COR2ED

THE HEART OF MEDICAL EDUCATION

GU CONNECT

MEETING SUMMARY
RENAL CANCER HIGHLIGHTS FROM ASCO 2023

Prof. Thomas Powles, MD
Medical Oncologist, Bart's Cancer Centre, UK

JUNE 2023

DEVELOPED BY GU CONNECT

This programme is developed by GU CONNECT, an international group of experts in the field of genitourinary oncology.

Acknowledgement and disclosures

This GU CONNECT programme is supported through an independent educational grant from Eisai Europe Limited. The programme is therefore independent, the content is not influenced by the supporter and is under the sole responsibility of the experts.

Please note: The views expressed within this programme are the personal opinions of the experts. They do not necessarily represent the views of the experts' institutions, or the rest of the GU CONNECT group.

Expert Disclaimers:

- **Prof. Thomas Powles** has received financial support/sponsorship for research support, consultation, or speaker fees from the following companies: Astellas, AstraZeneca, BMS, Eisai, Exelixis, Incyte, Ipsen, Johnson & Johnson, Mashup Ltd, Merck Serono, MSD, Novartis, Pfizer, Roche, Seattle Genetics

CLINICAL TAKEAWAYS

- **CONTACT-03:** For patients with mRCC, adding the atezolizumab to cabozantinib did not improve clinical outcomes compared with treatment with cabozantinib alone and higher toxicities were also observed in the combination arm
- **KEYNOTE-426:** Pembrolizumab + axitinib continued to demonstrate improved OS, PFS, and ORR versus sunitinib for patients with previously untreated clear cell RCC and no new safety signals were observed
- **CLEAR:** The combination of lenvatinib plus pembrolizumab remains superior to sunitinib on clinical outcomes as first-line treatment for advanced renal cell carcinoma after 4-years follow-up with no new safety signals detected
- Long-term follow up data from KEYNOTE-426 and the CLEAR trial re-confirms current clinical practice of frontline combination immunotherapy/TKI for IDMC intermediate/poor risk patients

IDMC, International Metastatic RCC Database Consortium; (m)RCC, (metastatic) renal cell carcinoma; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; TKI, tyrosine kinase inhibitor

EDUCATIONAL OBJECTIVES

- Help physicians translate the latest Renal cell carcinoma data from ASCO 2023 into clinical practice

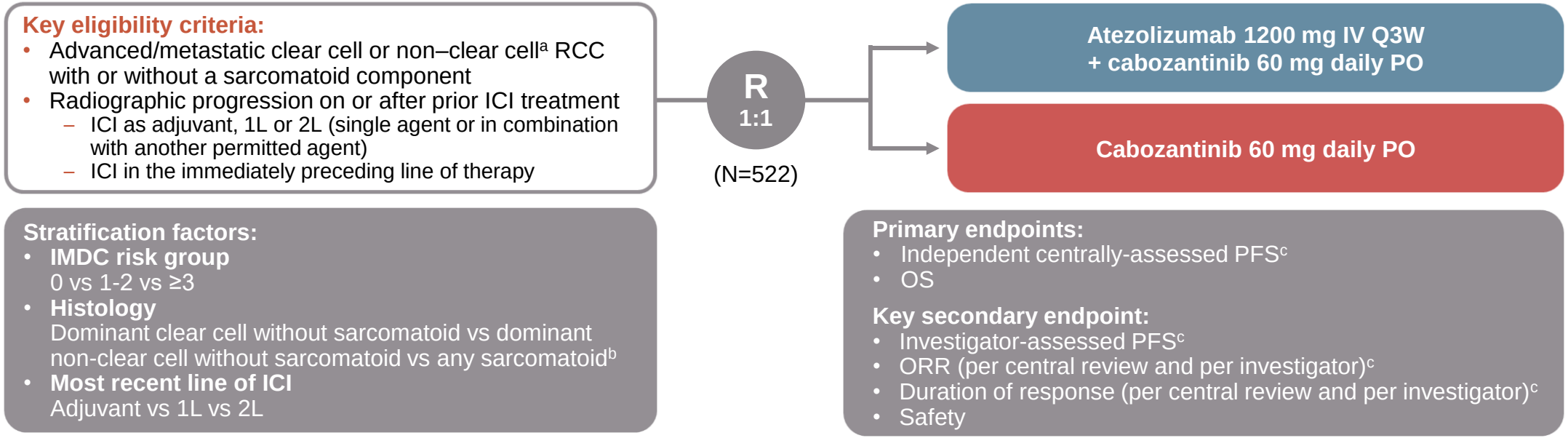
EFFICACY AND SAFETY OF ATEZOLIZUMAB PLUS CABOZANTINIB VS CABOZANTINIB ALONE AFTER PROGRESSION WITH PRIOR ICI TREATMENT IN mRCC: PRIMARY PFS ANALYSIS FROM THE PHASE 3, RANDOMISED, OPEN-LABEL CONTACT-03 STUDY

Choueiri T, et al. ASCO 2023. Abstract #LBA4500

ICI, immune checkpoint inhibitor; PFS, progression-free survival; mRCC, metastatic renal cell carcinoma

CONTACT-03: BACKGROUND AND STUDY DESIGN

- ICI-based regimens are the standard of care for first-line treatment of metastatic clear cell RCC
- Treatment options following disease progression during or after ICI therapy are limited but can include single-agent TKIs, such as cabozantinib (cabo)
- CONTACT-03 evaluated anti–PD-L1 atezolizumab + cabo vs cabo alone in patients with mRCC that progressed during or after prior ICI treatment



ClinicalTrials.gov ID, NCT04338269. IMDC, International Metastatic RCC Database Consortium. Patients were enrolled between July 28, 2020 and December 27, 2021

[a] Papillary, chromophobe or unclassified (chromophobe requires sarcomatoid differentiation); [b] Clear cell or non-clear cell; [c] Assessed according to RECIST 1.1

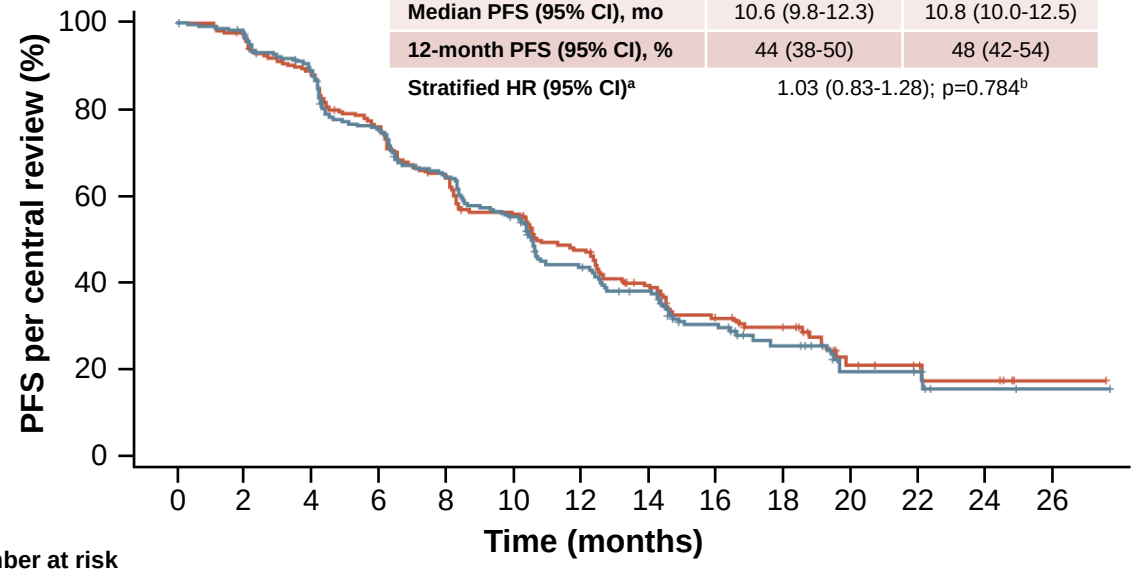
1L, first line; 2L, second line; ICI, immune checkpoint inhibitors; IDMC, International Metastatic RCC Database Consortium; IV, intravenously; (m)RCC, (metastatic) renal cell carcinoma; ORR, objective response rate; OS, overall survival; PD-L1, programmed death-ligand 1; PFS, progression-free survival; PO, oral administration; Q3W, every 3 weeks; R, randomisation; RECIST, response evaluation criteria in solid tumours; TKI, tyrosine kinase inhibitor

Choueiri T, et al. J Clin Oncol. 2023;41 (suppl 17): abstr LBA4500 (ASCO 2023 oral presentation)

CONTACT-03: EFFICACY RESULTS

rPFS (Centrally Reviewed)

	Atezo + cabo (N=263)	Cabo (N=259)
PFS events, n (%)	171 (65)	166 (64)
Median PFS (95% CI), mo	10.6 (9.8-12.3)	10.8 (10.0-12.5)
12-month PFS (95% CI), %	44 (38-50)	48 (42-54)
Stratified HR (95% CI)[a]	1.03 (0.83-1.28); p=0.784[b]	

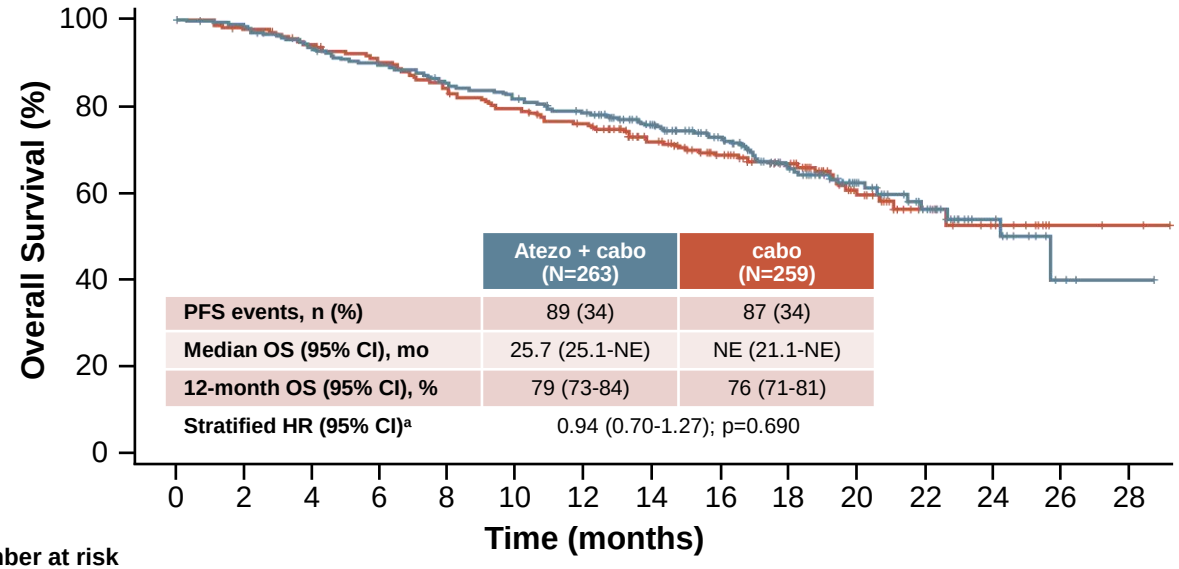


Number at risk														
Atezo + cabo	263	253	226	188	158	133	100	68	43	22	7	6	2	1
Cabo	259	242	216	183	153	130	109	71	52	34	12	8	5	1

[a] Stratified for IMCD risk group; [b] Non-significant at α=0.02

OS (INTERIM ANALYSIS)

	Atezo + cabo (N=263)	cabo (N=259)
PFS events, n (%)	89 (34)	87 (34)
Median OS (95% CI), mo	25.7 (25.1-NE)	NE (21.1-NE)
12-month OS (95% CI), %	79 (73-84)	76 (71-81)
Stratified HR (95% CI)[a]	0.94 (0.70-1.27); p=0.690	



Number at risk															
Atezo + cabo	263	259	240	229	215	207	196	157	127	91	50	31	15	3	1
Cabo	259	247	235	221	207	195	182	145	113	88	50	22	11	3	2

[a] Stratified for IMDC risk group

atezo, atezolizumab; cabo, cabozantinib; CI, confidence interval; HR, hazard ratio; IDMC, International Metastatic RCC Database Consortium; NE, not evaluable; OS, overall survival; (r)PFS, (radiographic) progression-free survival

Choueiri T, et al. J Clin Oncol. 2023;41 (suppl 17): abstr LBA4500 (ASCO 2023 oral presentation)

CONTACT-03: SAFETY RESULTS

Adverse event, n (%)	Atezo + cabo (N=262)	Cabo (N=256)
Any-cause AE	262 (100)	254 (99.2)
Any-cause treatment-related AE	252 (96.2)	249 (97.3)
Grade 3 or 4 AE	177 (67.6)	158 (61.7)
Grade 3 or 4 treatment-related AE	145 (55.3)	121 (47.3)
Death due to AE	17 (6.5)	9 (3.5)
Death due to treatment-related AE	3 (1.1)[a]	0
Serious AE	126 (48.1)	84 (32.8)
Serious treatment-related AE	63 (24.0)	30 (11.7)
AE leading to withdrawal from a trial drug	41 (15.6)	10 (3.9)
AE leading to withdrawal from atezo	29 (11.1)	–
AE leading to withdrawal from cabo	25 (9.5)	10 (3.9)
AE leading to interruption or reduction of a trial drug	240 (91.6)	223 (87.1)
AE leading to interruption of atezo[b]	159 (60.7)	–
AE leading to interruption or reduction of cabo	234 (89.3)	223 (87.1)

[a] Treatment-related AEs leading to death were immune-mediated enterocolitis and renal failure (both related to atezo) and intestinal perforation (related to cabo)
[b] Dose reduction of atezo was not permitted

AE, adverse events; atezo, atezolizumab; cabo, cabozantinib

Choueiri T, et al. J Clin Oncol. 2023;41 (suppl 17): abstr LBA4500 (ASCO 2023 oral presentation)

CONTACT-03: SUMMARY

- For patients with mRCC, adding the PD-L1 inhibitor atezolizumab to cabozantinib did not improve clinical outcomes compared with treatment with cabozantinib alone
- Higher toxicities were also observed in the combination arm

Clinical Perspective

- **CONTACT-03 is the first randomised, phase 3 oncology trial to test the benefit of PD-(L)1 inhibitor continuation by direct addition to a standard control arm; the results prompt caution with this approach in other cancers**

mRCC, metastatic renal cell carcinoma; PD1, programmed cell death protein 1; PD-L1, programmed death-ligand 1

Choueiri T, et al. J Clin Oncol. 2023;41 (suppl 17): abstr LBA4500 (ASCO 2023 oral presentation)

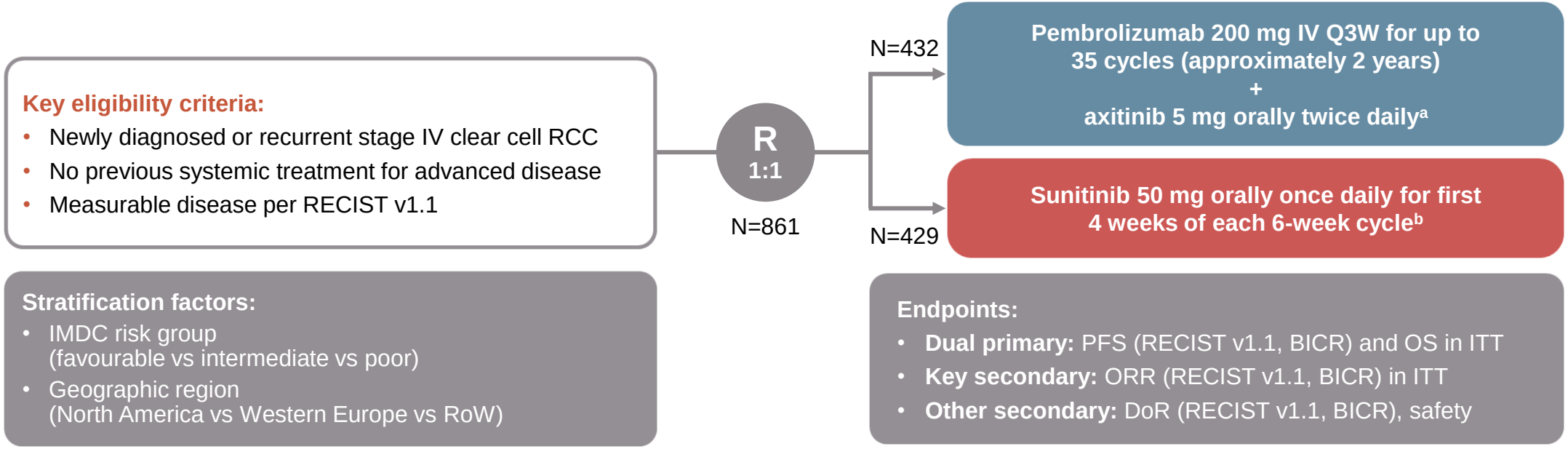
PEMBROLIZUMAB PLUS AXITINIB VERSUS SUNITINIB AS FIRST-LINE THERAPY FOR ADVANCED ccRCC: 5-YEAR ANALYSIS OF KEYNOTE-426

Rini B, et al. ASCO 2023. Abstract #LBA4501

ccRCC, clear cell renal cell carcinoma

KEYNOTE-426: BACKGROUND AND STUDY DESIGN

- At the first interim analysis of the randomised, open-label, phase 3 KEYNOTE-426 study, first-line pembrolizumab + axitinib showed statistically significant OS, PFS, and ORR over sunitinib for advanced ccRCC
- Long-term results after a median follow-up of 67 months (minimum 60 months) are reported



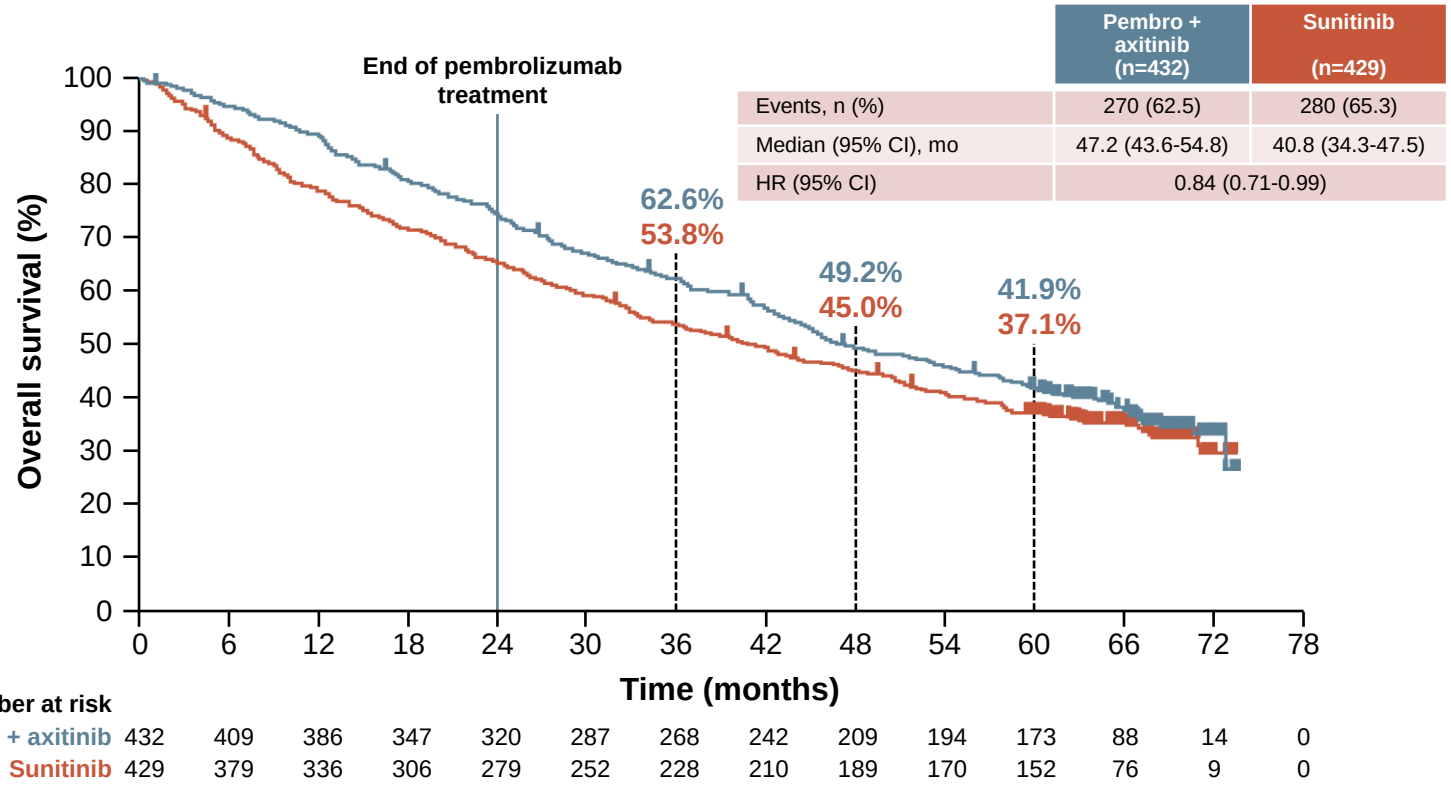
[a] Axitinib dose could be increased to 7 mg, then 10 mg, twice daily if safety criteria were met; dose could be reduced to 3 mg, then 2 mg, twice daily to manage toxicity
[b] Sunitinib dose could be decreased to 37.5 mg, then 25 mg, once daily for the first 4 weeks of each 6-week cycle to manage toxicity. Data cut-off: January 23, 2023

BICR, blinded central independent review; (cc)RCC, (clear cell) renal cell carcinoma; DoR, duration of response; IMDC, International Metastatic RCC Database Consortium; ITT, intention-to-treat; IV, intravenously; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; Q3W, every 3 weeks; R, randomised; RECIST v1.1, Response Evaluation Criteria in Solid Tumours version 1.1; RoW, rest of world

Rini B, et al. J Clin Oncol. 2023;41 (suppl 17): abstr LBA4501 (ASCO 2023 oral presentation)

KEYNOTE-426: EFFICACY RESULTS (ITT POPULATION)

FINAL OS ANALYSIS



	Pembro + axitinib (n=432)	Sunitinib (n=429)
Events, n (%)	270 (62.5)	280 (65.3)
Median (95% CI), mo	47.2 (43.6-54.8)	40.8 (34.3-47.5)
HR (95% CI)	0.84 (0.71-0.99)	

Number at risk

Pembro + axitinib	432	409	386	347	320	287	268	242	209	194	173	88	14	0
Sunitinib	429	379	336	306	279	252	228	210	189	170	152	76	9	0

Data cut-off: January 23, 2023

EFFICACY SUMMARY

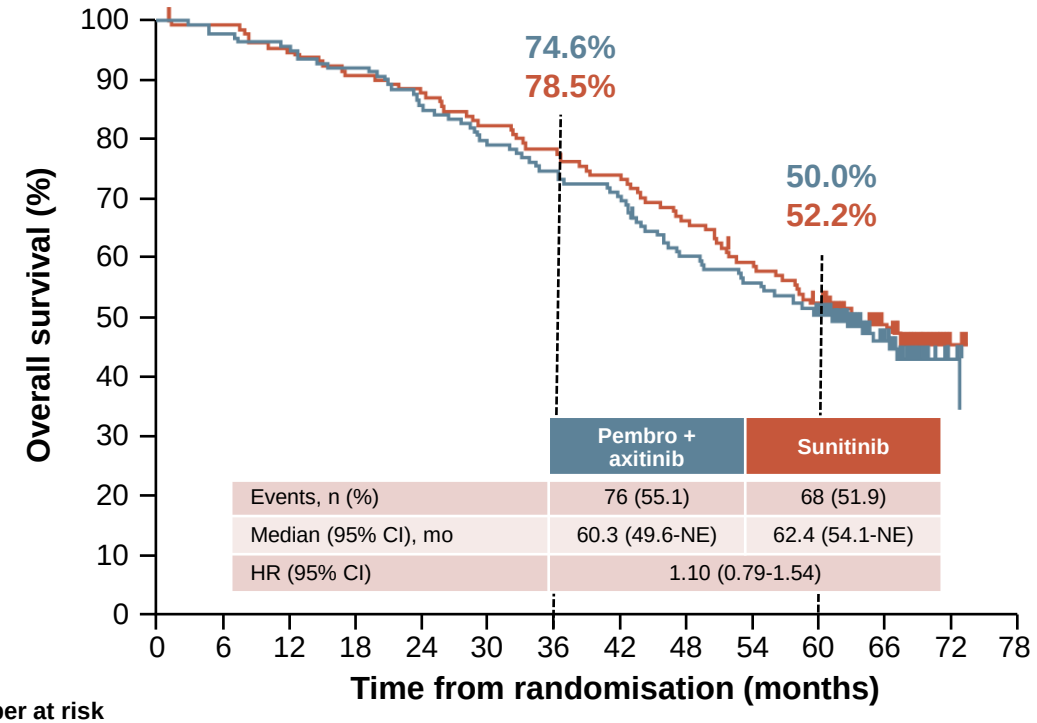
	Pembro + axitinib (n=432)	Sunitinib (n=429)
Progression-free survival		
Events, n	306	311
Median (95% CI), mo	15.7 (13.6-20.2)	11.1 (8.9-12.5)
HR (95% CI)	0.69 (0.59-0.81)	
Best Overall Response		
ORR, %	60.6	39.6
CR, %	11.6	4.0%
Duration of Response		
Pts with response, n	262	170
Median, mo	23.6	15.3
(95% CI)	(1.4+ to 68.6+)	(2.3-68.3)

CI, confidence interval; CR, complete response; DoR, duration of response; HR, hazard ratio; ITT, intention-to-treat; mo, months; ORR, objective response rate; OS, overall survival; pembro, pembrolizumab; PFS, progression-free survival

Rini B, et al. J Clin Oncol. 2023;41 (suppl 17): abstr LBA4501 (ASCO 2023 oral presentation)

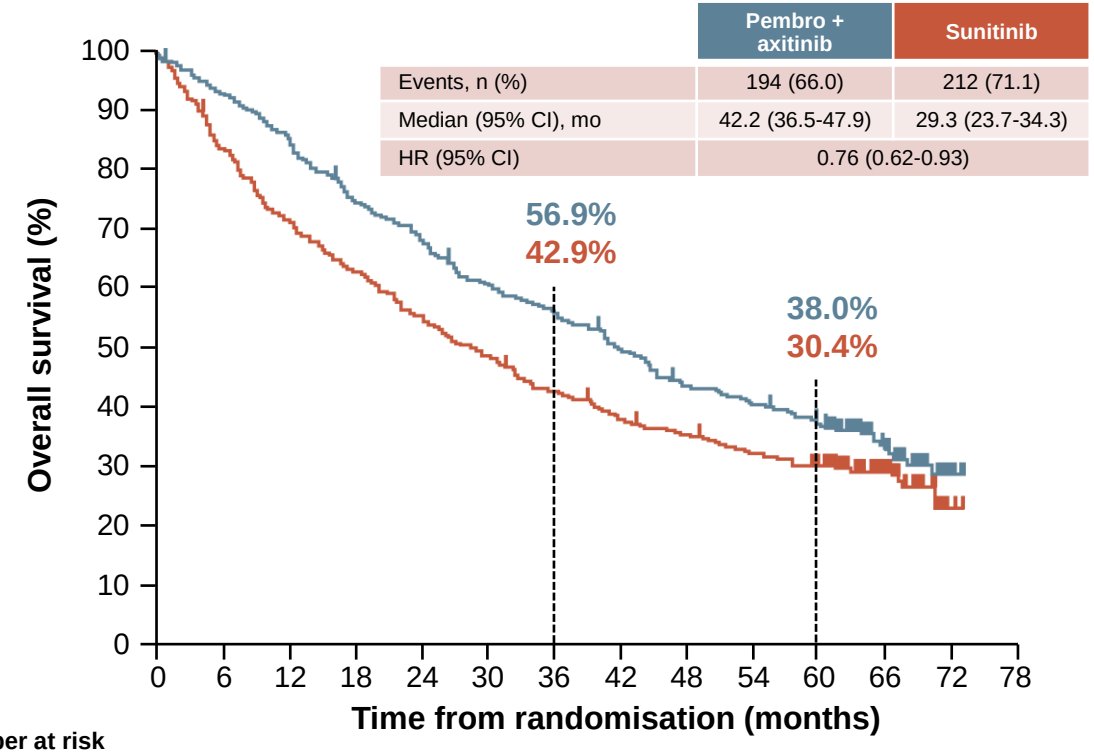
KEYNOTE-426: FINAL OS IN IDMC RISK SUBGROUPS

FAVOURABLE RISK



Number at risk														
Pembro + axitinib	138	135	132	127	118	109	103	97	83	77	67	36	5	0
Sunitinib	131	129	123	118	114	107	102	96	86	76	66	33	3	0

INTERMEDIATE/POOR RISK



Number at risk														
Pembro + axitinib	294	274	254	220	202	178	165	145	128	117	106	52	9	0
Sunitinib	298	250	213	188	165	145	126	114	103	94	86	43	6	0

CI, confidence interval; HR, hazard ratio; IDMC, International Metastatic RCC Database Consortium; mo, months; NE, not evaluable; OS, overall survival; pembro, pembrolizumab

Rini B, et al. J Clin Oncol. 2023;41 (suppl 17): abstr LBA4501 (ASCO 2023 oral presentation)

KEYNOTE-426: SAFETY SUMMARY

- No new safety signals were observed

	Pembrolizumab + axitinib N=429	Sunitinib N=425
Any adverse event	422 (98.4)	425 (100)
Treatment-related adverse event	413 (96.3)	415 (97.6)
Grade 3 to 5 treatment-related adverse event	291 (67.8)	270 (63.5)
Serious treatment-related adverse event	126 (29.4)	69 (16.2)
Discontinuation of any drug because of a treatment-related adverse event	143 (33.3)	58 (13.6)
Death from treatment-related adverse event	5 (1.2)	6 (1.4)

Values are n (%). Data cut-off: January 23, 2023

Rini B, et al. J Clin Oncol. 2023;41 (suppl 17): abstr LBA4501 (ASCO 2023 oral presentation)

KEYNOTE-426: SUMMARY

- KEYNOTE-426 represents the longest follow-up to date of the combination of a checkpoint inhibitor plus a VEGFR-TKI for the first-line clear cell RCC
- Pembrolizumab + axitinib continued to demonstrate improved overall survival, progression free survival, and objective response rate versus sunitinib for patients with previously untreated clear cell RCC
  - Benefit was observed despite a greater proportion of patients in the sunitinib arm receiving therapy, including predominantly PD-(L)1 inhibitors, and more lines of therapy
- No new safety signals were observed in this updated analysis

Clinical Perspective

- **Long-term follow up data re-confirms current clinical practice for IDMC intermediate/poor risk patients**

IDMC, International Metastatic RCC Database Consortium; PD1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; RCC, renal cell carcinoma; VEGFR-TKI, vascular endothelial growth factor receptor tyrosine kinase inhibitor

Rini B, et al. J Clin Oncol. 2023;41 (suppl 17): abstr LBA4501 (ASCO 2023 oral presentation)

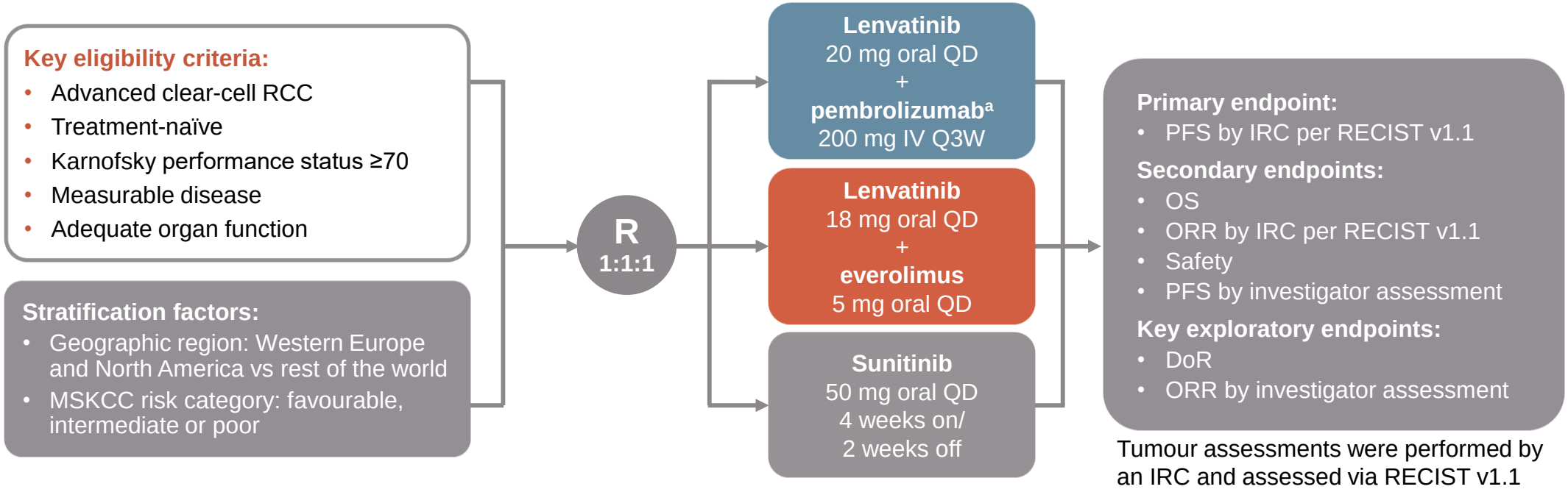
FINAL PRESPECIFIED OS ANALYSIS OF CLEAR: 4-YEAR FOLLOW-UP OF LENVATINIB PLUS PEMBROLIZUMAB VS SUNITINIB IN PATIENTS WITH aRCC

Motzer RJ, et al. ASCO 2023. Abstract #4502

aRCC, advanced renal cell carcinoma; OS, overall survival

CLEAR: BACKGROUND AND STUDY DESIGN

- In the phase 3 CLEAR trial, lenvatinib + pembrolizumab showed clinically meaningful and statistically significant benefits in PFS and OS, and improved ORR compared with sunitinib in 1L aRCC
- 4-yr follow-up results from the final prespecified OS analysis of CLEAR are reported (data cutoff: 31 Jul 2022)



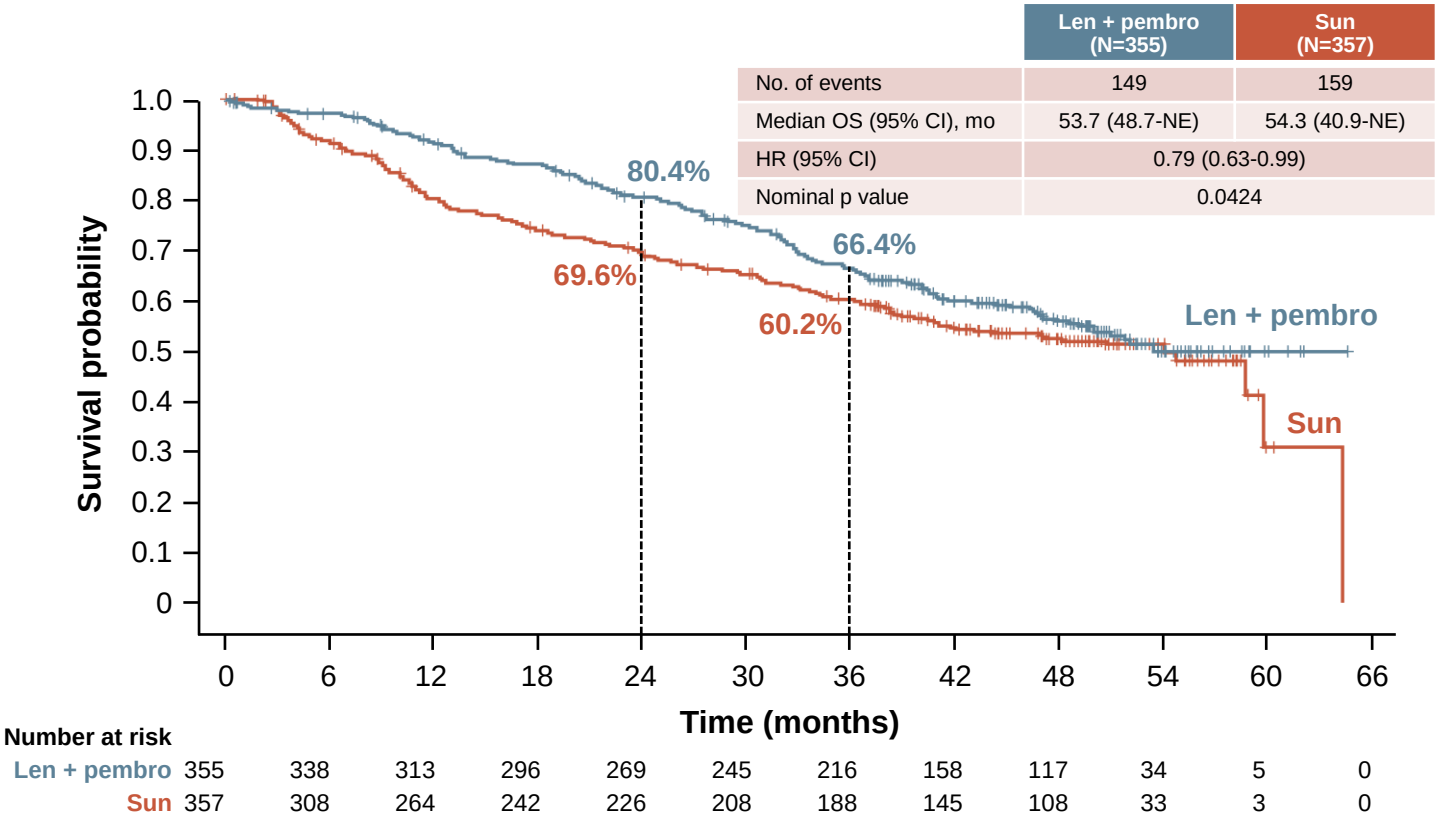
[a] Patients could receive a maximum of 35 pembrolizumab treatments

1L, first line; (a)RCC, (advanced) renal cell carcinoma; DoR, duration of response; HRQoL, health-related quality of life; IRC, independent review committee; IV, intravenously; MSKCC, Memorial Sloan Kettering Cancer Center; ORR, objective response rate; QD, once daily; OS, overall survival; PFS, progression-free survival; Q3W, once every 3 weeks; R, randomisation; RECIST v1.1, Response Evaluation Criteria In Solid Tumours version 1.1

Motzer R, et al. N Eng J Med 2021; 384 (14):1289-1300; Motzer R, et al. J Clin Oncol 2023;41 (suppl 16): abstr 4502 (ASCO 2023, oral presentation)

CLEAR: EFFICACY RESULTS

FINAL OS ANALYSIS



At median OS follow-up time of **49.8 months** (IQR: 41.4-53.1) in the lenvatinib plus pembrolizumab group and **49.4 months** (IQR: 41.6-52.8) in the sunitinib group

EFFICACY SUMMARY

	Len + pembro (N=N55)	Sun (N=357)
Median follow-up (95% CI), mo	49.8 (48.8-50.4)	49.4 (48.1-50.1)
PFS HR vs sunitinib (95% CI)	0.47 (0.38-0.57); p<0.0001[a]	
PFS rate at 24/36 mo, %	49.0/37.3	23.4/17.6
ORR (95% CI), % CR, %	71.3 (66.6-76.0); 18.3	36.7 (31.7-41.7); 4.8
Median DoR (95% CI), mo	26.7 (22.8-34.6)	14.7 (9.4-18.2)

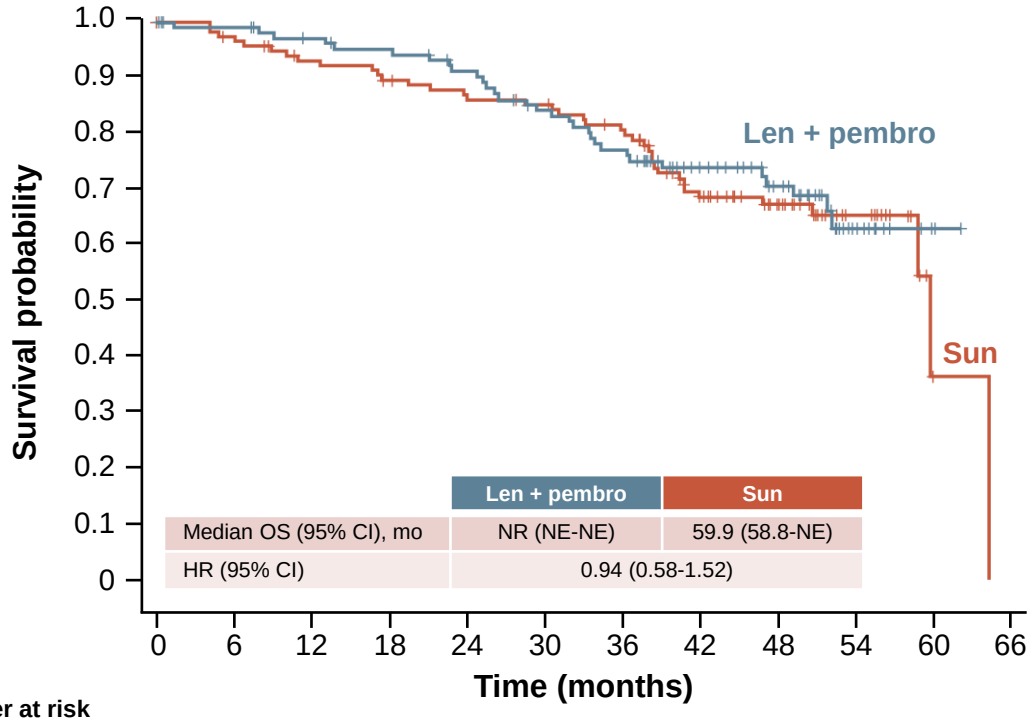
[a]Nominal p-values

CI, confidence interval; CR, complete response; DoR, duration of response; HR, hazard ratio; IQR, inter-quartile range; len, lenvatinib; mo, months; NE, not evaluable; ORR, objective response rate; OS, overall survival; pembro, pembrolizumab; PFS, progression-free survival; sun, sunitinib

Motzer R, et al. J Clin Oncol 2023;41 (suppl 16): abstr 4502 (ASCO 2023, oral presentation)

CLEAR: FINAL OS IN IDMC RISK SUBGROUPS

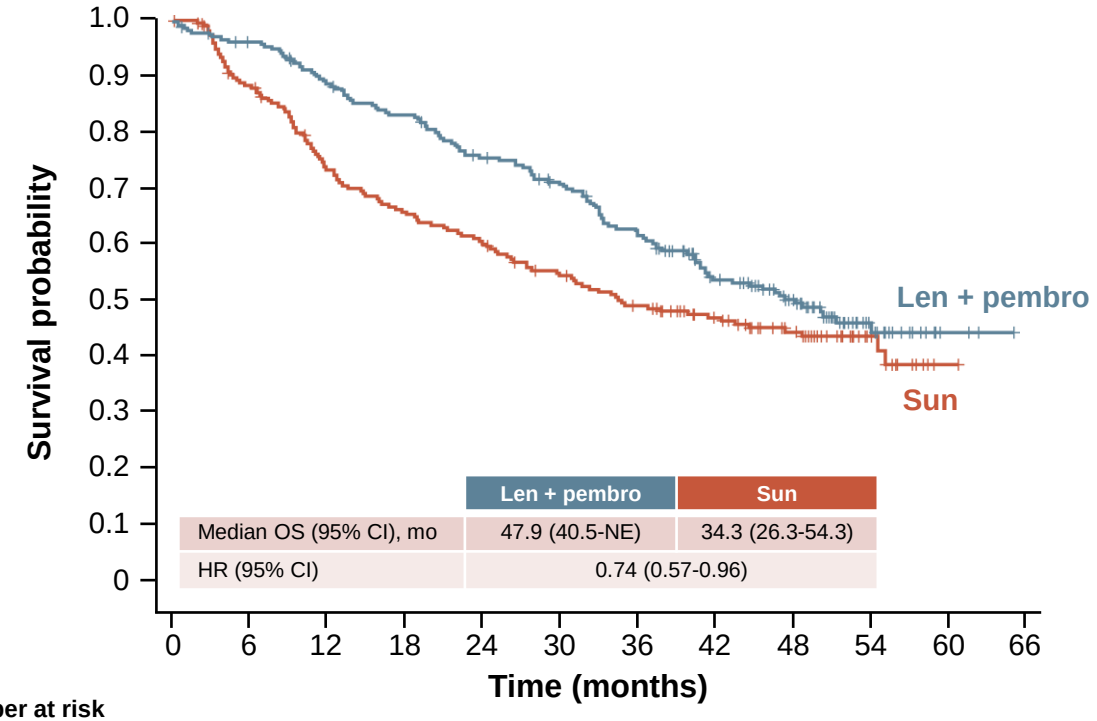
FAVOURABLE



Number at risk

Len + pembro	110	106	101	98	92	83	76	57	42	11	2	0
Sun	124	115	107	102	98	95	88	65	46	15	2	0

INTERMEDIATE + POOR



Number at risk

Len + pembro	243	230	210	196	176	161	139	101	75	23	3	0
Sun	229	190	155	138	127	112	99	79	61	18	1	0

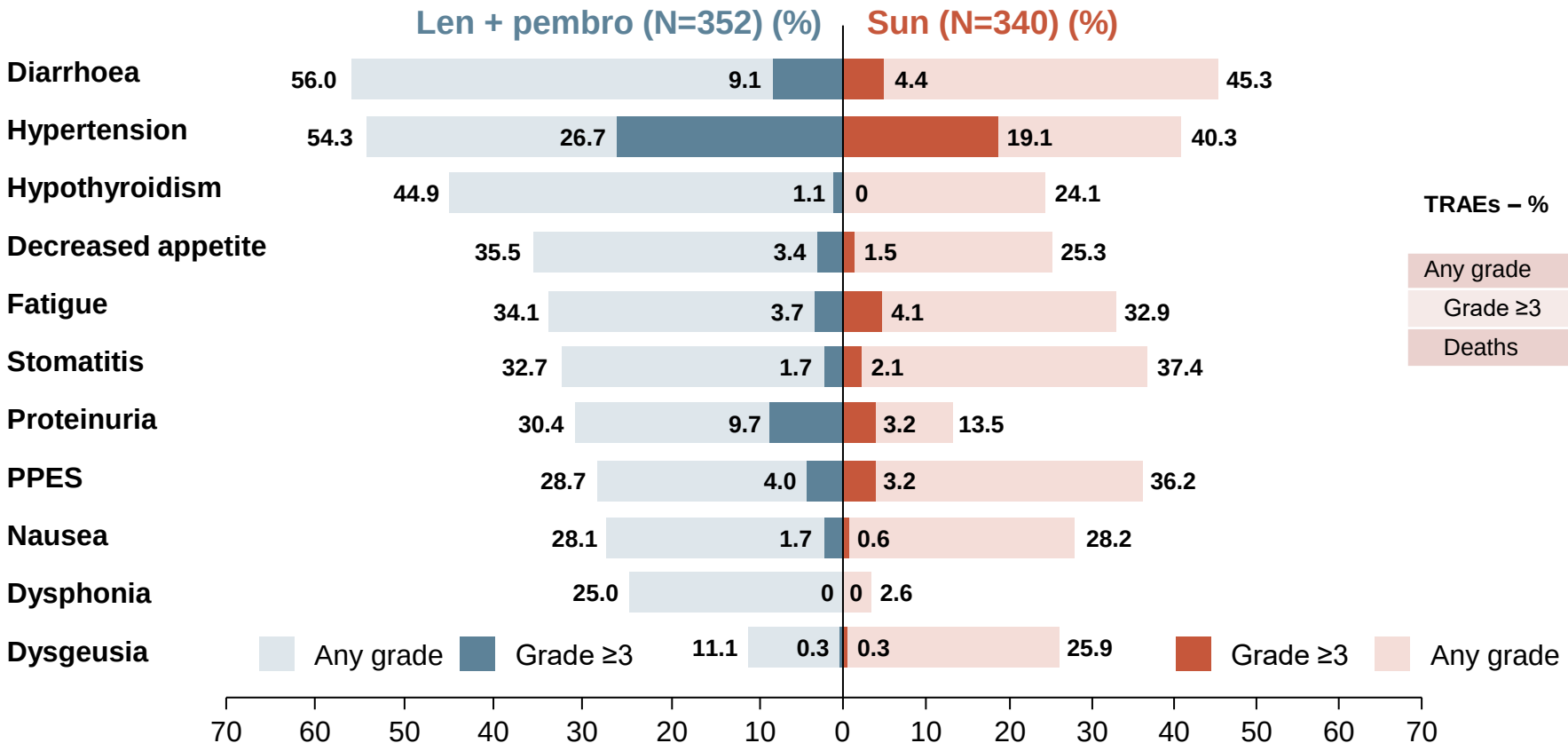
IMDC risk group was not a stratification factor and relevant data were derived programmatically. Hazard ratio is for lenvatinib + pembrolizumab vs sunitinib based on a Cox regression model with treatment as a factor. The Efron method was used for correction of tied events. Medians were estimated by the Kaplan-Meier method, and the 95% CIs were estimated with a generalised Brookmeyer and Crowley method

CI, confidence interval; HR, hazard ratio; IDMC, International Metastatic RCC Database Consortium; len, lenvatinib; NE, not evaluable; NR, not reached; OS, overall survival; pembro, pembrolizumab; sun, sunitinib

Motzer R, et al. J Clin Oncol 2023;41 (suppl 16): abstr 4502 (ASCO 2023, oral presentation)

CLEAR: SAFETY RESULTS (TRAEs ≥25%[a])

- No new safety signals were detected



TRAEs – %	Len + pembro (N=352)	Sun (N=340)
Any grade	96.9	92.1
Grade ≥3	74.1	60.3
Deaths	1.1	0.3

The median duration of treatment was 22.6 months (IQR: 9.4-37.1) in the Len + pembro group and 7.8 months (3.7-19.4) in the Sun group

[a]TRAEs ≥ 25% in either group

QR, interquartile range; len, lenvatinib; pembro, pembrolizumab; PPES, palmar–plantar erythrodysesthesia syndrome; sun, sunitinib; TRAE, treatment related adverse event

Motzer R, et al. J Clin Oncol 2023;41 (suppl 16): abstr 4502 (ASCO 2023, oral presentation)

CLEAR: SUMMARY

- With extended 4-year follow-up data, the combination of lenvatinib plus pembrolizumab remains superior to sunitinib on clinical outcomes as first-line treatment for advanced renal cell carcinoma
- There were no new safety signals and adverse events were managed with dose modifications as necessary
- These results support the robustness of the primary analysis data from CLEAR

Clinical Perspective

- **Long-term follow up data re-confirms current clinical practice of frontline combination immunotherapy/TKI for IDMC intermediate/poor risk patients**

IDMC, International Metastatic RCC Database Consortium; TKI, tyrosine kinase inhibitor

Motzer R, et al. J Clin Oncol 2023;41 (suppl 16): abstr 4502 (ASCO 2023, oral presentation)

COR2ED

THE HEART OF MEDICAL EDUCATION

For more information visit

GU connect®

POWERED BY COR2ED

Connect on
LinkedIn @GU CONNECT

Watch on
YouTube @COR2ED

Email
info@cor2ed.com

Visit us at
https://cor2ed.com/

Follow us on
Twitter @guconnectinfo

Heading to the heart of Independent Medical Education since 2012