

Phase IB/II Trial of Lenvatinib Plus Pembrolizumab in Patients With Advanced Renal Cell Carcinoma, Endometrial Cancer, and Other Selected Advanced Solid Tumors

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PURPOSE Modulation of vascular endothelial growth factor–mediated immune suppression via angiogenesis inhibition may augment the activity of immune checkpoint inhibitors. We report results from the dose-finding and initial phase II expansion of a phase Ib/II study of lenvatinib plus pembrolizumab in patients with selected advanced solid tumors.

METHODS Eligible patients had metastatic renal cell carcinoma (RCC), endometrial cancer, squamous cell carcinoma of the head and neck (SCCHN), melanoma, non–small-cell lung cancer (NSCLC), or urothelial cancer. The primary objective of phase Ib was to determine the maximum tolerated dose (MTD) for lenvatinib plus pembrolizumab (200 mg intravenously every 3 weeks). In the preplanned phase II cohort expansion, the primary objective was objective response rate at week 24 (ORR_{week 24}) at the recommended phase II dose.

RESULTS Overall, 137 patients were enrolled during phase Ib (n = 13) and the initial phase II expansion (n = 124). Two dose-limiting toxicities (DLTs; grade 3 arthralgia and grade 3 fatigue) were reported in the initial dose level (lenvatinib 24 mg/d plus pembrolizumab). No DLTs were observed in the subsequent dose–de-escalation cohort, establishing the MTD and recommended phase II dose at lenvatinib 20 mg/d plus pembrolizumab. ORR_{week 24} was as follows: RCC, 63% (19/30; 95% CI, 43.9% to 80.1%); endometrial cancer, 52% (12/23; 95% CI, 30.6% to 73.2%); melanoma, 48% (10/21; 95% CI, 25.7% to 70.2%); SCCHN, 36% (8/22; 95% CI, 17.2% to 59.3%); NSCLC, 33% (7/21; 95% CI, 14.6% to 57.0%); and urothelial cancer 25% (5/20; 95% CI, 8.7% to 49.1%). The most common treatment-related adverse events were fatigue (58%), diarrhea (52%), hypertension (47%), and hypothyroidism (42%).

CONCLUSION Lenvatinib plus pembrolizumab demonstrated a manageable safety profile and promising anti-tumor activity in patients with selected solid tumor types.

J Clin Oncol 38:1154-1163. © 2020 by American Society of Clinical Oncology

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INTRODUCTION

Vascular endothelial growth factor (VEGF), a regulator of angiogenesis in solid malignancies, is an important target in anticancer therapy.¹⁻³ VEGF also affects immune suppression by promoting the expansion of suppressive immune cell populations, such as regulatory T cells and myeloid-derived suppressor cells.³ VEGF suppresses effector T cell development, recruits tumor-associated macrophages to the tumor site, and inhibits the maturation and stimulatory function of dendritic cells.³ This causes inadequate presentation of tumor antigens, resulting in the impaired induction of T-cell–mediated immune responses directed at tumor antigens.³

Preclinical and clinical studies suggest that modulation of VEGF-mediated immune suppression via angiogenesis inhibition could potentially augment

the immunotherapeutic activity of immune checkpoint inhibitors.³⁻⁵ Lenvatinib is a multitargeted tyrosine kinase inhibitor of VEGF receptor 1-3, fibroblast growth factor (FGF) receptor 1-4, platelet-derived growth factor receptor α , RET, and KIT.⁶⁻⁸ Of note, upregulation of FGF has been described as a resistance mechanism to VEGF inhibition.^{9,10} As such, the combined inhibition of VEGF and FGF signaling may contribute to the therapeutic efficacy of lenvatinib.¹¹ Studies in mouse tumor models showed that treatment with lenvatinib combined with an anti–programmed cell death-1 (PD-1) monoclonal antibody demonstrated superior antitumor activity compared with either compound individually.^{4,5,12} These studies provide a strong rationale for the combination of lenvatinib plus pembrolizumab, an anti-PD-1 monoclonal antibody capable of producing significant antitumor immune responses in various solid tumors.¹³

ASSOCIATED CONTENT

Data Supplement Protocol

Author affiliations and support information (if applicable) appear at the end of this article.

Accepted on November 21, 2019 and published at ascopubs.org/journal/jco on January 21, 2020; DOI <https://doi.org/10.1200/JCO.19.01598>

METHODS

Study Design and Treatment

This phase Ib/II, multicenter, open-label study was designed to evaluate the safety, tolerability, and antitumor activity of lenvatinib plus pembrolizumab in patients with advanced renal cell carcinoma (RCC), endometrial cancer, melanoma, squamous cell carcinoma of the head and neck (SCCHN), non–small-cell lung cancer (NSCLC), and urothelial cancer (ClinicalTrials.gov identifier: [NCT02501096](#)). The tumor types were selected based on preliminary evidence of efficacy with lenvatinib and/or a PD-1 inhibitor in other studies where the agents were individually administered.^{4,5,12}

The maximum tolerated dose (MTD) was investigated in the phase Ib dose-finding portion of the study using a dose–deescalation strategy with a 3 + 3 design (Data Supplement). In the phase II portion of the study, all patients received the recommended phase II dose of lenvatinib 20 mg/day with pembrolizumab 200 mg every 3 weeks until disease progression or development of unacceptable toxicity.

The protocol was approved by the relevant institutional review boards or ethics committees and was conducted in accordance with the principles of the Declaration of Helsinki and Good Clinical Practice Guidelines. All patients provided written informed consent prior to study enrollment.

Patients

Key eligibility criteria for phase Ib included histologically or cytologically confirmed metastatic RCC, endometrial cancer, melanoma, SCCHN, NSCLC, or urothelial cancer that progressed after approved therapies or for which no standard therapies were available. There was no limit on the number of prior anticancer therapies during the phase Ib portion of the trial. Key entry criteria for phase II included age \geq 18 years, measurable disease according to immune-related Response Evaluation Criteria in Solid Tumors (irRECIST),¹⁴ \leq 2 prior lines of systemic therapies, Eastern Cooperative Oncology Group performance status score of 0 or 1, blood pressure \leq 150/90 mmHg, and adequate bone marrow, hepatic, and renal function. Patients were not preselected based on any biomarker, including microsatellite instability or programmed cell death-ligand 1 (PD-L1) expression. Key exclusion criteria included prior anticancer treatment within 28 days of the first dose of study drugs, significant cardiovascular impairment, inadequate recovery from toxicities and/or complications resulting from major surgery, and prior therapy with lenvatinib.

Clinical Assessments

The primary objective for phase Ib was to determine the MTD and recommended phase II dose for lenvatinib plus pembrolizumab. The phase II primary endpoint was objective response rate at 24 weeks ($\text{ORR}_{\text{week24}}$), which was defined as best overall response as of week 24. Secondary endpoints for phase II included the overall objective response

rate (ORR), progression-free survival (PFS), and duration of response (DOR).

Tumor responses were evaluated based on investigator assessment per irRECIST using computed tomography or magnetic resonance imaging.¹⁴ Complete and partial responses were confirmed no less than 4 weeks after the initial response. Tumor assessments were performed at baseline, every 6 weeks until week 24, and every 9 weeks thereafter. Radiographic evidence of disease progression was confirmed with repeat imaging at least 4 weeks later. Additional methods are included in the Data Supplement.

Statistical Analysis

The total number of patients required for the phase Ib portion of this study was dependent on the toxicities observed as the study progressed. A sample size of approximately 10 to 30 patients in phase Ib was planned to assess the MTD. For the phase II portion of the study, a sample size of 10 patients was enrolled per cohort, with the possibility of expansion to 20 patients per cohort based on sponsor and investigator evaluation of the efficacy and safety results observed with the initial 10 patients.

The point estimates of response rates and their 2-sided 95% CIs were calculated using the Clopper-Pearson method. Median PFS and DOR and their 2-sided 95% CIs were estimated using the Kaplan-Meier method. All statistical analyses were performed using SAS version 9.0 or higher (SAS Institute, Cary NC).

RESULTS

Patients

Between July 31, 2015, and March 1, 2018, 137 patients were enrolled at 7 centers in the United States. Thirty patients (22%) had RCC, 23 (17%) had endometrial cancer, 22 (16%) had SCCHN, 21 (15%) had melanoma, 21 (15%) had NSCLC, and 20 (15%) had urothelial cancer (Table 1). Most patients (75%) received at least 1 prior systemic therapy before enrollment. The list of prior treatments received by patients is presented in the Data Supplement. At the time of data cutoff (March 1, 2018), 30 patients (22%) were still receiving treatment, and 107 (78%) had discontinued treatment. Sixty-three patients (46%) discontinued treatment because of disease progression, and 27 (20%) discontinued because of adverse events (AEs).

Determination of MTD/Recommended Phase II Dose

Two dose-limiting toxicities (DLTs) were observed in the dose-finding portion of the study in 3 patients (RCC, $n = 2$; NSCLC, $n = 1$) who received the initial starting dose of lenvatinib 24 mg/day and pembrolizumab 200 mg. DLTs consisted of grade 3 arthralgia and grade 3 fatigue. No DLTs were observed in the 10 patients enrolled in the subsequent cohort treated with lenvatinib 20 mg/day plus pembrolizumab 200 mg every 3 weeks. Therefore, oral

TABLE 1. Baseline Demographic and Clinical Characteristics by Tumor Type

Characteristic	RCC (n = 30)	Endometrial (n = 23)	SCCHN (n = 22)	Melanoma (n = 21)	NSCLC (n = 21)	Urothelial (n = 20)	All Cohorts (N = 137)
Phase of enrollment							
Phase IB	8 (27)	2 (9)	0 (0)	1 (5)	2 (10)	0 (0)	13 (9)
Phase II	22 (73)	21 (91)	22 (100)	20 (95)	19 (90)	20 (100)	124 (91)
Median age, years (range)	62.0 (42–76)	64.0 (51–80)	65.5 (47–74)	57.0 (31–80)	65.0 (45–87)	72.0 (40–87)	65 (31–87)
Sex							
Male	25 (83)	0 (0)	18 (82)	17 (81)	10 (48)	14 (70)	84 (61)
Female	5 (17)	23 (100)	4 (18)	4 (19)	11 (52)	6 (30)	53 (39)
Race							
White	25 (83)	20 (87)	20 (91)	19 (91)	18 (86)	19 (95)	121 (88)
Black	2 (7)	0 (0)	2 (9)	0 (0)	3 (14)	0 (0)	7 (5)
Asian	1 (3)	2 (9)	0 (0)	0 (0)	0 (0)	0 (0)	3 (2)
Other	2 (7)	1 (4)	0 (0)	1 (5)	0 (0)	1 (5)	5 (4)
ECOG performance status							
0	20 (67)	7 (30)	9 (41)	9 (43)	6 (29)	6 (30)	57 (42)
1	10 (33)	16 (70)	13 (59)	12 (57)	15 (71)	14 (70)	80 (58)
PD-L1 status							
Positive	12 (40)	12 (52)	18 (82)	14 (67)	10 (48)	10 (50)	76 (56)
Negative	14 (47)	8 (35)	0 (0)	5 (24)	4 (19)	8 (40)	39 (29)
Unknown	4 (13)	3 (13)	4 (18)	2 (10)	7 (33)	2 (10)	22 (16)
No. of prior anticancer therapies							
0	12 (40)	0 (0)	2 (9)	13 (62)	3 (14)	4 (20)	34 (25)
1	10 (33)	6 (26)	14 (64)	7 (33)	7 (33)	11 (55)	55 (40)
2	3 (10)	14 (61)	4 (18)	1 (5)	10 (48)	5 (25)	37 (27)
≥ 3	5 (17)	3 (13)	2 (9)	0 (0)	1 (5)	0 (0)	11 (8)
Prior therapy							
Anti-PD-1/PD-L1	0 (0)	0 (0)	1 (5)	2 (10)	11 (52)	0 (0)	14 (10)
Anti-CTLA-4	0 (0)	0 (0)	0 (0)	7 (33)	0 (0)	0 (0)	7 (5)
Platinum based	1 (3)	23 (100)	17 (77)	0 (0)	18 (86)	16 (80)	75 (55)
Anti-VEGF	17 (57)	1 (4)	0 (0)	0 (0)	2 (10)	0 (0)	20 (15)

NOTE. Values are presented as No. (%) unless otherwise indicated.

Abbreviations: CTLA-4, cytotoxic T-lymphocyte antigen-4; ECOG, Eastern Cooperative Oncology Group; NSCLC, non-small-cell lung cancer; PD-1, programmed cell death-1; PD-L1, programmed cell death-ligand 1; RCC, renal cell carcinoma; SCCHN, squamous cell carcinoma of the head and neck; VEGF, vascular endothelial growth factor.

lenvatinib 20 mg/day and intravenous pembrolizumab 200 mg every 3 weeks was established as the MTD and the recommended phase II dose.

Safety

Treatment-related AEs (TRAEs) were reported in 97% (133/137) of patients (Table 2). Because AEs were similar across the cohorts, the overall safety profile is described in aggregate (Data Supplement). The most common any-grade TRAEs across all cohorts were fatigue (58%; 79/137), diarrhea (52%; 71/137), hypertension (47%; 64/137), hypothyroidism (42%; 58/137), and decreased

appetite (39%; 54/137). Grade 3-4 TRAEs were reported in 67% (92/137) of patients. The most common grade 3-4 TRAEs across all cohorts were hypertension (20%; 28/137), fatigue (12%; 17/137), diarrhea (9%; 12/137), proteinuria (8%; 11/137), and increased lipase levels (7%; 9/137; Table 2).

TRAEs resulted in the following treatment modifications: lenvatinib dose reduction and/or interruption (85%; 116/137), lenvatinib discontinuation (13%; 18/137), pembrolizumab dose interruption (45%; 62/137), and pembrolizumab discontinuation (15%; 20/137; Table 2). The most common AEs reported as reasons for lenvatinib

TABLE 2. Summary of Treatment-Related AEs (any-grade frequency of $\geq 10\%$, grade 3 frequency of $\geq 2\%$, and all grade 4)

		Lenvatinib Plus Pembrolizumab (N = 137), No. (%)		
Parameter				
Patients with treatment-related AEs		133 (97)		
Grade 3		82 (60)		
Grade 4		10 (7)		
Serious AEs		35 (26)		
Deaths ^a		2 (2)		
Patients with treatment-related AEs leading to:				
Lenvatinib dose reduction and/or interruption		116 (85)		
Lenvatinib discontinuation		18 (13)		
Patients with treatment-related AEs leading to:				
Pembrolizumab dose interruption		62 (45)		
Pembrolizumab discontinuation		20 (15)		
Patients with treatment-related AEs	Any Grade	Grade 3	Grade 4	
Fatigue	79 (58)	17 (12)	0 (0)	
Diarrhea	71 (52)	12 (9)	0 (0)	
Hypertension	64 (47)	28 (20)	0 (0)	
Hypothyroidism	58 (42)	1 (1)	0 (0)	
Decreased appetite	54 (39)	3 (2)	0 (0)	
Proteinuria	49 (36)	11 (8)	0 (0)	
Nausea	44 (32)	0 (0)	0 (0)	
Dysphonia	41 (30)	2 (2)	0 (0)	
Stomatitis	41 (30)	1 (1)	0 (0)	
Arthralgia	38 (28)	3 (2)	0 (0)	
Decreased weight	29 (21)	2 (2)	0 (0)	
Palmar-plantar erythrodysesthesia syndrome	27 (20)	3 (2)	0 (0)	
Vomiting	26 (19)	0 (0)	0 (0)	
Oropharyngeal pain	18 (13)	4 (3)	0 (0)	
Pruritus	17 (12)	1 (1)	0 (0)	
Dry skin	16 (12)	0 (0)	0 (0)	
Cough	15 (11)	0 (0)	0 (0)	
Maculopapular rash	15 (11)	1 (1)	0 (0)	
Headache	14 (10)	0 (0)	0 (0)	
Increased lipase	14 (10)	5 (4)	4 (3)	
Oral pain	14 (10)	1 (1)	0 (0)	
Dry mouth	13 (10)	0 (0)	0 (0)	
Dehydration	9 (7)	5 (4)	0 (0)	
Increased ALT	8 (6)	3 (2)	0 (0)	
Increased AST	7 (5)	2 (2)	1 (1)	
Colitis	5 (4)	2 (2)	0 (0)	
Hyponatremia	5 (4)	4 (3)	0 (0)	
Decreased platelet count	5 (4)	2 (2)	0 (0)	
Acute kidney injury	4 (3)	2 (2)	0 (0)	
Increased amylase	4 (3)	2 (2)	0 (0)	
Cholecystitis	2 (2)	2 (2)	0 (0)	

(continued on following page)

TABLE 2. Summary of Treatment-Related AEs (any-grade frequency of $\geq 10\%$, grade 3 frequency of $\geq 2\%$, and all grade 4) (continued)

Parameter	Lenvatinib Plus Pembrolizumab (N = 137), No. (%)		
Pulmonary embolism	2 (2)	2 (2)	0 (0)
Adrenal insufficiency	9 (7)	1 (1)	1 (1)
Hypomagnesemia	9 (7)	1 (1)	1 (1)
Pneumonitis	4 (3)	0 (0)	1 (1)
Hypertensive encephalopathy	2 (2)	1 (1)	1 (1)
Gastrointestinal perforation	1 (1)	0 (0)	1 (1)

NOTE. The 3 patients who received lenvatinib 24 mg/day in the dose-finding portion of the study were included in this analysis. Of note, analysis without these patients did not substantially alter the data presented here.

Abbreviation: AE, adverse event.

^aTwo grade 5 events were considered to be treatment related: gastrointestinal hemorrhage (n = 1) and pulmonary hemorrhage (n = 1).

dose reduction and/or interruption were fatigue (26%; 35/137), diarrhea (23%; 31/137), hypertension (17%; 23/137), decreased appetite (16%; 22/137), and proteinuria (11%; 15/137). The most common AEs leading to pembrolizumab dose interruption were fatigue (10%; 13/137), diarrhea (7%; 10/137), decreased appetite (5%; 7/137), dyspnea (4%; 5/137), and nausea (4%; 4/137). Of the 5 patients with dyspnea, 1 patient experienced pneumonitis. AEs leading to lenvatinib or pembrolizumab discontinuation are shown in the Data Supplement.

In total, 21 deaths occurred in the study. Two were deemed treatment related: 1 patient with NSCLC (pulmonary hemorrhage) and 1 patient with urothelial cancer (gastrointestinal hemorrhage).

Prespecified AEs of special interest (ie, previously associated with drug exposure) were recorded also. For pembrolizumab, these were considered to be immune mediated. Potentially immune related, TRAEs occurred in 52% (71/137) of patients; grade 3 or 4 immune-related AEs occurred in 8% (11/137) and 2% (2/137) of patients, respectively (Table 3). The most common immune-related grade 3 and 4 TRAEs of special interest for pembrolizumab were adrenal insufficiency and colitis (1.5% each).

TRAEs of special interest for lenvatinib occurred in 80% (110/137) of patients; grade 3 or 4 TRAEs of special interest occurred in 33% (45/137) and 2% (3/137) of patients, respectively. The most common grade 3 and 4 TRAEs of special interest for lenvatinib were hypertension (20%), AST increased, ALT increased, and palmar-plantar erythrodysesthesia syndrome (2% each).

Efficacy

Among patients in the RCC cohort, the primary endpoint of ORR_{week24} was 63% (19/30; 95% CI, 43.9% to 80.1%) and, at data cutoff, the overall ORR was 70% (21/30; 95% CI, 50.6% to 85.3%; Table 4). The median DOR was 20.0 months (95% CI, 9.0 to 22.9 months), and the median PFS was 19.8 months (95% CI, 9.9 to 24.1 months).

Overall, 30% (9/30) of patients with RCC were still receiving treatment at the time of data cutoff for this analysis.

The ORR_{week24} and overall ORR for patients with endometrial cancer were both 52% (12/23; 95% CI, 30.6% to 73.2%; Table 4). The median DOR was not reached (95% CI, 2.6 months to not evaluable [NE]), and the median PFS was 9.7 months (95% CI, 4.2 months to NE).

TABLE 3. Potentially Immune-Related Adverse Events

Patients With Adverse Events ^a	Any Grade	Grade 3	Grade 4
	No. (%)	No. (%)	No. (%)
Hypothyroidism ^b	58 (42)	1 (1)	0 (0)
Adrenal insufficiency	9 (7)	1 (1)	1 (1)
Hyperthyroidism	8 (6)	0 (0)	0 (0)
Colitis	5 (4)	2 (2)	0 (0)
Thyroiditis, autoimmune thyroiditis	5 (4)	0 (0)	0 (0)
Pneumonitis	4 (3)	0 (0)	1 (1)
Maculopapular rash	1 (1)	1 (1)	0 (0)
Pancreatitis, acute pancreatitis	2 (2)	1 (1)	0 (0)
Erythematous rash	1 (1)	1 (1)	0 (0)
Pruritus	1 (1)	1 (1)	0 (0)
Myasthenic Syndrome	1 (1)	1 (1)	0 (0)
Rhabdomyolysis, myositis	1 (1)	1 (1)	0 (0)
Drug eruption	1 (1)	1 (1)	0 (0)
Autoimmune nephritis	1 (1)	0 (0)	0 (0)

NOTE. Immune-related adverse events were predefined adverse events with a potential immune-mediated etiology and associated with pembrolizumab treatment. The 3 patients who received lenvatinib 24 mg/day were included in this analysis. Analysis without these patients did not substantially alter the data presented here. Of note, the only potentially immune-related adverse event that occurred in patients who received lenvatinib 24 mg/day was hypothyroidism (n = 2; grade 2).

^aAdverse event terms were coded using *Medical Dictionary for Drug Regulatory Affairs* version 20.1.³⁷

^bAdverse events can also be associated with lenvatinib treatment.

TABLE 4. Efficacy Outcomes (investigator review, immune-related RECIST)

Parameter	RCC (n = 30)	Endometrial (n = 23)	SCCHN (n = 22)	Melanoma (n = 21)	NSCLC (n = 21)	Urothelial (n = 20)
Best overall response						
Complete response	0 (0)	2 (9)	1 (5)	1 (5)	1 (5)	1 (5)
Partial response	21 (70)	10 (44)	9 (41)	9 (43)	6 (29)	4 (20)
Stable disease	8 (27)	10 (44)	10 (46)	7 (33)	10 (48)	9 (45)
Progressive disease	1 (3)	1 (4)	0 (0)	3 (14)	2 (10)	2 (10)
Unknown	0 (0)	0 (0)	2 (9)	1 (5)	2 (10)	4 (20)
ORR ^a	21 (70)	12 (52)	10 (46)	10 (48)	7 (33) ^b	5 (25)
(95% CI)	(50.6 to 85.3)	(30.6 to 73.2)	(24.4 to 67.8)	(25.7 to 70.2)	(14.6 to 57.0)	(8.7 to 49.1)
ORR _{Week24}	19 (63)	12 (52)	8 (36)	10 (48)	7 (33)	5 (25)
(95% CI)	(43.9 to 80.1)	(30.6 to 73.2)	(17.2 to 59.3)	(25.7 to 70.2)	(14.6 to 57.0)	(8.7 to 49.1)
Median DOR, months (95% CI)	20.0 (9.0 to 22.9)	NE (2.6 to NE)	8.2 (2.2 to 12.6)	12.5 (2.7 to NE)	10.9 (2.4 to NE)	NE (6.5 to NE)
Median PFS, months (95% CI)	19.8 (9.9 to 24.1)	9.7 (4.2 to NE)	4.7 (4.0 to 9.8)	5.5 (2.6 to 15.8)	5.9 (2.3 to 13.8)	5.4 (1.3 to NE)

NOTE. Values are presented as No. (%) unless otherwise indicated.

Abbreviations: DOR, duration of response; NE, not evaluable; NSCLC, non–small-cell lung cancer; ORR, objective response rate; ORR_{week24}, objective response rate at week 24; PFS, progression-free survival; RCC, renal cell carcinoma; SCCHN, squamous cell carcinoma of the head and neck.

^aORR is defined as the proportion of patients who had a confirmed complete or partial response per independent review by immune-related RECIST at the time of data cutoff. Four patients achieved a response after week 24 (2 patients in the RCC cohort and 2 patients in the SCCHN cohort).

^bTwo patients in the NSCLC cohort with a response (1 complete response and 1 partial response) had received prior programmed cell death-1/programmed cell death-ligand 1 therapy (both nivolumab).

At the time of data cutoff, 30% (7/23) of patients with endometrial cancer were still receiving treatment.

Among patients with melanoma, the ORR_{week24} and overall ORR were both 48% (10/21; 95% CI, 25.7% to 70.2%; Table 4). The median DOR was 12.5 months (95% CI, 2.7 months to NE), and the median PFS was 5.5 months (95% CI, 2.6 to 15.8 months). As of the data cutoff, 10% (2/21) of patients with melanoma remained on treatment.

Patients with SCCHN achieved an ORR_{week24} of 36% (8/22; 95% CI, 17.2% to 59.3%) and an overall ORR of 46% (10/22; 95% CI, 24.4% to 67.8%) (Table 4). The median DOR was 8.2 months (95% CI, 2.2 to 12.6 months), and the median PFS was 4.7 months (95% CI, 4.0 to 9.8 months). In total, treatment was ongoing for 14% (3/22) of patients with SCCHN at the time of data cutoff.

The ORR_{week24} and overall ORR for patients with NSCLC were both 33% (7/21; 95% CI, 14.6% to 57.0%; Table 4). The median DOR was 10.9 months (95% CI, 2.4 months to NE), and the median PFS was 5.9 months (95% CI, 2.3 to 13.8 months). Overall, 29% (6/21) of patients with NSCLC continued to receive treatment at the time of data cutoff.

Patients in the urothelial cancer cohort achieved an ORR_{week24} and overall ORR of 25% (5/20; 95% CI, 8.7% to 49.1%; Table 4). The median DOR was not reached (95% CI, 6.5 months to NE), and the median PFS was 5.4 months (95% CI, 1.3 months to NE). At the time of data cutoff, treatment was ongoing for 15% (3/20) of patients with urothelial cancer.

Maximum changes in tumor size are shown in Figure 1. Overall, 47% (65/137) of patients achieved a complete or partial response (Fig 2). Efficacy outcomes by PD-L1 status are summarized for each tumor type in the Data Supplement.

DISCUSSION

In this phase Ib/II study, lenvatinib plus pembrolizumab demonstrated an acceptable safety profile and encouraging antitumor activity in patients with selected solid tumors. The MTD and recommended phase II dose were determined to be lenvatinib 20 mg once daily plus pembrolizumab 200 mg every 3 weeks.

The safety profile of lenvatinib plus pembrolizumab was consistent with that observed in prior lenvatinib and pembrolizumab monotherapy trials, with no unexpected AEs.¹⁵⁻²³ In general, toxicities were manageable with supportive care medications, treatment interruption and discontinuation, and/or lenvatinib dose reductions.

Hypothyroidism is commonly observed in patients treated with lenvatinib or pembrolizumab monotherapies.^{15,16,19,20,22-24} However, because of overlapping toxicities, the incidence of hypothyroidism was higher in patients treated with the lenvatinib plus pembrolizumab combination (42%) than in patients who received lenvatinib (16% to 35%) or pembrolizumab (6% to 10%) monotherapy in previous clinical trials.^{15,16,19,20,22-24}

Overall, in this study, TRAEs resulted in dose reductions and interruptions for 87 (64%) and 96 (70%) patients, respectively; the median time to dose reduction was

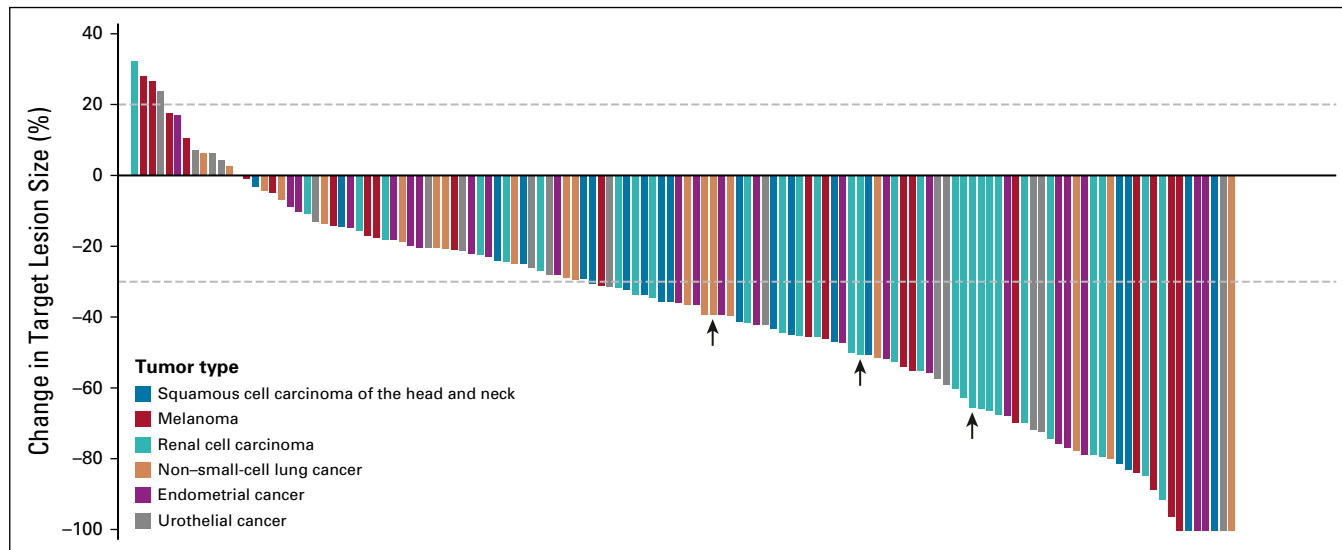


FIG 1. Maximum change in target lesion size by tumor type (investigator review, immune-related RECIST). Arrows indicate patients from phase Ib treated with lenvatinib 24 mg/day.

approximately 2 months. The rates of dose reduction reported in previous clinical trials with lenvatinib monotherapy were 68% and 62% for patients with differentiated thyroid cancer and RCC, respectively.^{16,17} Starting lenvatinib at a high dose and using dose reductions to ameliorate toxicities has been a successful strategy across several trials with lenvatinib and may contribute to the efficacy of lenvatinib. This strategy allows for strong inhibition of VEGF for several months before dose reduction (the median time to first dose reduction was 3 months in patients with differentiated thyroid cancer¹⁷). Although a significant number of patients required lenvatinib dose reductions because of TRAEs in the current study, several of these patients continued to have a durable response for several months after dose reduction.

Treatment discontinuation due to TRAEs in our study was observed in 16% of patients. Similarly, Schlumberger et al¹⁷ reported that 14% of patients with differentiated thyroid cancer discontinued treatment because of lenvatinib-related toxicities. In a phase II study of lenvatinib and everolimus in RCC, treatment-emergent AEs led to treatment discontinuation in 25% of patients who received single-agent lenvatinib.¹⁶

Across cohorts, ORRs ranged from 25% to 70%, with the most favorable responses seen among patients with RCC (70%), endometrial cancer (52%), and melanoma (48%). These encouraging response rates are particularly interesting when viewed in the context of clinical trial results with either lenvatinib or pembrolizumab given as monotherapies to patients with these tumor types. Lenvatinib monotherapy resulted in an ORR of 27% in the second-line treatment of RCC in a previously reported study.¹⁶ The Keynote 427 trial that evaluated pembrolizumab as first-line therapy in patients with advanced clear-cell RCC showed an

ORR of 34%.²⁵ Additionally, response rates in our trial for patients with RCC were promising compared with the response rates of recently approved tyrosine kinase/immune checkpoint inhibitor combinations. In 2 separate phase III studies of previously untreated advanced clear-cell RCC, pembrolizumab plus axitinib showed an ORR of 59%, and avelumab plus axitinib demonstrated an ORR of 55% (in patients with PD-L1-positive tumors).^{26,27} Our results suggest that combined inhibition of VEGF and immune checkpoint signaling pathways may result in enhanced antitumor activity in solid tumors, and in particular, advanced RCC, which is known to be sensitive to tyrosine kinase inhibitor therapy, as well as a range of other tumor types considered to be insensitive to VEGF inhibitors. Of note, the ability of lenvatinib to inhibit both FGF receptors 1-4, and VEGF receptors may contribute to the efficacy of lenvatinib plus pembrolizumab in various advanced cancers.

Preclinical studies using murine tumor models demonstrated that lenvatinib pretreatment decreased immunosuppressive tumor-associated macrophages and increased interferon- γ - and granzyme B-producing CD8+ T cells, resulting in significantly greater antitumor activity compared with anti-PD-1 treatment alone. Addition of an anti-PD-1 antibody further upregulated IFN signaling pathways, promoting an angiostatic and immune-activating tumor microenvironment.^{4,5,12,28} Recent clinical trials evaluating combinations of VEGF and PD-1/PD-L1 inhibitors have shown encouraging antitumor activity for the first-line treatment of patients with metastatic RCC.^{26,29} Collectively, the results of preclinical studies and recent clinical trials of anti-VEGF and anti-PD-1/PD-L1 combination therapies provide a strong rationale for this combination.

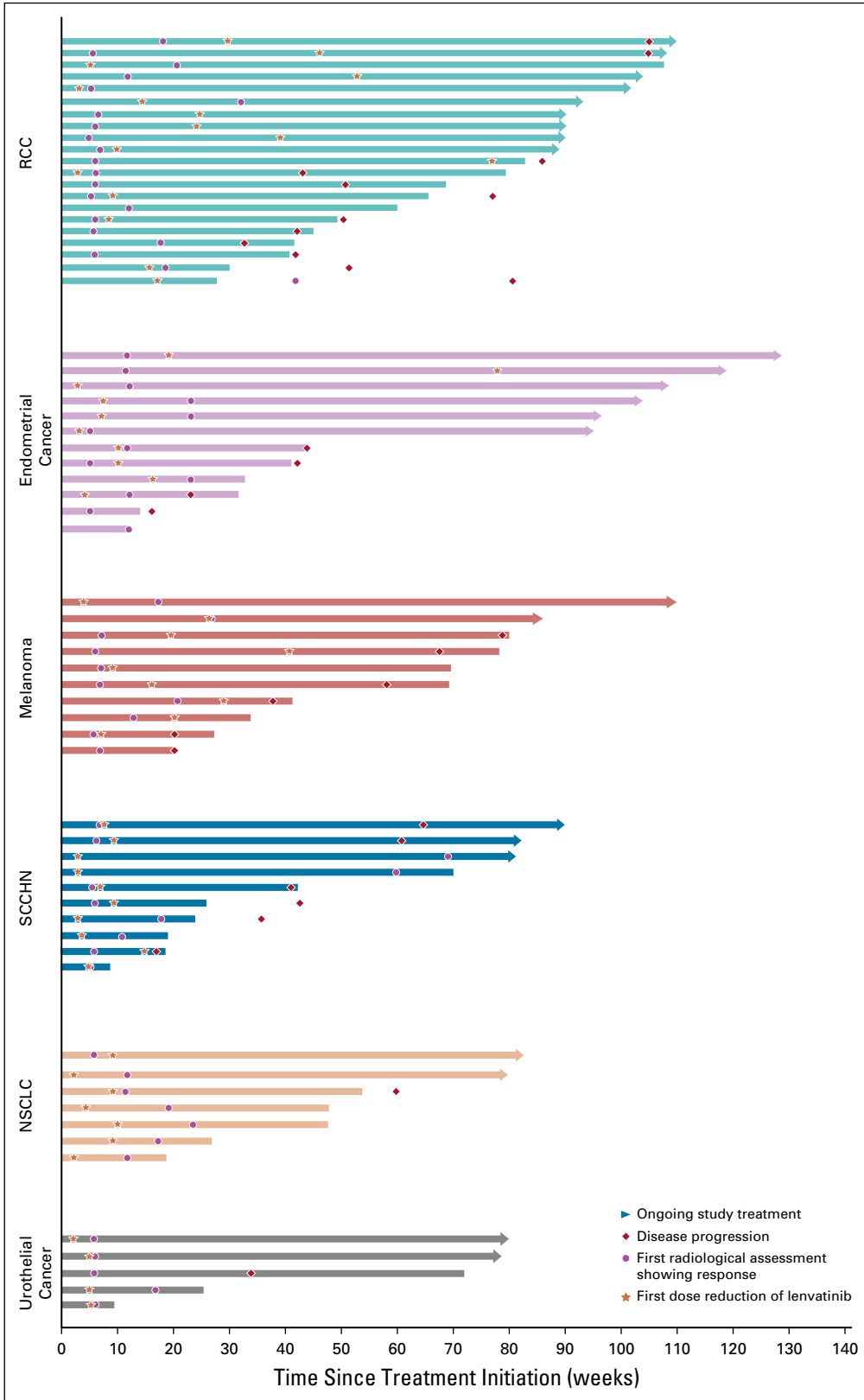


FIG 2. Treatment response and duration for patients achieving a partial response or complete response (investigator review, immune-related RECIST). NSCLC, non-small-cell lung cancer; RCC, renal cell carcinoma; SCCHN, squamous cell carcinoma of the head and neck.

The efficacy observed in patients with advanced endometrial cancer is particularly encouraging. In this clinical trial, 48% of patients with endometrial cancer had been

previously treated with systemic therapy in the metastatic setting. This cohort showed an ORR of 52% and a median PFS of 9.7 months. Interestingly, neither lenvatinib nor

pembrolizumab showed particularly robust clinical activity in this patient population as monotherapies, with reported ORRs of 22% and 13%, respectively.^{30,31} Although pembrolizumab is typically indicated for patients with microsatellite instability–high (MSI-H) tumors, only 25%–35% of patients with endometrial carcinoma are MSI-H.³² In both the RCC and endometrial cancer cohorts, our data suggest that this treatment combination is at least additive.

The Keynote 006 trial showed that pembrolizumab monotherapy in patients with advanced melanoma resulted in an ORR of 36%.³³ Lenvatinib monotherapy in patients with advanced melanoma resulted in an ORR of just 9.7%.³⁴ As such, the ORR of 48% in our combination of lenvatinib plus pembrolizumab represents an encouraging improvement. Additionally, one of the more striking improvements in ORR compared with pembrolizumab monotherapy occurred in the SCCHN cohort. Although the Keynote 012 clinical trial of pembrolizumab in patients with advanced SCCHN showed an ORR of 16% to 18%,^{35,36} this study resulted in an ORR of 45%.

Of note, PD-L1 status did not correlate with ORR in this trial. However, the sample sizes in each cohort were relatively small, and PD-L1 status was not available for several patients. PD-L1 and other biomarkers are being evaluated in ongoing phase III clinical trials with the lenvatinib plus pembrolizumab combination.

Limitations of this study are typical of an early-phase clinical trial and include small numbers of patients treated,

a heterogeneous patient population that was not randomly assigned, and the lack of a comparator treatment arm. Additionally, the PD-L1 status could be determined at any time point (including from archival tissue), and the PD-L1 expression assay has not yet been validated for patients with RCC, SCCHN, endometrial cancer, urothelial cancer, or melanoma.

In conclusion, lenvatinib plus pembrolizumab resulted in a manageable toxicity profile and promising antitumor activity in patients with selected solid tumors. Based on the clinical activity of the combination regimen in this study, additional clinical trials for patients with gastric cancer (ClinicalTrials.gov identifier: [NCT03609359](#)), gastroesophageal cancer (ClinicalTrials.gov identifier: [NCT03321630](#)), and differentiated thyroid cancer (ClinicalTrials.gov identifier: [NCT02973997](#)) are currently under way. Furthermore, the results of this study laid the foundation for 4 large phase III clinical trials in patients with RCC (ClinicalTrials.gov identifier: [NCT02811861](#)), endometrial cancer (ClinicalTrials.gov identifier: [NCT03517449](#)), melanoma (ClinicalTrials.gov identifier: [NCT03820986](#)), and NSCLC (ClinicalTrials.gov identifier: [NCT03829332](#)), which are currently ongoing. In the future, we also plan to study lenvatinib plus pembrolizumab in patients with RCC who have had disease progression after treatment with immune checkpoint inhibitors.

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PRIOR PRESENTATION

Presented at the European Society for Medical Oncology Congress, Copenhagen, Denmark, October 7–11, 2016.

CLINICAL TRIAL INFORMATION

[NCT02501096](#).

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST AND DATA AVAILABILITY STATEMENT

Disclosures provided by the authors and data availability statement (if applicable) are available with this article at DOI <https://doi.org/10.1200/JCO.19.01598>.

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ACKNOWLEDGMENT

We thank the patients, their families, the investigators, and the teams who participated in this trial. We also thank Emmett Schmidt, MD, PhD (Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ); Marcia Brose, MD, PhD (Department of Otorhinolaryngology – Head and Neck Surgery, Abramson Cancer Center of the University of Pennsylvania, Philadelphia, PA); Peter Kubiak, PhD (Eisai Inc., Woodcliff Lake, NJ); and Lea Dutta, Pharm.D (Eisai Inc., Woodcliff Lake, NJ) for their contributions. This study was funded by Eisai Inc., Woodcliff Lake, NJ, and was also supported by Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ. Patients treated at Memorial Sloan Kettering Cancer Center were supported in part by a Memorial Sloan Kettering Cancer Center Support Grant/Core Grant (P30 CA008748). Medical writing and editorial support was provided by Oxford PharmaGenesis Inc., Newtown, PA, and was funded by Eisai Inc., Woodcliff Lake, NJ, and Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST**Phase IB/II Trial of Lenvatinib Plus Pembrolizumab in Patients With Advanced Renal Cell Carcinoma, Endometrial Cancer, and Other Selected Advanced Solid Tumors**

The following represents disclosure information provided by authors of this manuscript. All relationships are considered compensated unless otherwise noted. Relationships are self-held unless noted. I = Immediate Family Member, Inst = My Institution. Relationships may not relate to the subject matter of this manuscript. For more information about ASCO's conflict of interest policy, please refer to www.asco.org/rwc or ascopubs.org/journal/jco/site/ffc.

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No other potential conflicts of interest were reported.