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Platinum Priority – Urothelial Cancer

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Pembrolizumab with or Without Lenvatinib as First-line Therapy for Patients with Advanced Urothelial Carcinoma (LEAP-011): A Phase 3, Randomized, Double-Blind Trial

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Abstract

Background: Pembrolizumab plus lenvatinib has shown antitumor activity and acceptable safety in patients with platinum-refractory urothelial carcinoma (UC).
Objective: To evaluate pembrolizumab plus either lenvatinib or placebo as first-line therapy for advanced UC in the phase 3 LEAP-011 study.
Design, setting, and participants: Patients with advanced UC who were ineligible for cisplatin-based therapy or any platinum-based chemotherapy were enrolled.
Intervention: Patients were randomly assigned (1:1) to pembrolizumab 200 mg intravenously every 3 wk plus either lenvatinib 20 mg or placebo orally once daily.
Outcome measurements and statistical analysis: Dual primary endpoints were progression-free survival (PFS) and overall survival (OS). An external data monitoring committee (DMC) regularly reviewed safety and efficacy data every 3 mo.
Results and limitations: Between June 25, 2019 and July 21, 2021, 487 patients were allocated to receive lenvatinib plus pembrolizumab (n = 245) or placebo plus pembrolizumab (n = 242). The median time from randomization to the data cutoff date

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Urothelial carcinoma

(July 26, 2021) was 12.8 mo (interquartile range, 6.9–19.3). The median PFS was 4.5 mo in the combination arm and 4.0 mo in the pembrolizumab arm (hazard ratio [HR] 0.90 [95% confidence interval {CI} 0.72–1.14]). The median OS was 11.8 mo for the combination arm and 12.9 mo for the pembrolizumab arm (HR 1.14 [95% CI 0.87–1.48]). Grade 3–5 adverse events attributed to trial treatment occurred in 123 of 241 patients (51%) treated with lenvatinib plus pembrolizumab and in 66 of 242 patients (27%) treated with placebo plus pembrolizumab. This trial was terminated earlier than initially planned based on recommendation from the DMC.

Conclusions: The benefit-to-risk ratio for first-line lenvatinib plus pembrolizumab was not considered favorable versus pembrolizumab plus placebo as first-line therapy in patients with advanced UC.

Patient summary: Lenvatinib plus pembrolizumab was not more effective than pembrolizumab plus placebo in patients with advanced urothelial carcinoma.

1. Introduction

First-line standard of care for patients with locally advanced, unresectable, or metastatic urothelial carcinoma (UC; herein termed as advanced UC) is cisplatin-based combination chemotherapy with either gemcitabine or methotrexate, vinblastine, and doxorubicin (known as dose-dense MVAC chemotherapy), followed by switch maintenance avelumab in the absence of disease progression [1]. However, up to half of patients with advanced UC do not tolerate cisplatin-based regimens owing to renal impairment, poor performance status, or other medical comorbidities [2,3]. For these patients, treatment options include carboplatin plus gemcitabine with switch maintenance avelumab for those without disease progression. However, a proportion of patients may not be eligible for any platinum-based chemotherapy because of carboplatin-related toxicities [3,4]. Furthermore, approximately half of all patients may not receive any systemic therapy for advanced UC based on real-world data [5]. Tolerable and effective non–platinum-based first-line treatment regimens for a subset of patients with advanced UC are urgently needed.

Treatment with programmed death 1 (PD-1)/programmed death ligand 1 (PD-L1) inhibitors has expanded the treatment options available for advanced UC. Atezolizumab and pembrolizumab are recommended first-line treatments in the USA for patients who are ineligible for platinum-based chemotherapy [1,6]. In the single-arm phase 2 KEYNOTE-052 trial, pembrolizumab monotherapy was demonstrated to have durable antitumor activity in patients with advanced UC who were ineligible for cisplatin-based chemotherapy [7,8]. The objective response rate (ORR) was 28.6%, median duration of response (DOR) was 30.1 mo, and median overall survival (OS) was 11.3 mo. With a median follow-up of 56.3 mo, ORR was 28.9% and median DOR was 33.4 mo [9]. Based on these results, pembrolizumab was approved by the European Medicines Agency in the first-line setting for cisplatin-ineligible patients whose tumors express PD-L1 (combined positive score [CPS] of $\geq$10), and by the US Food and Drug Administration for patients who are not eligible for any platinum-containing chemotherapy regardless of PD-L1 status [10,11]. The US Food and Drug Administration has since restricted pembrolizumab for use as a single agent for the treatment of patients who are not eligible for any platinum-containing chemotherapy, or who have disease progression during or following platinum-containing chemotherapy or within 12 mo of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy, or for use in combination with enfortumab vedotin for patients who are not eligible for cisplatin-containing chemotherapy [12]. Despite anti–PD-1/L1 agents demonstrating durable responses in the first-line and salvage settings, most patients with advanced UC will experience disease progression and overall poor outcomes [13].

Combination therapy that targets different aspects of tumor biology may overcome resistance and improve antitumor activity [14]. Upregulation of vascular endothelial growth factor (VEGF) is well established in promoting angiogenesis in solid tumors, whereas alterations in the fibroblast growth factor receptor (*FGFR*) gene are common in patients with UC [15,16]. Lenvatinib, a multikinase inhibitor of VEGF receptors, FGFR receptors, and other receptors and oncogenes, in combination with pembrolizumab, showed promising antitumor activity across solid tumors [17]. In preclinical models, lenvatinib decreased the tumor-associated macrophage population, which is an immune regulator in the tumor microenvironment and, thus, increased immune activation [18]. This immune-modulating effect of lenvatinib resulted in a potent and complementary combined effect with anti–PD-1/PD-L1 agents in colorectal and lung cancer models. In the phase 1b/2 KEYNOTE-146/study 111 trial, patients with previously treated advanced UC treated with lenvatinib plus pembrolizumab had an ORR of 25%, and nine patients (45%) had a best response of stable disease, resulting in a 70% disease control rate [17]. This combination also showed a manageable safety profile. We hypothesized that lenvatinib plus pembrolizumab would be effective with a manageable safety profile as first-line treatment for patients who are ineligible to receive cisplatin-based chemotherapy.

LEAP-011 is a randomized phase 3 trial investigating the efficacy and safety of pembrolizumab plus lenvatinib versus pembrolizumab plus placebo for patients with previously untreated advanced UC who either were ineligible for cisplatin-based chemotherapy and had tumors with a CPS of ≥10 or were considered ineligible for any platinum-based chemotherapy irrespective of CPS.

2. Patients and methods

2.1. Study design and patients

LEAP-011 (NCT03898180) was a randomized, double-blind, multicenter, phase 3 trial that enrolled patients aged ≥18 yr with a histologically or cytologically confirmed diagnosis of advanced UC. Patients had at least one measurable target lesion as per RECIST v1.1 and had not received prior systemic chemotherapy for advanced or metastatic UC (neoadjuvant platinum-based chemotherapy for the treatment of muscle-invasive UC with recurrence >12 mo from the completion of chemotherapy and adjuvant platinum-based chemotherapy following radical surgery with recurrence >12 mo from the completion of chemotherapy were permitted). Eligible patients had an Eastern Cooperative Oncology Group performance status (ECOG PS) score of 0–2, had tumors with PD-L1–positive status (CPS ≥10), and were ineligible to receive cisplatin-based chemotherapy, or had an ECOG PS score of 2 and were considered ineligible to receive any platinum-based chemotherapy, regardless of PD-L1 status.

The protocol and its amendments were approved by the appropriate ethics committee at each center, and the trial was conducted as per Good Clinical Practice guidelines and in accordance with the principles of the Declaration of Helsinki. All patients provided written informed consent.

2.2. Randomization and masking

Patients were assigned randomly using an interactive response technology system. All eligible patients received a treatment/randomization number that identified the patient for all procedures occurring after treatment randomization. Once a treatment/randomization number was assigned to a patient, it could never be reassigned to another patient. A single patient could not have been assigned more than one treatment/randomization number. Randomization was stratified by: (1) patients ineligible for cisplatin-based chemotherapy who had a PD-L1 CPS of ≥10 and an ECOG PS score of 2, (2) patients ineligible for cisplatin-based chemotherapy who had a PD-L1 CPS of ≥10 and an ECOG PS score of 0 or 1, (3) patients considered ineligible for any platinum-based chemotherapy who had a PD-L1 CPS of ≥10 and an ECOG PS score of 2, and (4) patients considered ineligible for any platinum-based chemotherapy who had a PD-L1 CPS of <10 and an ECOG PS score of 2. Patients were randomly assigned (1:1) to receive pembrolizumab plus lenvatinib or pembrolizumab plus placebo. Masking to treatment assignments was maintained at all investigational sites. For platinum-ineligible patients, the investigator was masked to the PD-L1 CPS result. For patients who were ineligible for cisplatin-based chemotherapy, the investigator had knowledge of PD-L1 CPS status (CPS ≥10) but remained masked to the specific CPS.

2.3. Treatment

Lenvatinib 20 mg or placebo was administered orally once daily continually. Patients in both treatment groups received pembrolizumab 200 mg intravenously every 3 wk for up to 35 cycles (approximately 24 mo) until disease progression according to RECIST v1.1, intolerable toxicity, or physician or patient decision to withdraw from the study. If one drug in the combination group was discontinued (eg, because of toxicity), the other drug could be continued. All patients could continue treatment beyond initial RECIST v1.1–defined disease progression if they received clinical benefit as per the investigator and tolerated the treatment. Patients who completed 35 treatment cycles of pembrolizumab and had a best response of stable disease or better, or attained an investigator-determined complete response (CR) after at least eight cycles of pembrolizumab treatment, were eligible for 17 additional cycles of pembrolizumab if they experienced radiographic progressive disease after stopping initial treatment.

2.4. Assessments and endpoints

Disease assessments were performed with computed tomography (CT) or magnetic resonance imaging of the abdomen and pelvis, CT of the chest, and radiographic bone imaging at baseline; response evaluations were done at week 6 and then every 6 wk until week 24, then every 9 wk through week 60, and every 12 wk thereafter. Tumor imaging was performed at the time of treatment discontinuation, and follow-up after treatment occurred every 12 wk until the start of a new anticancer therapy, disease progression, death, withdrawal of consent, or the end of the trial, whichever occurred first. Patient survival status was assessed every 12 wk during follow-up.

Adverse events (AEs) were monitored by investigators throughout treatment and for 30 d thereafter (90 d for serious AEs) or before the initiation of a new anticancer therapy, whichever occurred first. AEs were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0. Clinically relevant AEs for lenvatinib and AEs of special interest for pembrolizumab were based on a prespecified list of terms regardless of attribution to study treatment by the investigator. The dual primary endpoints were progression-free survival (PFS) as per RECIST v1.1 by blinded independent central review (BICR) and OS. The secondary endpoints were ORR as per RECIST v1.1 by BICR, and safety and tolerability.

2.5. Statistical considerations

Planned enrollment was approximately 694 eligible patients, with approximately 347 patients allocated to each treatment group. Prior to the most recent protocol amendment, interim analyses were planned. The first interim analysis was to be performed when at least 530 PFS events and 386 deaths occurred.

An external data monitoring committee (DMC) regularly reviewed safety and efficacy data every 3 mo and determined the benefit-to-risk ratio of lenvatinib plus pembrolizumab. For the sixth DMC review, a nonbinding futility analysis to evaluate efficacy was requested by the DMC and was performed as permitted under the DMC charter. The futility bounds for the difference in proportions of patients with response and PFS were −1% and hazard ratio (HR) ≥1.1, respectively. There was no futility bound for OS. Although first-line lenvatinib plus pembrolizumab showed a manageable safety profile and the criteria for the futility analysis were not met, the DMC recommended trial termination because the benefit-to-risk ratio of lenvatinib plus pembrolizumab was not considered favorable. Patients enrolled already were allowed to continue to receive pembrolizumab monotherapy. The trial was stopped due to a lack of efficacy in the context of added toxicity, but not due to concerns about the safety profile of lenvatinib plus pembrolizumab.

Owing to the early termination of the trial, the protocol was amended to remove hypothesis testing and multiplicity adjustment. The current analysis was not a formal interim analysis and was performed in the 487 participants who were randomly assigned at the study termination.

PFS and OS for each treatment group were estimated using a non-parametric Kaplan-Meier method. A stratified Cox proportional hazard model with the Efron method of tie handling was used to assess the HR and 95% confidence intervals (CIs) for PFS and OS. The stratification factors used for randomization were applied to both the stratified log-rank test and the stratified Cox model. The proportion of patients with an objective response was estimated by treatment group, and 95% CIs were provided by the Clopper-Pearson method.

Safety was assessed in all patients who received at least one dose of study treatment as of the data cutoff. Efficacy was assessed in the intention-to-treat population (all randomized patients). All statistical analyses were performed with SAS, version 9.4 (SAS Institute, Cary, NC, USA). This study is registered with ClinicalTrials.gov (number NCT03898180).

3. Results

3.1. Disposition, demographics, and exposure

Overall, 487 patients were allocated randomly to receive lenvatinib plus pembrolizumab (n = 245 [50%]) or placebo plus pembrolizumab (n = 242 [50%]; Fig. 1). Patient demographics and baseline disease characteristics were well balanced across treatment groups (Table 1). The median age was 74 yr (interquartile range [IQR], 66–79) in the combination arm and 73 yr (IQR, 67–78) in the pembrolizumab arm. In both arms, 83% of patients had an ECOG PS score of 2 and 81% of patients were ineligible for any platinum-based chemotherapy. The median time from randomization to data cutoff date (July 26, 2021) was 12.8 mo (IQR, 6.9–19.3). Patients in the combination arm received a median of five cycles (IQR, 3.0–11) of pembrolizumab and 19.6 mg/d (IQR, 15.2–20.0) of lenvatinib. Patients in the pembrolizumab arm received a median of five cycles (IQR, 3.0–12.0) of pembrolizumab.

At data cutoff, 147 patients in the combination arm and 152 patients in the pembrolizumab arm had discontinued treatment permanently. The primary reasons for treatment discontinuation in both groups were radiographic progression (59 patients in the combination arm and 99 patients in the pembrolizumab arm) and AEs (60 patients in the combination arm and 32 patients in the pembrolizumab arm). The median duration of treatment was 3.9 mo (IQR, 1.5–8.0) in the combination arm and 3.8 mo (IQR, 1.8–8.5) in the pembrolizumab arm.

3.2. Efficacy

The median PFS was 4.5 mo in the combination arm versus 4.0 mo in the pembrolizumab arm (HR 0.90 [95% CI 0.72–1.14]; Fig. 2A). Among patients ineligible for cisplatin-based chemotherapy, the median PFS was 9.5 mo in the combination arm and 7.6 mo in the pembrolizumab arm (HR 0.82 [95% CI 0.45–1.49]; Supplementary Fig. 1A). Among patients ineligible for any platinum-based chemotherapy, the median PFS was 4.1 mo in the combination arm and 2.8 mo in the pembrolizumab arm (HR 0.92 [95% CI 0.72–1.19]; Supplementary Fig. 1B).

At the time of data cutoff, 217 patients had died, including 109 patients in the combination arm and 108 patients in the pembrolizumab arm. The median OS was 11.8 mo in the combination arm versus 12.9 mo in the pembrolizumab arm (HR 1.14 [95% CI 0.87–1.48]; Fig. 2B). Among patients ineligible for cisplatin-based chemotherapy, the median OS was not reached (NR) in both the combination arm and the pembrolizumab arm (HR 0.79 [95% CI 0.36–1.73];

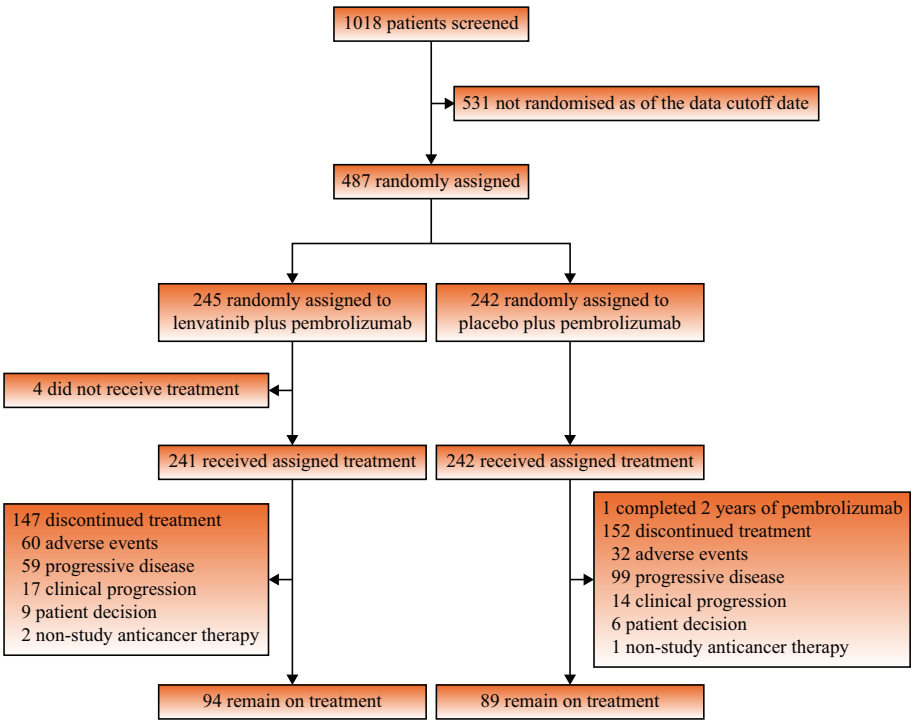

Fig. 1 – CONSORT diagram.

Table 1 – Baseline demographics and disease characteristics

Characteristic	Lenvatinib plus pembrolizumab (n = 245)	Placebo plus pembrolizumab (n = 242)
Age		
Median (IQR)	74 (66–79)	73 (67–78)
<65 yr	47 (19)	46 (19)
Sex		
Male	169 (69)	184 (76)
Region of enrollment		
North America	14 (5.7)	13 (5.4)
Western Europe	91 (37)	94 (39)
Rest of the world	140 (57)	135 (56)
ECOG PS		
2	203 (83)	200 (83)
Chemotherapy-ineligible status[a]		
Considered ineligible for any platinum-based chemotherapy	198 (81)[b]	195 (81)[c]
Metastasis location		
Visceral disease	183 (75)	186 (77)
Liver	61 (25)	63 (26)
Lymph node only	59 (24)	50 (21)
No metastatic visceral disease	3 (1.2)	6 (2.5)

CPS = combined positive score; ECOG PS = Eastern Cooperative Oncology Group performance status; IQR = interquartile range; IVRS = Interactive Voice Response System.
Data are median (range) or n (%).
[a] As per case report form.
[b] Eighty-two (33%) patients had tumors with a CPS of ≥10 per IVRS.
[c] Eighty-one (33%) patients had tumors with a CPS of ≥10 per IVRS.

Supplementary Fig. 2A). Among patients ineligible for any platinum-based chemotherapy, the median OS was 9.7 mo in the combination arm and 10.1 mo in the pembrolizumab arm (HR 1.19 [95% CI 0.90–1.58]; Supplementary Fig. 2B).

ORR was 33% in the combination arm and 29% in the pembrolizumab arm (Table 2); 15 patients (6.1%) in the combination arm and 18 patients (7.4%) in the pembrolizumab arm had a CR. The median DOR was 12.8 mo (95% CI 9.9–NR) in the combination arm and 19.3 mo (95% CI 11.1–NR) in the pembrolizumab arm (Supplementary Fig. 3A). Among patients ineligible for cisplatin-based chemotherapy, ORR was 43% (95% CI 28.3–57.8) in the combination arm and 45% (95% CI 30.2–59.9) in the pembrolizumab arm. The median DOR was NR (95% CI 6.9 mo–NR) in the combination arm and NR (95% CI 6.2 mo–NR) in the pembrolizumab arm (Supplementary Fig. 3B). Among patients ineligible for any platinum-based chemotherapy, ORR was 31% (95% CI 24.5–37.7) in the combination arm and 25% (95% CI 19.2–31.8) in the pembrolizumab arm. The median DOR was 10.8 mo (95% CI 6.2–15.2) in the combination arm and 19.3 mo (95% CI 11.1–NR) in the pembrolizumab arm (Supplementary Fig. 3C).

3.3. *Safety*

Treatment-related AEs were reported in 211 patients (88%) in the combination arm and 167 patients (69%) in the pembrolizumab arm (Table 3). Grade ≥3 treatment-related AEs were reported in 123 patients (51%) in the combination arm and 66 patients (27%) in the pembrolizumab arm. A total of 48 patients (20%) in the combination arm and 22 patients (9%) in the pembrolizumab arm discontinued any therapy because of a treatment-related AE. A total of 54 patients (22%) in the combination arm and 24 patients (10%) in the pembrolizumab arm had a serious treatment-related AE. Six treatment-related deaths attributed to study treatment occurred in the combination arm (pneumonitis [n = 2], cardiac failure [n = 1], cachexia [n = 1], sepsis [n = 1], and unknown cause [n = 1]). One death occurred in the pembrolizumab arm (renal failure).

AEs considered clinically relevant for lenvatinib occurred in 200 patients (83%) in the combination arm and 148 patients (61%) in the pembrolizumab arm (Supplementary Table 1); 107 patients (44%) in the combination arm and 56 patients (23%) in the pembrolizumab arm had grade ≥3 AEs considered clinically relevant for lenvatinib. The most common clinically relevant AEs of any grade were proteinuria (n = 100 [41%]), hypertension (n = 99 [41%]), and hypothyroidism (n = 89 [37%]) in the combination arm and proteinuria (n = 60 [25%]), hypothyroidism (n = 21 [8.7%]), and hematuria (n = 30 [12%]) in the pembrolizumab arm.

AEs of special interest were reported in 116 patients (48%) in the combination arm and 49 patients (20%) in the pembrolizumab arm (Supplementary Table 2). The most common AE of special interest was hypothyroidism in both the combination arm (n = 89; 37%) and the pembrolizumab arm (n = 21; 8.7%). Grade ≥3 AEs of interest occurred in 24 patients (10%) in the combination arm and 15 patients (6.2%) in the pembrolizumab arm.

4. Discussion

First-line lenvatinib plus pembrolizumab showed a manageable safety profile, and although the criteria for the futility analysis were not met, the DMC recommended trial termination because the benefit-to-risk ratio of lenvatinib plus pembrolizumab was not considered favorable. Enrolled patients may continue to receive pembrolizumab monotherapy. The trial was stopped because of a lack of added efficacy in the context of added toxicity, but not because of new concerns about the established safety profile of lenvatinib plus pembrolizumab.

The phase 1b/2 KEYNOTE-146/study 111 trial of lenvatinib plus pembrolizumab showed promising activity in treating advanced UC and several solid tumor types, including renal cell carcinoma, endometrial carcinoma, non–small cell lung cancer, head and neck squamous cell carcinoma, and melanoma [19–21]. Furthermore, lenvatinib plus pembrolizumab is approved by the US Food and Drug Administration and European Medicines Agency for the treatment of advanced renal cell carcinoma and advanced endometrial carcinoma [10,12] However, this study showed no benefit of adding lenvatinib to pembrolizumab as first-line treatment for advanced UC in cisplatin-ineligible patients.

The safety profile of each combination therapy was consistent with previous reports [21,22]. As expected for a combination therapy, a greater proportion of patients in the pembrolizumab plus lenvatinib group experienced treatment-related AEs than those in the placebo plus pembrolizumab group. In addition to the combination therapy effect, this was a relatively frail population, and most

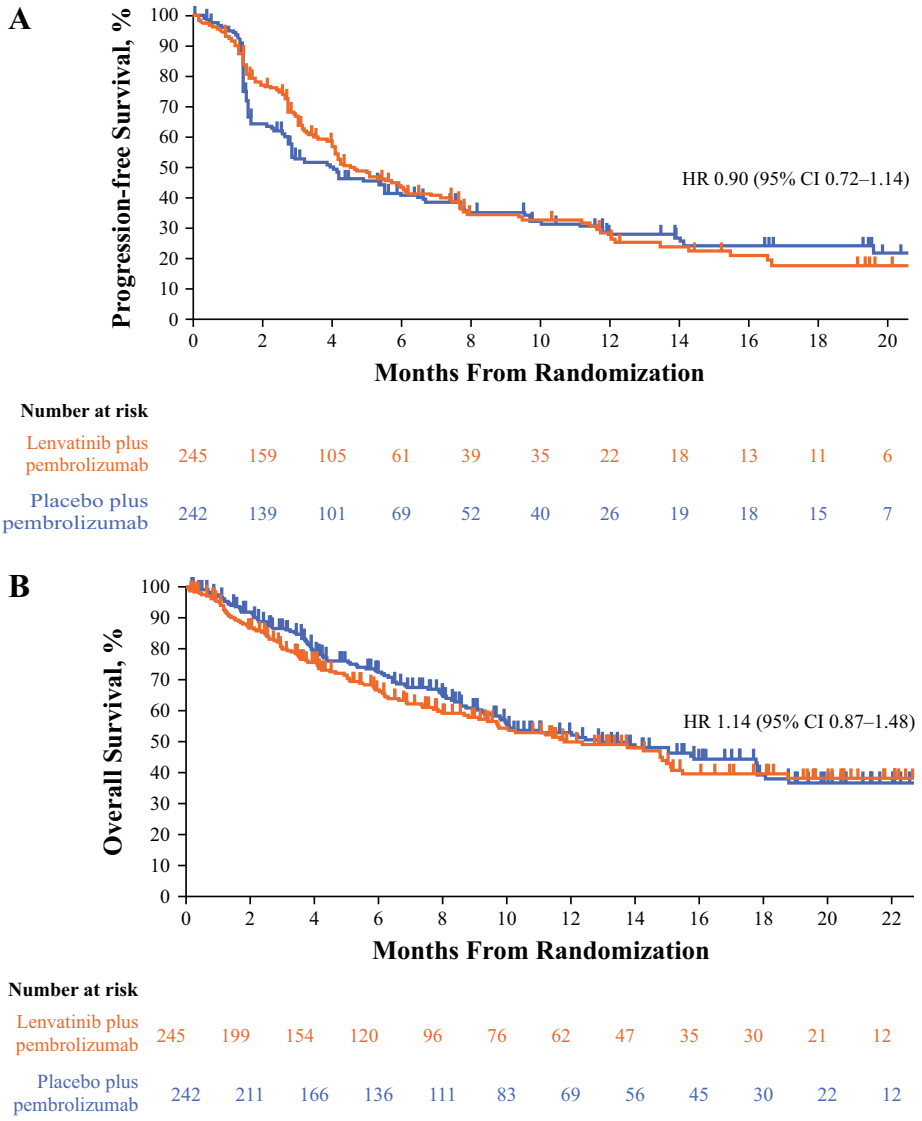

Fig. 2 – Kaplan-Meier estimates of (A) progression-free survival and (B) overall survival in the intention-to-treat population. CI = confidence interval; HR = hazard ratio.

Table 2 – Summary of confirmed objective response assessed as per RECIST version 1.1 by blinded independent central review

Variable	Intention-to-treat population	
	Lenvatinib plus pembrolizumab (*n* = 245)	Placebo plus pembrolizumab (*n* = 242)
Objective response rate (%)	33	29
Best overall response, *n* (%)		
Complete response	15 (6.1)	18 (7.4)
Partial response	66 (27)	52 (21)
Stable disease	83 (34)	66 (27)
Progressive disease	26 (11)	76 (31)
Nonevaluable[a]	13 (5.3)	8 (3.3)
No assessment[b]	42 (17)	22 (9.1)

[a] Patients with insufficient data for the assessment of a response as per RECIST version 1.1.
[b] No postbaseline assessment available for response evaluation.

patients were considered platinum ineligible, had an ECOG PS score of 2, and had visceral metastasis. Traditionally, patients who are defined as cisplatin ineligible have an ECOG PS score of at least 2. In our study eligibility criteria, patients had an ECOG PS score of 0–2, had tumors with CPS ≥10, and were ineligible to receive cisplatin-based chemotherapy, or had an ECOG PS score of 2 and were considered ineligible to receive any platinum-based

Table 3 – Treatment-related adverse events[a,b]

Adverse event	Lenvatinib plus pembrolizumab (n = 241)				Placebo plus pembrolizumab (n = 242)			
	Grade 1 or 2	Grade 3	Grade 4	Grade 5	Grade 1 or 2	Grade 3	Grade 4	Grade 5
Any	88 (37)	99 (41)	18 (7.5)	6 (2.5)	101 (42)	56 (23)	9 (3.7)	1 (0.41)
Proteinuria	63 (26)	28 (12)	0	0	37 (15)	8 (3.3)	0	0
Hypothyroidism	87 (36)	1 (0.41)	0	0	17 (7.0)	0	0	0
Hypertension	40 (17)	43 (18)	1 (0.41)	0	12 (5.0)	5 (2.1)	0	0
Diarrhea	39 (16)	11 (4.6)	0	0	22 (9.1)	3 (1.2)	0	0
Decreased appetite	31 (13)	4 (1.7)	0	0	14 (5.8)	0	0	0
Fatigue	29 (12)	5 (2.1)	1 (0.41)	0	24 (9.9)	5 (2.1)	0	0
Asthenia	25 (10)	4 (1.7)	0	0	11 (4.5)	1 (0.41)	0	0
Lipase level increased	14 (5.8)	8 (3.3)	7 (2.9)	0	6 (2.5)	7 (2.9)	4 (1.7)	0
Nausea	26 (11)	2 (0.83)	0	0	19 (7.9)	1 (0.41)	0	0
Pruritus	27 (11)	0	0	0	35 (14)	0	0	0
Dysphonia	26 (11)	0	0	0	1 (0.41)	0	0	0
Rash	20 (8.3)	4 (1.7)	0	0	13 (5.4)	1 (0.41)	0	0
Pneumonitis	5 (2.1)	1 (0.41)	0	2 (0.83)	4 (1.7)	1 (0.41)	1 (0.41)	0
Cardiac failure	0	2 (0.83)	0	1 (0.41)	0	0	0	0
Renal failure	0	2 (0.83)	0	0	1 (0.41)	1 (0.41)	0	1 (0.41)
Cachexia	0	0	0	1 (0.41)	0	0	0	0
Death	0	0	0	1 (0.41)	0	0	0	0
Sepsis	0	0	0	1 (0.41)	0	0	0	0

[a] Data are presented as n (%). The table shows treatment-related adverse events that occurred in ≥10% of patients in either group, the corresponding grade 3 or 4 events, and all grade 5 events.
[b] Data are from the as-treated population.

chemotherapy, regardless of PD-L1 status. As there was no consensus definition for defining platinum ineligibility, inclusion criteria were determined based on working definitions described in the literature, which include an ECOG PS score of ≥2 [23,24]. Future studies should better define the platinum-ineligible population using consensus-based criteria, whereas dedicated clinical trials should be designed to assess the safety and tolerability of novel agents [23,25].

Several studies have investigated novel first-line treatment for patients who are ineligible for cisplatin-based chemotherapy. In Checkmate-901, ipilimumab plus nivolumab did not prolong OS compared with platinum-based chemotherapy in patients whose tumor cells express PD-L1 ≥1% [26]. The phase 2 BAYOU study of durvalumab plus olaparib did not meaningfully improve PFS compared with durvalumab plus placebo in unselected patients, although very promising activity has been observed in the phase 1/2 EV-103 trial of enfortumab vedotin plus pembrolizumab and the phase 2 NORSE trial of erdafitinib plus cetrelimab [27–30]. The phase 3 EV-302 study is evaluating enfortumab vedotin plus pembrolizumab versus platinum-based chemotherapy in previously untreated advanced UC (switch maintenance avelumab in the control arm was allowed with a later amendment). Durvalumab in combination with tremelimumab plus platinum-based chemotherapy is also being evaluated as treatment for previously untreated advanced UC in the phase 3 NILE trial [31].

Although lenvatinib plus pembrolizumab did not show superior efficacy to pembrolizumab plus placebo, the antitumor activity observed with pembrolizumab plus placebo was consistent with previous results of first-line pembrolizumab monotherapy in advanced UC [8,32]. In the KEYNOTE-052 trial, ORR was 29% in cisplatin-ineligible patients with advanced UC [8,9]. In the phase 3 KEYNOTE-361 trial, ORR was 30.3% with pembrolizumab [32]. The US Food and Drug Administration indication approval at the time of study initiation has since been restricted to platinum-ineligible patients based on the results of the KEYNOTE-361 trial. In both trials, most patients had an ECOG PS score of 0 or 1, whereas most patients in this trial had an ECOG PS score of 2. A subgroup analysis of older patients in KEYNOTE-052, including those with an ECOG PS score of 2, showed a durable benefit with pembrolizumab that was consistent with the overall study population [33]. For context, in the EORTC study 30986 phase 2/3 trial, treatment with gemcitabine plus carboplatin resulted in median OS of 9.3 mo, with an ORR of 25% in cisplatin-ineligible patients with an ECOG PS score of 2 and a glomerular filtration rate of <60 ml/min [34]. Furthermore, LEAP-011 was a randomized, double-blind trial enrolling a higher number of patients in the control arm than the KEYNOTE-052 trial, and the results support the use of pembrolizumab monotherapy as a safe and effective first-line treatment option for patients with advanced UC who may not tolerate platinum-based chemotherapy [12].

Limitations should be considered when interpreting the results. As this trial was terminated earlier than initially planned, there was a relatively short period to evaluate a PFS or OS analysis. The definition of ineligibility to any platinum-based chemotherapy was based on investigator assessment, which may have introduced a selection bias, unmeasured confounding, variability, and heterogeneity into our data. Furthermore, biomarker or patient-reported outcomes are not reported in this manuscript; however, a biomarker analysis has been pursued in other trials evaluating pembrolizumab and may guide future translational research efforts [35].

5. Conclusions

Overall, lenvatinib plus pembrolizumab had a safety profile consistent with previous analyses and did not show a favor-

able benefit-to-risk ratio compared with pembrolizumab plus placebo. First-line pembrolizumab monotherapy remains a standard-of-care option in the USA for patients who are ineligible for any platinum-based chemotherapy regardless of PD-L1 status and in Europe for patients who are cisplatin ineligible and have tumors that express PD-L1 with CPS $\geq$10.

Author contributions: Yohann Loriot 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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Data sharing: Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA (MSD) is committed to providing qualified scientific researchers access to anonymized data and clinical study reports from the company's clinical trials for the purpose of conducting legitimate scientific research. MSD is also obligated to protect the rights and privacy of trial participants and, as such, has a procedure in place for evaluating and fulfilling requests for sharing company clinical trial data with qualified external scientific researchers. The MSD data sharing website (available at: http://engagezone.msd.com/ds_documentation.php) outlines the process and requirements for submitting a data request. Applications will be assessed promptly for completeness and policy compliance. Feasible requests will be reviewed by a committee of MSD subject matter experts to assess the scientific validity of the request and the qualifications of the requestors. In line with data privacy legislation, submitters of approved requests must enter into a standard data-sharing agreement with MSD before data access is granted. Data will be made available for request after product approval in the USA and EU or after product development is discontinued. There are circumstances that may prevent MSD from sharing requested data, including country- or region-specific regulations. If the request is declined, it will be communicated to the investigator. Access to genetic or exploratory biomarker data requires a detailed, hypothesis-driven statistical analysis plan that is collaboratively developed by the requestor and MSD subject matter experts; after approval of the statistical analysis plan and execution of a data-sharing agreement, MSD will either perform the proposed analyses and share the results with the requestor, or construct biomarker covariates and add them to a file with clinical data that are uploaded to an analysis portal so that the requestor can perform the proposed analyses.

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