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Phase 3 CLEAR Trial in Advanced Renal Cell Carcinoma: Outcomes in Subgroups and Toxicity Update

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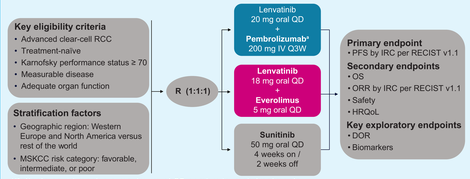
INTRODUCTION

- The phase 3 multicenter, open-label, randomized CLEAR trial (Study 307/KEYNOTE-581) compared the efficacy and safety of lenvatinib + pembrolizumab or everolimus versus sunitinib alone as a first-line treatment for patients with advanced renal cell carcinoma (RCC).[1]
- In the primary analysis of CLEAR, lenvatinib + pembrolizumab demonstrated significantly improved outcomes versus sunitinib.[1]
  - Progression-free survival (PFS) was 24 months versus 9 months (hazard ratio [HR] 0.39; 95% confidence interval [CI] 0.32–0.49; $P < 0.001$).
  - Overall survival (OS) was not reached for either arm (HR 0.66; 95% CI 0.49–0.88; $P = 0.005$).
  - Objective response rate (ORR) was 71% versus 36% (relative risk with lenvatinib + pembrolizumab versus sunitinib, 1.97; 95% CI 1.69–2.29).
- This analysis explored efficacy outcomes in patients with or without adverse prognostic features (eg, sarcomatoid histology, bone metastases, liver metastases, and no prior nephrectomy) in the lenvatinib + pembrolizumab and sunitinib arms (data cutoff date: August 28, 2020).
- We also report on the number of patients who received high-dose corticosteroids to manage immune-mediated adverse events (AEs).

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; QD, once daily; PFS, progression-free survival; Q3W, once every 3 weeks; RCC, renal cell carcinoma; R, randomization; RECIST v1.1; Response Evaluation Criteria In Solid Tumors version 1.1.

- Patients were randomly assigned (1:1:1) to receive 1 of 3 treatments:
  - Lenvatinib 20 mg orally once daily + pembrolizumab 200 mg intravenously once every 3 weeks.
  - Lenvatinib 18 mg + everolimus 5 mg orally once daily.
  - Sunitinib 50 mg orally once daily (4 weeks on/2 weeks off).
- Key eligibility criteria included: advanced RCC with no prior systemic therapy; ≥ 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 geographic region (Western Europe and North America or rest of the world) and Memorial Sloan Kettering Cancer Center prognostic risk group (favorable, intermediate, or poor risk).
- Tumor assessments were performed by an independent review committee (IRC) and assessed via RECIST v1.1.
- The primary endpoint was PFS (as assessed by an IRC); key secondary endpoints included OS and ORR (as assessed by an IRC).
- This preplanned subgroup analysis compared PFS, OS, and ORR in the lenvatinib + pembrolizumab arm versus the sunitinib arm based on selected baseline prognostic features, including sarcomatoid histology, bone metastases, liver metastases, and no prior nephrectomy.
- Median PFS and OS for the lenvatinib + pembrolizumab and sunitinib arms were estimated using the Kaplan–Meier method; HR and 95% CIs comparing lenvatinib + pembrolizumab versus sunitinib arms were estimated by a stratified Cox model.
- Odds ratios were used to compare ORRs for the lenvatinib + pembrolizumab and sunitinib arms.
- The number of patients requiring corticosteroids (≥ 40 mg prednisone daily equivalent) to manage immune-mediated AEs for any duration was tracked during the study.

RESULTS

Patients

- Of the 1069 patients randomly assigned to treatment in CLEAR, 355 were randomly assigned to receive lenvatinib + pembrolizumab and 357 to receive sunitinib.
- Baseline characteristics of patients in these 2 arms are shown in **Table 1**.

Table 1. Baseline Characteristics of Lenvatinib + Pembrolizumab and Sunitinib Arms in CLEAR[a]

Characteristic	Lenvatinib + Pembrolizumab (n = 355)	Sunitinib (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 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
PD-L1 combined positive score, %		
≥ 1 / < 1 / not available	30.1 / 31.5 / 38.3	33.3 / 28.9 / 37.8
Number of metastatic organs or sites[b], %		
1 / ≥ 2	27.3 / 71.5	30.3 / 68.9
Sarcomatoid features, %	7.9	5.9
Bone metastases[b], %	23.9	27.2
Liver metastases[b], %	16.9	17.1
Prior nephrectomy, %	73.8	77.0

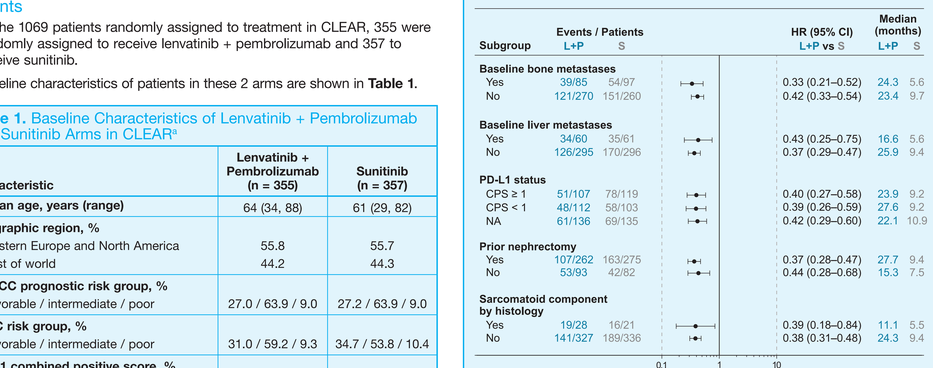
[a]Motzer et al 2021[1] previously reported baseline characteristics in full; [b]as assessed by the investigators.

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

Efficacy by Subgroups

- PFS, as assessed by IRC per RECIST v1.1, was longer with lenvatinib + pembrolizumab versus sunitinib treatment across baseline-characteristic subgroups of interest (**Figure 2**).
  - Specifically, PFS results favored lenvatinib + pembrolizumab (median 11.1 months) versus sunitinib (median 5.5 months) treatment in patients with sarcomatoid features (HR 0.39; 95% CI 0.18–0.84) and in those without sarcomatoid features (median 24.3 vs 9.4 months, respectively; HR 0.38; 95% CI 0.31–0.48).
  - Patients with bone metastases in the lenvatinib + pembrolizumab arm had a median PFS of 24.3 months versus 5.6 months in the sunitinib arm (HR 0.33; 95% CI 0.21–0.52); those without bone metastases in the lenvatinib + pembrolizumab arm had a median PFS of 23.4 months versus 9.7 months in the sunitinib arm (HR 0.42; 95% CI 0.33–0.54).
  - Patients with liver metastases in the lenvatinib + pembrolizumab arm had a median PFS of 16.6 months versus 5.6 months in the sunitinib arm (HR 0.43; 95% CI 0.25–0.75); those without liver metastases in the lenvatinib + pembrolizumab arm had a median PFS of 25.9 months versus 9.4 months in the sunitinib arm (HR 0.37; 95% CI 0.29–0.47).
  - PFS also favored lenvatinib + pembrolizumab (median 27.7 months) versus sunitinib (median 9.4 months) in patients with prior nephrectomy (HR 0.37; 95% CI 0.28–0.47) and in those without prior nephrectomy (median 15.3 vs 7.5 months, respectively; HR 0.44; 95% CI 0.28–0.68).

Figure 2. Forest Plot of PFS for Lenvatinib + Pembrolizumab Versus Sunitinib Treatment by IRC per RECIST v1.1



CI, confidence interval; CPS, combined positive score; HR, hazard ratio; IRC, independent review committee; L+P, lenvatinib + pembrolizumab; NA, not available; PD-L1, programmed cell death ligand-1; PFS, progression-free survival; RECIST v1.1, Response Evaluation Criteria In Solid Tumors version 1.1; S, sunitinib.

- OS results also favored lenvatinib + pembrolizumab versus sunitinib treatment across baseline-characteristic subgroups of interest (**Figure 3**).
  - Specifically, OS results favored lenvatinib + pembrolizumab (median not estimable [NE]) versus sunitinib (median NE) treatment in patients with sarcomatoid features (HR 0.91; 95% CI 0.32–2.58) and in those without sarcomatoid features (median NE in both arms; HR 0.64; 95% CI 0.47–0.87).
  - OS favored lenvatinib + pembrolizumab (median NE) versus sunitinib (median 24.8 months) treatment in patients with bone metastases (HR 0.50; 95% CI 0.30–0.83) and in those without bone metastases (median NE in both arms; HR 0.79; 95% CI 0.54–1.14).
  - Patients with liver metastases in the lenvatinib + pembrolizumab arm had a median OS of 33.6 months, while median OS in the sunitinib arm was NE (HR 0.52; 95% CI 0.27–0.99); median OS was NE in patients without liver metastases in the lenvatinib + pembrolizumab arm and in the sunitinib arm (HR 0.66; 95% CI 0.47–0.93).
  - OS favored lenvatinib + pembrolizumab (median NE) versus sunitinib (median NE) in patients with prior nephrectomy (HR 0.71; 95% CI 0.49–1.03) and in those without prior nephrectomy (median 33.1 vs 24.0 months, respectively; HR 0.52; 95% CI 0.31–0.86).

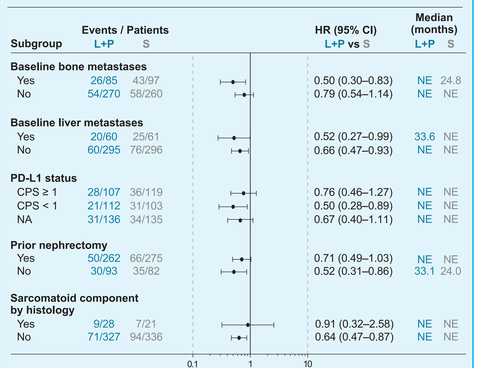
Table 2. ORR and Odds Ratios for Lenvatinib + Pembrolizumab Versus Sunitinib Treatment in Subgroups of Interest

	Sarcomatoid Features				Bone Metastases				Liver Metastases				Prior Nephrectomy			
	Yes		No		Yes		No		Yes		No		Yes		No	
Parameter	**L+P n = 28**	**S n = 21**	**L+P n = 327**	**S n = 336**	**L+P n = 85**	**S n = 97**	**L+P n = 270**	**S n = 260**	**L+P n = 60**	**S n = 61**	**L+P n = 295**	**S n = 296**	**L+P n = 262**	**S n = 275**	**L+P n = 93**	**S n = 82**
ORR,[a] n (%)	17 (60.7)	5 (23.8)	235 (71.9)	124 (36.9)	55 (64.7)	22 (22.7)	197 (73.0)	107 (41.2)	40 (66.7)	21 (34.4)	212 (71.9)	108 (36.5)	193 (73.7)	110 (40.0)	59 (63.4)	19 (23.2)
Odds ratio, (95% CI)	8.85 (2.07–37.84)		4.40 (3.16–6.12)		6.94 (3.51–13.74)		3.84 (2.66–5.55)		4.03 (1.84–8.82)		4.47 (3.15–6.35)		4.13 (2.87–5.94)		6.29 (3.14–12.60)	

[a]As assessed by IRC per RECIST v1.1.

CI, confidence interval; IRC, independent review committee; L+P, lenvatinib + pembrolizumab; ORR, objective response rate; RECIST v1.1, Response Evaluation Criteria In Solid Tumors version 1.1; S, sunitinib.

Figure 3. Forest Plot of OS for Lenvatinib + Pembrolizumab Versus Sunitinib Treatment



CI, confidence interval; CPS, combined positive score; HR, hazard ratio; L+P, lenvatinib + pembrolizumab; NA, not available; NE, not estimable; OS, overall survival; PD-L1, programmed cell death ligand-1; S, sunitinib.

- ORR results favored lenvatinib + pembrolizumab versus sunitinib treatment across all subgroups of interest (**Table 2**).

Safety in Patients Given Lenvatinib + Pembrolizumab

- Safety was assessed among patients who received at least 1 dose of study treatment.
- Overall, 52 (14.8%) of 352 patients given lenvatinib + pembrolizumab received high-dose corticosteroids (≥ 40 mg prednisone daily equivalent) for any duration to manage immune-mediated AEs.
- The most frequent immune-mediated AEs treated with high-dose corticosteroids were pneumonitis (3.7%), hypothyroidism (2.8%), adrenal insufficiency, and rash (1.7% each).
- 18 (5.1%) and 6 (1.7%) patients received high-dose corticosteroids for ≥ 14 days and ≥ 30 days consecutively, respectively.

CONCLUSIONS

- In this exploratory analysis, PFS, OS, and ORR efficacy outcomes favored lenvatinib + pembrolizumab versus sunitinib, regardless of presence of adverse prognostic features at baseline—including sarcomatoid histology, bone metastases, liver metastases, and no prior nephrectomy.
- These findings are similar to the efficacy outcomes observed in the intention-to-treat population.[1]
- 14.8% Of patients received high-dose corticosteroids to manage immune-mediated AEs.
- These results support lenvatinib + pembrolizumab combination treatment as a new first-line option for patients with advanced RCC.

Reference

1. Motzer R et al. *N Engl J Med*. 2021;384:1289-1300.

Conflict of Interest

Toni K. Choueiri: Advisory board or speaker: BMS; Pfizer; Lilly; Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA; Exelixis; AstraZeneca; EMD Serono; Calithera; Ipsen; Infinity; Surface Oncology; Peerview; PER; ResearchToPractice; NAMC; ASCO-SITC; Aptitude Health; Advent Health; UAE Society of Oncology; MJH Life Sciences; MDACC; Cancernet; France Foundation; Springer; WebMed; ASiM (CE); Caribou Publishing; Kidney Cancer Association. Other (consultancy; grant review): Analysis Group; ORIEN. Stocks/shares: Pionyr; Tempest (neither publicly traded). Licensing fees/royalties: Up-to-Date online textbook; filed patents related to biomarkers of immune checkpoint blockers, and circulating free methylated DNA. Research grant/funding (to institution): BMS; Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA; Roche; Exelixis; Pfizer; AstraZeneca; EMD-Serono; Takeda; Tracon; Peloton; Lilly; Surface Oncology; Eisai; GSK; ALLIANCE Cooperative Group; Exelixis; and Roche. Nonfinancial interests: Kidney Cancer Research Summit of KidneyCan, and multiple academic and industry entities. Nonfinancial benefits: ASCO; ESMO; Foundation Med; Guardant; Invitae; AACR; various journals (eg, *NEJM*, *Lancet*, *JCO*); and medical communication assistance. Memberships: ASCO, AACR. Other: Dana-Farber Cancer Institute and Harvard Medical School.

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