Poster No. E41

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 (CLEAR Study)

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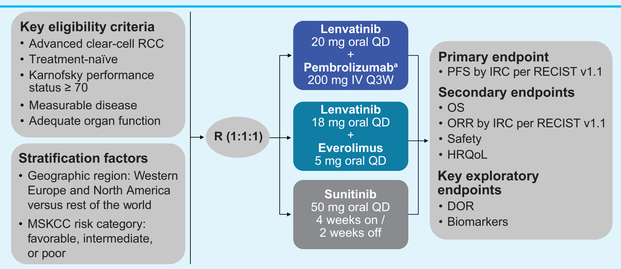
INTRODUCTION

- The randomized phase 3 CLEAR study (data cutoff date: August 28, 2020; median overall survival (OS) follow-up: 26.6 months) demonstrated significantly improved efficacy outcomes with lenvatinib (LEN) + pembrolizumab (PEMBRO) versus sunitinib (SUN) in the first-line treatment of patients with advanced renal cell carcinoma (RCC).[1,2]
  - Progression-free survival (PFS) by independent review committee (IRC) per Response Evaluation Criteria In Solid Tumors version 1.1 (RECIST v1.1), the primary endpoint, was significantly longer with LEN + PEMBRO versus SUN (hazard ratio [HR] 0.39; 95% confidence interval [CI] 0.32–0.49; $P < 0.001$).
  - OS was also significantly longer with LEN + PEMBRO versus SUN treatment (HR 0.66; 95% CI 0.49–0.88; $P = 0.005$).
  - Confirmed objective response rate (ORR) by IRC per RECIST v1.1 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 OS 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; PFS and ORR at the updated data cutoff date were also assessed (by investigator assessment per RECIST v1.1).

METHODS

- The CLEAR study design is summarized in **Figure 1**.

Figure 1. 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.

- Adult patients (≥ 18 years of age) with advanced treatment-naïve RCC with a clear cell component were randomly assigned to receive 1 of 3 treatments:
  - LEN 20 mg orally once daily + PEMBRO 200 mg intravenously every 3 weeks.
  - LEN 18 mg + everolimus 5 mg orally once daily.
  - SUN 50 mg orally once daily (4 weeks on/2 weeks off).
- Key eligibility criteria included ≥ 1 measurable lesion per Response Evaluation Criteria In Solid Tumors version 1.1 (RECIST v1.1) and a Karnofsky performance-status score ≥ 70.
- Randomization was stratified by geographical region and by Memorial Sloan Kettering Cancer Center (MSKCC) prognostic risk group.
- PFS and tumor responses for this follow-up analysis were assessed only by investigator per RECIST v1.1.
- PFS and OS were calculated with Kaplan-Meier estimates and two-sided CIs.
- PFS and OS in LEN + PEMBRO versus SUN arms were compared using a stratified-log rank test, and the HR and the corresponding 95% CI were estimated using a stratified Cox regression model.
- Objective response rates in LEN + PEMBRO versus SUN arms were compared using a stratified Cochran-Mantel-Haenszel test.

RESULTS

Patients

- Baseline demographic and clinical characteristics for all patients randomly assigned to receive LEN + PEMBRO (n = 355) or SUN (n = 357) are shown in **Table 1**.

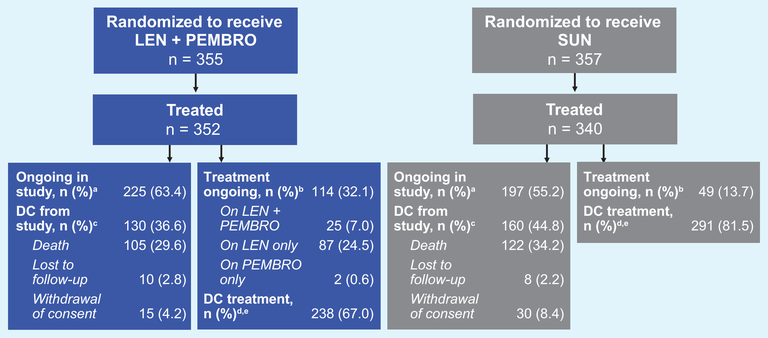
Table 1. Demographic and Clinical Characteristics

Characteristic	LEN + PEMBRO (n = 355)	SUN (n = 357)
Median age, years (range)	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; LEN, lenvatinib; MSKCC, Memorial Sloan Kettering Cancer Center; PD-L1, programmed cell death ligand-1; PEMBRO, pembrolizumab; SUN, sunitinib.

- Patient disposition at the updated data cutoff date (March 31, 2021) is shown in **Figure 2**.
  - 114 (32.1%) Patients in the LEN + PEMBRO arm and 49 (13.7%) patients in the SUN arm were receiving ongoing treatment at the data cutoff date.
  - 225 (63.4%) Patients in the LEN + PEMBRO arm and 197 (55.2%) patients in the SUN arm were ongoing in the study at the data cutoff date.

Figure 2. Patient Disposition at Updated Data Cutoff Date (March 31, 2021)



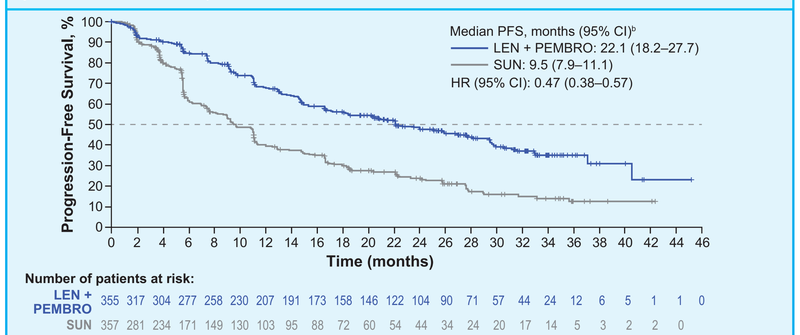
[a]Refers to patients who were on study treatment or in survival follow-up as of the cutoff date; [b]refers to patients who were on study treatment as of the cutoff date; [c]refers to patients who were no longer followed-up for survival as of the cutoff date; [d]refers to patients who discontinued SUN 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; LEN, lenvatinib; PEMBRO, pembrolizumab; SUN, sunitinib.

Progression-Free Survival Outcomes

- Median PFS by investigator assessment per RECIST v1.1 was 22.1 months (95% CI 18.2–27.7) in the LEN + PEMBRO arm and 9.5 months (95% CI 7.9–11.1) in the SUN arm (HR 0.47; 95% CI 0.38–0.57) (**Figure 3**).

Figure 3. Progression-Free Survival (Investigator Assessment per RECIST v1.1)[a]



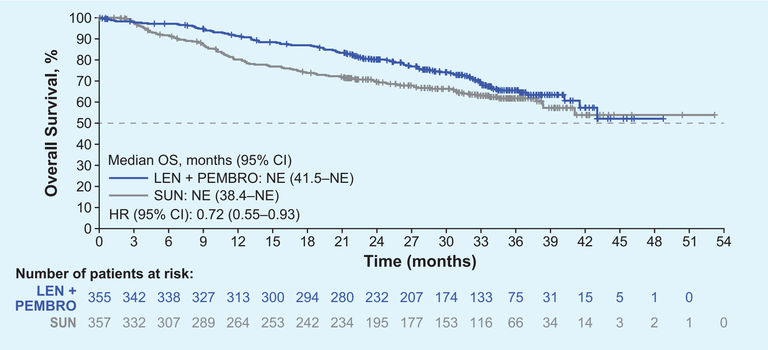
[a]Data cutoff occurred on March 31, 2021; [b]at the earlier (August 28, 2020) data cutoff, the median PFS by investigator per RECIST v1.1 was 22.1 months (95% CI 17.1–26.9) in the LEN + PEMBRO arm and 9.5 months (95% CI 7.9–11.1) in the SUN arm (HR 0.47; 95% CI 0.38–0.58).

CI, confidence interval; HR, hazard ratio; LEN, lenvatinib; PEMBRO, pembrolizumab; PFS, progression-free survival; RECIST v1.1, Response Evaluation Criteria In Solid Tumors version 1.1; SUN, sunitinib.

Overall Survival Outcomes

- Median durations of follow-up for OS were 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.
- Median OS was not estimable (NE) in both the LEN + PEMBRO arm (95% CI 41.5–NE) and in the SUN arm (95% CI 38.4–NE); the HR was 0.72 (95% CI 0.55–0.93) (**Figure 4).**
- Of patients in the LEN + PEMBRO and SUN arms, 250 (70.4%) and 235 (65.8%) were censored, respectively.

Figure 4. Overall Survival in LEN + PEMBRO and SUN arms[a]

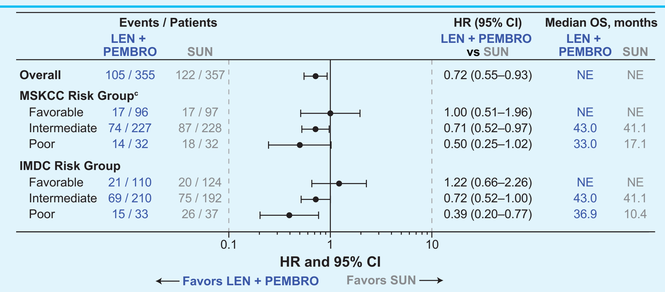


[a]Data cutoff occurred on March 31, 2021.

CI, confidence interval; HR, hazard ratio; LEN, lenvatinib; NE, not estimable; OS, overall survival; PEMBRO, pembrolizumab; SUN, sunitinib.

- OS in MSKCC and International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) risk groups is shown in **Figure 5**.
  - Similar to the previous data cutoff results, OS continued to favor LEN + PEMBRO over SUN in the MSKCC and IMDC intermediate and poor risk groups.
  - Owing to the low number of events and wide CI, interpretation of the HR is limited in the MSKCC and IMDC favorable risk groups.

Figure 5. Overall Survival in MSKCC and IMDC Risk Groups[a,b]



[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; LEN, lenvatinib; MSKCC, Memorial Sloan Kettering Cancer Center; NE, not estimable; OS, overall survival; PEMBRO, pembrolizumab; SUN, sunitinib.

Tumor Response

- A summary of tumor response outcomes is outlined in **Table 2**.
  - ORR was 68.7% in the LEN + PEMBRO arm versus 34.5% in the SUN arm (relative risk 2.00; 95% CI 1.70–2.34).
  - Complete responses were observed in 37 (10.4%) and 7 (2.0%) patients in the LEN + PEMBRO and SUN arms, respectively; partial responses were observed in 207 (58.3%) and 116 (32.5%) patients in the LEN + PEMBRO and SUN arms, respectively.

Table 2. Summary of Tumor Response (Investigator Assessment per RECIST v1.1)[a]

Parameter	LEN + PEMBRO (n = 355)	SUN (n = 357)
Objective response rate,[b] n (%)	244 (68.7)	123 (34.5)
95% CI	63.9–73.6	29.5–39.4
Relative risk (95% CI)	2.00 (1.70–2.34)	
Complete response, n (%)	37 (10.4)	7 (2.0)
Partial response, n (%)	207 (58.3)	116 (32.5)
Stable disease, n (%)	74 (20.8)	158 (44.3)
Progressive disease, n (%)	22 (6.2)	33 (9.2)
Unknown/NE,[c] n (%)	15 (4.2)	43 (12.0)
TTR, months, median (range)	1.94 (1.41–20.14)	2.00 (1.51–17.28)
DOR, months, median (95% CI)	27.9 (22.1–36.8)	14.8 (11.6–17.3)

[a]Data cutoff occurred on March 31, 2021; [b]at the earlier (August 28, 2020) data cutoff, the ORR by investigator per RECIST v1.1 was 68.7 (95% CI 63.9–73.6) in the LEN + PEMBRO arm and 34.2 (95% CI 29.3–39.1) in the SUN arm (relative risk 2.01; 95% CI 1.72–2.36); [c]best overall response was unknown or could not be evaluated for patients who had no postbaseline tumor assessment, ≥ 1 lesion that could not be evaluated, or early SD (SD < 7 weeks).

CI, confidence interval; DOR, duration of response; LEN, lenvatinib; NE, not evaluable; PEMBRO, pembrolizumab; RECIST v1.1, Response Evaluation Criteria In Solid Tumors version 1.1; SUN, sunitinib; TTR, time to response.

CONCLUSIONS

- The efficacy (ie, PFS, OS, and ORR) benefit previously observed with LEN + PEMBRO versus SUN in the CLEAR study was also maintained with longer follow-up in the intention-to-treat population.
  - No substantial changes in efficacy endpoints were observed from the original data cutoff date (August 28, 2020).
  - Notably, PFS and ORR were assessed only by investigator assessment per RECIST v1.1 at the updated data cutoff date (March 31, 2021).
- 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 analysis further supports LEN + PEMBRO as a first-line treatment for patients with advanced RCC.[3,4]

References

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.
3. Lenvima [package insert]. Woodcliff Lake, NJ: Eisai Inc.
4. Keytruda. Prescribing information. Merck Sharp & Dohme Corp., Whitehouse Station, NJ, USA; 2021.

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