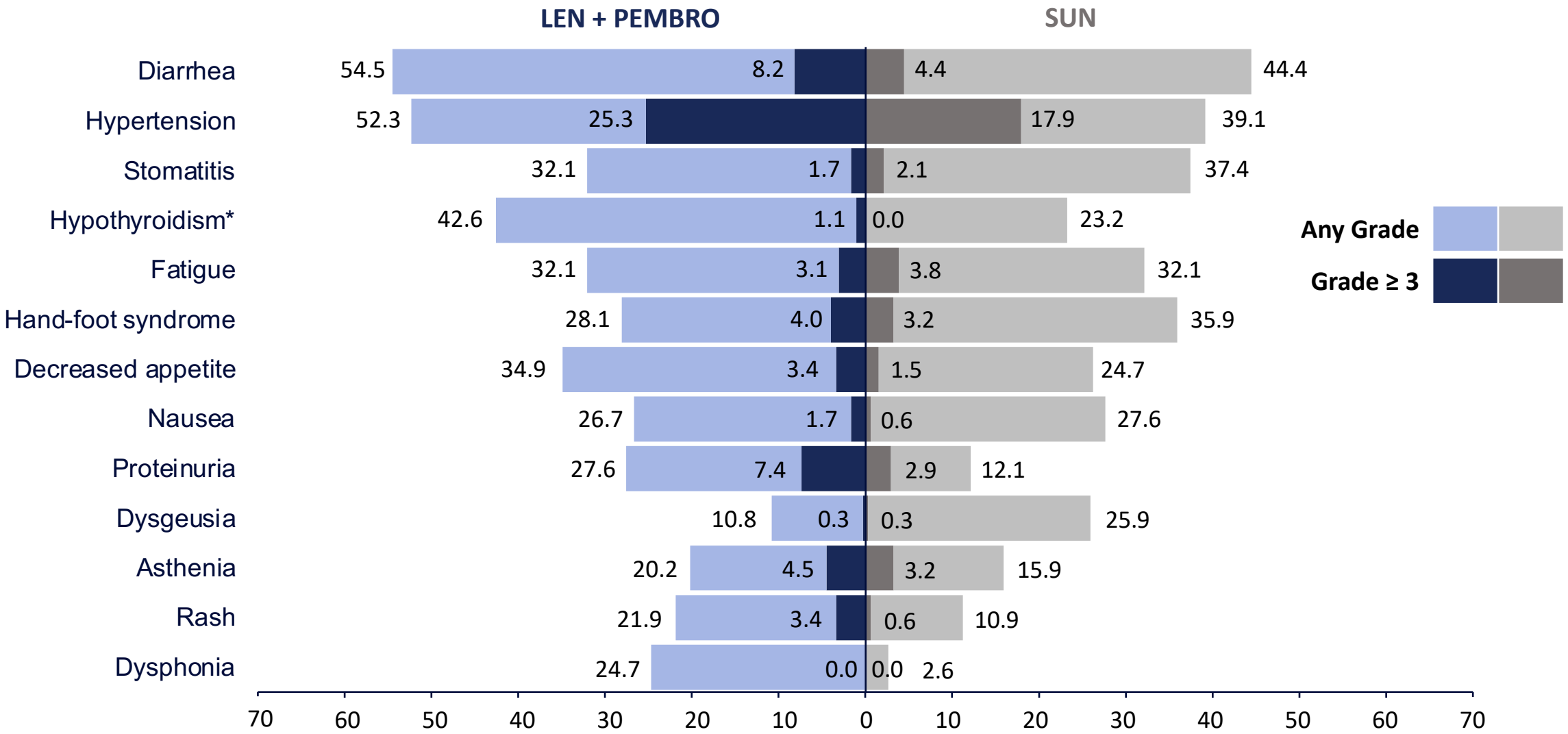


Confirmed Objective Response Rate*

	LEN + PEMBRO (n = 355)	LEN + EVE (n = 357)	SUN (n = 357)
Objective response rate (95% CI) — %	71.0 (66.3–75.7)	53.5 (48.3–58.7)	36.1 (31.2–41.1)
Best overall response — %			
Complete response	16.1	9.8	4.2
Partial response	54.9	43.7	31.9
Stable disease	19.2	33.6	38.1
Progressive disease	5.4	7.3	14.0
Unknown / not evaluable	4.5	5.6	11.8
Relative risk versus SUN (95% CI)	1.97 (1.69–2.29)	1.48 (1.26–1.74)	--
P-value	< 0.001	< 0.001	--

*By Independent Review Committee per RECIST v1.1.

TRAEs With Frequency ≥ 20%



Alanine aminotransferase/aspartate aminotransferase increased in 9.7/9.4% (grade 3: 3.1/2.6%) of patients in the LEN + PEMBRO arm and 8.8/8.8% of patients (grade 3: 1.8/0.6%) in the SUN arm.
*Adverse event of interest for pembrolizumab.

Indirect comparison of the 4 regimens available.

	CheckMate 214 (Ipi/Nivo)[1] (n=550 vs n=546)	KEYNOTE-426 (Axi/Pembro)[2] (n=432 vs n=429)	CheckMate 9ER (Cabo/Nivo)[3] (n=323 vs n=328)	CLEAR (Len/Pembro)[4] (N=355 vs n=357)
mOS, months HR (CI);	NR vs 38.4 **0.69** (0.59–0.81);	NR vs 35.7 **0.68** (0.55-0.85);	NR vs NR **0.60** (0.40–0.89);	NR vs NR **0.66** (0.49-0.88)
Landmark OS 12 mo Landmark OS 24 mo	**83%** vs. 78% **71%** vs. 61%	**90%** vs. 79% **74%** vs. 66%	**87%** vs. 78% (est) **74%** vs 60% (est)	**90%** vs 79% (est.) **79%** vs. 70%
mPFS, months HR (CI)	**12.2** vs 12.3 0.89 (0.76–1.05)	**15.4** vs 11.1 0.71 (0.60–0.84)	**16.6** vs 8.3 0.51 (0.41–0.64)	**23.9** vs 9.2 0.39 (0.32-0.49)
ORR, %	**39** vs 32	**60** vs 40	**56** vs 27	**71** vs 36
CR, %	**11** vs 3	**9** vs 3	**8** vs 5	**16** vs 4
Med f/u, months	**55**	**30.6**	**18.1**	**27**
Prognostic risk, % Favorable Intermediate Poor	 23 61 17	 32 55 13	 23 58 19	 31 59 9
Prior nephrectomy	82%	83%	69%	74%
Subsequent systemic therapies for sunitinib arm, %	Overall (69%) IO (42%)	Overall (69%) IO (48%)	Overall (40%) IO (29%)	NR

Please handle with care….

Indirect comparison of the 4 regimens available.

	CheckMate 214 (Ipi/Nivo)[1] (n=550 vs n=546)	KEYNOTE-426 (Axi/Pembro)[2] (n=432 vs n=429)	CheckMate 9ER (Cabo/Nivo)[3] (n=323 vs n=328)	CLEAR (Len/Pembro)[4] (N=355 vs n=357)
mOS, months HR (CI);	NR vs 38.4 **0.69** (0.59–0.81);			
Landmark OS 12 mo Landmark OS 24 mo	**83%** vs. 78% **71%** vs. 61%			
mPFS, months HR (CI)	**12.2** vs 12.3 0.89 (0.76–1.05)			
ORR, %	**39** vs 32			
CR, %	**11** vs 3			
Med f/u, months	**55**			
Prognostic risk, % Favorable Intermediate Poor	 23 61 17			
Prior nephrectomy	82%			
Subsequent systemic therapies for sunitinib arm, %	Overall (69%) IO (42%)			

Please handle with care….

Case 2

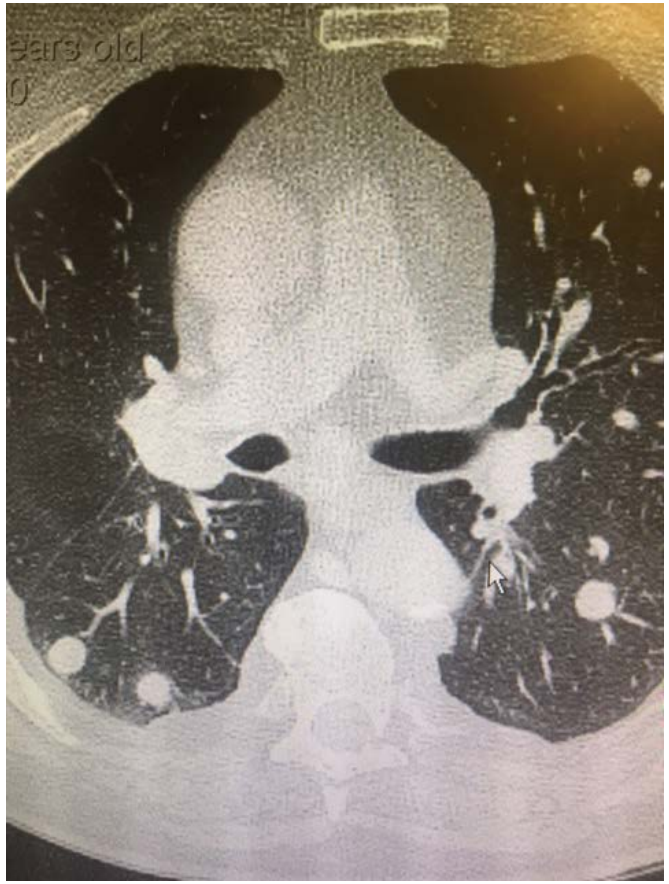
Patient characteristics	72 year old male Performance status 1 Past medical history of heavy smoker. Osteoarthritis and well controlled hypertension.
Tumor characteristics	18 months ago: Nephrectomy for G2 T3 clear cell renal cancer. 3 months ago: New lung mets in both lungs. Max 17mm. N=16. CT scan after surveillance for 3 months showed 2mm increase in size of lesions with no change in IMDC score (good risk).
Options	Biopsy? Continued surveillance? VEGF TKI + PD-1 therapy? VEGF therapy?

Case 2 continued

Patient characteristics

72 year old male
Performance status 1
Past medical history: Osteoarthritis and well controlled hypertension.

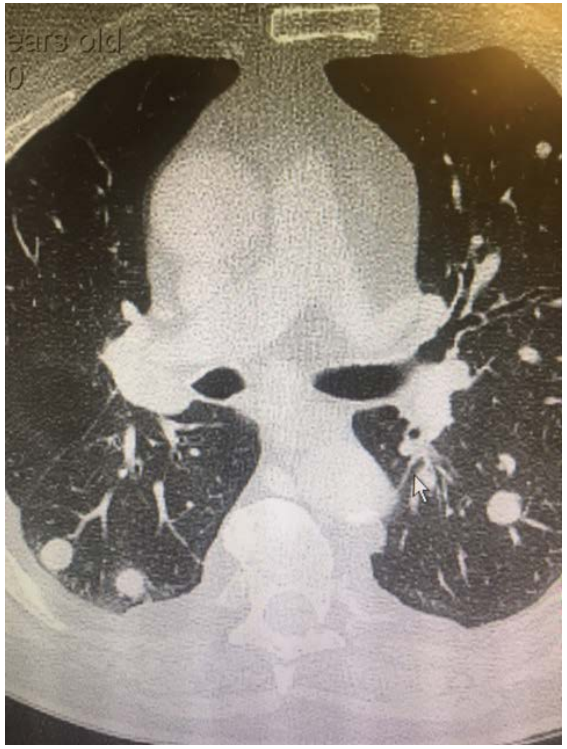
Tumor characteristics



Options

Case 2 continued

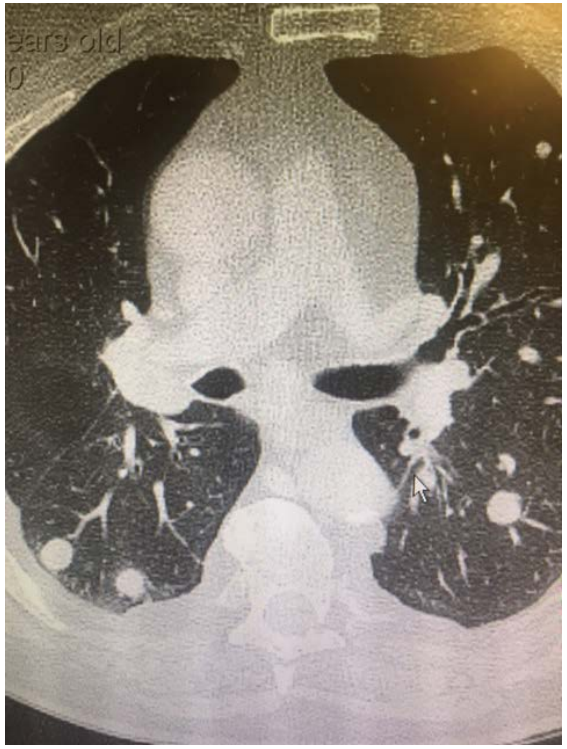
We chose axitinib and pembrolizumab

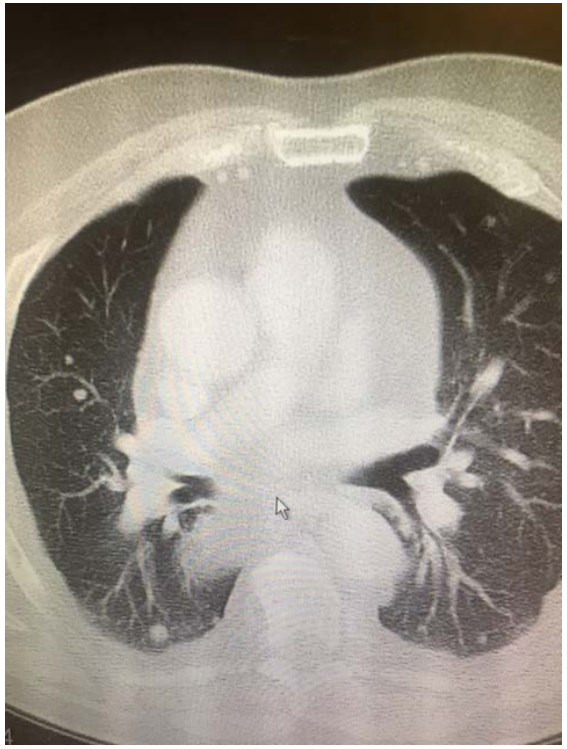


- Axitinib 5mg PO BD with pembrolizumab (3 weekly).
- Week 3: fatigue grade 1, Hypertension grade 1, pyrexia grade 1.
- Week 6: no new toxicity dose increase to 7mg BD.

Case 2 continued

Partial response at week 9 CT scan.

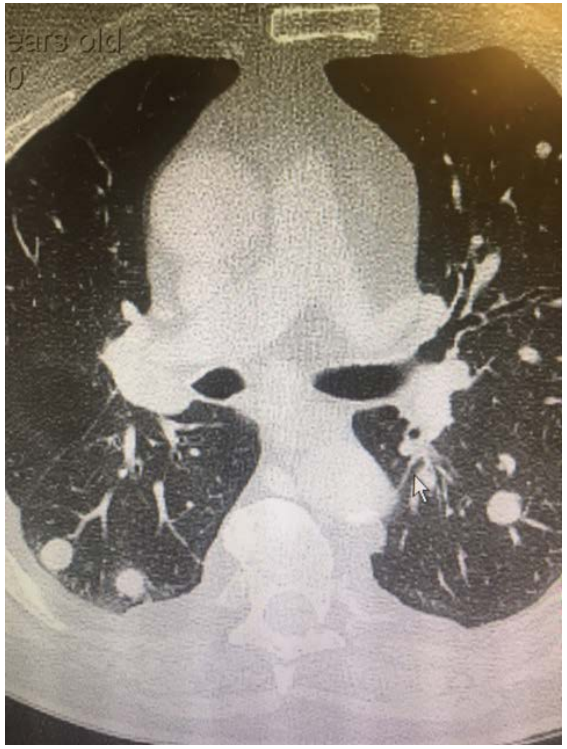


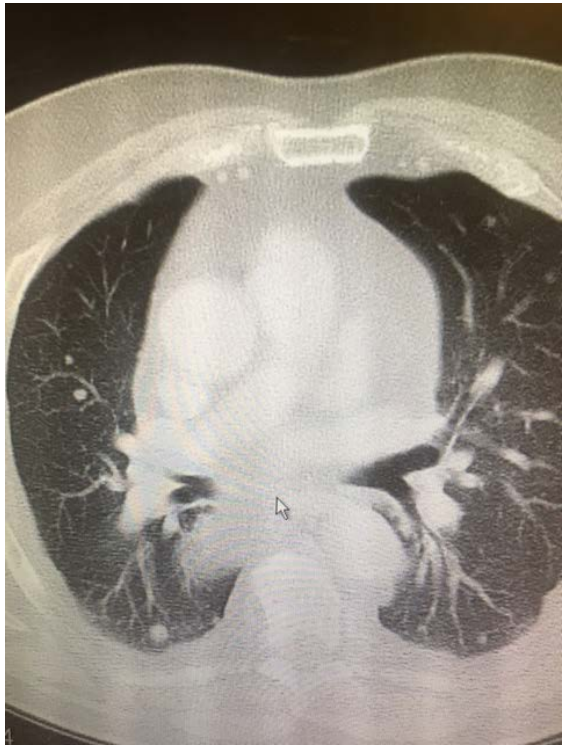


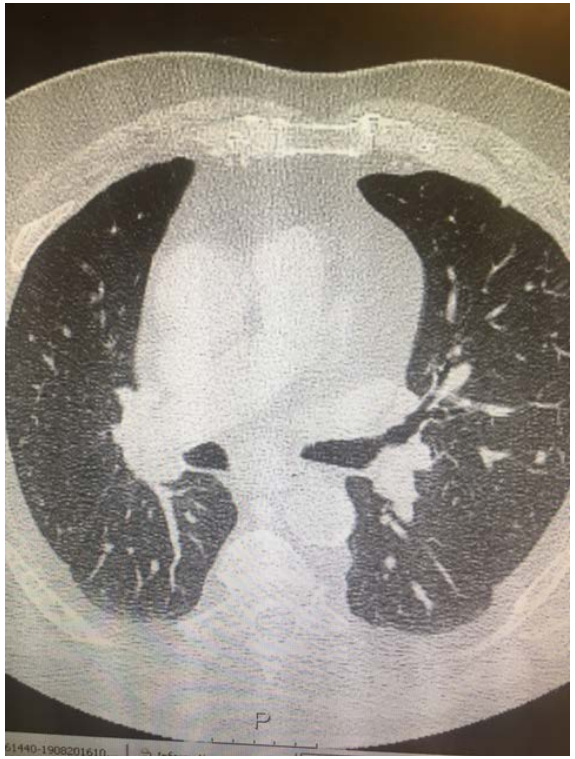
- Fatigue increases to grade 2
- Grade 1 diarrhoea (With dose escalation) thought to be TKI related.

Case 2 continued

Week 18 CT ongoing good response to therapy.



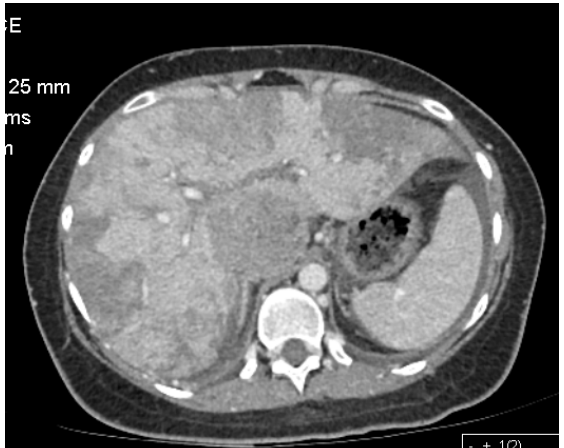




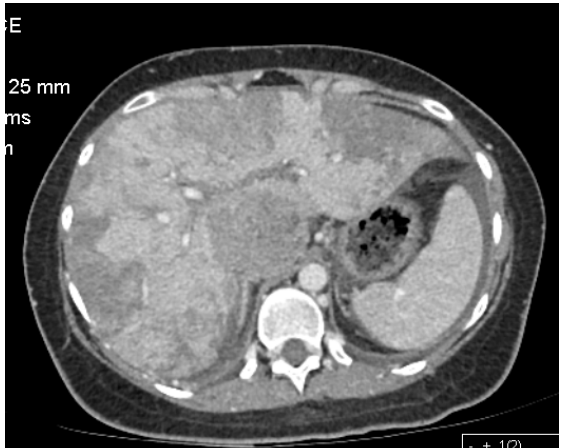
- Reduction of axitinib back to 5mg BD due to fatigue. Held axitinib for 1 week.

How long should the pembro continue?

Case 3

Patient characteristics	45 year old male Performance status 1 Past medical history: Nil of note (marathon runner)
Tumor characteristics	Relapse with liver and bone metastases 6 months after nephrectomy (G3T2). CT (including brain) + bone scan showed 4 liver metastases (max 8cm) and significant bone met in Left femur. Anaemia and high platelets. IMDC poor risk disease.
Options	

Case 3 continued

Patient characteristics	45 year old male Performance status 1 Past medical history: Nil of note (marathon runner)
Tumor characteristics	Relapse with liver and bone metastases 6 months after nephrectomy (G3T2). CT (including brain) + bone scan showed 4 liver metastases (max 8cm) and significant bone met in Left femur. Anaemia and high platelets. IMDC poor risk disease.
Options	 → Any of the three VEFG/IO combos!!!