Poster No. 66

Characterization of Tumor Response With Lenvatinib Plus Pembrolizumab in Patients With Advanced Renal Cell Carcinoma: Final Overall Survival Analysis of the CLEAR Study (4-Year Median Follow Up)

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BACKGROUND

- In the phase 3 CLEAR study of lenvatinib + pembrolizumab or lenvatinib + everolimus versus sunitinib for the treatment of advanced renal cell carcinoma (aRCC), lenvatinib + pembrolizumab showed clinically/statistically significant benefits versus sunitinib in progression-free survival (PFS), overall survival (OS), and objective response rate (ORR); tumors were assessed per independent review using Response Evaluation Criteria In Solid Tumors version 1.1 (RECIST v1.1) (**Figure 1**).[1]
- Based on results from the primary analysis of CLEAR,[1] lenvatinib + pembrolizumab was approved by regulatory agencies for the first-line treatment of adult patients with aRCC.[2,3]

Figure 1. Prior Results of the Primary CLEAR Analysis[1]

Key eligibility criteria
- Advanced clear cell RCC
- Treatment-naïve
- KPS ≥ 70
- Measurable disease
- Adequate organ function

Stratification factors
- Region
- MSKCC risk groups

R 1:1:1

Median follow-up: 26.6 months	Lenvatinib 20 mg oral QD + Pembrolizumab[a] 200 mg IV Q3W (N = 355)	Lenvatinib 18 mg oral QD + Everolimus 5 mg oral QD (N = 357)	Sunitinib 50 mg oral QD 4 weeks on / 2 weeks off (N = 357)
PFS,[b] median (95% CI), months	23.9 (20.8–27.7)	14.7 (11.1–16.7)	9.2 (6.0–11.0)
HR (95% CI) vs SUN	0.39 (0.32–0.49)	0.65 (0.53–0.80)	
P-value	< 0.001	< 0.001	
OS, median (95% CI), months	NR (33.6–NE)	NR (NE–NE)	NR (NE–NE)
HR (95% CI) vs SUN	0.66 (0.49–0.88)	1.15 (0.88–1.50)	
P-value	0.005	0.30	
ORR (95% CI),[b] %	71.0 (66.3–75.7)	53.5 (48.3–58.7)	36.1 (31.2–41.1)
Complete response, %	16.1	9.8	4.2
Time to response, median (range), months	1.94 (1.41, 18.50)	1.91 (1.41, 14.36)	1.94 (1.61, 16.62)

[a]Patients could receive a maximum of 35 pembrolizumab treatments; [b]per independent imaging review by RECIST v1.1.

CI, confidence interval; HR, hazard ratio; IV, intravenous; KPS, Karnofsky performance status; MSKCC, Memorial Sloan Kettering Cancer Center; NE, not estimable; NR, not reached; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; Q3W, once every 3 weeks; QD, once daily; R, randomization; RECIST v1.1, Response Evaluation Criteria In Solid Tumors version 1.1; RCC, renal cell carcinoma.

- At the final prespecified OS analysis, lenvatinib + pembrolizumab continued to demonstrate clinically meaningful and durable benefit versus sunitinib in the first-line treatment of patients with aRCC (data cutoff date: 31 July 2022; median OS follow up: lenvatinib + pembrolizumab, 49.8 months [IQR 41.4, 53.1]; sunitinib, 49.4 months [41.6, 52.8]).[4]
  - Lenvatinib + pembrolizumab showed improved PFS (HR 0.47 [95% CI 0.38–0.57]; nominal *P*-value < 0.0001), OS (HR 0.79 [95% CI 0.63–0.99]; nominal *P*-value = 0.0424), and ORR (relative risk 1.94 [95% CI 1.67–2.26]) versus sunitinib.
  - Median duration of response (DOR) was also increased among patients given lenvatinib + pembrolizumab compared with sunitinib (HR 0.57 [95% CI 0.43–0.76]).
- Here, we characterize patients with an objective response in the lenvatinib + pembrolizumab arm of the CLEAR study at the final analysis, with a median follow-up duration of approximately 4 years.

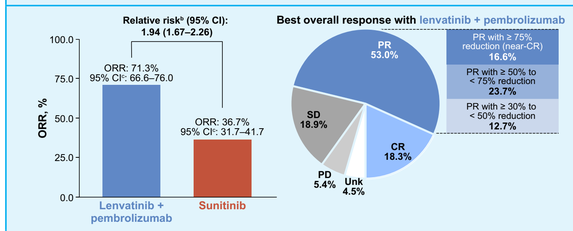
METHODS

- Treatment-naïve patients (n = 1069) who had aRCC with a clear cell component were randomly assigned (1:1:1) to receive either lenvatinib 20 mg orally per day (QD) + pembrolizumab 200 mg IV every 3 weeks, lenvatinib 18 mg + everolimus 5 mg orally QD (not further reported on herein), or sunitinib 50 mg orally QD (4 weeks on/2 weeks off) (**Figure 1**).
- Stratification factors were geographic region and MSKCC prognostic risk group (**Figure 1**).
- IMDC risk groups were not a stratification factor and were derived programmatically.
- Tumor responses were assessed per independent imaging review using RECIST v1.1.
- The analyses presented here use the data cutoff date of the final prespecified OS analysis (31 July 2022), with 23 months of additional follow up from the primary analysis (data cutoff date: 28 August 2020).
- Patients with complete response (CR), partial response (PR)—with maximum tumor shrinkage ≥ 75% from baseline termed "near-CR," or other PR, were characterized by baseline characteristics.
- Median OS and DOR in responders were calculated using the Kaplan-Meier method; 95% CIs were estimated with a generalized Brookmeyer and Crowley method.
- OS rates and 95% CIs were calculated using the Kaplan-Meier product-limit method and Greenwood formula.

RESULTS

- In the final OS analysis dataset, ORR was greater with lenvatinib + pembrolizumab versus sunitinib (relative risk 1.94 [95% CI 1.67-2.26]) (**Figure 2**).

Figure 2. ORR per Independent Review[a]



Percentages may not total 100 due to rounding.

[a]ORR was per RECIST v1.1; [b]relative risk was calculated using the Cochran-Mantel-Haenszel (CMH) method, stratified by IxRS stratification factors; [c]95% CI were constructed using the method of normal approximation.

CI, confidence interval; CR, complete response; IxRS, interactive web-response system; ORR, objective response rate; PD, progressive disease; PR, partial response; SD, stable disease; Unk, unknown.

- Baseline characteristics of patients with tumor responses are shown in **Table 1**.
  - Tumor responses (CR, near-CR, or PR) were observed in patients irrespective of baseline programmed death ligand-1 (PD-L1) status (**Table 1**).

Table 1. Demographics and Baseline Characteristics of Responders in the Lenvatinib + Pembrolizumab Arm, Grouped by Tumor Shrinkage From Baseline

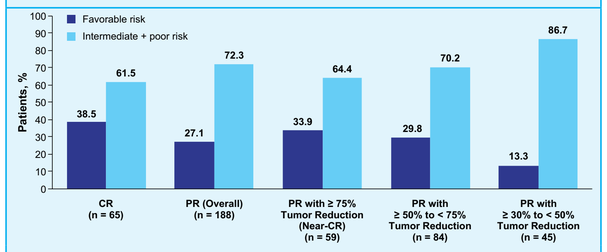
Parameter	CR (n = 65)	PR (Overall) (n = 188)	PR With ≥ 75% Tumor Reduction (Near-CR) (n = 59)	PR With ≥ 50% to < 75% Tumor Reduction (n = 84)	PR With ≥ 30% to < 50% Tumor Reduction (n = 45)
Age (years)					
Median	58.0	64.0	64.0	65.0	61.0
Minimum, maximum	34.0, 78.0	38.0, 84.0	39.0, 77.0	38.0, 84.0	43.0, 78.0
Sex, n (%)					
Men	45 (69.2)	147 (78.2)	51 (86.4)	59 (70.2)	37 (82.2)
Women	20 (30.8)	41 (21.8)	8 (13.6)	25 (29.8)	8 (17.8)
Geographic region,[a] n (%)					
Western Europe + N. America	35 (53.8)	106 (56.4)	33 (55.9)	48 (57.1)	25 (55.6)
Rest of the world	30 (46.2)	82 (43.6)	26 (44.1)	36 (42.9)	20 (44.4)
Baseline KPS score group, n (%)					
100–90	60 (92.3)	154 (81.9)	52 (88.1)	65 (77.4)	37 (82.2)
80–70	5 (7.7)	34 (18.1)	7 (11.9)	19 (22.6)	8 (17.8)
Lesion organ / site locations,[b,c] n (%)					
Lung	44 (67.7)	140 (74.5)	45 (76.3)	58 (69.0)	37 (82.2)
Lymph node	34 (52.3)	76 (40.4)	18 (30.5)	41 (48.8)	17 (37.8)
Bone	4 (6.2)	44 (23.4)	17 (28.8)	14 (16.7)	13 (28.9)
Kidney	4 (6.2)	59 (31.4)	11 (18.6)	25 (29.8)	23 (51.1)
Liver	5 (7.7)	30 (16.0)	10 (16.9)	12 (14.3)	8 (17.8)
Adrenal	8 (12.3)	29 (15.4)	10 (16.9)	11 (13.1)	8 (17.8)
Brain	0	4 (2.1)	1 (1.7)	1 (1.2)	2 (4.4)
Other	9 (13.8)	71 (37.8)	23 (39.0)	35 (41.7)	13 (28.9)
Number of metastatic organs / sites involved,[c,d] patient n (%)					
0	0	5 (2.7)	0 (0.0)	4 (4.8)	1 (2.2)
1	36 (55.4)	50 (26.6)	17 (28.8)	22 (26.2)	11 (24.4)
2	23 (35.4)	75 (39.9)	24 (40.7)	31 (36.9)	20 (44.4)
≥ 3	6 (9.2)	58 (30.9)	18 (30.5)	27 (32.1)	13 (28.9)
MSKCC prognostic group at baseline,[a] n (%)					
Favorable risk	20 (30.8)	48 (25.5)	20 (33.9)	20 (23.8)	8 (17.8)
Intermediate + poor risk	45 (69.2)	140 (74.5)	39 (66.1)	64 (76.2)	37 (82.2)
PD-L1 status,[e] n (%)					
Positive (CPS ≥ 1)	26 (40.0)	53 (28.2)	18 (30.5)	27 (32.1)	8 (17.8)
Negative (CPS < 1)	19 (29.2)	69 (36.7)	18 (30.5)	28 (33.3)	23 (51.1)
Not available	20 (30.8)	66 (35.1)	23 (39.0)	29 (34.5)	14 (31.1)
Prior nephrectomy, n (%)					
Yes	61 (93.8)	133 (70.7)	51 (86.4)	60 (71.4)	22 (48.9)
No	4 (6.2)	55 (29.3)	8 (13.6)	24 (28.6)	23 (51.1)

[a]Per interactive web response system; [b]patients may be represented in > 1 category; [c]derivation based on information obtained from independent imaging review; [d]the kidney is not included in the number of metastatic organs/sites; [e]PD-L1 status was determined using an investigational version of the PD-L1 immunohistochemistry 22C3 pharmDx and a provisional combined positive score which is defined as the number of PD-L1–staining cells (tumor cells, lymphocytes, macrophages) divided by the total number of viable tumor cells, multiplied by 100. The combined positive score cutoff value is 1.

CR, complete response; CPS, combined positive score; KPS, Karnofsky Performance Status; MSKCC, Memorial Sloan Kettering Cancer Center; N. America, North America; PD-L1, programmed death ligand 1; PR, partial response.

- Patients with CR, near-CR, or PR were similarly distributed across IMDC risk groups (**Figure 3**).

Figure 3. Tumor Response by IMDC[a] Risk Group at Baseline in the Lenvatinib + Pembrolizumab Arm



[a]IMDC prognostic group at baseline is based on total risk score from 6 prognostic factors at baseline: KPS, hemoglobin, corrected serum calcium, neutrophils, platelets, and time from first renal cell cancer diagnosis to randomization.

CR, complete response; IMDC, International Metastatic Renal Cell Carcinoma Database Consortium; KPS, Karnofsky Performance Status; PR, partial response.

- In patients who experienced a tumor response (responders), the median DORs (95% CI) were 26.7 months (22.8–34.6) with lenvatinib + pembrolizumab and 14.7 months (9.4–18.2) with sunitinib.
- The median DOR by best overall response in the lenvatinib + pembrolizumab arm is summarized in **Table 2**.

Table 2. Summary of Duration of Response in the Lenvatinib + Pembrolizumab Arm by Depth of Tumor Response per RECIST v1.1

Parameter	CR (n = 65)	PR (Overall) (n = 188)	PR With ≥ 75% Tumor Reduction (Near-CR) (n = 59)	PR With ≥ 50% to < 75% Tumor Reduction (n = 84)	PR With ≥ 30% to < 50% Tumor Reduction (n = 45)
Duration of objective response (months)[a]					
Median (95% CI)	43.7 (39.2–NE)	20.4 (17.0–25.7)	30.5 (22.4–NE)	19.6 (13.0–25.8)	14.7 (8.9–20.2)
Q1 (95% CI)	33.3 (20.3–39.2)	10.1 (9.3–12.0)	14.8 (11.1–23.4)	9.5 (7.4–12.5)	7.4 (3.8–9.4)
Q3 (95% CI)	NE (NE–NE)	40.6 (31.7–NE)	NE (36.4–NE)	35.2 (25.8–45.0)	22.8 (18.6–NE)
Range (minimum, maximum)	(5.5, 55.9+)	(1.6+, 49.7+)	(1.6+, 49.7+)	(2.1+, 46.2+)	(1.8+, 41.2+)
Patients, n (%), with a duration of response of:					
≥ 6 months	64 (98.5)	155 (82.4)	54 (91.5)	70 (83.3)	31 (68.9)
≥ 12 months	60 (92.3)	107 (56.9)	43 (72.9)	48 (57.1)	16 (35.6)
≥ 18 months	55 (84.6)	80 (42.6)	35 (59.3)	32 (38.1)	13 (28.9)

Duration of objective response (months) = (Date of progressive disease / death, or censor date – date of first objective response + 1) × 12/365.25, for patients with an objective response.

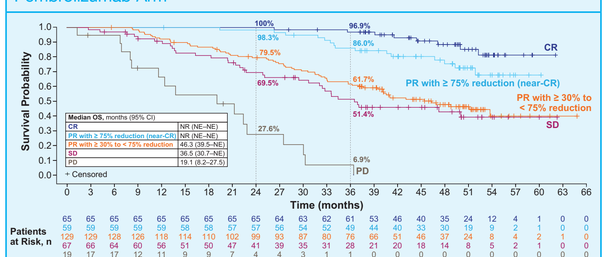
[a]Quartiles are estimated by Kaplan-Meier method and 95% CIs are estimated with a generalized Brookmeyer and Crowley method.

"+" indicates the time is censored.

CI, confidence interval; CR, complete response; NE, not estimable; PR, partial response; Q, quartile; RECIST v1.1., Response Evaluation Criteria In Solid Tumors version 1.1.

- For patients with a CR or near-CR, median OS (95% CI) was not reached (NE–NE); for patients with PR who had a maximum tumor reduction of ≥ 30% to < 75%, median OS (95% CI) was 46.3 months (39.5–NE) (**Figure 4**).

Figure 4. OS for Categories of Responders in the Lenvatinib + Pembrolizumab Arm

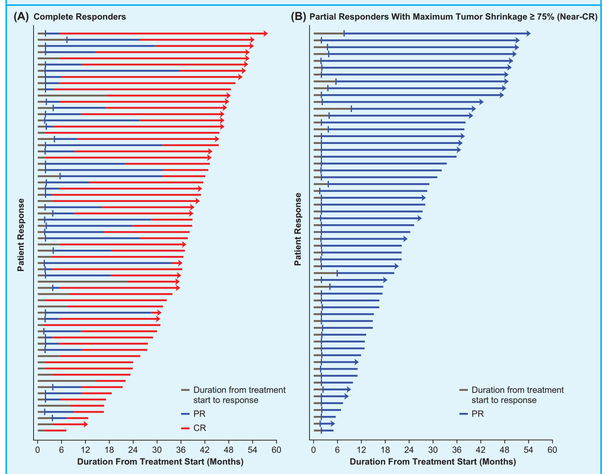


"Near-CR" refers to patients who had a PR with a maximum tumor reduction of ≥ 75%.

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

- Tumor responses to lenvatinib + pembrolizumab treatment were durable, particularly among patients with CR and near-CR (**Figure 5**).

Figure 5. Characterization of Patients With a Confirmed CR (A) or Near-CR (PR With Maximum Tumor Reduction ≥ 75%; B) in the Lenvatinib + Pembrolizumab Arm



Patients were allowed a maximum of 35 cycles of pembrolizumab treatment (approximately 2 years).

Arrow heads at the right end of the lines denote an ongoing response.

CR, complete response; PR, partial response.

- The median time to first dose reduction (months [range]) of lenvatinib for patients with tumor response were: CR (n = 56), 3.12 (0.10, 41.2); PR with ≥ 30% to < 50% tumor reduction (n = 36), 2.12 (0.49, 24.87); PR with ≥ 50% to < 75% tumor reduction (n = 64), 2.22 (0.26, 29.67); PR with ≥ 75% tumor reduction (n = 49), 1.87 (0.26, 26.25).
- Overall median duration of treatment was 36.5 months (range 4.4, 59.1) among patients with a CR. Median duration of treatment was similar in patients with near-CR (26.6 months [range 2.8, 56.7]) and PR (23.8 months [range 2.8, 56.7]).

CONCLUSIONS

- At the final prespecified OS analysis (data cutoff date: 31 July 2022), objective responses were approximately two times as frequent with lenvatinib + pembrolizumab (71.3%) than with sunitinib (36.7%).
- Objective responses (median [range]) were durable across patients with CR (43.7 months [5.5, 55.9+]) or PR (20.4 months [1.6+, 49.7+]), including patients with near-CR (30.5 months [1.6+, 49.7+]).
- Median OS was not reached in patients with either CRs or near-CRs.
- Tumor response was observed regardless of PD-L1 status and MSKCC/IMDC risk group.
- These results corroborate data from the primary analysis,[1] with early, deep, and durable responses in patients with aRCC; and further support the use of lenvatinib + pembrolizumab as a standard-of-care first-line treatment.

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