Final Prespecified Overall Survival Analysis of CLEAR: 4-Year Follow-Up of Lenvatinib Plus Pembrolizumab Versus Sunitinib in Advanced Renal Cell Carcinoma

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INTRODUCTION

- In the phase 3 open-label CLEAR study, we compared the efficacy and safety of lenvatinib + pembrolizumab and lenvatinib + everolimus versus sunitinib in patients with advanced clear cell renal cell carcinoma (RCC).[1]
- At the primary analysis (median survival follow-up duration: 26.6 months), lenvatinib + pembrolizumab showed statistically significant and clinically meaningful improvements versus sunitinib in progression-free survival (PFS; final analysis: hazard ratio [HR] 0.39 [95% CI 0.32–0.49]; *P* < 0.001) and overall survival (OS; interim analysis: HR 0.66 [95% CI 0.49–0.88]; *P* = 0.005).[1]
  - The objective response rate (ORR) was also improved with lenvatinib + pembrolizumab versus sunitinib (71.0% [95% CI, 66.3–75.7] vs 36.1% [95% CI, 31.2–41.1]; relative risk 1.97 [95% CI, 1.69–2.29]).[1]
  - The safety profile of the combination was consistent with the known safety profiles of each monotherapy.[1–3]
  - Based on results from the primary analysis of CLEAR, lenvatinib + pembrolizumab was approved by regulatory agencies for the first-line treatment of adult patients with advanced RCC.
- Here, we present results from the final prespecified OS analysis of lenvatinib + pembrolizumab versus sunitinib with a median follow-up of 4 years (data cutoff date: 31 July 2022).

METHODS

- Treatment-naïve patients (n = 1069) with advanced RCC were randomly assigned (1:1:1) to receive lenvatinib 20 mg once daily (QD) + pembrolizumab 200 mg once every 3 weeks (Q3W); or lenvatinib 18 mg + everolimus 5 mg QD; or sunitinib 50 mg QD (4 weeks on/2 weeks off).
- This final prespecified OS analysis (data cutoff date: 31 July 2022), with 23 months of additional follow-up from the primary analysis (data cutoff date: 28 August 2020), was triggered by ~304 OS events in 2 groups.
- All analyses presented are descriptive and noninferential; *P*-values are nominal.
- HRs and 2-sided 95% CIs were estimated by a stratified Cox proportional hazards model with Efron's method for ties, stratified by region and Memorial Sloan Kettering Cancer Center (MSKCC) prognostic groups.
- The International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) risk group was not a stratification factor and relevant data were derived programmatically.
- Median OS with 2-sided 95% CIs was calculated using Kaplan–Meier estimates.
- Post hoc analyses of OS adjusting for the impact of imbalance in subsequent therapies between treatment groups were based on the 2-stage estimation method.
- Updated results are provided for OS, PFS, ORR, duration of response (DOR), safety, and exploratory subgroups analyses for the MSKCC and IMDC risk groups.
- Tumors were assessed by independent review using Response Evaluation Criteria In Solid Tumors (RECIST) version 1.1.
- Herein, analyses are presented for lenvatinib + pembrolizumab and sunitinib.

RESULTS

Patients

- Baseline characteristics of patients enrolled in the lenvatinib + pembrolizumab (n = 355) and sunitinib (n = 357) arms are reported in **Table 1**.

Table 1. Baseline Characteristics

Category	Lenvatinib + Pembrolizumab (n = 355)	Sunitinib (n = 357)
Age, median (range), years	64 (34–88)	61 (29–82)
Geographic region, % Western Europe or North America / rest of world	56 / 44	56 / 44
MSKCC prognostic group[a], % Favorable / intermediate / poor	27 / 64 / 9	27 / 64 / 9
IMDC risk group[b], % Favorable / intermediate / poor	31 / 59 / 9	35 / 54 / 10
Sarcomatoid features, %	8	6

Total % may not = 100 due to rounding. 1 Patient in the lenvatinib + pembrolizumab group had carcinoma without a clear cell component.

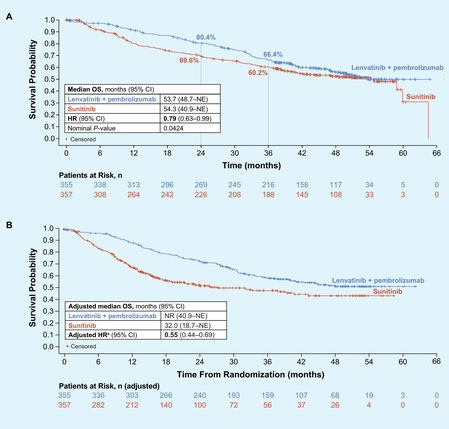
[a]MSKCC scores: 0 indicates favorable risk, 1 or 2 intermediate risk, and 3 or higher poor risk; [b]IMDC scores: 0 indicates favorable risk, 1 or 2 intermediate risk, and 3 to 6 poor risk. IMDC risk group was not a stratification factor and relevant data were derived programmatically.

IMDC, International Metastatic Renal Cell Carcinoma Database Consortium; MSKCC, Memorial Sloan Kettering Cancer Center.

Efficacy

- Median OS follow-up time (interquartile range [IQR]) was 49.8 months (41.4–53.1) in the lenvatinib + pembrolizumab arm and 49.4 months (41.6–52.8) in the sunitinib arm.
- With an HR of 0.79 (95% CI, 0.63–0.99; nominal *P*-value = 0.0424) for the lenvatinib + pembrolizumab versus sunitinib comparison, median OS (95% CI) was 53.7 months (48.7–not estimable [NE]) in the lenvatinib + pembrolizumab arm versus 54.3 months (40.9–NE) in the sunitinib arm (**Figure 1A**).
- Overall, 181 (51.0%) and 246 (68.9%) patients received subsequent systemic anticancer medication in the lenvatinib + pembrolizumab and sunitinib arms, respectively.
  - In the lenvatinib + pembrolizumab arm, 163 (45.9%) patients received subsequent antivascular endothelial growth factor therapy and 56 (15.8%) patients received subsequent programmed death/programmed death ligand-1 checkpoint inhibitors.
  - In the sunitinib arm, 162 (45.4%) patients received subsequent anti-vascular endothelial growth factor therapy, and 195 (54.6%) patients received subsequent programmed death/programmed death ligand-1 checkpoint inhibitors.
- The OS adjusted for subsequent therapy is shown in **Figure 1B**; the adjusted HR (95% CI) was 0.55 (0.44–0.69).

Figure 1. Kaplan–Meier Plot of Final OS Analysis (A) and Final OS Analysis Adjusted for Subsequent Anticancer Medications (B)[a]



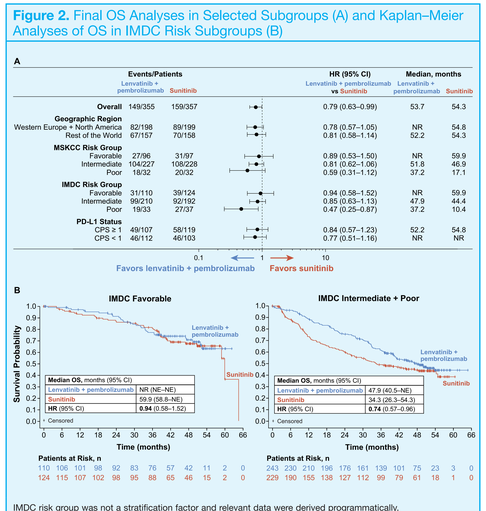
At median OS follow-up time (IQR) of 49.8 months (41.4–53.1) in the lenvatinib plus pembrolizumab group and 49.4 months (41.6–52.8) in the sunitinib group, 308 target OS events had occurred (lenvatinib + pembrolizumab, 149 events; sunitinib, 159 events).

[a]A 2-stage estimation post hoc method of adjusting OS for any effects of subsequent anticancer medications was used. Patients were classified as switchers and nonswitchers, depending on whether the patients received subsequent anticancer medication. Within each treatment arm, survival times were compared between switchers and nonswitchers following the treatment discontinuation, then an acceleration factor was derived to adjust the impact of subsequent anticancer medications. With the derived acceleration factor, switcher survival time was scaled down to get the counterfactual OS time (defined as the OS time for switchers had they not received any subsequent anticancer medications).

CI, confidence interval; HR, hazard ratio; IQR, interquartile range; NE, not estimable; NR, not reached; OS, overall survival.

- The HR for OS favored lenvatinib + pembrolizumab versus sunitinib across subgroups of interest (**Figure 2**).
- Median follow-up time (IQR) for PFS was 39.2 months (22.1–48.5) in the lenvatinib + pembrolizumab arm and 20.6 months (5.5–41.2) in the sunitinib arm.
- Median PFS (95% CI) was 23.9 months (20.8–27.7) in the lenvatinib + pembrolizumab arm and 9.2 months (6.0–11.0) in the sunitinib arm (**Figure 3A**).
- PFS benefit was observed irrespective of risk subgroups (**Figure 3B**).

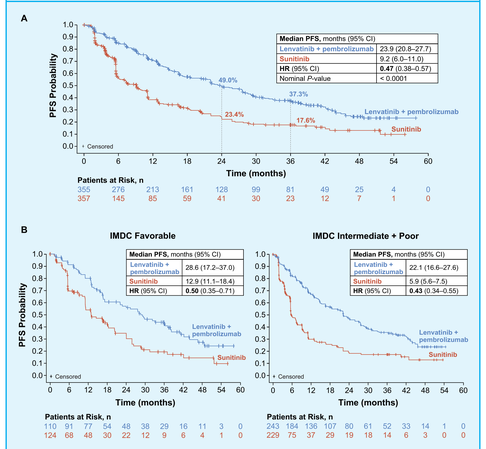
Figure 2. Final OS Analyses in Selected Subgroups (A) and Kaplan–Meier Analyses of OS in IMDC Risk Subgroups (B)



IMDC risk group was not a stratification factor and relevant data were derived programmatically.

CI, confidence interval; CPS, combined positive score; HR, hazard ratio; IMDC, International Metastatic Renal Cell Carcinoma Database Consortium; MSKCC, Memorial Sloan Kettering Cancer Center; NE, not estimable; NR, not reached; OS, overall survival; PD-L1, programmed death ligand 1.

Figure 3. Kaplan–Meier Plot of Final Analysis of PFS by IIR per RECIST v1.1 (A) and in IMDC Risk Subgroups (B)

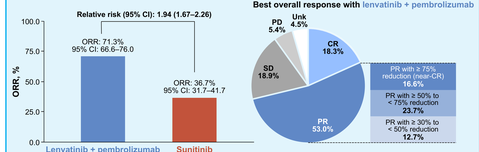


IMDC risk group was not a stratification factor and relevant data were derived programmatically.

CI, confidence interval; HR, hazard ratio IIR, independent imaging review; IMDC, International Metastatic Renal Cell Carcinoma Database Consortium; PFS, progression-free survival; RECIST v1.1, Response Evaluation Criteria In Solid Tumors version 1.1.

- ORR (95% CI) was 71.3% (66.6–76.0) with lenvatinib + pembrolizumab and 36.7% (31.7–41.7) with sunitinib (relative risk 1.94; 95% CI 1.67–2.26) (**Figure 4**).
  - Median DOR (95% CI) was 26.7 months (22.8–34.6) and 14.7 months (9.4–18.2) in the lenvatinib + pembrolizumab and sunitinib arms, respectively (HR 0.57; 95% CI 0.43–0.76).
  - In the lenvatinib + pembrolizumab arm, median DOR (95% CI) was 43.7 months (39.2–NE) for patients with a complete response and 30.5 months (22.4–NE) for patients with a near-complete response (ie, partial response with a tumor reduction ≥ 75%).

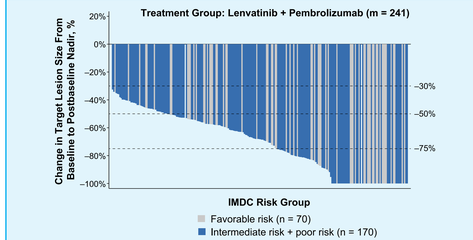
Figure 4. Updated ORR by IIR per RECIST v1.1 in Patients With Advanced RCC



CI, confidence interval; CR, complete response; IIR, independent imaging review; ORR, objective response rate; PD, progressive disease; PR, partial response; RCC, renal cell carcinoma; RECIST v1.1, Response Evaluation Criteria In Solid Tumors version 1.1; SD, stable disease; Unk, unknown.

- Deep tumor responses were observed across IMDC risk groups in the lenvatinib + pembrolizumab arm (**Figure 5**).

Figure 5. Change in Target Lesion Size in Responders

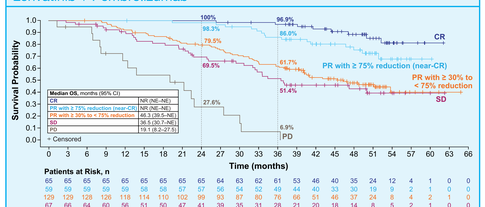


Per independent review. This figure includes patients (m) with both baseline and at least 1 postbaseline target lesion assessment.

IMDC, International Metastatic Renal Cell Carcinoma Database Consortium.

- Median OS was not reached in patients with a complete or near-complete tumor response (**Figure 6**).

Figure 6. Final OS Analyses by Best Overall Response: Lenvatinib + Pembrolizumab



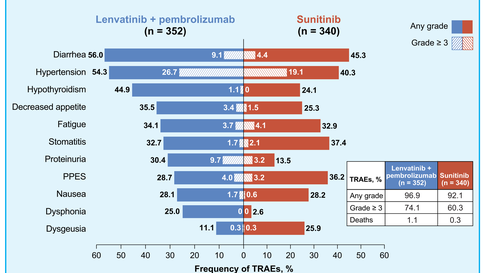
Near-CR refers to partial responders who showed a maximum tumor reduction of ≥ 75%.

CI, confidence interval; CR, complete response; NE, not estimable; NR, not reached; OS, overall survival; PD, progressive disease; PR, partial response; SD, stable disease.

Safety

- The safety profile of lenvatinib + pembrolizumab was consistent with that of the primary analysis[1] and of the known profile of each monotherapy[2,3]; adverse events were managed with dose modifications as necessary.
- The most common treatment-related adverse event was diarrhea in both the lenvatinib + pembrolizumab (56.0%) and sunitinib (45.3%) arms (**Figure 7**).

Figure 7. TRAEs With Frequency ≥ 25% in Any Group



The median duration of treatment (IQR) was 22.6 months (9.4–37.1) in the lenvatinib + pembrolizumab arm and 7.8 months (3.7–19.4) in the sunitinib arm.

IQR, interquartile range; PPES, palmar-plantar erythrodysesthesia; TRAE, treatment-related adverse event.

CONCLUSIONS

- Lenvatinib + pembrolizumab continued to demonstrate clinically meaningful and durable benefit in OS, PFS, and ORR versus sunitinib in the first-line treatment of patients with advanced RCC at the final analysis (with a median follow-up of 4 years).
- No new safety signals were identified; adverse events were managed with dose modifications as necessary.

References

1. Motzer R et al. *N Engl J Med*. 2021;384(14):1289-1300.
2. Lenvima (lenvatinib) prescribing information. Nutley, NJ, USA: Eisai Inc., 2022.
3. Keytruda (pembrolizumab) prescribing information. Rahway, NJ, USA: Merck Sharp & Dohme LLC, 2023.

ClinicalTrials.gov identifier: NCT02811861

Acknowledgment: We would like to thank all the patients, their families, and/or caregivers, as well as the investigators and their teams who participated in the CLEAR study. We would like to thank the late Dr. Anil Kapoor for his contributions to this study.

Funding source: This study was sponsored by Eisai Inc., Nutley, NJ, USA, and Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA. Medical writing support was provided by Oxford PharmaGenesis Inc., Newtown, PA, USA, with funding by Eisai Inc., Nutley, NJ, USA, and Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA.

Originally presented at the American Society of Clinical Oncology Symposium; June 2–6, 2023; Chicago, IL, USA, and in Virtual Format.

Poster presented at: NCODA Fall Summit; October 25–27, 2023; Orlando, FL, USA