Kidney Cancer Research Summit KCRS21

A phase 3 trial of lenvatinib plus pembrolizumab versus sunitinib as a first-line treatment for patients with advanced renal cell carcinoma: overall survival follow-up analysis (the CLEAR study)

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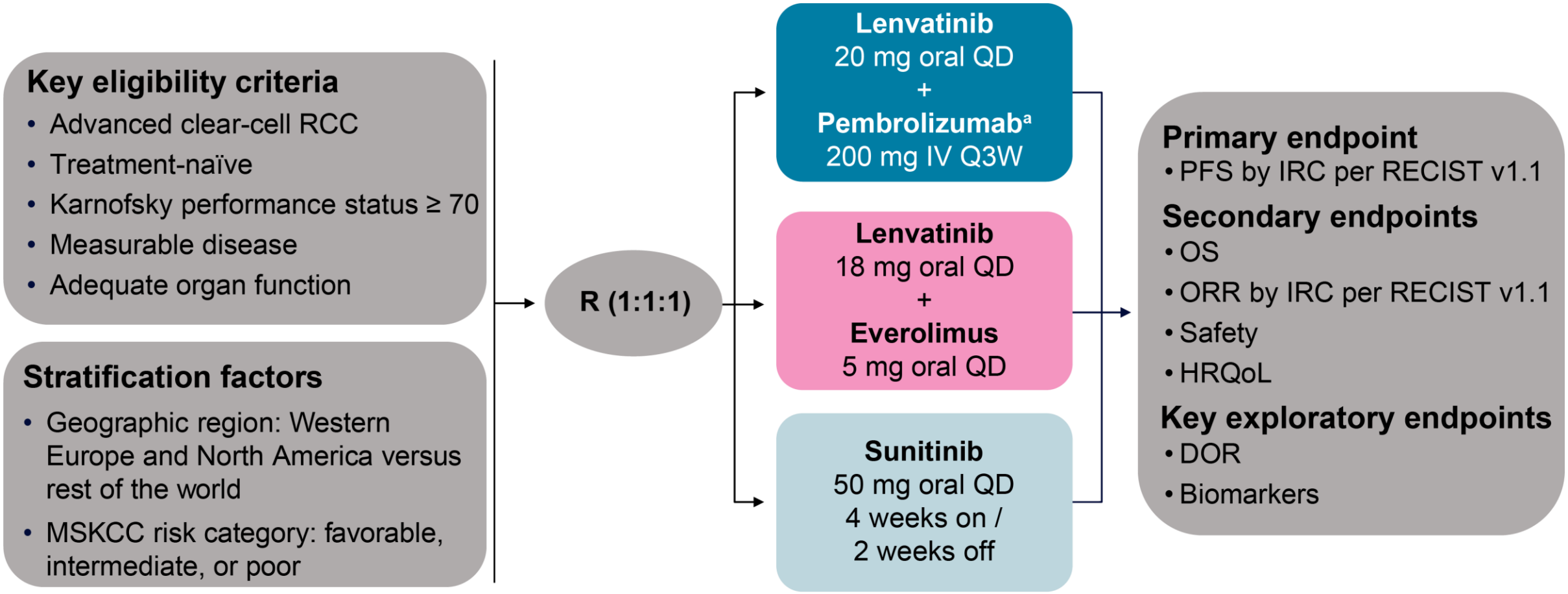
Introduction

- The randomized phase 3 CLEAR study (data cutoff date: Aug 28, 2020; median OS follow-up: 26.6 mo) demonstrated significantly improved efficacy outcomes with lenvatinib (LEN) + pembrolizumab (PEMBRO) versus sunitinib (SUN) in the first-line treatment of patients with advanced RCC[1,2]
    - PFS (primary endpoint) was significantly improved with LEN + PEMBRO versus SUN (HR, 0.39; 95% CI, 0.32–0.49, $P < 0.001$)
    - OS was also significantly improved with LEN + PEMBRO versus SUN (HR, 0.66; 95% CI, 0.49–0.88; $P = 0.005$)
    - ORR was 71.0% with LEN + PEMBRO and 36.1% with SUN (relative risk, 1.97 [95% CI, 1.69–2.29]; nominal $P < 0.001$)
- This follow-up analysis (data cutoff date: March 31, 2021; median follow-up: 33.7 months for LEN + PEMBRO arm and 33.4 months for SUN arm) assessed OS in LEN + PEMBRO versus SUN arms from the CLEAR study

1. Motzer RJ et al. *N Engl J Med.* 2021;14:1289-1300; 2. Motzer RJ et al. Orally presented at: ASCO Genitourinary Cancers Virtual Symposium; February 11-13, 2021. #269.
CI, confidence interval; HR, hazard ratio; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; RCC, renal cell carcinoma.

CLEAR Study Design



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

DOR, duration of response; HRQoL, health-related quality of life; IRC, independent review committee; IV, intravenous; MSKCC, Memorial Sloan Kettering Cancer Center; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; QD, once daily; Q3W, once every 3 weeks; R, randomization; RCC, renal cell carcinoma; RECIST v1.1; Response Evaluation Criteria In Solid Tumors version 1.1.

Patients and Methods

- Adult patients (≥ 18 years of age) with advanced treatment-naïve RCC with a clear cell component were randomly assigned to receive LEN 20 mg QD + PEMBRO 200 mg IV Q3W; or LEN 18 mg + everolimus 5 mg QD; or SUN 50 mg QD (4 weeks on/2 weeks off)

- Key eligibility criteria included ≥ 1 measurable lesion per RECIST v1.1 and a Karnofsky performance-status score ≥ 70

- Randomization was stratified by geographical region and by MSKCC prognostic risk group

- This follow-up analysis[a] compared OS in LEN + PEMBRO versus SUN arms using a stratified log-rank test

- The HR and the corresponding 95% CI were estimated using a stratified Cox regression model

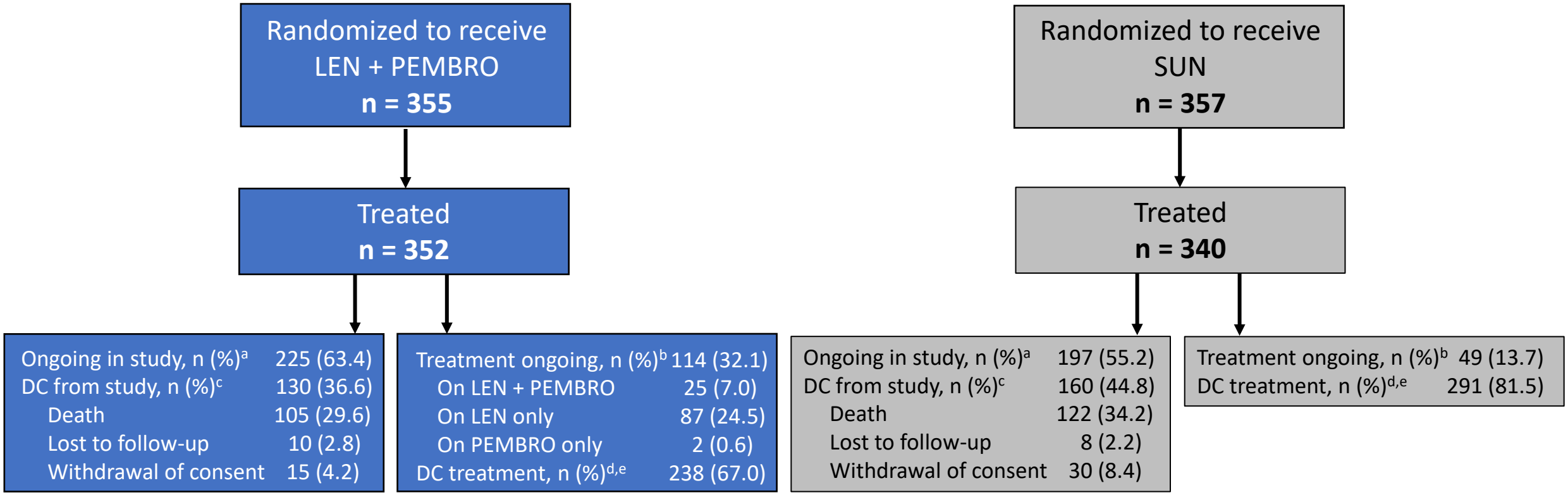
[a]Data cutoff occurred on March 31, 2021.
CI, confidence interval; HR, hazard ratio; IV, intravenous; MSKCC, Memorial Sloan Kettering Cancer Center; OS, overall survival; QD, once daily; Q3W, once every 3 weeks; RCC, renal cell carcinoma; RECIST v1.1; Response Evaluation Criteria In Solid Tumors version 1.1.

Baseline Characteristics

	LEN + PEMBRO (n = 355)	SUN (n = 357)
Median age (range) — years	64 (34–88)	61 (29–82)
Geographic region — %		
Western Europe and North America	55.8	55.7
Rest of the World	44.2	44.3
MSKCC prognostic risk group — %		
Favorable / Intermediate / Poor	27.0 / 63.9 / 9.0	27.2 / 63.9 / 9.0
IMDC risk group — %		
Favorable / Intermediate / Poor	31.0 / 59.2 / 9.3	34.7 / 53.8 / 10.4
Sarcomatoid features — %	7.9	5.9
PD-L1 expression — %		
≥ 1 / < 1 / not available	30.1 / 31.5 / 38.3	33.3 / 28.9 / 37.8
Prior nephrectomy — %	73.8	77.0

IMDC, International Metastatic RCC Database Consortium; MSKCC, Memorial Sloan Kettering Cancer Center; PD-L1, programmed cell death ligand-1.

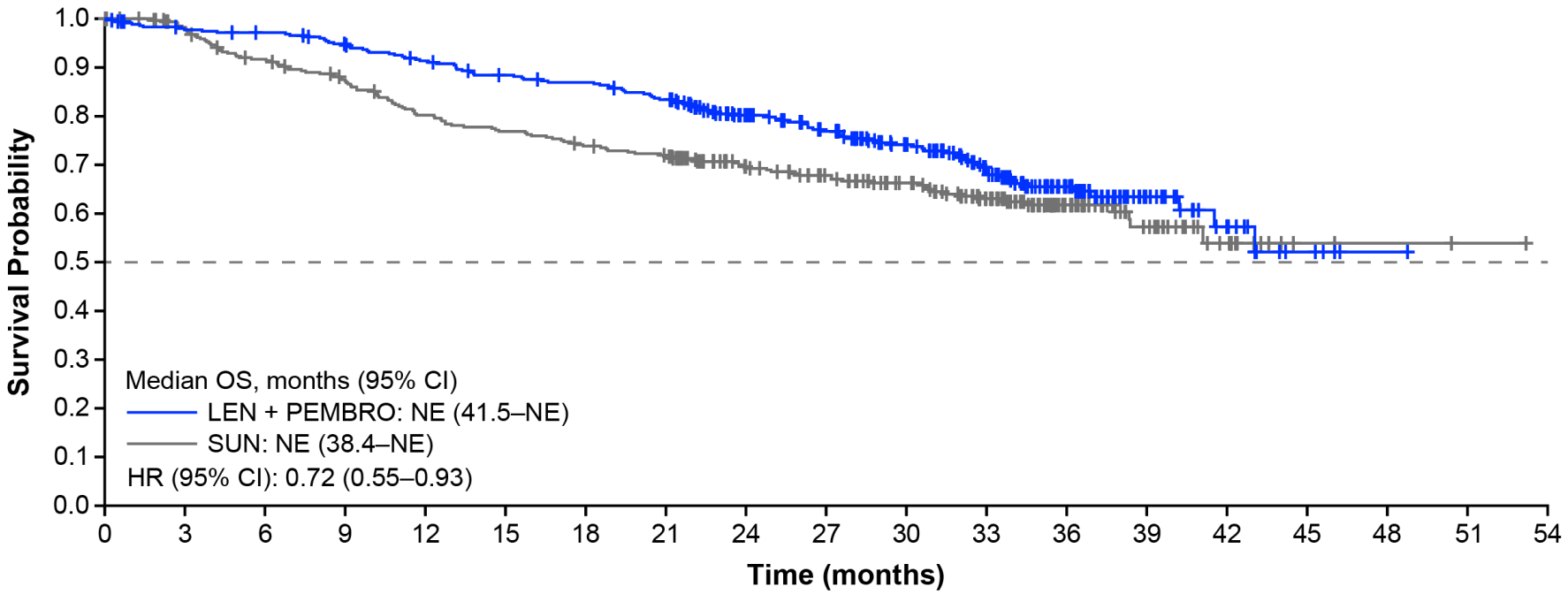
Patient Disposition at Updated Data Cutoff Date (March 31, 2021)



- 114 (32.1%) vs 49 (13.7%) patients in the LEN + PEMBRO and SUN arms were receiving treatment at the time of data cutoff, respectively
- 225 (63.4%) vs 197 (55.2%) patients in the LEN + PEMBRO and SUN arms were ongoing in the study at the time of data cutoff, respectively

[a]Refers to patients who were on study treatment or in survival follow-up as of the cutoff date; [b]Refers to patients who were on study treatment as of the cutoff date; [c]Refers to patients who were no longer followed up for survival as of the cut-off date; [d]Refers to patients who discontinued sunitinib or both study drugs in combination therapy; [e]The most common reason for treatment discontinuation in both arms was radiological disease progression (LEN+PEMBRO, n = 108; SUN, n = 185), followed by adverse event (LEN+PEMBRO, n = 68; SUN, n = 43).
DC, discontinued.

Overall Survival[a]



Number of patients at risk:

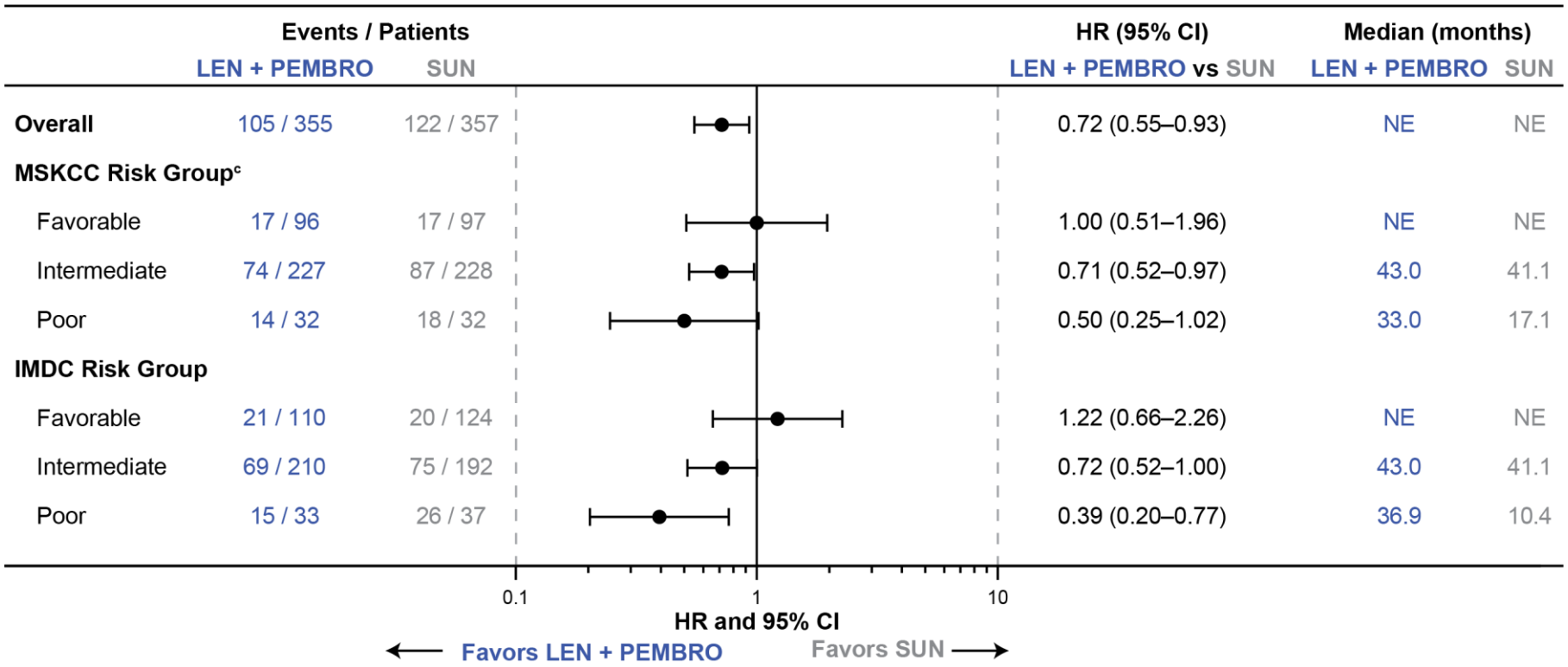
LEN + PEMBRO	355	342	338	327	313	300	294	280	232	207	174	133	75	31	15	5	1	0
SUN	357	332	307	289	264	253	242	234	195	177	153	116	66	34	14	3	2	1	0

- Median duration of follow-up for OS was 33.7 months (95% CI, 32.8–34.4) in the LEN + PEMBRO arm and 33.4 months (95% CI, 32.5–34.1) in the SUN arm
- 250 (70.4%) and 235 (65.8%) patients in the LEN + PEMBRO and SUN arms were censored, respectively

[a]Data cutoff occurred on March 31, 2021.

CI, confidence interval; HR, hazard ratio; NE, not estimable; OS, overall survival.

Overall Survival in MSKCC and IMDC Risk Groups[a,b]



- OS continues to favor LEN + PEMBRO over SUN in the MSKCC and IMDC intermediate and poor risk groups
- Due to the low number of events and wide CI, interpretation of the HR is limited in the MSKCC and IMDC favorable risk groups

[a]Data cutoff occurred on March 31, 2021; [b]Patients were stratified by MSKCC risk group but not IMDC risk group; [c]Per IxRS.
CI, confidence interval; HR, hazard ratio; IMDC, International Metastatic Renal Cell Carcinoma Database Consortium; IxRS, interactive voice and web response system; MSKCC, Memorial Sloan Kettering Cancer Center; NE, not estimable; OS, overall survival.

Conclusions

- The OS benefit observed with LEN + PEMBRO versus SUN in the CLEAR study was maintained with longer follow-up[a] in the intention to treat population
    - An OS benefit continues to be observed with additional follow-up of patients with intermediate or poor risk as defined by MSKCC or IMDC criteria
    - The interpretation of OS in patients with favorable risk (as defined by MSKCC or IMDC criteria) is limited by the low number of events
- Along with the previously observed efficacy benefits with LEN + PEMBRO, this follow-up OS analysis further supports LEN + PEMBRO as a first-line treatment for patients with advanced RCC[1,2]

[a]Data cutoff occurred on March 31, 2021.

IMDC, International Metastatic Renal Cell Carcinoma Database Consortium; MSKCC, Memorial Sloan Kettering Cancer Center; OS, overall survival; RCC, renal cell carcinoma.

1. Lenvima [package insert]. Woodcliff Lake, NJ: Eisai Inc; 2. Keytruda [package insert]. Whitehouse Station, NJ, USA: Merck Sharp & Dohme Corp.

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