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SHORT REPORT

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Clinical outcomes by baseline metastases in patients with renal cell carcinoma treated with lenvatinib plus pembrolizumab versus sunitinib: Post hoc analysis of the CLEAR trial

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Abstract

Lenvatinib plus pembrolizumab significantly improved efficacy versus sunitinib in treatment of advanced renal cell carcinoma (aRCC) in the phase 3 CLEAR study. We report results of an exploratory post hoc analysis of tumor response data based on baseline metastatic characteristics of patients who received lenvatinib plus pembrolizumab versus sunitinib, at the final overall survival analysis time point of CLEAR (cutoff: July 31, 2022). Treatment-naïve adults with aRCC were randomized to: lenvatinib (20 mg PO QD in 21-day cycles) plus pembrolizumab ($n = 355$; 200 mg IV Q3W); lenvatinib plus everolimus (not reported here); or sunitinib ($n = 357$; 50 mg PO QD; 4 weeks on/2 weeks off). The most common (lenvatinib plus pembrolizumab; sunitinib, respectively) metastatic site was lung (71.0%; 63.9%), followed by lymph node (45.6%; 43.7%), bone (22.5%; 24.9%), and liver (17.7%; 19.6%). Across treatment arms, ≥65% had two or more metastatic organs/sites involved, >80% of patients had nontarget lesions, and ∼45% had baseline sums of diameters of target lesions ≥60 mm. Lenvatinib plus pembrolizumab demonstrated greater progression-free survival, objective response rate, and duration of response versus sunitinib across evaluable subgroups regardless of site or size of baseline metastasis or number of metastatic sites at baseline. Overall survival generally trended to favor lenvatinib plus pembrolizumab versus sunitinib; and tumor shrinkage was greater across sites (lung, lymph node, liver, and bone) for patients in the lenvatinib-plus-pembrolizumab arm versus the sunitinib arm. These results further support lenvatinib plus pembrolizumab as a standard-of-care in patients with aRCC regardless of site or size of baseline metastasis or the number of metastatic sites.

KEYWORDS
pembrolizumab, lenvatinib, lenvatinib plus pembrolizumab, renal cell carcinoma

What's New?

In the CLEAR trial, lenvatinib plus pembrolizumab showed better efficacy than sunitinib in the treatment of patients with advanced renal cell carcinoma. In this exploratory post hoc subgroup analysis, the authors report a greater progression-free survival, response rate, and response duration for the drug combination than for sunitinib regardless of the patients' baseline metastatic characteristics. The findings support the use of lenvatinib plus pembrolizumab as a standard-of-care in all patients with advanced renal cell carcinoma, regardless of the site or size of baseline metastasis or the number of metastatic sites.

1 | INTRODUCTION

Clinicopathological features observed in patients with advanced renal cell carcinoma (aRCC), including the site of tumor metastasis, number of metastatic sites, and/or tumor size, may affect the prognosis of the disease.[1–4] Per data from an international cohort study of the International Metastatic RCC Database Consortium (IMDC)[1] that included more than 10,000 patients with metastatic RCC, the most common sites of metastasis in patients were lung (70%), lymph nodes (45%), bone (32%), liver (18%), and brain (8%). Overall survival (OS) varied among patients by sites of metastasis, with metastases to endocrine glands associated with improved survival and metastases to liver or brain associated with shorter OS.[1] Furthermore, the involvement of multiple metastatic sites corresponded with shorter OS.[2]

The phase 3, multicenter, open-label, randomized CLEAR trial (Study 307/KEYNOTE-581) compared the efficacy and safety of lenvatinib plus pembrolizumab versus sunitinib as a first-line treatment for patients with aRCC.[5] In the primary analysis of the CLEAR trial (data cutoff: August 28, 2020), with a median survival follow-up of 26.6 months, lenvatinib plus pembrolizumab demonstrated significantly improved progression-free survival (PFS: final analysis; hazard ratio [HR] 0.39 [95% CI 0.32–0.49]; $p < .001$) and OS (interim analysis; HR 0.66 [95% CI 0.49–0.88]; $p = .005$) versus sunitinib.[5] The objective response rate (ORR) also favored lenvatinib plus pembrolizumab

(71.0% [95% CI 66.3–75.7]) versus sunitinib (36.1% [95% CI 31.2–41.1]; relative risk 1.97 [95% CI 1.69–2.29]).[5] Analysis of corresponding data by subgroups of patients at this data cutoff date showed that efficacy outcomes were improved after treatment with lenvatinib plus pembrolizumab versus sunitinib, irrespective of the presence or absence of prognostic indicators of the disease,[1,2,6,7] including baseline lung metastases, baseline bone metastases, baseline liver metastases, prior nephrectomy, or sarcomatoid features.[8]

At the final prespecified OS analysis, with a median survival follow-up of approximately 4 years (data cutoff: July 31, 2022), lenvatinib plus pembrolizumab continued to show clinically meaningful efficacy compared with sunitinib in the first-line treatment of patients with aRCC.[9] In this exploratory post hoc analysis, we examined outcome data based on the baseline characteristics of the site of metastasis, number of metastatic sites, and baseline sums of diameters of target lesions in patients who received lenvatinib plus pembrolizumab versus sunitinib, at the final OS analysis time point of CLEAR with 23 additional months of follow-up from the primary analysis. These analyses could potentially inform the choice of personalized therapy in patients with aRCC.

2 | MATERIALS AND METHODS

2.1 | Patients and study design

Eligibility criteria for the open-label, multicenter, randomized CLEAR trial were published previously.[5] Briefly, treatment-naïve patients with aRCC that had a clear-cell component were eligible if they had at least one measurable lesion per Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1); a Karnofsky performance status score of 70 or higher; and adequate organ function.

Patients were randomly assigned (1:1:1) to receive either lenvatinib 20 mg orally once daily plus pembrolizumab 200 mg intravenously once every 3 weeks, lenvatinib 18 mg plus everolimus 5 mg orally once daily (not reported here), or sunitinib 50 mg orally once daily (4 weeks on/2 weeks off). Randomization was stratified by geographic region (Western Europe and North America or the rest of the world) and by Memorial Sloan Kettering Cancer Center (MSKCC) prognostic risk group (favorable, intermediate, or poor risk).

The primary and key secondary objectives of the trial were met, in which lenvatinib plus pembrolizumab showed statistically significant and/or clinically meaningful improvements in OS, PFS, and ORR (data cutoff date: August 28, 2020).[5] Data presented here correspond to the data cutoff date of the final prespecified OS analysis (July 31, 2022),[9] with 23 months of additional follow-up beyond the primary analysis of CLEAR for a total follow-up time of ~4 years.[5] Our analyses focus on the approved combination of lenvatinib plus pembrolizumab versus sunitinib; given the differences in mechanism of action of lenvatinib plus everolimus, related data are not presented here and may be explored later.

2.1.1 | Statistics

In this exploratory post hoc analysis, baseline characteristics related to lesion organ/site and non-target lesions were derived based on independent imaging review. We examined the endpoints of PFS, tumor response, and duration of response (DOR) by independent imaging review per RECIST v1.1 and OS in patients with the following baseline metastatic characteristics: patients with lung, lymph node, bone, liver, or brain metastases; patients with one metastatic site versus those with two or more metastatic sites; and patients with baseline sums of diameters of target lesions ≥60 mm or <60 mm. The cutoff of 60 mm was chosen because the median sums of diameters of target lesions was 60.06 mm in the lenvatinib-plus-pembrolizumab arm and 57.96 mm in the sunitinib arm.

Median PFS, OS, and DOR were estimated with the Kaplan–Meier product-limit method, and 95% CIs were constructed with a generalized Brookmeyer and Crowley method. HR was based on a Cox proportional hazards model stratified by interactive voice/web response system stratification factors (geographic region and MSKCC prognostic groups), including the treatment group as a factor; the Efron method was used for ties. Odds ratios were calculated using the Cochran–Mantel–Haenszel method, stratified by geographic region and MSKCC prognostic groups.

Waterfall plots with the percentage change in sums of diameters of target lesions at nadir by the site of metastasis are also included. These plots include data from patients with baseline and at least one post-baseline target lesion assessment for the specified site.

3 | RESULTS

3.1 | Patients and baseline characteristics

Baseline characteristics of the 1069 patients randomized across treatment arms in the CLEAR trial have been previously described[5,9] and are summarized in Table S1. Of the randomized patients, 355 were in the lenvatinib-plus-pembrolizumab arm, and 357 were in the sunitinib arm. In both treatment arms, patients were similarly distributed across IMDC favorable (lenvatinib plus pembrolizumab, 31.0%; sunitinib, 34.7%), intermediate (59.2% and 53.8%, respectively), and poor risk subgroups (9.3% and 10.4%, respectively) (Table S1). In the lenvatinib-plus-pembrolizumab arm, 252 (71%) patients had lung metastases, 162 (45.6%) patients had lymph node metastases, 80 (22.5%) patients had bone metastases, and 63 (17.7%) patients had liver metastases. Correspondingly, in the sunitinib arm, 228 (63.9%) patients had lung metastases, 156 (43.7%) had lymph node metastases, 89 (24.9%) patients had bone metastases, and 70 (19.6%) patients had liver metastases. The number of patients with baseline brain metastasis across treatment arms was very low (≤10); thus, corresponding data should be interpreted with caution.

Across treatment arms, approximately one third of patients had one metastatic organ/site involved, whereas ≥65% had two or more metastatic organs/sites involved (Table S1). More than 80% of patients across treatment arms had non-target lesions (Table S1).

Approximately 45% of patients had ≥60 mm baseline sums of target lesions across treatment arms (Table S1).

3.2 | Efficacy

3.2.1 | Progression-free survival

The PFS highly favored lenvatinib plus pembrolizumab versus sunitinib across all subgroups with baseline metastasis in the: lung (median 22.1 vs. 6.0 months; HR 0.41 [95% CI 0.32–0.52]), lymph node (median 22.0 vs. 7.5 months; HR 0.49 [95% CI 0.37–0.66]), bone (median 17.2 vs. 5.6 months; HR 0.50 [95% CI 0.33–0.77]), or liver (median 14.6 vs. 4.2 months; HR 0.48 [95% CI 0.31–0.77]) (Figure 1A). Similar results were seen in patients without baseline metastasis in the: lung (median 29.5 vs. 12.7 months; HR 0.51 [95% CI 0.34–0.75]), lymph node (median 27.6 vs. 10.9 months; HR 0.45 [95% CI 0.34–0.60]), bone (median 27.6 vs. 9.9 months; HR 0.45 [95% CI 0.36–0.57]), or liver (median 27.6 vs. 10.9 months; HR 0.46 [95% CI 0.36–0.57]) (Figure 1A). In patients with brain metastases, the CIs for HR were wide (0.32, 95% CI 0.07–1.59), likely due to the small number of patients. Among patients without brain metastases, PFS highly favored the combination versus sunitinib (median 24.0 vs. 9.2 months; HR 0.47 [95% CI 0.38–0.57]) (Figure 1A).

PFS also favored lenvatinib plus pembrolizumab versus sunitinib in patients with one (median 32.2 vs. 13.8 months; HR 0.60 [95% CI 0.41–0.87]) or two or more (median 20.8 vs. 5.6 months; HR 0.40 [95% CI 0.31–0.50]) metastatic organ(s)/site(s) involvement and in patients with baseline sums of diameters of target lesions ≥60 mm (median 22.1 vs. 5.7 months; HR 0.39 [95% CI 0.29–0.53]) or <60 mm (median 25.3 vs. 11.1 months; HR 0.53 [95% CI 0.40–0.71]) (Figure 1A).

3.2.2 | Overall survival

The OS trended to favor lenvatinib plus pembrolizumab versus sunitinib in the following subgroups of patients with baseline metastasis in the: lung (median 51.8 vs. 44.4 months; HR 0.75 [95% CI 0.57–0.97]), lymph node (median 49.3 vs. 38.9 months; HR 0.78 [95% CI 0.56–1.07]), or bone (median 36.9 vs. 31.5 months; HR 0.67 [95% CI 0.44–1.02]) (Figure 1B). In patients with liver metastasis, the HR for comparison had wide CIs (HR 0.95 [95% CI 0.60–1.51]), so these data should be interpreted with caution (Figure 1B).

The OS trended to favor lenvatinib plus pembrolizumab versus sunitinib in the following subgroups without baseline metastasis in the: lung (median not estimable vs. 59.9 months; HR 0.85 [95% CI 0.55–1.31]), lymph node (median not estimable vs. 59.9 months; HR 0.77 [95% CI 0.55–1.06]), bone (median not estimable vs. 58.8 months; HR 0.85 [95% CI 0.65–1.11]), or liver (median not estimable vs. 58.8 months; HR 0.76 [95% CI 0.58–0.98]) (Figure 1B). Very few patients had baseline brain metastases; this was reflected by the relatively wide CI for HR (0.29, 95% CI 0.05–1.56). Among patients without brain metastases, the OS trended to favor the combination versus sunitinib (HR 0.81 [95% CI 0.65–1.02]) (Figure 1B).

OS trended to favor lenvatinib plus pembrolizumab versus sunitinib in patients with two or more metastatic organs/sites (median 49.3 vs. 38.3 months; HR 0.74 [95% CI 0.57–0.96]) and in patients with baseline sums of diameters of target lesions ≥60 mm (median 43.0 vs. 38.4 months; HR 0.84 [95% CI 0.62–1.14]) or <60 mm (median not estimable vs. 59.9 months; HR 0.75 [95% CI 0.53–1.08]) (Figure 1B). In patients with one metastatic organ/site involvement, the HR was 1.00 (95% CI 0.63–1.60), but the number of death events were <40 in each arm (Figure 1B), which was also reflected by the relatively wide CI.

3.2.3 | Objective response rate and duration of response

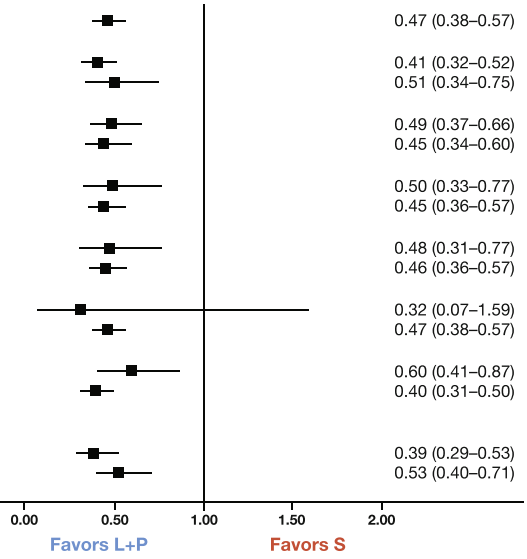
ORR highly favored lenvatinib plus pembrolizumab versus sunitinib across all subgroups with baseline metastasis in the: lung (73.0% vs. 35.1%; odds ratio 5.19 [95% CI 3.48–7.72]), lymph node (67.9% vs. 37.2%; odds ratio 3.66 [95% CI 2.28–5.88]), bone (60.0% vs. 27.0%; odds ratio 4.09 [95% CI 2.11–7.94]), or liver (55.6% vs. 25.7%; odds ratio 3.51 [95% CI 1.68–7.30]) (Figure 2). Among the few patients with brain metastases, ORR favored the combination versus sunitinib (66.7% vs. 30.0%; odds ratio 3.00 [95% CI 0.43–20.72]). Additionally, ORR highly favored lenvatinib plus pembrolizumab versus sunitinib across all subgroups without baseline metastasis in the: lung (67.0% vs. 39.8%; odds ratio 3.02 [95% CI 1.75–5.20]), lymph node (74.1% vs. 36.5%; odds ratio 4.83 [95% CI 3.14–7.43]), bone (74.5% vs. 40.1%; odds ratio 4.30 [95% CI 2.97–6.20]), liver (74.7% vs. 39.5%; odds ratio 4.53 [95% CI 3.17–6.47]), or brain (71.3% vs. 37.0%; odds ratio 4.29 [95% CI 3.11–5.92]) (Figure 2).

ORR also highly favored lenvatinib plus pembrolizumab versus sunitinib in patients with one (72.3% vs. 46.5%; odds ratio 2.98 [95% CI 1.71–5.21]) or two or more (70.1% vs. 31.8%; odds ratio 5.06 [95% CI 3.40–7.53]) metastatic organ(s)/site(s) involvement, and in patients with baseline sums of diameters of target lesions ≥60 mm (72.2% vs. 23.0%; odds ratio 10.50 [95% CI 6.08–18.13]) or <60 mm (77.5% vs. 53.1%; odds ratio 3.14 [95% CI 1.94–5.07]) (Figure 2).

Additionally, the DOR favored lenvatinib plus pembrolizumab versus sunitinib across all subgroups with baseline metastasis in the: lung (median 25.8 vs. 11.1 months), lymph node (median 25.9 vs. 9.5 months), bone (median 22.0 vs. 16.6 months), or liver (median 20.1 vs. 9.2 months) (Figure 2). Correspondingly, the DOR favored lenvatinib plus pembrolizumab versus sunitinib across all subgroups without baseline metastasis in the: lung (median 39.2 vs. 19.0 months), lymph node (median 27.9 vs. 15.8 months), bone (median 30.5 vs. 13.1 months), liver (median 27.9 vs. 14.8 months), or brain (median 27.1 vs. 14.7 months) (Figure 2). DOR also favored lenvatinib plus pembrolizumab versus sunitinib in patients with one (median 39.2 vs. 29.5 months) or two or more (median 23.4 vs. 9.5 months) metastatic organ(s)/site(s) involvement and patients

(A)

	Events[a]/Patients		Median PFS, mos		HR (95% CI)[b]
	L+P	S	L+P	S	
Overall	207/355	214/357	23.9	9.2	0.47 (0.38–0.57)
Baseline Lung Metastasis					
Yes	155/252	147/228	22.1	6.0	0.41 (0.32–0.52)
No	52/103	67/128	29.5	12.7	0.51 (0.34–0.75)
Baseline Lymph Node Metastasis					
Yes	106/162	99/156	22.0	7.5	0.49 (0.37–0.66)
No	101/193	115/200	27.6	10.9	0.45 (0.34–0.60)
Baseline Bone Metastasis					
Yes	48/80	49/89	17.2	5.6	0.50 (0.33–0.77)
No	159/275	165/267	27.6	9.9	0.45 (0.36–0.57)
Baseline Liver Metastasis					
Yes	42/63	46/70	14.6	4.2	0.48 (0.31–0.77)
No	165/292	168/286	27.6	10.9	0.46 (0.36–0.57)
Baseline Brain Metastasis[c]					
Yes	4/6	8/10	9.2	6.0	0.32 (0.07–1.59)
No	203/349	206/346	24.0	9.2	0.47 (0.38–0.57)
No. of Metastatic Organs/Sites Involved					
1	61/119	56/114	32.2	13.8	0.60 (0.41–0.87)
≥ 2	145/231	155/236	20.8	5.6	0.40 (0.31–0.50)
Baseline Sums of Diameters of Target Lesions					
≥ 60 mm	97/162	97/161	22.1	5.7	0.39 (0.29–0.53)
< 60 mm	94/160	107/175	25.3	11.1	0.53 (0.40–0.71)



(B)

	Events[a]/Patients		Median OS, mos		HR (95% CI)[b]
	L+P	S	L+P	S	
Overall	149/355	159/357	53.7	54.3	0.79 (0.63–0.99)
Baseline Lung Metastasis					
Yes	114/252	109/228	51.8	44.4	0.75 (0.57–0.97)
No	35/103	50/128	NE	59.9	0.85 (0.55–1.31)
Baseline Lymph Node Metastasis					
Yes	80/162	78/156	49.3	38.9	0.78 (0.56–1.07)
No	69/193	81/200	NE	59.9	0.77 (0.55–1.06)
Baseline Bone Metastasis					
Yes	41/80	53/89	36.9	31.5	0.67 (0.44–1.02)
No	108/275	106/267	NE	58.8	0.85 (0.65–1.11)
Baseline Liver Metastasis					
Yes	37/63	41/70	32.9	36.6	0.95 (0.60–1.51)
No	112/292	118/286	NE	58.8	0.76 (0.58–0.98)
Baseline Brain Metastasis[c]					
Yes	3/6	7/10	NE	14.2	0.29 (0.05–1.56)
No	146/349	152/346	53.7	54.8	0.81 (0.65–1.02)
No. of Metastatic Organs/Sites Involved					
1	37/119	35/114	NE	59.9	1.00 (0.63–1.60)
≥ 2	111/231	122/236	49.3	38.3	0.74 (0.57–0.96)
Baseline Sums of Diameters of Target Lesions					
≥ 60 mm	84/162	83/161	43.0	38.4	0.84 (0.62–1.14)
< 60 mm	56/160	67/175	NE	59.9	0.75 (0.53–1.08)

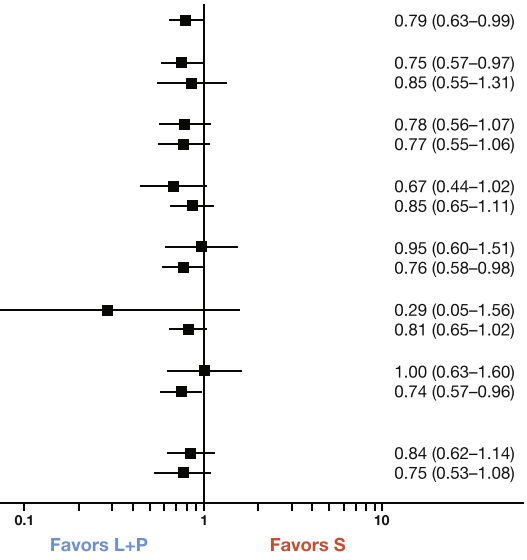


FIGURE 1 Progression-free survival by independent imaging review per RECIST v1.1 (A), and overall survival (B) in subgroups of the lenvatinib plus pembrolizumab versus sunitinib arms. Data for all subgroups in (A) were derived based on information obtained from the independent imaging review. Median PFS and OS were estimated with Kaplan–Meier method, and 95% CI was constructed with a generalized Brookmeyer and Crowley method. Stratification factors were geographic region (Region 1: Western Europe and North America, Region 2: Rest of the world) and MSKCC prognostic groups (favorable, intermediate, and poor risk) in the interactive voice/web response system. If a stratification factor was within its own subgroup, this factor was excluded from stratified analysis. [a]Patients who died or had progressive disease (for PFS); patients who died (for OS); [b]Hazard ratio was based on a Cox proportional hazards model including treatment group as a factor; Efron method was used for ties. Stratification factors were geographic region (Region 1: Western Europe and North America, Region 2: Rest of the world) and MSKCC prognostic groups (favorable, intermediate, and poor risk) in the interactive voice/web response system; [c]The number of patients with baseline brain metastasis was very low. The data should be interpreted cautiously, considering this. CI, confidence interval; DOR, duration of response; HR, hazard ratio; L + P, lenvatinib plus pembrolizumab; MSKCC, Memorial Sloan Kettering Cancer Center; NE, not estimable; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version v1.1; S, sunitinib.

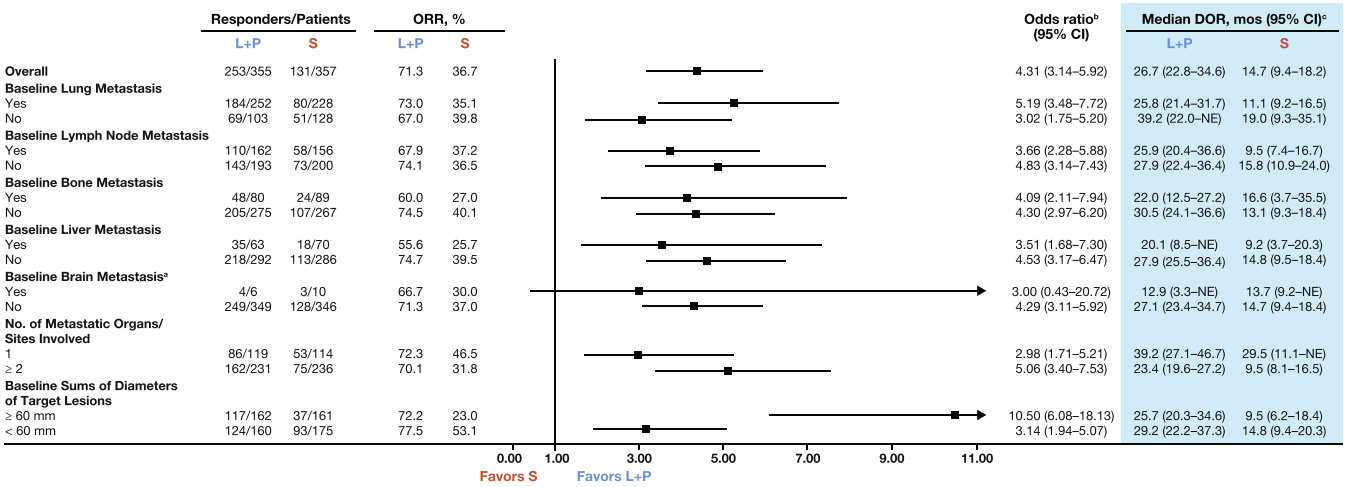


FIGURE 2 Tumor response and duration of response by independent imaging review per RECIST v1.1 in subgroups of the lenvatinib plus pembrolizumab versus sunitinib arms. [a]The number of patients with baseline brain metastasis was very low. The data should be interpreted cautiously, considering this; [b]Odds ratios were calculated using the Cochran–Mantel–Haenszel method, stratified by interactive voice/web response system stratification factors; [c]Median DOR is for all responders. Medians were estimated with Kaplan–Meier product-limit method and 95% CIs were constructed with a generalized Brookmeyer and Crowley method. Derivation of data was based on information obtained from the independent imaging review. Stratification factors were geographic region (Region 1: Western Europe and North America, Region 2: Rest of the world) and MSKCC prognostic groups (favorable, intermediate, and poor risk) in the interactive voice/web response system. If a stratification factor was within its own subgroup, this factor was excluded from stratified analysis. Arrows indicate 95% CI values that fall outside the scale of the graph. CI, confidence interval; DOR, duration of response; L + P, lenvatinib plus pembrolizumab; MSKCC, Memorial Sloan Kettering Cancer Center; NE, not estimable; ORR, objective response rate; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version v1.1; S, sunitinib.

with baseline sums of diameters of target lesions ≥60 mm (median 25.7 vs. 9.5 months) or <60 mm (median 29.2 vs. 14.8 months) (Figure 2). In the small subgroup of patients with brain metastases, median DOR was similar with lenvatinib plus pembrolizumab (12.9 months) and sunitinib (13.7 months).

3.2.4 | Change in sums of diameters of target lesions

Greater depth and breadth of tumor shrinkage at nadir was observed in target lesions in specific organ sites (lung, lymph node, liver, and bone) for patients in the lenvatinib-plus-pembrolizumab arm versus the sunitinib arm (Figure 3). No patients had target lesions in the brain. Patients only had non-target lesions in the brain.

4 | DISCUSSION

Patterns of sites of metastatic involvement in aRCC may reflect differences in the underlying disease biology and may affect clinical outcomes,[1] with metastases to organs like liver, bone, and/or brain typically associated with poor outcomes.[10–12] In this exploratory post hoc subgroup analysis of the CLEAR trial with extended follow-up of 23 additional months from the primary analysis, OS trended to favor lenvatinib plus pembrolizumab across most subgroups; lenvatinib plus pembrolizumab also demonstrated greater PFS, ORR, and DOR versus sunitinib across evaluable subgroups regardless of site of metastasis (lung, lymph nodes, bones, or liver). These benefits in PFS and tumor response with the combination treatment were also observed regardless of the number of metastatic sites (one or two or more) and baseline sums of diameters of target lesions (≥60 mm or <60 mm). Subgroup analyses were stratified by region and MSKCC prognostic risk groups, consistent with the primary analyses. Results from these subgroups are consistent with outcomes observed in the intent-to-treat population at this extended data cutoff date with a median survival follow-up of ~4 years[9] and further confirm and supplement the results from the previous exploratory analysis of CLEAR conducted at an earlier data cutoff date.[8]

Although cross-trial comparisons should be made carefully considering differences in inclusion/exclusion criteria, study design, and methods, subgroup data analysis results from studies in aRCC that used sunitinib as a comparator are briefly summarized for context. In CheckMate-214 (median follow-up time of 25.2 months), subgroup OS analysis results favored nivolumab plus ipilimumab over sunitinib across most subgroups, including in patients who did not have bone metastases, in patients irrespective of liver metastases, and in patients with lung metastases.[13] At the extended follow-up (median 32.9 months) of CheckMate-9ER, nivolumab plus cabozantinib showed superior efficacy over sunitinib across subgroups of patients with baseline liver metastasis, with bone metastasis, or with lung metastasis.[14] In a subgroup analysis of the JAVELIN Renal 101 study that showed improved PFS with avelumab plus axitinib versus sunitinib in the overall population, the observed PFS among patients with baseline brain metastasis ($n = 23$ in each arm) was similar between the two treatment arms, with the HR and median PFS numerically favoring the avelumab

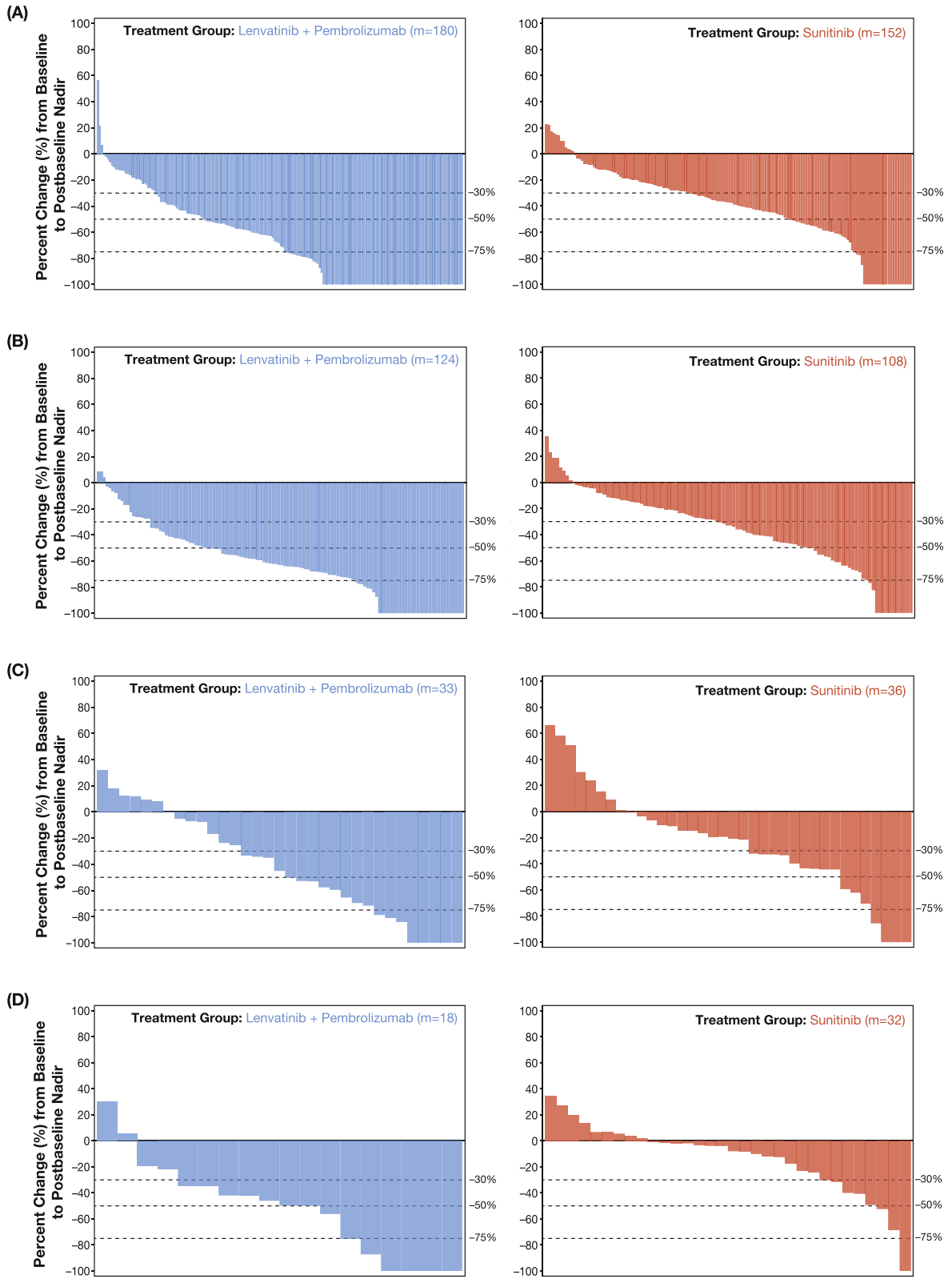


FIGURE 3 Percentage change in the sum of diameters of target lesions in the lung (A), lymph nodes (B), liver (C), and bone (D) from baseline to postbaseline nadir. These figures include patients (m) with baseline and at least 1 postbaseline target lesion assessment in the respective organ per independent imaging review.

arm.[15] Also, in the phase 3 KEYNOTE-426 trial, PFS and OS results for subgroups of patients with one or two or more metastatic organs favored pembrolizumab plus axitinib versus sunitinib.[16] These results emphasize the benefit of immunotherapy-based combination treatments versus sunitinib in particular prognostic groups. This is in line with observations from our analyses where results of OS, PFS, ORR,

and DOR generally favored lenvatinib plus pembrolizumab versus sunitinib across most subgroups of interest. These results emphasize the benefit of combination therapies in treatment of patients with aRCC, compared to previous standard-of-care treatments (i.e., sunitinib).

Limitations of presented data include the exploratory nature of our analyses with a lack of statistical power relating to comparisons in individual subgroups and a low number of patients with brain metastases, subgroup data for which should be interpreted with caution. Despite these limitations, the results from these subgroup analyses can provide valuable aid in the selection of personalized treatment strategies for patients and support the use of lenvatinib plus pembrolizumab as a standard-of-care treatment across patients with aRCC, regardless of site or size of baseline metastasis or the number of metastatic sites.

In conclusion, lenvatinib plus pembrolizumab showed clinically relevant efficacy in subgroups of interest, including in subgroups based on the site of metastasis, number of metastatic sites, and metastatic tumor size at baseline. Tumor responses favored lenvatinib plus pembrolizumab versus sunitinib in all subgroups of interest. The median DOR was generally longer with lenvatinib plus pembrolizumab versus sunitinib across subgroups of interest. Greater depth and breadth of tumor shrinkage was observed across organ sites (lung, lymph node, liver, and bone) for patients in the lenvatinib-plus-pembrolizumab arm versus the sunitinib arm.

Results of this post hoc analysis further support the early, deep, and durable tumor response benefit with lenvatinib plus pembrolizumab versus sunitinib observed in the CLEAR trial[5,9,17] and support the use of lenvatinib plus pembrolizumab as a standard-of-care in all patients with aRCC regardless of site or size of baseline metastasis or the number of metastatic sites.

AUTHOR CONTRIBUTIONS

Viktor Grünwald: Conceptualization; investigation; writing – original draft; writing – review and editing. **Rana R. McKay:** Investigation; writing – original draft; writing – review and editing. **Tomas Buchler:** Investigation; writing – original draft; writing – review and editing. **Masatoshi Eto:** Investigation; writing – original draft; writing – review and editing. **Se Hoon Park:** Investigation; writing – original draft; writing – review and editing. **Toshio Takagi:** Investigation; writing – original draft; writing – review and editing. **Sylvie Zanetta:** Investigation; writing – original draft; writing – review and editing. **Daniel Keizman:** Investigation; writing – original draft; writing – review and editing. **Cristina Suárez:** Investigation; writing – original draft; writing – review and editing. **Sylvie Négrier:** Investigation; writing – original draft; writing – review and editing. **Jae Lyun Lee:** Investigation; writing – original draft; writing – review and editing. **Daniele Santini:** Investigation; writing – original draft; writing – review and editing. **Jens Bedke:** Investigation; writing – original draft; writing – review and editing. **Michael Staehler:** Investigation; writing – original draft; writing – review and editing. **Christian Kollmannsberger:** Investigation; writing – original draft; writing – review and editing. **Toni K. Choueiri:** Investigation; writing – original draft; writing – review and editing. **Robert J. Motzer:** Investigation; writing – original draft; writing – review and editing. **Joseph E. Burgents:** Writing – original draft; writing – review and editing. **Ran Xie:** Conceptualization; formal analysis; writing – original draft; writing – review and editing. **Chinyere E. Okpara:** Conceptualization; writing – original draft; writing – review and editing. **Thomas Powles:** Investigation; writing – original draft; writing – review and editing.

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DATA AVAILABILITY STATEMENT

To access the datasets, contact Eisai Inc. Further information, models, and the code that support the findings of this study are available from the corresponding author upon reasonable request.

ETHICS STATEMENT

The CLEAR trial was conducted in accordance with the International Council for Harmonisation Good Clinical Practice Guidelines and the principles of the 2013 Declaration of Helsinki. The protocol and related documents were approved by Institutional Review Boards or independent ethics committees. All patients provided written informed consent. Efficacy and safety data were monitored by an independent data and safety monitoring committee. ClinicalTrials.gov registration ID: NCT02811861.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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