Lenvatinib Plus Pembrolizumab Versus Sunitinib in First-Line Treatment of Advanced Renal Cell Carcinoma: Final Prespecified Overall Survival Analysis of CLEAR, a Phase III Study

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ABSTRACT

Clinical trials frequently include multiple end points that mature at different times. The initial report, typically based on the primary end point, may be published when key planned co-primary or secondary analyses are not yet available. Clinical trial updates provide an opportunity to disseminate additional results from studies, published in JCO or elsewhere, for which the primary end point has already been reported.

We present the final prespecified overall survival (OS) analysis of the open-label, phase III CLEAR study in treatment-naïve patients with advanced renal cell carcinoma (aRCC). With an additional follow-up of 23 months from the primary analysis, we report results from the lenvatinib plus pembrolizumab versus sunitinib comparison of CLEAR. Treatment-naïve patients with aRCC were randomly assigned to receive lenvatinib (20 mg orally once daily in 21-day cycles) plus pembrolizumab (200 mg intravenously once every 3 weeks) or sunitinib (50 mg orally once daily [4 weeks on/2 weeks off]). At this data cutoff date (July 31, 2022), the OS hazard ratio (HR) was 0.79 (95% CI, 0.63 to 0.99). The median OS (95% CI) was 53.7 months (95% CI, 48.7 to not estimable [NE]) with lenvatinib plus pembrolizumab versus 54.3 months (95% CI, 40.9 to NE) with sunitinib; 36-month OS rates (95% CI) were 66.4% (95% CI, 61.1 to 71.2) and 60.2% (95% CI, 54.6 to 65.2), respectively. The median progression-free survival (95% CI) was 23.9 months (95% CI, 20.8 to 27.7) with lenvatinib plus pembrolizumab and 9.2 months (95% CI, 6.0 to 11.0) with sunitinib (HR, 0.47 [95% CI, 0.38 to 0.57]). Objective response rate also favored the combination over sunitinib (71.3% *v* 36.7%; relative risk 1.94 [95% CI, 1.67 to 2.26]). Treatment-emergent adverse events occurred in >90% of patients who received either treatment. In conclusion, lenvatinib plus pembrolizumab achieved consistent, durable benefit with a manageable safety profile in treatment-naïve patients with aRCC.

ACCOMPANYING CONTENT

Appendix
Data Supplement
Protocol

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INTRODUCTION

At the primary analysis point of the phase III open-label, CLEAR study (Study 307/KEYNOTE-581), with a median survival follow-up of 26.6 months, lenvatinib plus pembrolizumab showed superior efficacy versus sunitinib in the first-line treatment of patients with advanced renal cell carcinoma (aRCC).[1] Lenvatinib plus pembrolizumab showed significant improvements versus sunitinib in progression-free survival (PFS: final analysis; hazard ratio [HR], 0.39 [95% CI, 0.32 to 0.49]; $P < .001$) and overall survival (OS: interim analysis; HR, 0.66 [95% CI, 0.49 to 0.88]; $P = .005$). The objective response rate (ORR) was also improved with the combination versus sunitinib (relative risk, 1.97 [95% CI, 1.69 to 2.29]), and the safety profile was consistent with the known safety profiles of each monotherapy.[1-3] An update with an additional follow-up of 7 months supported these efficacy results.[4]

Here, we present the results of the final prespecified OS analysis (median survival follow-up, about 4 years) for the lenvatinib plus pembrolizumab versus sunitinib comparison

from CLEAR, along with updated PFS, PFS on the next line of therapy (PFS2), ORR, exposure, and safety results.

METHODS

The CLEAR study design was described previously[1] (Data Supplement, online only). The protocol and related documents were approved by institutional review boards or independent ethics committees. All patients provided written informed consent.

This final prespecified OS analysis (data cutoff: July 31, 2022), with an additional follow-up of 23 months beyond the primary analysis (data cutoff: August 28, 2020), was triggered by approximately 304 OS events in the two groups. Analyses presented are descriptive and noninferential; *P* values are nominal. HR and two-sided 95% CI were estimated using a stratified Cox proportional hazards model with Efron's method for ties, stratified by region and Memorial Sloan Kettering Cancer Center (MSKCC) prognostic groups. Median OS and OS rate with two-sided 95% CIs were calculated using Kaplan-Meier product-limit estimates. A post hoc two-stage estimation method, adjusting for the impact of subsequent anticancer medications on OS, was applied separately (Data Supplement).

Updated PFS, ORR, and duration of response (DOR) were determined by independent imaging review (IIR), and PFS2 by investigator review, both per RECIST version 1.1 (RECIST v1.1). Methodologies used in all prespecified analyses here were identical to those used in the primary analysis.[1] Efficacy was assessed in all randomly assigned patients regardless of the treatment received; safety was assessed in all patients who received at least one dose of study drug.

RESULTS

Disposition and Baseline Characteristics

At this data cutoff date (July 31, 2022), 58 (16.3%) patients in the lenvatinib plus pembrolizumab group and 24 (6.7%) patients in the sunitinib group remained on study treatment (Data Supplement, Fig S1). Most patients in this study belonged to the intermediate (MSKCC/International Metastatic Renal Cell Carcinoma Database Consortium [IMDC]) risk groups (Table 1). In the lenvatinib plus pembrolizumab group, approximately 34% of patients completed the full 35 cycles of pembrolizumab treatment and continued lenvatinib monotherapy.

OS

At the median OS follow-up time (IQR) of 49.8 months (IQR, 41.4-53.1) in the lenvatinib plus pembrolizumab group and 49.4 months (IQR, 41.6-52.8) in the sunitinib group, 308 OS events had occurred (lenvatinib plus pembrolizumab, 149; sunitinib, 159). With an HR of 0.79 (95% CI, 0.63 to 0.99; nominal *P* value = .0424), the median OS (95% CI) was 53.7 months (95% CI, 48.7 to not estimable [NE]) in the lenvatinib plus pembrolizumab group versus 54.3 months (95% CI, 40.9 to NE) in the sunitinib group (Fig 1A); OS rates at 36 months (95% CI) were 66.4% (95% CI, 61.1 to 71.2) and 60.2% (95% CI, 54.6 to 65.2), respectively. In patients who completed 35 cycles of pembrolizumab and continued lenvatinib monotherapy, the OS rate at 36 months was 94.2% (95% CI, 88.2 to 97.2; Data Supplement, Fig S2).

Fewer patients in the lenvatinib plus pembrolizumab group (51.0%) received subsequent anticancer medications compared with those in the sunitinib group (68.9%); the proportion of patients who received PD-1/PD-L1 inhibitors as subsequent therapy in the lenvatinib plus pembrolizumab group was more than three times lower than that in the sunitinib group (15.8% *v* 54.6%, respectively; Data Supplement, Table S1). A two-stage estimation was used to assess the impact of subsequent anticancer therapies, which are known confounders of OS estimates[5] (Data Supplement). The adjusted OS HR for lenvatinib plus pembrolizumab versus sunitinib was 0.55 (95% CI, 0.44 to 0.69; Data Supplement, Fig S3A).

Lenvatinib plus pembrolizumab improved OS compared with sunitinib in both the intermediate- plus poor-risk IMDC (HR, 0.74 [95% CI, 0.57 to 0.96]; Fig 2A) and MSKCC (HR, 0.77 [95% CI, 0.60 to 0.99]) subgroups. OS was similar in the favorable-risk group; however, there were a low number of events in this subgroup and these analyses were not powered to detect such differences (Fig 2A; Data Supplement, Figs S4A and S5).

PFS

PFS events occurred in 207 patients in the lenvatinib plus pembrolizumab group and 214 patients in the sunitinib group. The median follow-up time (IQR) for PFS was 39.2 months (IQR, 22.1-48.5) with lenvatinib plus pembrolizumab and 20.6 months (IQR, 5.5-41.2) with sunitinib. The median PFS (95% CI) was 23.9 months (95% CI, 20.8 to 27.7) with lenvatinib plus pembrolizumab and 9.2 months (95% CI, 6.0 to 11.0) with sunitinib (HR, 0.47 [95% CI, 0.38 to 0.57]; nominal *P* value < .0001; Fig 1B). PFS favored lenvatinib plus pembrolizumab over sunitinib across all IMDC and MSKCC risk subgroups (Fig 2B; Data Supplement, Figs S4B and S6).

The median PFS2 (95% CI) was 43.3 months (95% CI, 37.2 to 50.4) with lenvatinib plus pembrolizumab and 25.9 months (95% CI, 21.3 to 32.0) with sunitinib (HR, 0.63 [95% CI, 0.51 to 0.77]; Data Supplement, Fig S3B).

ORR

The ORR (95% CI) was 71.3% (95% CI, 66.6 to 76.0) with lenvatinib plus pembrolizumab and 36.7% (95% CI, 31.7 to 41.7) with sunitinib (relative risk, 1.94 [95% CI, 1.67 to 2.26];

TABLE 1. Summary of Baseline Characteristics of Patients in the CLEAR Study and Updated ORR by IIR per RECIST v1.1

Parameter[a]	Lenvatinib + Pembrolizumab (n = 355)	Sunitinib (n = 357)
Age, years, median (range)	64 (34-88)	61 (29-82)
Geographic region, No. (%)		
Western Europe or North America	198 (55.8)	199 (55.7)
Rest of the world	157 (44.2)	158 (44.3)
MSKCC prognostic risk group,[b] No. (%)		
Favorable	96 (27.0)	97 (27.2)
Intermediate	227 (63.9)	228 (63.9)
Poor	32 (9.0)	32 (9.0)
IMDC risk group,[c] No. (%)		
Favorable	110 (31.0)	124 (34.7)
Intermediate	210 (59.2)	192 (53.8)
Poor	33 (9.3)	37 (10.4)
Sarcomatoid features, No. (%)	28 (7.9)	21 (5.9)
PD-L1 expression,[d] No. (%)		
≥1	107 (30.1)	119 (33.3)
<1	112 (31.5)	103 (28.9)
Not available	136 (38.3)	135 (37.8)
Previous nephrectomy, No. (%)	262 (73.8)	275 (77.0)
Updated efficacy analysis		
Best overall response, No. (%)		
CR	65 (18.3)	17 (4.8)
Near CR[e]	59 (16.6)	25 (7.0)
PR	188 (53.0)	114 (31.9)
Stable disease	67 (18.9)	134 (37.5)
Progressive disease	19 (5.4)	50 (14.0)
Unknown/not evaluable	16 (4.5)	42 (11.8)
ORR (CR + PR), No. (%)	253 (71.3)	131 (36.7)
95% CI[f]	66.6 to 76.0	31.7 to 41.7
Difference, % (95% CI)[f]	34.6 (27.7 to 41.4)	
OR (95% CI)[g]	4.31 (3.14 to 5.92)	
Relative risk (95% CI)[g]	1.94 (1.67 to 2.26)	
Nominal *P* value	<.0001	
Time to first objective response (months)		
Patients with objective response, No.	253	131
Mean (standard deviation)	3.38 (2.897)	3.71 (3.963)
Median	1.94	1.97
Q1, Q3	1.87, 3.75	1.87, 3.75
Minimum, maximum	1.41, 22.60	1.61, 34.96

Abbreviations: CR, complete response; DOR, duration of response; HR, hazard ratio; IHC, immunohistochemistry; IMDC, International Metastatic Renal Cell Carcinoma Database Consortium; IxRS, interactive voice/web response system; MSKCC, Memorial Sloan Kettering Cancer Center; NE, not estimable; NR, not reached; OR, odds ratio; ORR, objective response rate; OS, overall survival; PFS; progression-free survival; PR, partial response.

[a]Percentages may not total 100 because of rounding. One patient in the lenvatinib plus pembrolizumab group had carcinoma without a clear-cell component. Patients randomly assigned to receive lenvatinib plus pembrolizumab received lenvatinib at a starting dose of 20 mg orally once daily in 21-day cycles plus pembrolizumab at a dose of 200 mg intravenously once every 3 weeks (on day 1 of each 21-day cycle). Patients randomly assigned to receive sunitinib received a starting dose of 50 mg orally once every day (4 weeks on/2 weeks off).

[b]An MSKCC score of 0 indicates favorable risk, a score of 1 or 2 intermediate risk, and a score of 3 or higher poor risk.

[c]An IMDC score of 0 indicates favorable risk, a score of 1 or 2 intermediate risk, and a score of 3 to 6 poor risk.

[d]PD-L1 expression was assessed using the PD-L1 IHC 22C3 pharmDx assay (Agilent Technologies, Santa Clara, CA) and reported as the combined positive score, defined as the number of PD-L1–staining cells (tumor cells, lymphocytes, and macrophages) divided by the total number of viable tumor cells, then multiplied by 100.

[e]Partial response with a ≥75% change from baseline in sum of target lesion diameters.

[f]95% CI is constructed using the method of normal approximation.

[g]OR and relative risk are calculated using the Cochran-Mantel-Haenszel method, stratified by IxRS stratification factors.

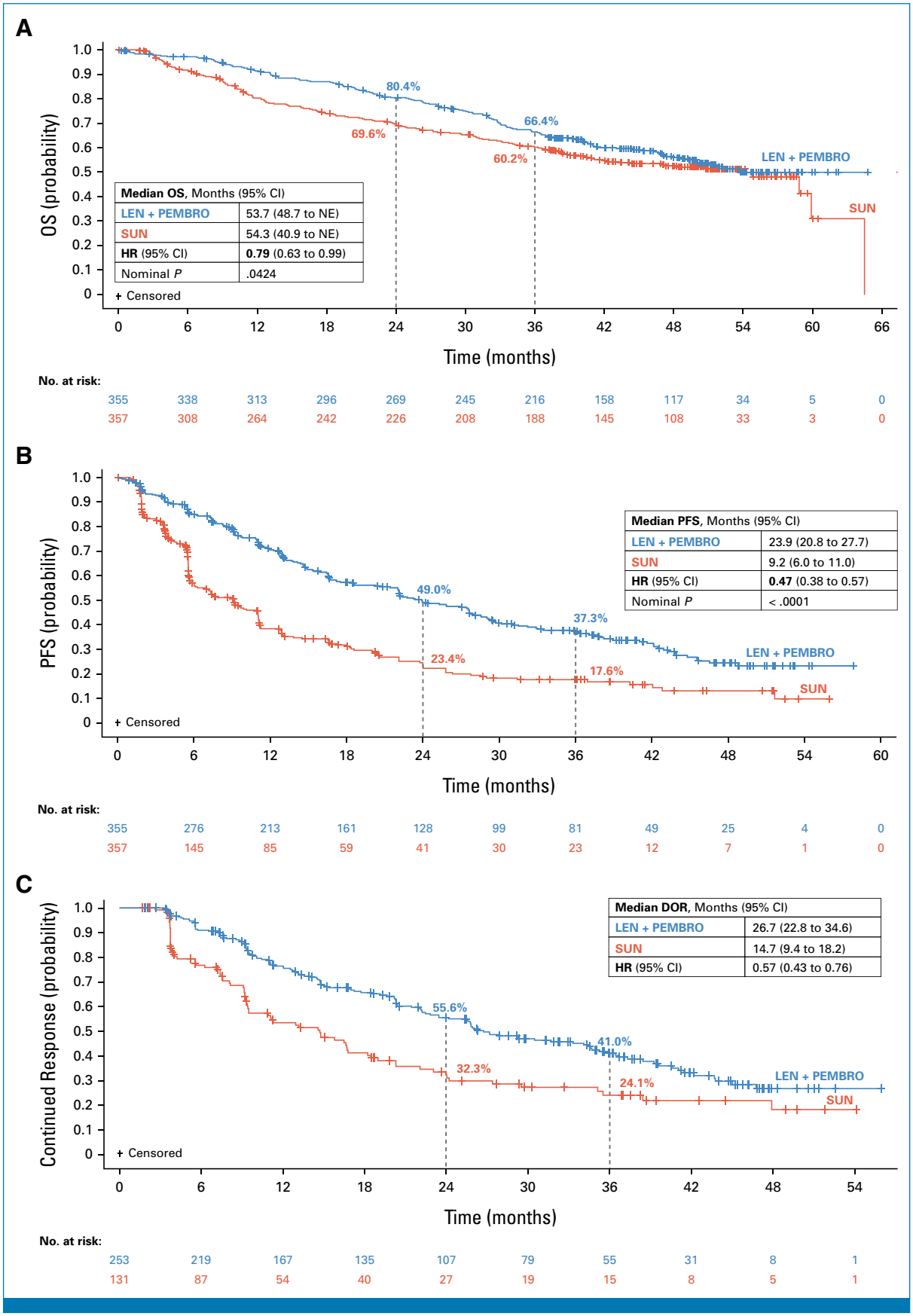

FIG 1. Kaplan-Meier plots of final analysis of (A) OS (unadjusted), (B) PFS by IIR per RECIST v1.1, and (C) duration of response by IIR per RECIST v1.1. The 95% CIs are estimated using a generalized Brookmeyer and Crowley method. HR is based on a Cox proportional hazards model including the treatment group as a factor; the Efron method (continued on following page)

FIG 1. (Continued). was used for ties and stratified by 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 IxRS. CR, complete response; DOR, duration of response; HR, hazard ratio; IIR, independent imaging review; IxRS, interactive voice/web response system; LEN, lenvatinib; MSKCC, Memorial Sloan Kettering Cancer Center; NE, not estimable; OS, overall survival; PEMBRO, pembrolizumab; PFS, progression-free survival; PR, partial response; SUN, sunitinib.

nominal *P* value < .0001; Table 1). Complete responses were achieved by 65 patients (18.3%) in the lenvatinib plus pembrolizumab group and 17 patients (4.8%) in the sunitinib group. A best overall response of progressive disease was reported in 19 patients (5.4%) in the lenvatinib plus pembrolizumab group and 50 patients (14.0%) in the

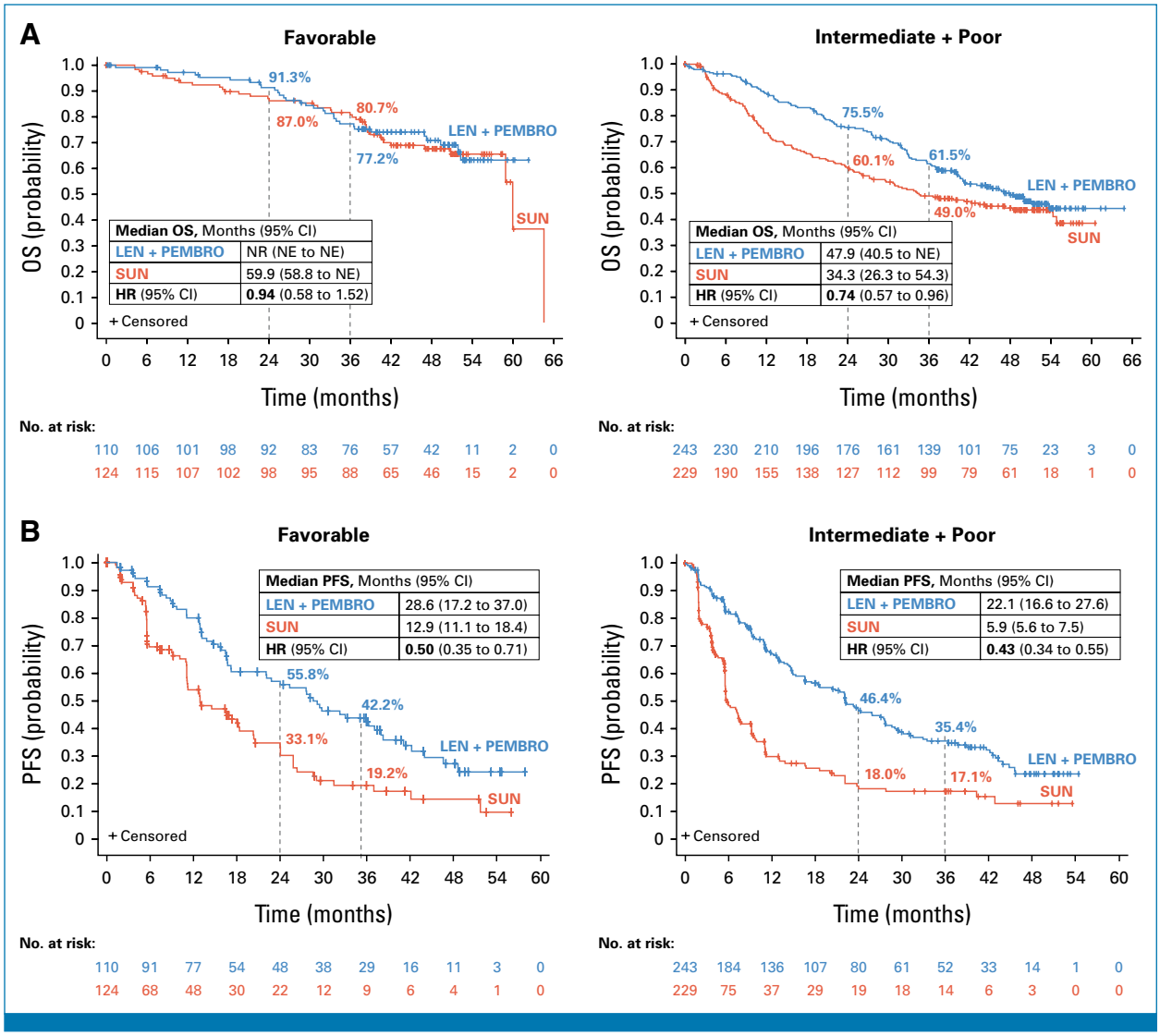

FIG 2. Kaplan-Meier plots of (A) final OS and (B) PFS analysis in favorable-risk and intermediate- plus poor-risk IMDC subgroups. PFS was determined by independent imaging review per RECIST v1.1. The IMDC risk group was not a stratification factor, and relevant data were derived programmatically. Medians were estimated using the Kaplan-Meier method, and 95% CIs were estimated using a generalized Brookmeyer and Crowley method. HR is based on a Cox proportional hazards model including the treatment group as a factor; the 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 IxRS. HR, hazard ratio; IMDC, International Metastatic Renal Cell Carcinoma Database Consortium; IxRS, interactive web/voice-response system; LEN, lenvatinib; MSKCC, Memorial Sloan Kettering Cancer Center; NE, not estimable; NR, not reached; OS, overall survival; PEMBRO, pembrolizumab; PFS, progression-free survival; SUN, sunitinib.

sunitinib group. In responders, the median DOR (95% CI) was 26.7 months (95% CI, 22.8 to 34.6) with lenvatinib plus pembrolizumab and 14.7 months (95% CI, 9.4 to 18.2) with sunitinib (Fig 1C).

Exposure and Safety

The median overall duration of treatment (range) in the safety analysis population was 22.6 months (range, 0.1-62.1) in patients who received lenvatinib plus pembrolizumab (352 patients) and 7.8 months (range, 0.1-57.5) in patients who received sunitinib (340 patients).

In both groups, most patients had treatment-emergent adverse events (TEAEs; Data Supplement, Table S2). Grade ≥3 TEAEs occurred in 84.9% of patients treated with lenvatinib plus pembrolizumab and 74.7% of patients treated with sunitinib. Diarrhea was the most common TEAE, and hypertension was the most common grade ≥3 TEAE across treatment groups (Data Supplement, Table S2). Fatal TEAEs occurred in 16 (4.5%) patients treated with lenvatinib plus pembrolizumab and 12 (3.5%) patients treated with sunitinib (Data Supplement, Table S3); fatal treatment-related adverse events occurred in 4 (1.1%) and 1 (0.3%) patient(s) in respective groups (Data Supplement, Table S4).

DISCUSSION

In the final prespecified OS analysis, with a median OS follow-up time of about 4 years, lenvatinib plus pembrolizumab continued to show clinically meaningful efficacy compared with sunitinib as a first-line treatment for aRCC. The OS HR of 0.79 (95% CI, 0.63 to 0.99) represents a 21% reduction in the risk of death. The 36-month OS rate of 66.4% with lenvatinib plus pembrolizumab versus 60.2% with sunitinib highlights the sustained benefit with the combination treatment over sunitinib.

PFS, ORR, and response duration benefits for lenvatinib plus pembrolizumab versus sunitinib were maintained with long-term follow-up and highlight the magnitude and durability of response for this treatment combination. The ORR (71.3%) and percentage of patients with a complete response (18.3%) with lenvatinib plus pembrolizumab treatment are notable.

Safety results were consistent with those from the primary analysis and with the established safety profiles of each monotherapy and of the combination in patients with other solid tumors.[2,3,6-8] In conclusion, lenvatinib plus pembrolizumab achieved consistent, durable benefit with a manageable safety profile in treatment-naïve patients with aRCC.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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Consulting or Advisory Role: Bristol Myers Squibb, AstraZeneca, Ipsen, Pfizer, Novartis, Seagen, Roche, Exelixis, MSD, Merck Serono, Astellas Pharma, Johnson & Johnson, Eisai, MashupMD, Merck, Incyte
Research Funding: AstraZeneca, Roche, Bristol Myers Squibb, Exelixis, Ipsen, MSD, Novartis, Pfizer, Seagen, Merck Serono, Astellas Pharma, Johnson & Johnson, Eisai
Travel, Accommodations, Expenses: Pfizer, MSD, AstraZeneca, Roche, Ipsen

Viktor Grünwald
Employment: University Hospital Essen
Stock and Other Ownership Interests: MSD, Bristol Myers Squibb, AstraZeneca, Seagen, Genmab
Honoraria: Bristol Myers Squibb, Pfizer, Ipsen, Eisai, MSD Oncology, Merck Serono, AstraZeneca, EUSA Pharma, Janssen-Cilag, Advanced Accelerator Applications/Novartis, Apogepha, Nanobiotix, Ono Pharmaceutical, Astellas Pharma, Amgen
Consulting or Advisory Role: Bristol Myers Squibb, Pfizer, Novartis, MSD Oncology, Ipsen, Janssen-Cilag, Onkowissen, Cor2Ed, Eisai, Debiopharm Group, PCI Biotech, Gilead Sciences, Cureteq, Oncorena, Synthekine
Research Funding: Amgen (Inst), MSD Oncology (Inst), BMS (Inst), Seagen (Inst), Ipsen (Inst), Gilead Sciences (Inst)
Travel, Accommodations, Expenses: Pfizer, AstraZeneca, Janssen, Merck Serono

Thomas E. Hutson
Employment: Texas Oncology
Honoraria: Pfizer, Astellas Pharma, Bristol Myers Squibb, Exelixis, Eisai, Novartis, Johnson & Johnson, Bayer/Onyx
Consulting or Advisory Role: Bayer/Onyx, Pfizer, Novartis, Astellas Pharma, Johnson & Johnson, Bristol Myers Squibb, Eisai, Exelixis
Speakers' Bureau: Pfizer, Johnson & Johnson, Eisai, Exelixis, Astellas Pharma, Bristol Myers Squibb
Research Funding: Pfizer (Inst), Johnson & Johnson (Inst), Exelixis (Inst), Eisai (Inst), Bristol Myers Squibb (Inst)

Boris Alekseev
Honoraria: AstraZeneca, Astellas Pharma, Eisai, Janssen, Bayer, MSD, Merck, Pfizer, Roche, Bristol Myers Squibb
Consulting or Advisory Role: AstraZeneca, Astellas Pharma, Bayer, Bristol Myers Squibb, Janssen, Merck, Pfizer, MSD, Roche, Eisai
Speakers' Bureau: Janssen, Astellas Pharma, Pfizer, AstraZeneca, Bayer, Merck, Bristol Myers Squibb, MSD, Eisai, Roche
Research Funding: AstraZeneca, Merck, Bayer, Astellas Pharma, Janssen, Bristol Myers Squibb, Pfizer, ICON Clinical Research, Eisai, MSD, Roche
Travel, Accommodations, Expenses: AstraZeneca, Astellas Pharma, Bayer, Bristol Myers Squibb, Janssen, MSD, Pfizer, Sanofi

Sun Young Rha
Consulting or Advisory Role: MSD Oncology, Daiichi Sankyo, Eisai, LG Chem, Eutilex, Astellas Pharma, indivumed, AstraZeneca, Ono Pharmaceutical, Amgen
Speakers' Bureau: Lilly, Eisai, MSD Oncology, BMS/Ono, Amgen, Daiichi Sankyo/UCB Japan, AstraZeneca
Research Funding: MSD Oncology, Bristol Myers Squibb, Eisai, Roche/Genentech, ASLAN Pharmaceuticals, Sillajen, Bayer, Daichii Sankyo, Lilly, AstraZeneca, BeiGene, Zymeworks, Astellas Pharma, Indivumed, Amgen (Inst)

Jaime Merchan
Consulting or Advisory Role: Merck
Research Funding: Corvus Pharmaceuticals (Inst), Genentech/Roche (Inst), Tizona Therapeutics, Inc (Inst), Tocagen (Inst), Vyriad (Inst), Sillajen (Inst), Replimune (Inst), Peloton Therapeutics (Inst), Eisai (Inst), Seattle Genetics/Astellas (Inst), Merck (Inst), Rubius Therapeutics (Inst), BioNTech (Inst), Trishula Therapeutics (Inst), Exelixis (Inst), IMUGENE (Inst)
Patents, Royalties, Other Intellectual Property: UpToDate

Jeffrey C. Goh
Stock and Other Ownership Interests: Immutep, ICON Cancer Care
Honoraria: MSD Oncology, AstraZeneca
Consulting or Advisory Role: GlaxoSmithKline, MSD, BMS, Janssen Oncology
Speakers' Bureau: Ipsen, Janssen, AstraZeneca/MedImmune, MSD Oncology, Pfizer/EMD Serono, Eisai
Travel, Accommodations, Expenses: Pfizer/EMD Serono, Bayer

Aly-Khan A. Lalani
Honoraria: Pfizer, Roche/Genentech, Merck, Novartis, Astellas Pharma, Bayer, Bristol Myers Squibb, Eisai, Ipsen
Consulting or Advisory Role: Eisai, Merck, Ipsen, Pfizer, Roche/Genentech, Bristol Myers Squibb, AbbVie, Janssen, Bayer, Astellas Pharma
Research Funding: Bristol Myers Squibb (Inst), Novartis (Inst), Roche (Inst), Ipsen (Inst), EMD Serono (Inst), BioCanRx (Inst)

Ugo De Giorgi
Consulting or Advisory Role: Pfizer, Janssen, Astellas Pharma, Bristol Myers Squibb, Bayer, Ipsen, MSD, PharmaMar, Novartis, Dompé Farmaceutici, Clovis Oncology, AstraZeneca, Eisai, Amgen, the healthcare business of Merck KGaA, Darmstadt, Germany, Merck & Co, Kenilworth, NJ
Research Funding: Sanofi (Inst), AstraZeneca (Inst), Roche (Inst)
Travel, Accommodations, Expenses: Ipsen, Pfizer, AstraZeneca/Daiichi Sankyo

Bohuslav Melichar
Honoraria: Roche, Pfizer, Bristol Myers Squibb, Astellas Pharma, Novartis, MSD, Merck Serono, AstraZeneca, Eisai, Lilly
Consulting or Advisory Role: Roche, Pfizer, Bristol Myers Squibb, Astellas Pharma, Novartis, MSD, Merck Serono, AstraZeneca, Eisai, Lilly
Travel, Accommodations, Expenses: Bristol Myers Squibb, Merck Serono, AstraZeneca, MSD

Howard Gurney
Consulting or Advisory Role: Bristol Myers Squibb, Ipsen, Merck Sharp & Dohme, AstraZeneca, Janssen-Cilag, Pfizer, Roche, Merck Serono, Astellas Pharma
Speakers' Bureau: Merck Serono, AstraZeneca

María José Méndez-Vidal
Honoraria: Astellas Pharma, Roche, Bristol Myers Squibb, Ipsen
Consulting or Advisory Role: Janssen-Cilag, Pfizer, Astellas Pharma, Bristol Myers Squibb, Novartis, Roche, Ipsen, EUSA Pharma, Merck
Travel, Accommodations, Expenses: Janssen-Cilag, Pfizer, Astellas Pharma, Bristol Myers Squibb, Roche

Sergei Tjulandin
Stock and Other Ownership Interests: RosPharmTech
Consulting or Advisory Role: AstraZeneca, BioCad, Novartis, Servier
Speakers' Bureau: AstraZeneca, Novartis, R-Pharm
Research Funding: Merck (Inst), Eisai (Inst), AbbVie (Inst), Novartis (Inst), Bristol Myers Squibb Foundation (Inst), Servier

Teresa Alonso Gordoa
Consulting or Advisory Role: Ipsen, Pfizer, Bristol Myers Squibb, Janssen-Cilag, Astellas Pharma, Bayer, Eisai, Advanced Accelerator Applications/Novartis, Lilly, MSD Oncology
Research Funding: Ipsen, Janssen Oncology
Travel, Accommodations, Expenses: Janssen Oncology

Anna Alyasova
Research Funding: Eisai (Inst)

Eric Winquist
Consulting or Advisory Role: Merck, Bayer, Eisai, Roche, Ipsen, EMD Serono
Research Funding: Roche/Genentech (Inst), Merck (Inst)

Pablo Maroto
Consulting or Advisory Role: Astellas Pharma, Ipsen, BMS, Merck/Pfizer, Bayer, Janssen, Bayer
Travel, Accommodations, Expenses: Merck/Pfizer, Bayer

Miso Kim
Honoraria: Astellas Pharma, Yuhan, Novartis, Merck
Consulting or Advisory Role: Ipsen, Bristol Myers Squibb/Ono Pharmaceutical, Eisai, Yuhan, Pfizer, MSD, Roche, Janssen, Astellas Pharma, Bayer, Bayer, Merck, Boryung

Avivit Peer
Honoraria: MSD, BMS, Astellas Pharma, Janssen Oncology, Bayer, Exelixis, Medison, Roche, AstraZeneca, Merck Serono
Consulting or Advisory Role: Janssen-Cilag, Astellas Pharma, Pfizer, Novartis, Bayer, MSD Oncology, BMS, Eisai, Takeda, AstraZeneca, Merck Serono
Travel, Accommodations, Expenses: Pfizer, Astellas Pharma, BMS, MSD
Other Relationship: AstraZeneca

Giuseppe Procopio
Consulting or Advisory Role: Bayer, Bristol Myers Squibb (BMS), Janssen, Novartis, Pfizer, Ipsen, Merck Sharp & Dohme, AstraZeneca, Eisai, MSD Oncology, Roche
Research Funding: Astellas Pharma, Ipsen, Janssen Oncology

Toshio Takagi
Honoraria: Ezai Co, Ltd

Shirley Wong
Consulting or Advisory Role: Pfizer, Merk Sharpe & Dome

Jens Bedke
Consulting or Advisory Role: Bristol Myers Squibb, Eisai, EUSA Pharma, Ipsen, MSD Oncology, Roche, Pfizer, Merck KGaA
Speakers' Bureau: MSD Oncology, Bristol Myers Squibb, Merck KGaA, Pfizer, Ipsen, Astellas Pharma, Apogepha
Research Funding: Bristol Myers Squibb (Inst), Astellas Pharma (Inst), Ipsen (Inst), MSD Oncology (Inst), Novartis (Inst), Roche (Inst), Exelixis (Inst), Pfizer (Inst), SeaGen (Inst)

Manuela Schmidinger
Honoraria: BMS, Ipsen, MSD Oncology, EISAI, EUSA Pharma, Merck Sharp & Dohme, Janssen Oncology, AstraZeneca
Consulting or Advisory Role: BMS, Ipsen, MSD Oncology, EUSA Pharma, Eisai, AstraZeneca
Research Funding: IPSEN (Inst)
Travel, Accommodations, Expenses: BMS, Ipsen

Karla Rodriguez-Lopez
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Stock and Other Ownership Interests: Merck
Honoraria: Merck
Research Funding: Merck (Inst)
Travel, Accommodations, Expenses: Merck

Joseph Burgents
Employment: Merck
Stock and Other Ownership Interests: Merck

Chinyere E. Okpara
Employment: Eisai

Jodi McKenzie
Employment: Eisai

Toni K. Choueiri
Stock and Other Ownership Interests: Precede Bio, Osel, Tempest Therapeutics, Pionyr, Curesponse, Inndura, Primium
Honoraria: HiberCell, Pfizer, Bayer, Novartis, GlaxoSmithKline, Merck, Bristol Myers Squibb, Roche/Genentech, Eisai, Foundation Medicine, AstraZeneca, Exelixis, Prometheus, Ipsen, Sanofi/Aventis, Peloton Therapeutics, UpToDate, NCCN, Michael J. Hennessy Associates, Analysis Group, Clinical Care Options, PlatformQ Health, Navinata Health, Harborside Press, ASCO, The New England Journal of Medicine, Lancet Oncology, EMD Serono, Lilly, Tempest Therapeutics, Arcus Biosciences, Arcus Biosciences, Alkermes, Gilead Sciences, Scholar Rock, Janssen Oncology, Precede Bio, Aravive, Infinity Pharmaceuticals, ESMO, NiKang Therapeutics, Kanaph Therapeutics, Gilead Sciences
Consulting or Advisory Role: Pfizer, Bayer, Novartis, GlaxoSmithKline, Merck, Bristol Myers Squibb, Roche/Genentech, Eisai, Foundation Medicine, AstraZeneca, Exelixis, Prometheus, Ipsen, Sanofi/Aventis, Peloton Therapeutics, UpToDate, NCCN, Michael J. Hennessy Associates, Analysis Group, Clinical Care Options, PlatformQ Health, Navinata Health, Harborside Press, ASCO, The New England Journal of Medicine, Lancet Oncology, EMD Serono, Lilly, Tempest Therapeutics, Arcus Biosciences, alkermes, Gilead Sciences, Scholar Rock, Janssen Oncology, Precede Bio, Aravive, Infinity Pharmaceuticals, ESMO, NiKang Therapeutics, Kanaph Therapeutics, Gilead Sciences
Research Funding: Pfizer (Inst), Novartis (Inst), Merck (Inst), Exelixis (Inst), TRACON Pharma (Inst), GlaxoSmithKline (Inst), Bristol Myers Squibb (Inst), AstraZeneca (Inst), Peloton Therapeutics (Inst), Roche/Genentech (Inst), Agensys (Inst), Eisai (Inst), Takeda (Inst), Ipsen (Inst), Seattle Genetics/Astellas (Inst), Bayer (Inst), Roche (Inst), Calithera Biosciences (Inst), NiKang Therapeutics (Inst), Arcus Biosciences (Inst), AVEO (Inst)
Patents, Royalties, Other Intellectual Property: International Patent Application No. PCT/US2018/058430, titled “Biomarkers of Clinical Response and Benefit to Immune Checkpoint Inhibitor Therapy” (Inst), International Patent Application No. PCT/US2018/12209, titled “PBRM1 Biomarkers Predictive of Anti-Immune Checkpoint Response” (Inst), ctDNA technologies
Travel, Accommodations, Expenses: Pfizer, Bayer, Novartis, GlaxoSmithKline, Merck, Bristol Myers Squibb, Roche/Genentech, Eisai, Foundation Medicine, Cerulean Pharma, AstraZeneca, Exelixis, Prometheus, alligent, Ipsen, Corvus Pharmaceuticals, Lpath, Alexion Pharmaceuticals, Sanofi/Aventis, UpToDate, Peloton Therapeutics, NCCN, Michael J. Hennessy Associates, Analysis Group, Kidney Cancer Association, Clinical Care Options, PlatformQ Health, Harborside Press, Navinata Health, The New England Journal of Medicine, Lancet Oncology, EMD Serono, HERON, Lilly, ESMO
Other Relationship: Medical writing and editorial assistance support may have been funded by Communications companies funded by pharmaceutical companies such as ClinicalThinking, Health Interactions, Envision Pharma Group, Fishawack Group of Companies, Parexel

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APPENDIX

TABLE A1. CLEAR Study List of Countries, Sites, and Investigators

Country	Site Name	Principal Investigator
United States	Memorial Sloan Kettering Cancer Center	Robert J. Motzer
	Dana-Farber Cancer Institute	Toni Choueiri
	Texas Oncology, P.A.	Thomas Hutson
	GU Research Network	Luke Nordquist
	SCRI – Tennessee Oncology	David Spigel
	University of Miami	Jaime Merchan
	Roswell Park Comprehensive Cancer Center	Saby George
	Stanford School of Medicine	Sandhya Srinivas
	Providence Portland Medical Center	Brendan Curti
	Centricity Research IRT – DBA IACT Health Columbus Regional Research Institute	Andrew Pippas
	Karmanos Cancer Center	Elisabeth Heath
	Healthcare Research Network III, LLC	Subramanya Rao
	Medical University of South Carolina (MUSC)	Theodore Gourdin
	Cotton-O'Neil Clinical Research Center, Hematology and Oncology	Mehmood Hashmi
	Duly Health and Care	Nafisa Burhani
	Weill Cornell Medical College New York Presbyterian Hospital	Ana Molina
	Boca Raton Community Hospital	Alan Koletsky
	Temple University Hospital	Robert Alter
	AdventHealth	Carlos Alemany
	Montefiore Medical Center PRIME	Benjamin Gartrell
	Mount Sinai Medical Center	Mike Cusnir
	Cancer Center of Middle Georgia	Harsha Vyas
	Health Midwest Ventures Group, Inc d/b/a HCA MidAmerica Division, LLC	Stephanie Graff
	Cooper Research Institute	Christian Squillante
	Mid Ohio Oncology Hematology, Inc	Mark Knapp
	Florida Cancer Specialists North	Ivor Percent
	Florida Cancer Specialists North	Vijay Patel
	Florida Cancer Specialists East	Daniel Spitz
	Mission Hospital	Cameron Harkness
	Ochsner Clinic Foundation	Marc Matrana
	Wenatchee Valley Hospital & Clinics	Lindsay Overton
	Texas Oncology	Stephen Richey
	Texas Oncology, P.A. – Tyler	Donald Richards
	Texas Oncology McAllen	Habib Ghaddar
	Illinois Cancer Specialists	Robert Galamaga
	Nebraska Cancer Specialists	Ralph Hauke
	Associates in Oncology & Hematology, PC	Joseph Haggerty
	Broome Oncology, LLC	Ronald Harris
	Oncology/Hematology Care Clinical Trials, LLC	Mark Johns
	Minnesota Oncology Hematology, P.A.	Samith Kochuparambil

(continued in next column)

TABLE A1. CLEAR Study List of Countries, Sites, and Investigators (continued)

Country	Site Name	Principal Investigator
Canada	BC Cancer – Vancouver	Christian Kollmannsberger
	St Joseph's Healthcare Hamilton	Bobby Shayegan
	The Ottawa Hospital Cancer Center	Christina Canil
	London Health Sciences Center (LHSC) – Victoria Hospital	Eric Winquist
	Centre de santé et de services sociaux Champlain-Charles-Le Moyne	Catherine Sperlich
	Sunnybrook Research Institute	Georg Bjarnason
	Cross Cancer Institute	Naveen Basappa
Austria	Ordensklinikum Linz GmbH Elisabethinen	Wolfgang Loidl
	Medizinische Universität Innsbruck	Wolfgang Horninger
	AKH – Medizinische Universität Wien	Manuela Schmidinger
Belgium	CHU UCL Namur	Lionel D'Hondt
	ZNA Middelheim	Dirk Schrijvers
	GZA Ziekenhuizen	Annemie Rutten
	Onze Lieve Vrouw Ziekenhuis	Peter Schatteman
	Imeldaziekenhuis	Wim Wynendaele
	ETC Jessa Ziekenhuis	Daisy Luyten
	Institut Jules Bordet	Spyridon Sideris
	CHU de Liège	Christine Gennigens
Czech Republic	Fakultni nemocnice Olomouc	Bohuslav Melichar
	Fakultni nemocnice u sv. Anny v Brne	Jana Katolicka
	Masarykuv onkologicky ustav	Jiri Tomasek
	Fakultni nemocnice v Motole	Jana Prausova
	Fakultni Thomayerova nemocnice	Tomas Buchler
	Fakultni nemocnice Bulovka	Petra Holeckova
France	CHU Strasbourg – Nouvel Hôpital Civil	Philippe Barthelemy
	Institut du Cancer de Montpellier	Diego Tosi
	Groupe Hospitalier Pitie-Salpetriere	Baptiste Abbar
	Centre Leon Berard	Sylvie Negrier
	Hôpital Européen Georges Pompidou	Stephane Oudard
	Clinique Victor Hugo – Centre Jean Bernard	Eric Voog
	Centre Georges François Leclerc	Sylvie Zanetta
	ICO – Site Paul Papin	Frederic Rolland
Germany	Universitaetsklinikum Tuebingen	Jens Bedke
	Universitaetsklinikum des Saarlandes	Stefan Siemer
	Universitaetsklinikum Carl Gustav Carus TU Dresden	Manfred Wirth
	Klinikum Stuttgart-Katharinenhospital	Jan Schleicher
	Charité – Campus Charité Mitte	Maria De Santis
	Universitaetsklinikum Frankfurt Goethe-Universitaet	Lothar Bergmann
	LMU-Campus Grosshadern	Michael Staehler
	Medizinische Hochschule Hannover	Philipp Ivanyi
	Praxis f. Haematologie und Onkologie Koblenz	Christoph Lutz
	Universitaetsklinikum Hamburg-Eppendorf	Gunhild Von Amsberg
	Universitaetsklinikum Muenster	Martin Boegemann
	Universitaetsmedizin Greifswald	Uwe Zimmermann

(continued on following page)

TABLE A1. CLEAR Study List of Countries, Sites, and Investigators (continued)

Country	Site Name	Principal Investigator
Ireland	Adelaide and Meath Hospital Incorp The National Children's Hospital	Raymond McDermott
	Cork University Hospital	Richard Bambury
	University Hospital Galway	Paul Donnellan
	Beaumont Hospital	Oscar Breathnach
Israel	Shamir Medical Center (Assaf Harofe)	Raya Leibowitz-Amit
	Sapir Medical Center, Meir Hospital	Olesya Goldman
	Rambam Health Care Campus	Avivit Peer
	Tel Aviv Sourasky Medical Center	David Sarid
	Hadassah University Hospital – Ein Kerem	Hovav Nechushtan
	Chaim Sheba Medical Center	Raanan Berger
	Rabin MC	Victoria Neiman
Italy	Azienda Ospedaliera San Camillo Forlanini	Fabio Calabro
	Fondazione IRCCS Policlinico San Matteo	Paolo Pedrazzoli
	IRCCS Opedale Policlinico San Martino-IST	Francesco Boccardo
	Ospedale San Donato – ASL 8 Arezzo	Alketa Hamzaj
	Azienda Ospedaliera di Rilievo Nazionale A. Cardarelli	Ferdinando Riccardi
	IRCCS Istituto Scientifico Romagnolo Per Lo Studio Dei Tumori "Dino Amadori"—IRST	Ugo De Giorgi
	Istituto Nazionale Tumori Fondazione G. Pascale	Sandro Pignata
	Azienda Ospedaliera Santa Maria Degli Angeli	Sandra Santarossa
	Azienda Ospedaliera Universitaria Policlinico Sant'Orsola Malpighi IRCCS	Francesco Massari
	Università Campus Bio-Medico di Roma	Giuseppe Tonini
	Presidio Ospedaliero Vito Fazzi	Caterina Accettura
	Azienda Unità Sanitaria Locale- Ravenna	Francesco Carrozza
	A.O.U. Policlinico di Modena	Roberto Sabbatini
	Fondazione IRCCS Istituto Nazionale dei Tumori	Elena Verzoni
	I.R.C.S.S Fondazione Maugeri	Elisa Biscaldi
The Netherlands	UMC Utrecht	Britt Suelmann
	Amsterdam UMC, Locatie VUMC	Alfonsus van den Eertwegh
	Antoni van Leeuwenhoek	Hans van Thienen
Poland	Instytut MSF Sp. o.o	Ewa Kalinka
	Uniwersyteckie Centrum Kliniczne	Jacek Jassem
	SPWSZ w Szczecinie im. Marii Sklodowskiej-Curie	Violetta Sulzyc-Bielicka
	Dr n med. Slawomir Mandziuk Specjalistyczna Praktyka Lekarska	Slawomir Mandziuk
Russian Federation	FSBSI "Russian Oncological Scientific Center n.a. N.N. Blokhin"	Sergei Tjulandin
	FSBI "National Medical Research Radiological Center" of the MoH of the RF	Oleg Karyakin
	FBHI Privolzhskiy District Medical Center FMBA of Russia	Anna Alyasova
	FSBI "Moscow scientific research oncology institute n.a. P.A. Gertsen" of MoH of RF	Boris Alekseev
	Medicinskiy gorod	Alexander Zyrianov
	FSBSI "Russian Oncological Scientific Center n.a. N.N. Blokhin"	Vsevolod Matveev
	BHI of Omsk region "Clinical Oncology Dispensary"	Evgeny Kopyltsov
	SBHI of Novosibirsk region "Novosibirsk Regional Oncological Dispensary"	Vadim Kozlov

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TABLE A1. CLEAR Study List of Countries, Sites, and Investigators (continued)

Country	Site Name	Principal Investigator
Spain	Hospital General Universitario Gregorio Marañon	Jose Angel Arranz Arija
	Hospital San Pedro de Alcantara	Pablo Borrega Garcia
	Instituto Valenciano de Oncologia IVO	Miguel Angel Climent Duran
	Hospital Universitario Virgen del Rocio	Begona Perez Valderrama
	Hospital Universitario Central de Asturias	Emilio Esteban Gonzalez
	ICO l'Hospitalet – Hospital Duran i Reynals	Francisco Javier Garcia del Muro Solans
	Hospital Universitario HM Madrid Sanchinarro	Jesus Garcia-Donas Jimenez
	Hospital Universitario Ramon y Cajal	Teresa Alonso Gordoa
	Hospital de la Santa Creu i Sant Pau	Jose Pablo Maroto Rey
	Hospital Clinic de Barcelona	Begoña Mellado Gonzalez
	Hospital Universitario Reina Sofia	Maria Jose Mendez Vidal
	Hospital Universitario Clinico San Carlos	Javier Puente Vazquez
	Hospital Universitari Vall d'Hebron	Cristina Suarez Rodriguez
	MD Anderson Cancer Center	Enrique Grande Pulido
	Complejo Asistencial Universitario de Burgos	Guillermo Crespo
	Hospital Universitario Lucus Augusti	Natalia Fernandez Nuñez
	Hospital Universitario Marques de Valdecilla	Ignacio Duran Martinez
Switzerland	Inselspital – Universitaetsspital Bern	Joerg Beyer
	Kantonsspital Winterthur	Natalie Fischer
United Kingdom	Beatson West of Scotland Cancer Centre	Hilary Glen
	Velindre Cancer Centre	Ricky Frazer
	The Christie Hospital	Jennifer Allison
	Royal Free Hospital	Thomas Powles
	Western General Hospital	Jahangeer Malik
	St James's University Hospital	Christy Ralph
	Guy's Hospital	Sarah Rudman
	Royal Bournemouth Hospital	Thomas Geldart
Greece	General Hospital of Athens "Alexandra"	Aristotelis Bamias
	Interbalkan Hospital of Thessaloniki	Sofia Baka
	Metropolitan General Hospital	Vassilios Georgoulias
	Euromedica General Clinic of Thessaloniki	Konstantinos Papazisis
	University Hospital of Patra	Haralabos Kalofonos
	General Hospital Papageorgiou	Eleni Timotheadou
Republic of Korea	Seoul National University Bundang Hospital	Seok-Soo Byun
	Asan Medical Center	Bumjin Lim
	SEVERANCE HOSPITAL, YONSEI UNIVERSITY	Sun Young Rha
	Samsung Medical Center	Seong Il Seo
	National Cancer Center	Jinsoo Chung
	Seoul National University Hospital	Miso Kim
	The Catholic University of Korea, Seoul St Mary's Hospital	Sung-Hoo Hong
	Asan Medical Center	Jae Lyun Lee
	Samsung Medical Center	Se Hoon Park
	Kyungpook National University Chilgok Hospital	Tae Gyun Kwon

(continued on following page)

TABLE A1. CLEAR Study List of Countries, Sites, and Investigators (continued)

Country	Site Name	Principal Investigator
Australia	Box Hill Hospital	Ian Davis
	Sunshine Hospital	Shirley Wong
	Royal Hobart Hospital	Ian Byard
	Austin Health	Andrew Weickhardt
	Macquarie University Hospital	Howard Gurney
	Icon Cancer Centre Chermside	Jeffrey Goh
Japan	Hokkaido University Hospital	Takahiro Osawa
	Sapporo Medical University Hospital	Naoya Masumori
	Hirosaki University Hospital	Shingo Hatakeyama
	Akita University Hospital	Mitsuru Saito
	Niigata University Medical & Dental Hospital	Yoshihiko Tomita
	Toranomon Hospital	Yuji Miura
	Juntendo University Hospital	Masayoshi Nagata
	Nippon Medical School Hospital	Go Kimura
	Keio University Hospital	Mototsugu Oya
	Tokyo Women's Medical University Hospital	Toshio Takagi
	Kyorin University Hospital	Yu Nakamura
	Yokohama City University Hospital	Hisashi Hasumi
	Kitasato University Hospital	Masatsugu Iwamura
	Chiba University Hospital	Akira Komiya
	Chiba Cancer Center	Atsushi Komaru
	Saitama Medical University International Medical Center	Masafumi Oyama
	Nagoya University Hospital	Yoshihisa Matsukawa
	Aichi Cancer Center Hospital	Norihito Soga
	Osaka Metropolitan University Hospital	Minoru Kato
	Kindai University Hospital	Masahiro Nozawa
	Nara Medical University Hospital	Makito Miyake
	Kobe University Hospital	Yuzo Nakano
	Okayama University Hospital	Kohei Edamura
	Hiroshima University Hospital	Nobuyuki Hinata
	Kagawa University Hospital	Homare Okazoe
	Tokushima University Hospital	Masayuki Takahashi
	Kyushu University Hospital	Masatoshi Eto
	Nagasaki University Hospital	Kojiro Oba
	Kanagawa Cancer Center	Takeshi Kishida
	University Hospital, Kyoto Prefectural University of Medicine	Osamu Ukimura