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Assessing the Safety and Efficacy of Two Starting Doses of Lenvatinib Plus Everolimus in Patients with Renal Cell Carcinoma: A Randomized Phase 2 Trial

Sumanta K. Pal[a,*], *Javier Puente*[b], *Daniel Y.C. Heng*[c], *Hilary Glen*[d], *Piotr Koralewski*[e], *Daniil Stroyakovskiy*[f], *Boris Alekseev*[g], *Francis Parnis*[h], *Daniel Castellano*[i], *Tudor Ciuleanu*[j], *Jae Lyun Lee*[k], *Kaisa Sunela*[l], *Karen O'Hara*[m], *Terri A. Binder*[n,†], *Lixian Peng*[n,‡], *Alan D. Smith*[m], *Sun Young Rha*[o,*]

[a] *Department of Medical Oncology & Therapeutics, City of Hope Comprehensive Cancer Center, Duarte, CA, USA;* [b] *Medical Oncology Department, Hospital Clinico San Carlos, Instituto de Investigación Sanitaria del Hospital Clínico San Carlos (IdISSC), CIBERONC, Madrid, Spain;* [c] *Department of Oncology, Tom Baker Cancer Center, Calgary, Alberta, Canada;* [d] *Medical Oncology, Beatson West of Scotland Cancer Centre, Glasgow, UK;* [e] *Department of Oncology, Rydygier Hospital, Krakow, Poland;* [f] *Chemotherapeutic Department, Moscow City Oncology Hospital, Moscow, Russian Federation;* [g] *Moscow Hertzen Oncology Institute, Moscow, Russian Federation (Alekseev);* [h] *Medical Oncology, Adelaide Cancer Center, Adelaide, Australia;* [i] *Medical Oncology Department, Hospital Universitario 12 de Octubre (CIBERONC), Madrid, Spain;* [j] *Medical Oncology, Iuliu Hatieganu University of Medicine and Pharmacy, Ion Chiricuta Institute of Oncology, Cluj-Napoca, Romania;* [k] *Department of Oncology, University of Ulsan College of Medicine, Asan Medical Center, Seoul, South Korea;* [l] *Department of Oncology, Tampere University Hospital, Tampere, Finland;* [m] *Eisai Europe Ltd., Hatfield, UK;* [n] *Eisai Inc., Nutley, NJ, USA;* [o] *Department of Medical Oncology, Yonsei Cancer Center, Yonsei University Health System, Seoul, South Korea*

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Abstract

Background: Lenvatinib (18 mg) plus everolimus (5 mg) is approved for patients with advanced renal cell carcinoma (RCC) after one or more prior antiangiogenic therapies.
Objective: To assess whether a lower starting dose of lenvatinib has comparable efficacy with improved tolerability for patients with advanced RCC treated with lenvatinib plus everolimus.
Design, setting, and participants: A randomized, open-label, phase 2 global trial was conducted in patients with advanced clear cell RCC and disease progression after one prior vascular endothelial growth factor–targeted therapy (prior anti–programmed death-1/programmed death ligand-1 therapy permitted).
Intervention: Patients were randomly assigned 1:1 to the 14- or 18-mg lenvatinib starting dose, both in combination with everolimus 5 mg/d. Patients in the 14-mg arm were to be uptitrated to lenvatinib 18 mg at cycle 2, day 1, barring intolerable grade 2 or any

† Former employee and current consultant at Eisai Inc.
‡ Formerly of Eisai Inc.
* Corresponding authors. Department of Medical Oncology & Therapeutics, City of Hope Comprehensive Cancer Center, 1500 East Duarte Road, Duarte, CA 91010, USA. Tel. +1 626 256 4673; Fax: +1 626 301 8233 (S.K. Pal). Department of Medical Oncology, Yonsei Cancer Center, Yonsei University Health System, 50-1 Yonsei-ro, Seodaemun-gu, Seoul 03722, South Korea. Tel. +82 2 2228 8050, Fax: +82 2 362 5592 (S.Y. Rha).
E-mail addresses: spal@coh.org (S.K. Pal) rha7655@yuhs.ac (S.Y. Rha).

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Phase 2 trial
Renal cell carcinoma
Safety
Starting dose

grade ≥3 treatment-emergent adverse events (TEAEs) requiring dose reduction occurring in the first 28-d cycle.

Outcome measurements and statistical analysis: The primary efficacy endpoint was investigator-assessed objective response rate (ORR) as of week 24 (ORR_{wk24}); the noninferiority threshold of the 14- versus 18-mg arm was $p \leq 0.045$. The primary safety endpoint was the proportion of patients with intolerable grade 2 or any grade ≥3 TEAEs within 24 wk of randomization.

Results and limitations: The ORR_{wk24} for the 14-mg arm (32% [95% confidence interval {CI} 25–39]) was not noninferior to the ORR_{wk24} in the 18-mg arm (35% [95% CI 27–42]; odds ratio: 0.88; 90% CI 0.59–1.32; $p = 0.3$). The proportion of intolerable grade 2 or any grade ≥3 TEAEs was similar between the two arms (14 mg, 83% vs 18 mg, 80%; $p = 0.5$). The secondary endpoints of overall ORR, progression-free survival, and overall survival numerically favored the 18-mg arm. A limitation of this study was that the study design did not allow for a full comparison of progression-free survival between treatment arms.

Conclusions: The study findings support the approved dosing regimen of lenvatinib 18 mg plus everolimus 5 mg daily for patients with advanced RCC.

Patient summary: In this report, we examined two doses of lenvatinib (the approved 18-mg dose and a lower dose of 14 mg) in people with advanced renal cell carcinoma to determine whether the lower dose (which was increased to the approved 18-mg dose after the first treatment cycle) could improve safety without affecting efficacy. The results showed that the efficacy of the lower lenvatinib dose (14 mg) was not the same as that of the approved (18 mg) dose, although safety results were similar, so the approved lenvatinib 18-mg dose should still be used.

1. Introduction

The incidence of renal cell carcinoma (RCC) is increasing, and approximately 30% of patients present with regional or distant metastases at diagnosis [1]. The 5-yr survival rate for patients with advanced RCC is approximately 12% [1,2]. Despite the benefit of tyrosine kinase inhibitors and combinations with immunotherapy in the first-line setting, many patients experience disease progression [1,3]. Lenvatinib (18 mg) plus everolimus (5 mg) is an approved second-line treatment in patients with advanced RCC after one prior antiangiogenic therapy [4]. In Study 205 (a pivotal phase 2 study of patients with metastatic RCC) [5], treatment with lenvatinib plus everolimus significantly prolonged progression-free survival (PFS) compared with everolimus alone (hazard ratio [HR] 0.40, 95% confidence interval [CI] 0.24–0.68; $p = 0.0005$); the median PFS was 14.6 mo (95% CI 5.9–20.1), notably longer than the median PFS for other treatments in second- or later-line settings (range: 3.9–7.4 mo) [6–8]. The objective response rate (ORR) was 43% for patients with metastatic RCC who received lenvatinib plus everolimus [5]. Based on these results, the National Comprehensive Cancer Network granted lenvatinib plus everolimus a category 1 designation as a recommended treatment option for patients with advanced clear cell RCC in second- or later-line settings [9].

Despite improved efficacy, many patients treated with lenvatinib plus everolimus experience treatment-emergent adverse events (TEAEs), which often require dose interruptions/reductions and treatment discontinuations [10]. In Study 205, patients treated with the combination had TEAEs leading to lenvatinib dose reductions and study-drug discontinuations in 71% and 24%, respectively [5]. The most frequently reported TEAEs leading to dose reduction/interruption were diarrhea and vomiting [5].

In collaboration with the US Food and Drug Administration (FDA), a tumor-growth pharmacokinetic/pharmacodynamic model was created to evaluate the safety and efficacy of several dosing scenarios (eg, lower lenvatinib starting doses with or without uptitration or dosage interruption [eg, 2 wk on/1 wk off]). The model suggested that the efficacy of a lower starting dose of lenvatinib (ie, 14 mg) that allows uptitration to the 18-mg dose (both doses in combination with everolimus 5 mg) may result in equivalent or superior tumor reduction with a predicted ORR by week 24 (ORR_{wk24}) comparable to that with an 18-mg starting dose (unpublished data).

Herein, the results of a randomized, open-label, phase 2 study of lenvatinib (14 or 18 mg) in combination with everolimus (5 mg) in patients with advanced RCC after one prior vascular endothelial growth factor (VEGF)-targeted therapy are presented.

2. Patients and methods

This randomized trial was reported according to the CONsolidated Standards of Reporting Trials (CONSORT) statement guidelines [11].

2.1. Study design and patients

Eligible patients were ≥18 yr old with histologically or cytologically confirmed predominantly clear cell advanced RCC and evidence of disease progression on, or after, a prior VEGF-targeted therapy for RCC (one prior programmed death-1 [PD-1]/programmed death ligand-1 [PD-L1]–targeted therapy was also allowed). See the Supplementary material (Methods) for additional inclusion/exclusion criteria.

This study was reviewed and approved by the Institutional Review Board or Independent Ethics Committee, and conducted in accordance with the principles of the Declaration of Helsinki, Good Clinical Practice guidelines, and local regulations. All patients provided written informed consent.

2.2. Treatments

Patients were randomly assigned 1:1 to receive a starting dosage of lenvatinib (14 mg) plus everolimus (5 mg) orally once daily (QD) in 28-d cycles or of lenvatinib (18 mg) plus everolimus (5 mg) orally QD in 28-d cycles. For patients in the 14-mg treatment arm with no intolerable grade 2 or any grade ≥3 TEAEs that required dose reduction in the first 28-d cycle, lenvatinib was to be escalated to 18 mg at cycle 2, day 1. The predefined randomization scheme incorporated Memorial Sloan Kettering Cancer Center (MSKCC) prognostic groups (favorable, intermediate, or poor risk) and prior exposure to a PD-1/PD-L1–targeted treatment (yes or no) as stratification factors. The study was originally double blind. Study treatments were assigned according to an interactive voice and web response system; the investigators communicated with this system to assign the lenvatinib starting dose. After a dose-reassignment error introduced by a programmatic update to the interactive voice and web response system affected 33 patients, the study sponsor unblinded the study (after 11 mo) to ensure patient safety and continued the study as an open-label trial. All investigators had received unblinding information as of July 2018. No assigned doses exceeded lenvatinib 18 mg/d. Among the affected patients, 32 received two or more incorrect lenvatinib doses and were excluded from the efficacy analysis. The number of patients enrolled in the study was increased by 32 to ensure that enough patients would be included in the primary efficacy analysis set.

2.3. Study endpoints and assessments

The primary efficacy endpoint was the ORR as of week 24 (ORR_{wk24}) by investigator assessment according to RECIST v1.1 (Response Evaluation Criteria in Solid Tumors version 1.1). ORR_{wk24} was defined as the proportion of patients with a best overall response (BOR) of confirmed complete (CR) or partial (PR) response at or before the week 24 postrandomization time point. The primary safety endpoint was the proportion of patients with intolerable grade 2 or any grade ≥3 TEAEs within 24 wk after randomization. The secondary study endpoints included ORR as of the end of study treatment, PFS, and PFS on next-line therapy (defined as the date of disease progression from next-line therapy or death from any cause, whichever occurs first; all assessed by an investigator as per RECIST v1.1), overall survival (OS), and time to treatment failure due to toxicity (time from the date of randomization to the date that a patient discontinued study drug due to one or more TEAEs). Additional secondary endpoints included the overall safety profile and tolerability of lenvatinib in combination with everolimus, the proportion of patients who discontinued treatment due to a toxicity, lenvatinib and everolimus exposure parameters and pharmacokinetic and pharmacodynamic drug-drug interactions (to be reported in a future publication), and health-related quality of life (to be reported in a future publication). A subgroup analysis to assess efficacy (ORR, PFS [both by investigator assessment], and OS) among those patients who received a prior PD-1/PD-L1–targeted immune checkpoint inhibitor (ICI) therapy (the "prior ICI" subgroup) was conducted.

As a result of the study becoming unblinded, and after consultation with the regulatory agencies (ie, FDA and European Medicines Agency), blinded independent imaging review (IIR) assessments of ORR_{wk24}, ORR, and PFS were added as exploratory objectives to corroborate the investigator assessment.

2.4. Statistical analyses

The primary efficacy analysis set was the per-protocol analysis set 1 (PPAS1), which included all randomized patients except for those who received two or more incorrect lenvatinib doses. Sample size was calculated assuming 37% ORR_{wk24} in the lenvatinib 18-mg arm and 45% ORR_{wk24} in the lenvatinib 14-mg arm (with planned 1:1 randomization) and adjusting for the interim analyses; a total of 306 patients (153 per arm) in PPAS1 were required to achieve 80% statistical power at one-sided $\alpha = 0.05$. The number of patients required increased to approximately 338 as 32 patients received two or more incorrect lenvatinib doses due to dose-reassignment error and were excluded from the efficacy analysis.

The primary analysis of ORR_{wk24} was based on a noninferiority test of the ORR_{wk24} of the 14-mg arm compared with that of the 18-mg arm, with the noninferiority margin of the odds ratio (OR) being 0.76 (for additional details, see Supplementary Methods). The OR of ORR_{wk24} (14 vs 18 mg) along with the 90% CI was calculated using the Cochran-Mantel-Haenszel method stratified by MSKCC prognostic groups and prior anti–PD-1/PD-L1 treatment. Noninferiority in ORR_{wk24} could be claimed if the O'Brien-Fleming efficacy boundary was crossed at the primary analysis based on the PPAS1. The data cutoff for primary analysis occurred when the last patient enrolled completed the week-24 tumor assessments or discontinued study treatment before week 24. ORR_{wk24} was tested at the primary analysis for noninferiority using the following efficacy boundary: if the one-sided p value at the primary analysis was ≤0.045, noninferiority in ORR_{wk24} would be claimed for the lenvatinib 14-mg starting dose. The treatment difference in ORR_{wk24} for the two arms was estimated along with 90% CI based on the asymptotic normal approximation. The 90% CIs were used for between-treatment difference and OR in order to be consistent with the statistical design, since OR and one-sided $\alpha = 0.05$ were used to calculate sample size. For each treatment arm, 95% CIs were used as conventional interval estimates.

2.5. Safety

The primary safety endpoint was based on the per-protocol safety analysis set (PPSAS), which included all treated patients in the PPAS1. The primary safety analysis compared the proportion of patients with intolerable grade 2 and any grade ≥3 TEAEs within 24 wk after randomization in each of the treatment arms. Additional analyses were performed on the safety analysis set, which included all patients who were randomly assigned to a treatment arm and received one or more doses of study drug. Adverse events (AEs) were graded using Common Terminology Criteria for Adverse Events version 4.03, and the number of patients with TEAEs, serious AEs (defined in the Methods section in the Supplementary material), or TEAEs that led to study-drug discontinuation/dose reduction/dose interruption, together with any deaths, were recorded. The rates of TEAEs, intolerable grade 2 TEAEs, grade ≥3 TEAEs, and serious AEs were summarized using descriptive statistics.

3. Results

From the start of enrollment (August 17, 2017) to data cutoff (February 14, 2020), 343 patients were enrolled: 172 patients in the lenvatinib 14 mg (starting dose) plus everolimus 5 mg arm (the "14-mg arm") and 171 patients in the lenvatinib 18 mg plus everolimus 5 mg arm (the "18-mg arm"; Fig. 1). Baseline characteristics were generally similar between treatment arms and representative of an advanced RCC population (Table 1). At data

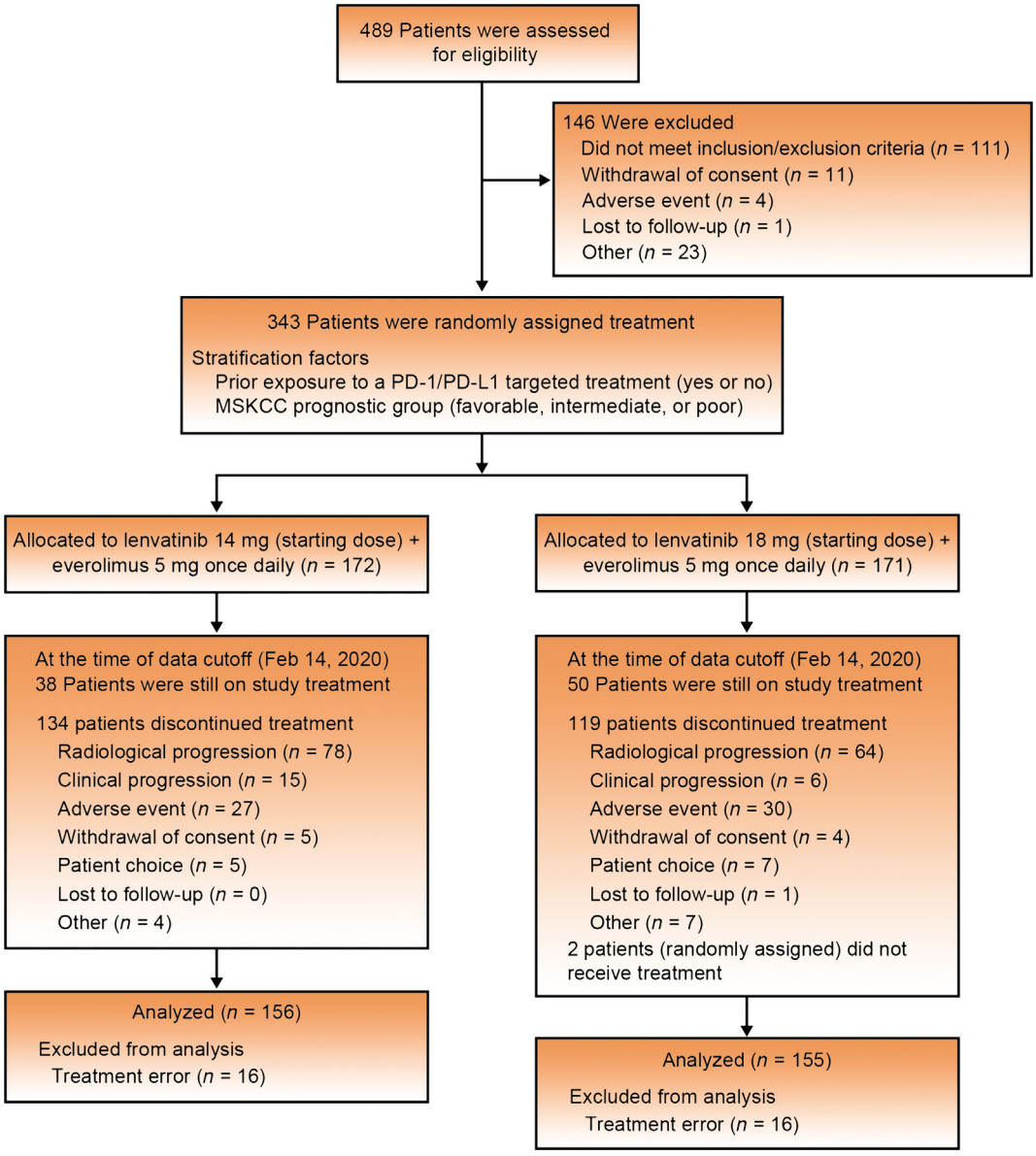

Fig. 1 – CONSORT diagram. Randomization 1:1 was stratified based on a predefined scheme using the following stratification factors: MSKCC prognostic groups (favorable, intermediate, or poor risk) and patient's prior exposure to a PD-1/PD-L1–targeted treatment (yes or no; ClinicalTrials.gov identifier: NCT03173560). CONSORT = CONsolidated Standards of Reporting Trials; MSKCC = Memorial Sloan Kettering Cancer Center; PD-1 = programmed death-1; PD-L1 = programmed death ligand-1.

cutoff, the most common reason for treatment discontinuation was radiological or clinical disease progression, which was higher in the 14-mg arm than in the 18-mg arm (radiological, 45% vs 37%; clinical, 8.7% vs 3.5%; Supplementary Table 1).

The ORR_{wk24} (primary efficacy endpoint; investigator assessed) was 32% (95% CI 25–39) in the 14-mg arm versus 35% (95% CI 27–42) in the 18-mg arm; the OR was 0.88 (90% CI 0.59–1.32) with a p value of 0.3 for the noninferiority test. The p value did not meet the noninferiority threshold ($p \leq 0.045$; Table 2); therefore, the noninferiority claim could not be made. At the time of data cutoff, in the 14-mg arm, one patient had a CR and 53 had a PR for an ORR of 35% (95% CI 27–42), by investigator assessment (Table 2). In the 18-mg arm, two patients had a CR and 61 had a PR for an ORR of 41% (95% CI 33–48; OR 0.77 [90% CI 0.52–1.14]; Table 2).

Most patients experienced tumor shrinkage (Supplementary Fig. 1). The median duration of response was 11.5 mo (95% CI 7.5–19.2) in the 14-mg arm and 11.7 mo (95% CI 9.1–not estimable [NE]) in the 18-mg arm.

The median PFS by investigator assessment was 11.1 mo (95% CI 9.0–12.9) for patients in the 14-mg arm versus 14.7 mo (95% CI 11.1–20.3) for patients in the 18-mg arm (Fig. 2A). The median OS was 27.0 mo (95% CI 18.3–NE) in the 14-mg arm and not reached (95% CI 23.8 months–NE) in the 18-mg arm (Fig. 2B). The median PFS following next-line therapy was 18.2 mo (95% CI 13.1–22.5) in the 14-mg arm versus 19.5 mo (95% CI 14.1–23.8) in the 18-mg arm.

Table 1 – Baseline demographics (full analysis set)

Characteristic	Lenvatinib 14 mg + everolimus (*n* = 172)	Lenvatinib 18 mg + everolimus (*n* = 171)
Age (yr), median (Q1, Q3)	61 (55, 67)	62 (55, 68)
Sex (male), *n* (%)	133 (77)	129 (75)
KPS score at baseline (>90), *n* (%)	128 (74)	124 (73)
ECOG performance status, *n* (%)		
0	128 (74)	124 (73)
≥1	44 (26)	44 (26)
Missing	0 (0)	3 (1.8)
IMDC prognostic risk group, *n* (%)		
Favorable risk	25 (15)	38 (22)
Intermediate risk	107 (62)	78 (46)
Poor risk	40 (23)	52 (30)
Missing	0 (0)	3 (1.8)
MSKCC prognostic risk group [a,b], *n* (%)		
Favorable risk	49 (28)	50 (29)
Intermediate risk	93 (54)	90 (53)
Poor risk	30 (17)	31 (18)
Number of metastatic sites by investigator, *n* (%)		
1	19 (11)	24 (14)
2	57 (33)	57 (33)
≥3	96 (56)	90 (53)
Sites of metastasis by investigator [c], *n* (%)		
Bone	59 (34)	64 (37)
Brain	8 (4.7)	9 (5.3)
Liver	42 (24)	43 (25)
Lung	114 (66)	124 (73)
Lymph node	97 (56)	99 (58)
Adrenal	41 (24)	25 (15)
Other	104 (60)	102 (60)
Prior nephrectomy, *n* (%)		
Yes	146 (85)	141 (82)
Prior anti–PD-1/PD-L1 treatment (yes) [b], *n* (%)	49 (28)	41 (24)
Number of prior anticancer therapy regimens, *n* (%)		
1	129 (75)	140 (82)
2	38 (22)	29 (17)
≥3	5 (2.9)	2 (1.2)

ECOG = Eastern Cooperative Oncology Group; IMDC = International Metastatic RCC Database Consortium; KPS = Karnofsky performance status; MSKCC = Memorial Sloan Kettering Cancer Center; PD-1 = programmed death-1; PD-L1 = programmed death ligand-1; Q1 = quartile 1; Q3 = quartile 3; RCC = renal cell carcinoma.

[a] MSKCC prognostic risk groups for the patients in this study (all previously treated) were based on three prognostic factors (low KPS [<80%], low serum hemoglobin level, and high corrected calcium level) [17].

[b] Based on data from the case report form.

[c] Patients may be present in more than one category.

Table 2 – Tumor responses by investigator assessment (PPAS1) [a]

Tumor response	Lenvatinib 14 mg + everolimus (*n* = 156)	Lenvatinib 18 mg + everolimus (*n* = 155)
Tumor response		
Objective response rate as of week 24 (complete response + partial response), % (95% CI)	32 (25–39)	35 (27–42)
Difference, % (90% CI)	−2.8 (−12 to 6.0)	
Odds ratio [b] (90% CI)	0.88 (0.59–1.32)	
p value [c], 1 sided	0.3	
Overall tumor response		
Best overall response, *n* (%)		
Complete response	1 (0.64)	2 (1.3)
Partial response	53 (34)	61 (39)
Stable disease	81 (52)	72 (46)
Progressive disease	7 (4.5)	7 (4.5)
Not evaluable	14 (9.0)	13 (8.4)
Objective response rate, % (95% CI)	35 (27–42)	41 (33–48)
Difference, % (90% CI)	−6.0 (−15 to 3.0)	
Odds ratio [b] (90% CI)	0.77 (0.52–1.14)	
Duration of response (mo), median (95% CI)	11.5 (7.5–19.2)	11.7 (9.1–NE)

CI = confidence interval; IRT = interactive response technology; MSKCC = Memorial Sloan Kettering Cancer Center; NE = not estimable; PD-1 = programmed death-1; PD-L1 = programmed death ligand-1; PPAS1 = per-protocol analysis set 1.

[a] Data are reported per primary efficacy population (PPAS1). This primary efficacy analysis set was evaluated per randomized treatment group, with randomization stratified by the MSKCC risk group (favorable, intermediate, or poor risk) and prior PD-1/PD-L1 inhibitor treatment (yes or no).

[b] The Cochran-Mantel-Haenszel test stratified by the randomization factors MSKCC risk group and prior PD-1/PD-L1 inhibitor treatment from IRT. The intermediate- and poor-risk groups were pooled in this analysis because some patients with MSKCC prognostic score 2 were misclassified into the intermediate-risk group instead of the poor-risk group on the IRT system.

[c] Noninferiority of the objective response rate as of week 24 will be claimed if the one-sided *p* value is ≤0.045.

Among patients in the prior ICI subgroup (14 mg, *n* = 43; 18 mg, *n* = 39), the investigator-assessed ORR was 30% (95% CI 17–46) versus 51% (95% CI 35–68) in the 14-mg versus 18-mg arm. In the prior ICI subgroup, the median PFS for the 14-mg versus 18-mg arm was 12.0 mo (95% CI 8.9–16.7) versus 12.9 mo (95% CI 8.4–NE), and the median OS was 17.1 mo (95% CI 10.6–NE) versus 18.0 mo (95% CI 13.1–NE; Supplementary Fig. 2).

Based on the exploratory analysis, ORR_{wk24} values by IIR were 39% (95% CI 31–47) in the 14-mg arm and 35% (95% CI 27–42) in the 18-mg arm (OR 1.20 [90% CI 0.82–1.76]). There was high concordance for ORR_{wk24} between investigator assessment and IIR for both the 14-mg (83%) and the 18-mg (82%) arm (Supplementary Table 2). Overall ORRs by IIR were 40% (95% CI 32–47) in the 14-mg arm and 39% (95% CI 31–46) in the 18-mg arm (OR 1.04 [90% CI 0.71–1.53]), which also showed high concordance in objective response versus nonresponse between investigator assessment and IIR (>80%). The median PFS by IIR was 11.0 mo (95% CI 9.3–12.9) in the 14-mg arm versus 12.9 mo (95% CI 9.2–17.1) in the 18-mg arm (HR 1.21 [90% CI 0.92–1.59]), which was comparable with the investigator-reported PFS.

The primary safety endpoint assessment indicated that the occurrence of intolerable grade 2 or any grade ≥3 TEAEs in the PPSAS (14 mg, *n* = 157; 18 mg, *n* = 152) was similar in both treatment arms (14 mg, n = 130 [83%] vs 18 mg, n = 121 [80%]; p = 0.5; Table 3).

Most patients (≥99%) in the safety analysis set (*n* = 341) experienced at least one TEAE (Table 4). The most common TEAEs of any grade were generally similar between the 14-mg and 18-mg arms, and included diarrhea (68% vs 72%), decreased appetite (35% vs 35%), hypertension (30% vs 36%), stomatitis (34% vs 28%), and nausea (31% vs 31%).

In the 14-mg arm, 115 of 173 patients (66%) received the increased 18-mg lenvatinib dose (+ everolimus 5 mg) at cycle 2, day 1, and 49 patients (28%) continued on the same dose or a reduced dose (ten of these patients were eligible to be uptitrated but did not receive the increased dose due to patient/clinician choice [*n* = 9] or dose allocation error in the computerized dose allocation system [*n* = 1]). The

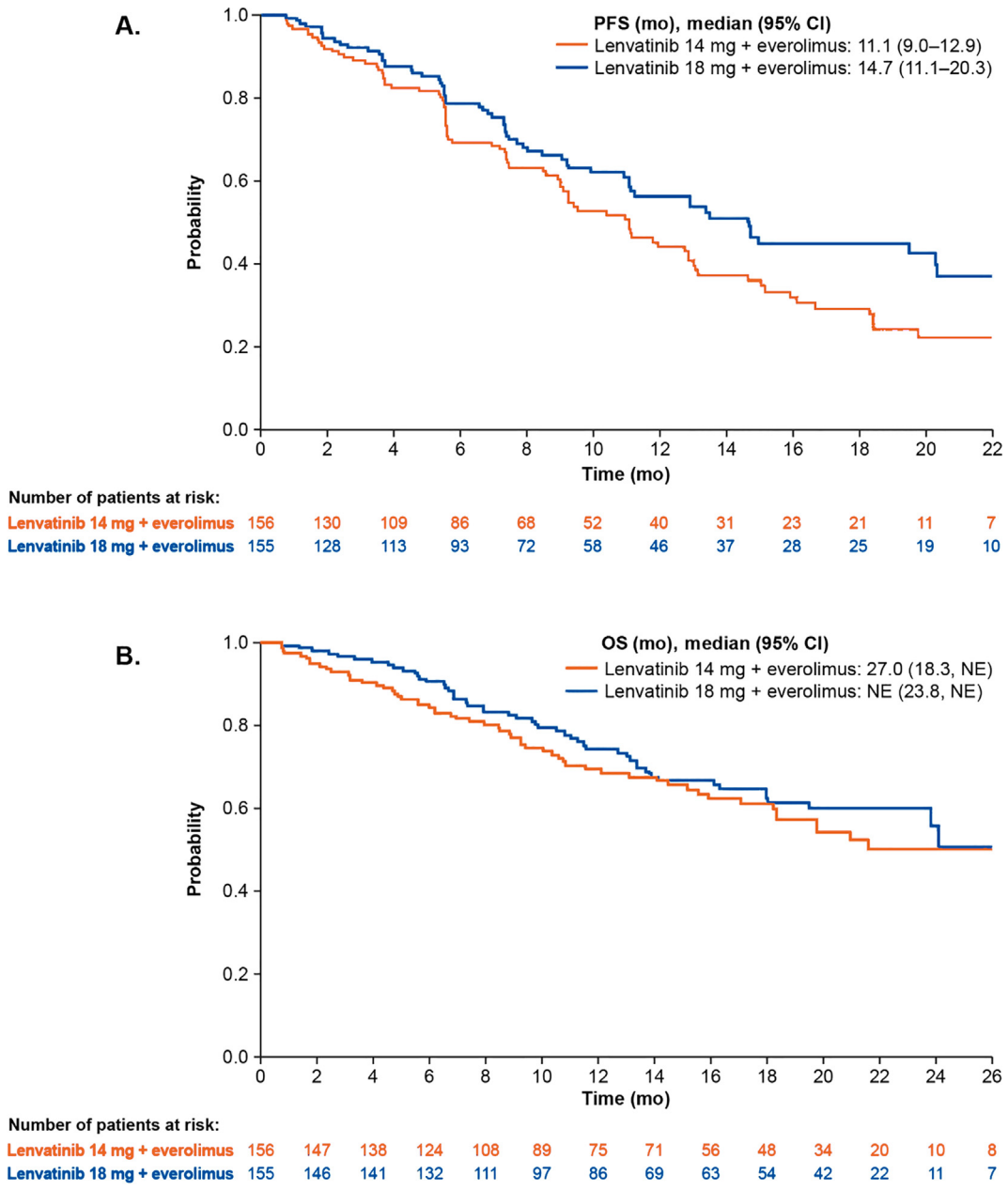

Fig. 2 – Kaplan-Meier estimates of (A) PFS by investigator assessment and (B) OS in the per-protocol analysis set 1. CI = confidence interval; NE = not estimable; OS = overall survival; PFS = progression-free survival.

remaining nine patients (5.2%) discontinued treatment by or as of cycle 2, day 1. Treatment discontinuation due to a TEAE occurred in 32% of patients in the 14-mg arm and 27% in the 18-mg arm (Table 3). The median time to treatment discontinuation due to an AE was 3.2 mo (interquartile range: 1.5, 7.4) for patients in the 14-mg arm versus 5.7 mo (interquartile range: 3.0, 8.0) for those in the 18-mg arm.

The duration of treatment was similar between the 14-mg and 18-mg treatment arms (7.7 vs 8.2 mo). Dose intensity of lenvatinib and everolimus was also similar between the 14-mg and 18-mg arms (13.3 vs 13.8 mg/d for lenvatinib; 4.7 vs 4.6 mg/d for everolimus). Additionally, the received percentage of planned dose was similar between the 14- and 18-mg arms for lenvatinib (80% vs 77%) and everolimus (94% vs 92%).

4. Discussion

Previous studies have demonstrated the benefit of lenvatinib plus everolimus in patients with RCC [5]. Owing to high rates of TEAEs leading to lenvatinib dose reductions and study-drug discontinuations associated with the combination [10], some consider the possibility of starting lenvatinib at a reduced dose. This phase 2 study, which tested a tumor-growth pharmacokinetic/pharmacodynamic model's prediction that a lower starting dose (ie, 14 mg QD) of

Table 3 – Summary of the primary safety endpoint, TEAEs, and treatment-related AEs

Parameter	Lenvatinib 14 mg + everolimus (n = 157) [a]	Lenvatinib 18 mg + everolimus (n = 152)
Patients with intolerable grade 2 or any grade ≥3 TEAEs within 24 wk after randomization in the PPSAS, % (95% CI) [b]	83 (77–89)	80 (73–86)
Difference, % (95% CI)	3.2 (−5.5 to 12)	
p value [c]	0.5	
Characteristic, n (%) in the safety analysis set [d]	**Lenvatinib 14 mg + everolimus (n = 173) [a]**	**Lenvatinib 18 mg + everolimus (n = 168)**
All-grade TEAEs, any cause	173 (100)	167 (99)
Treatment-related all-grade AEs	165 (95)	161 (96)
Intolerable grade 2 AEs	15 (8.7)	11 (6.5)
CTCAE v4.03 grade 3/4 TEAEs	124 (72)	129 (77)
Treatment-related grade 3/4 AEs	108 (62)	113 (67)
Serious AEs	85 (49)	82 (49)
CTCAE v4.03 grade 5 AEs [e]	24 (14)	15 (8.9)
Treatment-related grade 5 AEs [f]	3 (1.7)	3 (1.8)
TEAEs leading to discontinuation	56 (32)	45 (27)
Of both study drugs	41 (24)	32 (19)
Of lenvatinib	45 (26)	37 (22)
Of everolimus	55 (32)	43 (26)
TEAEs leading to dose reduction	117 (68)	117 (70)
Of both study drugs	16 (9.2)	23 (14)
Of lenvatinib	114 (66)	114 (68)
Of everolimus	29 (17)	30 (18)
TEAEs leading to dose interruption	129 (75)	140 (83)
Of both study drugs	100 (58)	111 (66)
Of lenvatinib	105 (61)	117 (70)
Of everolimus	126 (73)	137 (82)

AE = adverse event; CI = confidence interval; CTCAE v4.03 = Common Terminology Criteria for Adverse Events version 4.03; PD-1 = programmed death-1; PD-L1 = programmed death ligand-1; PPSAS = per-protocol safety analysis set; TEAE = treatment-emergent adverse event.

[a] One patient was randomly assigned to the 18-mg arm but received lenvatinib 14 mg as the starting dose and therefore was included in the 14-mg arm in all safety analysis sets.

[b] The PPSAS included all treated patients in the per-protocol analysis set 1.

[c] Cochran-Mantel-Haenszel stratified by Memorial Sloan Kettering Cancer Center risk group and prior PD-1/PD-L1 inhibitor treatment from interactive-response technology.

[d] The safety analysis set included all randomly assigned patients who received one or more doses of study drug.

[e] These CTCAE grade 5 AEs includes TEAEs that are due to disease progression.

[f] For lenvatinib 14 mg: pneumonitis, n = 1; sepsis, n = 1; intestinal sepsis, n = 1; cardiopulmonary failure, n = 1; and for lenvatinib 18 mg: upper gastrointestinal hemorrhage, n = 1; sudden death, n = 1; acute kidney injury, n = 1. In the lenvatinib 14-mg arm, pneumonitis and sepsis occurred in the same patient.

lenvatinib that allows uptitration to the higher dose (ie, 18 mg QD) may result in equivalent or superior tumor reduction, confirms lenvatinib 18 mg QD as the appropriate starting dose (in combination with everolimus 5 mg) for the treatment of patients with advanced RCC after one prior antiangiogenic treatment. To our knowledge, this is the largest and most robust dose-optimization study to date, examining a systemic therapy in patients with advanced RCC.

Based on the primary efficacy endpoint, the current study failed to prove that the 14-mg starting dose of lenvatinib was noninferior to the 18-mg starting dose, when used in combination with everolimus (ORR_{wk24} as per investigator assessment, OR 0.88; p = 0.3). This study also demonstrated a numerical benefit for patients in the 18-mg versus 14-mg arm for overall ORR (investigator assessed), median PFS (by both investigator and IIR assessments), and median OS. As assessed in the exploratory analysis, ORR_{wk24} by IIR was numerically higher for the lenvatinib 14-mg starting dose than for the 18-mg starting dose (OR 1.20). However, this advantage disappears when evaluating the overall ORR by IIR (14-mg arm, 40% [95% CI 32–47] vs 18-mg arm, 39% [95% CI 31–46]). The results demonstrated a high level of concordance (>80%) in the assessment of individual patient responses between investigator and IIR for both ORR and ORR_{wk24}. The discordances seen between investigator assessment and IIR in BOR were primarily because different target lesions were selected at baseline. Importantly, although the lenvatinib dose intensities were similar between the 14-mg and 18-mg starting-dose arms, starting with a lower dose and then escalating to the higher dose do not appear to provide comparable efficacy versus a regimen that starts with a higher lenvatinib dose. Altogether, these results support the approved starting dose of 18-mg lenvatinib plus 5-mg everolimus QD for the treatment of patients with advanced RCC.

The treatment landscape for patients with RCC now includes ICI therapy in the first-line setting, especially for patients in the intermediate/poor prognosis risk category [12]. Similar results (investigator assessed) were observed in this study in patients with prior ICI therapy; specifically, overall ORR, median PFS, and median OS were numerically higher in the 18-mg arm than in the 14-mg arm. Among patients with RCC and prior ICI therapy, both the median PFS of 13 mo and the ORR of 51% observed in this study (in the 18-mg arm) compare favorably with those reported in retrospective analyses (median PFS, range: 6.4–13.2 mo; ORR, range: 10–41%) [13–15]. Therefore, the current study suggests that lenvatinib plus everolimus may hold promise for patients with advanced RCC with disease progression on or after ICI therapy.

Further supporting the lenvatinib 18-mg starting dose, the rate of grade 2 intolerable and grade ≥3 TEAEs reported within the first 24 wk was similar between the two arms (14 mg, 83%; 18 mg, 80%; p = 0.5). The overall safety profile was also similar, including the rate of TEAEs leading to study-drug dose reduction (14 mg, 68%; 18 mg, 70%) or study-drug discontinuation (14 mg, 32%; 18 mg, 27%). Although proteinuria occurred at a lower frequency in the 14-mg (23%) versus 18-mg (36%) arm, this difference largely consisted of low-grade proteinuria events. Interestingly, the time to treatment discontinuation due to a TEAE was shorter in the 14-mg arm (3.2 mo) than in the 18-mg arm (5.7 mo), indicating that using a lower starting dose of lenvatinib (ie, 14 mg) does not necessarily result in longer time on treatment.

Although caution should be used when comparing studies, it is notable that the efficacy outcomes in the lenvatinib 18-mg arm in this study were comparable with those

Table 4 – Most common (frequency ≥10% in either treatment arm) TEAEs in the safety analysis set

Preferred term, *n* (%)	Lenvatinib 14 mg + everolimus (*n* = 173) [a]			Lenvatinib 18 mg + everolimus (*n* = 168)		
	Any grade	Grade 3	Grade 4	Any grade	Grade 3	Grade 4
Patients with any TEAEs [b]	173 (100)	105 (61)	19 (11)	167 (99)	105 (63)	24 (14)
Diarrhea	118 (68)	27 (16)	0	121 (72)	29 (17)	0
Hypertension	52 (30)	18 (10)	0	60 (36)	25 (15)	0
Proteinuria	39 (23)	13 (7.5)	0	60 (36)	16 (9.5)	1 (0.60)
Decreased appetite	61 (35)	6 (3.5)	0	58 (35)	12 (7.1)	0
Nausea	53 (31)	4 (2.3)	0	52 (31)	4 (2.4)	0
Fatigue	50 (29)	10 (5.8)	0	48 (29)	7 (4.2)	0
Stomatitis	59 (34)	8 (4.6)	0	47 (28)	6 (3.6)	0
Vomiting	41 (24)	7 (4.0)	0	42 (25)	7 (4.2)	0
Weight decreased	34 (20)	2 (1.2)	0	41 (24)	7 (4.2)	0
Asthenia	43 (25)	11 (6.4)	0	37 (22)	9 (5.4)	0
Hypertriglyceridemia	35 (20)	15 (8.7)	1 (0.58)	37 (22)	16 (9.5)	4 (2.4)
Hypothyroidism	30 (17)	0	0	31 (18)	0	0
Cough	10 (5.8)	1 (0.58)	0	30 (18)	3 (1.8)	0
Rash	27 (16)	0	0	28 (17)	2 (1.2)	0
Abdominal pain	28 (16)	3 (1.7)	0	26 (15)	6 (3.6)	0
PPES	23 (13)	3 (1.7)	0	26 (15)	0	0
Hypercholesterolemia	31 (18)	5 (2.9)	0	25 (15)	4 (2.4)	1 (0.60)
Epistaxis	26 (15)	1 (0.58)	0	25 (15)	1 (0.6)	0
Edema peripheral	19 (11)	1 (0.58)	0	25 (15)	3 (1.8)	0
Constipation	22 (13)	2 (1.2)	0	25 (15)	0	0
Blood creatinine increased	20 (12)	2 (1.2)	1 (0.58)	24 (14)	2 (1.2)	1 (0.60)
Anemia	31 (18)	11 (6.4)	0	24 (14)	8 (4.8)	0
Dysphonia	19 (11)	0	0	24 (14)	0	0
Dyspnea	15 (8.7)	1 (0.58)	0	22 (13)	4 (2.4)	0
Blood cholesterol increased	13 (7.5)	1 (0.58)	0	22 (13)	1 (0.6)	1 (0.60)
Headache	22 (13)	2 (1.2)	0	19 (11)	1 (0.6)	0
Hypokalemia	10 (5.8)	3 (1.7)	0	19 (11)	6 (3.6)	2 (1.2)
Back pain	16 (9.2)	3 (1.7)	0	17 (10)	4 (2.4)	0
Arthralgia	21 (12)	1 (0.58)	0	16 (9.5)	1 (0.6)	0
Lipase increased	19 (11)	9 (5.2)	4 (2.3)	14 (8.3)	5 (3.0)	3 (1.8)

TEAE = treatment-emergent adverse event; PPES = palmar-plantar erythrodysesthesia syndrome.

[a] One patient was randomly assigned to the 18-mg arm but received lenvatinib 14 mg as the starting dose and therefore was included in the 14-mg arm in all safety analysis sets.

[b] Adverse events terms were coded using Medical Dictionary for Regulatory Activities version 23.0. Grade 5 TEAEs occurred in 24 patients in the 14-mg arm and 15 patients in the 18-mg arm. Patients may have had more than one grade 5 TEAE. Grade 5 TEAEs for the 14-mg arm were large intestinal obstruction (*n* = 1), edema peripheral (*n* = 1), general physical health deterioration (*n* = 1), death (*n* = 2), localized edema (*n* = 1), pneumonitis (*n* = 2), pleural effusion (*n* = 1), pneumothorax (*n* = 1), acute respiratory distress syndrome (*n* = 1), pulmonary hemorrhage (*n* = 1), pneumonia (*n* = 3), sepsis (*n* = 2), appendicitis perforated (*n* = 1), intestinal sepsis (*n* = 1), cardiopulmonary failure (*n* = 1), cardiovascular disorder (*n* = 1), malignant neoplasm progression (*n* = 5), and metastases to lung (*n* = 1); grade 5 TEAEs for the 18-mg arm were intestinal perforation (*n* = 1), upper gastrointestinal hemorrhage (*n* = 1), sudden death (*n* = 1), dyspnea (*n* = 1), pleural effusion (*n* = 1), pneumonia (*n* = 1), encephalitis (*n* = 1), acute kidney injury (*n* = 1), cerebrovascular accident (*n* = 1), cardiac arrest (*n* = 1), cardiac failure (*n* = 1), malignant neoplasm progression (*n* = 4), and hepatic failure (*n* = 1).

previously reported in Study 205 (as assessed by investigator in both studies) [5]. Specifically, the ORR of 41% (95% CI 33–48) and the median PFS of 14.7 mo (95% CI 11.1–20.3) observed in the 18-mg arm of this study corroborate the findings of the pivotal study (Study 205: ORR, 43% [95% CI 29–58]; PFS, 14.6 mo [95% CI 5.9–20.1]) [5] and further demonstrate the promising antitumor efficacy of lenvatinib plus everolimus for patients with advanced RCC. Treatment discontinuations due to TEAEs (27% vs 24% [5]), lenvatinib dose reductions due to any cause (66% vs 71%), and treatment duration (8.2 vs 7.6 mo) were similar between the current (18-mg arm) and the prior (Study 205 [5]) study.

The study design did not allow for a full comparison of PFS between the two treatment arms because the randomized treatment phase of the study ended at the data cutoff date that was set per protocol to occur 6 mo (24 wk) after the last patient had randomly been assigned to treatment.

5. Conclusions

These primary efficacy results show that the lenvatinib 14-mg starting dose is not noninferior to the lenvatinib 18-mg starting dose, in combination with everolimus, for the treatment of patients with advanced RCC after a prior antiangiogenic therapy. Moreover, although we observed some evidence of improved efficacy for the 18-mg starting dose, this study was not designed to test for superiority of the 18-mg starting dose. Safety profiles were comparable between both treatment arms. These results support the currently approved regimen [4,16] of lenvatinib 18 mg plus everolimus 5 mg for the treatment of patients with advanced RCC (after a prior antiangiogenic therapy), with lenvatinib dose reductions as necessary.

***Author contributions*:** Sumanta K. Pal had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Pal, O'Hara, Binder, Peng, Smith.
Acquisition of data: Pal, Puente, Heng, Glen, Koralewski, Stroyakovskiy, Alekseev, Parnis, Castellano, Ciuleanu, Lee, Sunela, Rha.
Analysis and interpretation of data: All authors.
Drafting of the manuscript: Pal, O'Hara, Binder, Smith.
Critical revision of the manuscript for important intellectual content: All authors.

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***Data sharing*:** The data will not be available for sharing at this time because the data are commercially confidential. However, Eisai Inc. will consider written requests to share the data on a case-by-case basis. S.K. Pal (lead/corresponding author) confirms that he had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Appendix A – Supplementary data

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