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Lenvatinib plus pembrolizumab for patients with previously treated advanced ovarian cancer: Results from the phase 2 multicohort LEAP-005 study

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HIGHLIGHTS

- We evaluated lenvatinib plus pembrolizumab as fourth-line therapy in 31 patients with advanced ovarian cancer.
- Lenvatinib plus pembrolizumab had an objective response rate of 35% by blinded independent central review in this population.
- Median duration of response by blinded independent central review was 9.2 (1.5+ to 37.8+) months.
- Median progression-free survival was 6.2 months and median overall survival was 21.3 months.
- Treatment-related adverse events occurred in 94% of patients (grade 3–4, 77%; grade 5, 3%).

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ABSTRACT

Objectives. The phase 2, multicohort, open-label LEAP-005 study evaluated lenvatinib plus pembrolizumab in patients with previously treated advanced solid tumors. We report outcomes from the ovarian cancer cohort.

Methods. Eligible patients had metastatic/unresectable ovarian cancer and had received 3 previous lines of therapy. Patients received lenvatinib 20 mg/day plus pembrolizumab 200 mg every 3 weeks. Treatment continued until progression, unacceptable toxicity, or (for pembrolizumab) completion of 35 cycles. Primary endpoints were objective response rate (ORR) per RECIST version 1.1 and safety. Secondary endpoints included duration of response (DOR), progression-free survival (PFS), and overall survival (OS).

Results. Thirty-one patients were enrolled. 39% had high grade serous ovarian cancer, 23% were platinum-sensitive, 55% were platinum-resistant, 23% were platinum-refractory, and 84% had tumors that had a PD-L1 combined positive (CPS) score ≥1. ORR (95% CI) was 26% (12%–45%) by investigator assessment and 35% (19%–55%) by blinded independent central review (BICR). Per BICR, median DOR was 9.2 (1.5+ to 37.8+) months. ORRs (95% CI) by BICR were 35% (9/26 patients; 17%–56%) for PD-L1 CPS ≥ 1 disease and 50% (2/4 patients; 7%–93%) for PD-L1 CPS < 1 disease. Median (95% CI) PFS by BICR and OS were 6.2 (4.0–8.5) months

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and 21.3 (11.7–32.3) months, respectively. Treatment-related AEs occurred in 94% of patients (grade 3–4, 77%). One patient died from treatment-related hypovolemic shock.

Conclusions. Lenvatinib plus pembrolizumab demonstrated antitumor activity as fourth line therapy in patients with advanced ovarian cancer, and no unanticipated safety signals were identified. Responses were observed regardless of PD-L1 status.

1. Introduction

Approximately 80% of patients with high-grade ovarian cancer have disease that responds to standard of care therapy with chemotherapy; however, many of them experience disease recurrence, which is not curable [1,2]. Most patients with recurrent disease receive multiple subsequent courses of systemic therapy [3]. Systemic treatment options for those with recurrent disease include rechallenge with platinum-based chemotherapy (in patients for whom platinum is considered an option following a platinum-free interval), non-platinum chemotherapy, bevacizumab with or without chemotherapy, and poly(adenosine diphosphate-ribose) polymerase (PARP) inhibitors as maintenance therapy after response to platinum rechallenge [3–5].

The immune checkpoint protein, programmed cell death receptor 1 (PD-1), and its ligand, programmed death ligand 1 (PD-L1), are targets for PD-1 or PD-L1 monoclonal antibodies with recognized activity in many solid tumor types [6,7]. Initial studies of monotherapy with the anti–PD-1 monoclonal antibody pembrolizumab in patients with recurrent ovarian cancer have returned modest results, with objective response rates (ORRs) of 8% to 33%, regardless of PD-L1 status [8–10].

Vascular endothelial growth factor (VEGF) is expressed in nearly all ovarian tumors [11]. The anti-VEGF antibody bevacizumab is considered standard of care therapy for recurrent ovarian cancer in combination with chemotherapy [3,4], based in part on results from the phase 3 AURELIA study, in which the addition of bevacizumab to chemotherapy significantly improved median PFS (but not OS) in patients with platinum-resistant recurrent ovarian cancer [12]. Lenvatinib is a multiple receptor tyrosine kinase inhibitor that inhibits VEGFR1, VEGFR2, and VEGFR3 kinases and has demonstrated efficacy in several tumor types [13–15]. A phase 1 trial of lenvatinib combined with paclitaxel demonstrated a 71% ORR in patients with platinum resistant epithelial ovarian cancer and median progression-free survival (PFS) of 7.2 months [16]. Preclinical studies in murine tumor models demonstrated that the combination of lenvatinib and an anti–PD-1 antibody elicited greater antitumor activity and slower tumor growth compared with either treatment alone [17]. In the clinical setting, the combination of lenvatinib plus pembrolizumab has been shown in phase 3 trials to significantly improve OS and PFS in patients with previously treated advanced endometrial cancer [18] and in patients with previously untreated advanced renal cell carcinoma [19]. Results from these studies led to regulatory approval in these settings.

LEAP-005 (ClinicalTrials.gov, NCT03797326) is a multicohort, open-label phase 2 study evaluating lenvatinib plus pembrolizumab in patients with previously treated selected solid tumors. Herein we report results from the cohort of patients with advanced ovarian cancer who had received 3 prior lines of therapy.

2. Methods

2.1. Eligibility criteria

Patients were eligible for the ovarian cancer cohort if they were aged ≥18 years, had histologic or cytologic documentation of metastatic and/or unresectable epithelial ovarian cancer, and had received 3 prior lines of systemic therapy. Additionally, eligible patients had progression on or after the last treatment; radiologically measurable disease per Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 as confirmed by blinded independent central radiologic review (BICR); Eastern Cooperative Oncology Group performance status of 0 or 1; adequate hematologic, renal, hepatic, and coagulation function; and provision of an archival tumor tissue sample or newly obtained core or excisional biopsy of tumor lesion not previously irradiated for analysis of PD-L1 status. All systemic cytotoxic therapies (including antibody–drug conjugates with a cytotoxic warhead) were considered prior lines of therapy, as was neoadjuvant or adjuvant systemic cytotoxic chemotherapy used in the initial treatment (irrespective of timing). Patients with deleterious or suspected deleterious germline or somatic *BRCA*-mutated disease must have progressed on or had intolerance to PARP inhibition therapy before enrolling in LEAP-005. Key exclusion criteria were radiographic evidence of major blood vessel invasion or infiltration; clinically significant hemoptysis or tumor bleeding ≤2 weeks before starting study drug; significant cardiovascular impairment or arterial thromboembolism ≤12 months before starting study drug; history of arterial thromboembolism within 12 months of start of study drug; serious nonhealing wound, ulcer, or bone fracture; major surgery ≤3 weeks before starting study drug; receipt of biologic response modifiers ≤4 weeks before study entry; pre-existing grade ≥3 fistula; urine protein ≥1 g/24 h; QTc prolongation > 480 ms or left ventricular ejection fraction < 55%; active autoimmune disease that required systemic treatment ≤2 years before study entry; diagnosis of immunodeficiency or receipt of systemic steroid or immunosuppressive therapy ≤7 days before the first dose of study drug; active central nervous system metastasis or carcinomatous meningitis; tumors involving the brainstem; prior or current noninfectious pneumonitis requiring steroids; active infection requiring systemic therapy; prior therapy with lenvatinib, an anti–PD-1, anti–PD-L1, or anti–PD-L2 agent, or any agent directed to another stimulatory or coinhibitory T-cell receptor. Prior use of bevacizumab was not exclusionary.

2.2. Study design

In this phase 2, multicenter, multicohort, open-label study, patients received oral lenvatinib 20 mg/day and intravenous pembrolizumab 200 mg every 3 weeks. Treatment continued until progressive disease (PD) per RECIST version 1.1, unacceptable toxicity, initiation of a new anticancer treatment, pregnancy, intercurrent illness, or patient or physician decision to stop treatment. Pembrolizumab treatment continued for up to 35 administrations (approximately 2 years) or until discontinuation criteria were met; lenvatinib treatment could continue beyond 2 years if the patient experienced clinical benefit. Patients who experienced intolerable toxicity could discontinue one or both study drugs depending on which drug(s) was considered related to the adverse event (AE) by the investigator. In the event of toxicity, doses of study treatment could be adjusted per protocol-specified rules. For pembrolizumab, doses could be temporarily interrupted for certain AEs; for lenvatinib, dose reductions or interruptions were permitted if AEs occurred. Patients could continue pembrolizumab beyond RECIST version 1.1–defined PD if they tolerated treatment and the physician believed the patient would receive clinical benefit.

The study was conducted in compliance with the ethical principles originating from the Declaration of Helsinki and with the International Council on Harmonisation Good Clinical Practice guidelines and all applicable regulations. An institutional review board at each study site approved the protocol, amendments, and informed consent forms before the study began at that site. All patients provided written informed consent to participate.

2.3. Assessments

A central laboratory assessed tumor PD-L1 status using PD-L1 IHC 22C3 pharmDx (Agilent Technologies, Carpinteria, CA, USA). PD-L1 status was determined according to combined positive score (CPS), which was calculated as the number of PD-L1–staining cells (tumor cells, lymphocytes, and macrophages) divided by the total number of tumor cells, multiplied by 100. CPS raw scores were collected prospectively at the time that the samples were evaluated, and PD-L1 status of CPS ≥ 1 versus CPS < 1 was applied retrospectively based on these raw scores.

Tumor imaging by computed tomography or magnetic resonance imaging was done at baseline, every 9 weeks for the first 54 weeks, every 12 weeks until week 102, and every 24 weeks thereafter. Imaging assessments were done until confirmed PD or until patients began a new anticancer treatment or withdrew consent.

The incidence of AEs was monitored at all study visits and for 30 days (90 days for serious AEs) after the last dose. AEs were graded using the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.03.

2.4. Endpoints

The primary efficacy endpoint was ORR as determined by the investigator, with ORR defined as the proportion of patients with a best overall response of complete response (CR) or partial response (PR) per RECIST version 1.1 at any time during the study. Secondary efficacy endpoints included the duration of response (DOR), disease control rate (DCR) and PFS by the investigator; all of which were assessed by BICR in exploratory analyses; and OS. DOR was defined as the time from first documented CR or PR until first documented evidence of PD or death. DCR was defined as the proportion of patients with CR, PR, or stable disease). PFS was defined as the time from first dose of study drug until death or PD per RECIST version 1.1. OS was defined as the time from first dose of study drug until death. ORR by BICR was an exploratory endpoint.

2.5. Statistical analysis

Initially, the study was planned to enroll 30 patients with ovarian cancer, with the potential for cohort expansion up to a total of 100 patients (ie, an additional 70 patients in the expansion phase). Interim analyses, based on investigator assessment, occurred after 30 patients had been enrolled and had approximately 6 months follow-up after study entry. Results from interim analyses were reviewed by the study sponsor and recommendations for cohort expansion provided. Efficacy and safety analyses included all patients who received at least 1 dose of lenvatinib plus pembrolizumab. The ORR and DCR were estimated with point estimates and 95% exact Clopper-Pearson CIs. Summary statistics using the Kaplan-Meier method were provided for analyses of DOR, PFS, and OS. Statistical analyses were done using SAS version 9.4 (SAS Institute, Inc., Cary, NC, USA).

3. Results

3.1. Patient population

Thirty-one patients were enrolled in the ovarian cohort at 20 sites in 9 countries between March 6, 2019 and October 24, 2019. The median time from first dose to data cutoff (February 6, 2023) was 41.7 months (range, 38.5–46.3 months). As of data cutoff, 29 patients (94%) had discontinued study drug, 1 (3%) had completed treatment, and 1 (3%) was receiving ongoing treatment. Reasons for discontinuation were clinical or radiographic progression ($n = 19$ [61%]), AEs ($n = 9$ [29%]), and consent withdrawal (n = 1 [3%]). Sixteen patients (52%) received at least 6 months of treatment with lenvatinib plus pembrolizumab, and 5 (16%) received at least 21 months of treatment. Thirty patients (97%) had received at least 3 prior lines of therapy and 24 (77%) were resistant or refractory to platinum-based chemotherapy (Table 1).

3.2. Objective response

The primary efficacy endpoint of investigator-assessed ORR per RECIST version 1.1 was 26% (95% CI, 12%–45%), which included 1 patient with a CR (3%) and 7 with a PR (23%; Table 2). In the assessment by BICR, the ORR was 35% (95% CI, 19%–55%) and included 3 patients with a CR (adenocarcinoma, high grade serous, papillary serous; n = 1 each) and 8 with a PR (adenocarcinoma, $n = 5$; 2 high grade serous, $n = 2$, papillary serous, n = 1) (Table 2). The median DOR by BICR was 9.2 months (range, 1.5+ to 37.8+ months). Time to response and response duration for individual patients is shown in Fig. 1. Among patients with a response, 80% of patients were estimated (per Kaplan-Meier analysis) to have a response duration ≥6 months, 38% had an estimated response duration ≥12 months, and 25% had an estimated response duration ≥18 months. DCR per BICR assessment was 77% (95% CI, 59%–90%). Among 28 patients with ≥1 postbaseline tumor assessment, 24 patients (86%) had a reduction in tumor size relative to baseline (Fig. 2).

Table 1
Patient demographics and baseline disease characteristics.

	Patients $N = 31$
Age, median (range), y	62 (40–76)
ECOG performance status	
0	22 (71)
1	9 (29)
Metastatic stage	
M0	3 (10)
M1	23 (74)
M1b	5 (16)
PD-L1 status	
PD-L1 CPS ≥ 1	26 (84)
PD-L1 CPS < 1	4 (13)
Missing	1 (3)
No. of prior lines of systemic therapy	
2	1 (3)
3	29 (94)
4	1 (3)
Prior bevacizumab use	
Yes	19 (61)
No	12 (39)
Prior PARP inhibitor use	
Yes	10 (32)
No	21 (68)
Platinum sensitive/resistant status	
Sensitive	7 (23)
Refractory	7 (23)
Resistant	17 (55)
Histologic subtype	
Adenocarcinoma	11 (34)
Carcinosarcoma	1 (3)
Clear cell carcinoma	1 (3)
High-grade serous carcinoma	12 (39)
Low-grade serous carcinoma	1 (3)
Papillary serous (serous carcinoma NOS)	5 (16)

CPS, combined positive score; ECOG, Eastern Cooperative Oncology Group; PARP, poly(adenosine diphosphate-ribose) polymerase; PD-L1, programmed cell death ligand 1.
Unless specified otherwise, data are n (%).

Table 2
Antitumor activity per RECIST version 1.1.

	All Patients $N = 31$	Patients With PD-L1 CPS ≥ 1 Tumors $n = 26$	Patients With PD-L1 CPS < 1 Tumors $n = 4$
Response per investigator review			
ORR (95% CI), %	26 (12–45)	27 (12–48)	25 (1–81)
Best overall response, n (%)			
CR	1 (3)	1 (4)	0
PR	7 (23)	6 (23)	1 (25)
SD	16 (52)	13 (50)	3 (75)
PD	5 (16)	4 (15)	0
No assessment[a]	2 (6)	2 (8)	0
Disease control [CR + PR + SD], n (%)	24 (77)	20 (77)	3 (75)
Response per blinded independent central review			
ORR (95% CI), %	35 (19–55)	35 (17–56)	50 (7–93)
Best overall response, n (%)			
CR	3 (10)	2 (8)	1 (25)
PR	8 (26)	7 (27)	1 (25)
SD	13 (42)	11 (42)	1 (25)
PD	5 (16)	4 (15)	1 (25)
No assessment[a]	2 (6)	2 (8)	0
Disease control [CR + PR + SD], n (%)	24 (77)	20 (77)	3 (75)
Time to response, median (range), mo	2.0 (0.1–3.5)	2.1 (0.1–3.5)	1.9 (1.9–1.9)

CPS, combined positive score; CR, complete response; ORR, objective response rate; PD, progressive disease; PD-L1, programmed cell death ligand 1; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors; SD, stable disease.
[a] "No assessment" included patients who had a baseline assessment but no postbaseline assessment.

Among 26 patients with PD-L1 CPS ≥ 1 disease, 9 had an objective response, providing a BICR-assessed ORR of 35% (95% CI, 17%–56%; 2 CRs and 7 PRs). Among 4 patients with PD-L1 CPS < 1 disease, 2 had an objective response; the ORR was 50% (95% CI, 7%–93%; 1 CR and 1 PR).

3.3. Progression-free survival and overall survival

As of the data cutoff date, 24 patients (77%) had a PFS event. In the overall population, the median PFS was 6.2 months (95% CI, 4.0–8.5 months; Fig. 3A). The 6- and 12-month PFS rates were 51% and 20%, respectively. In 26 patients with PD-L1 CPS ≥ 1 disease, median PFS was 6.2 months (95% CI, 3.9–9.4 months), and in 4 patients with PD-L1 CPS < 1 disease median PFS was 6.3 months (95% CI, 1.8 months–not reached).

At the data cutoff date, 26 patients (84%) had died. The median OS was 21.3 months (95% CI, 11.7–32.3 months; Fig. 3B), and the 6- and 12-month OS rates were 81% and 68%, respectively. In 26 patients with PD-L1 CPS ≥ 1 disease, the median OS was 26.6 months (95% CI, 13.8–33.3 months); and in 4 patients with PD-L1 CPS < 1 disease, median OS was 13.0 months (95% CI, 4.9 months–not reached).

3.4. Safety

Treatment-related AEs were reported for 29 patients (94%), the most common of which were hypertension (68%), diarrhea (48%), fatigue (45%), and decreased appetite and hypothyroidism (42% each; Table 3). Grade 3 treatment-related AEs were reported for 21 patients (68%) and grade 4 treatment-related AEs for 3 patients (10%).

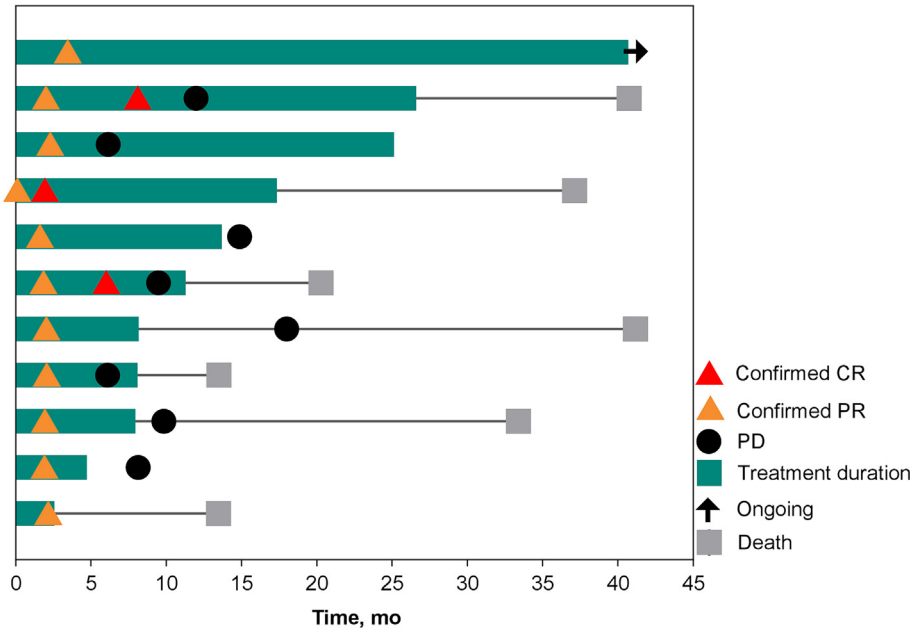

Fig. 1. Time on study treatment and response evaluation per RECIST version 1.1 by blinded independent central review for patients with an objective response (ie, patients with confirmed CR or PR). CR, complete response; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors.

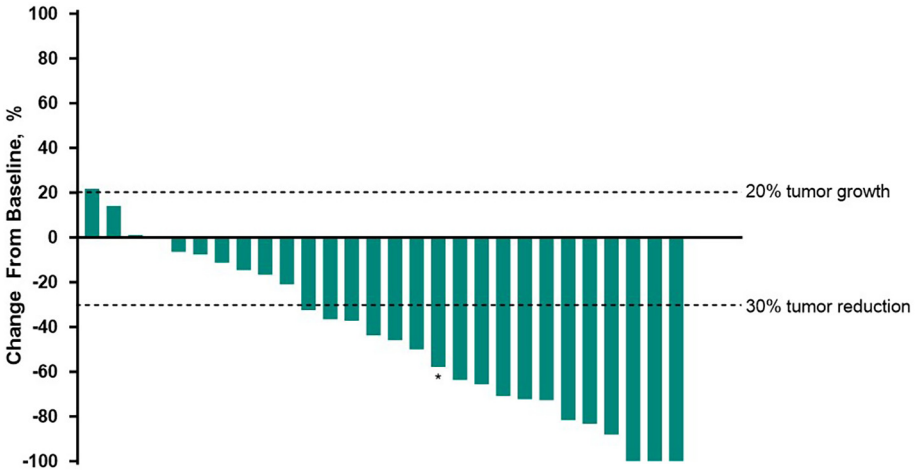

Fig. 2. Best percentage change from baseline in target lesion size per RECIST version 1.1 by blinded independent central review among patients with ≥1 postbaseline assessment. Percentage changes from baseline > 100% are presented as 100%. $n = 28$ (3 patients did not have 6 months of follow up). *Patients who remained on treatment at the time of data cutoff. RECIST, Response Evaluation Criteria in Solid Tumors.

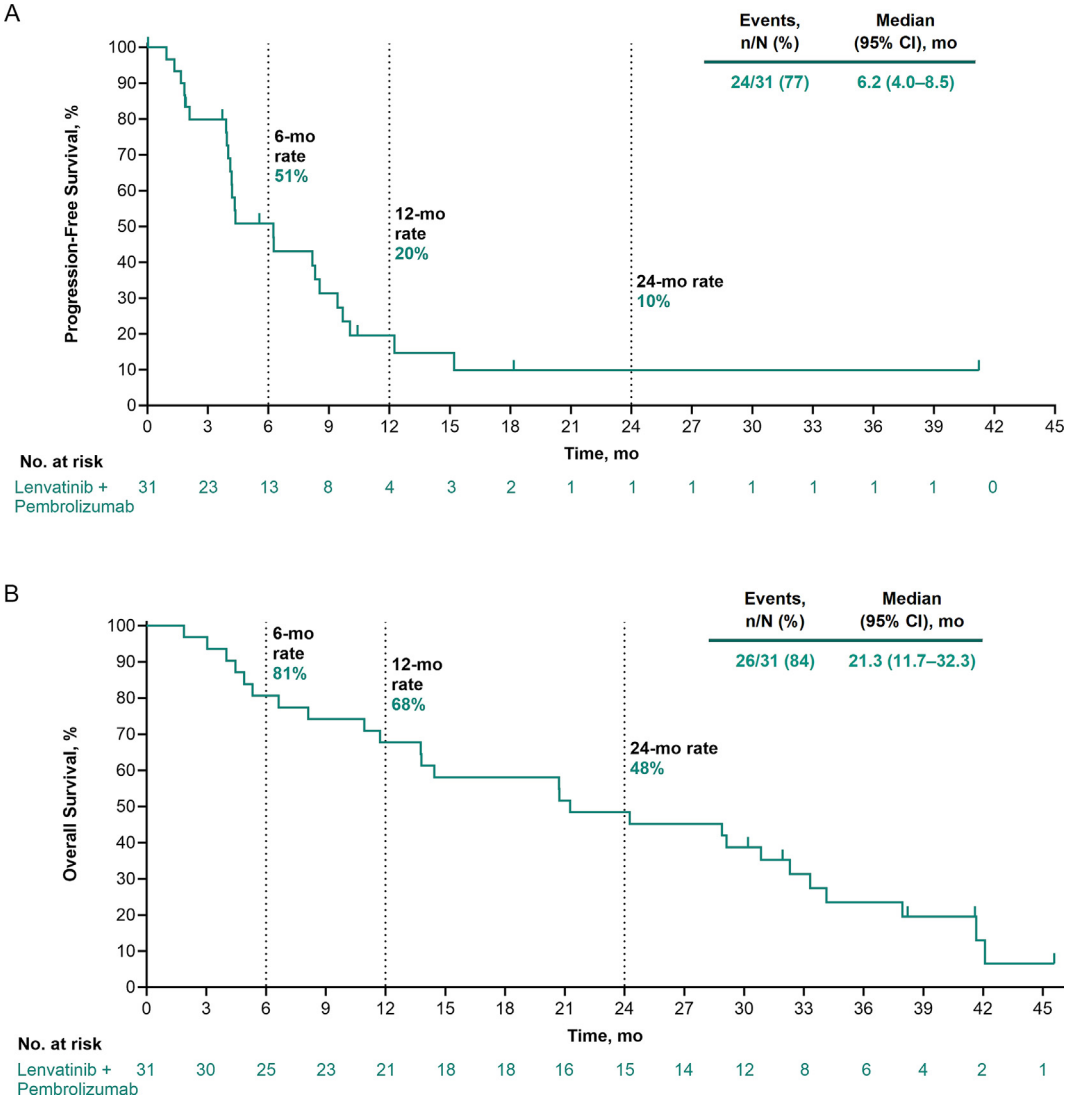

Fig. 3. (A) Progression-free survival per RECIST version 1.1 by blinded independent central review. (B) Overall survival. RECIST, Response Evaluation Criteria in Solid Tumors.

Table 3
Treatment-related adverse events.

	Patients $N = 31$	
Patients with any treatment-related AE[a]	29 (94)	
Grade 3	21 (68)	
Grade 4	3 (10)	
Grade 5[b]	1 (3)	
Led to treatment discontinuation	7 (23)	
	Any Grade	Grade 3/4[b]
Treatment-related AEs occurring in ≥10% of patients		
Hypertension	21 (68)	9 (29)
Diarrhea	15 (48)	3 (10)
Fatigue	14 (45)	4 (13)
Decreased appetite	13 (42)	1 (3)
Hypothyroidism	13 (42)	0
Proteinuria	11 (35)	2 (6)
Mucosal inflammation	10 (32)	0
Vomiting	10 (32)	2 (6)
Headache	9 (29)	1 (3)
Nausea	8 (26)	1 (3)
Myalgia	7 (23)	0
Abdominal pain	6 (19)	1 (3)
Increased alanine aminotransferase	6 (19)	3 (10)
Arthralgia	6 (19)	0
Increased aspartate aminotransferase	6 (19)	2 (6)
Dry mouth	6 (19)	0
Palmar-plantar erythrodysesthesia syndrome	5 (16)	1 (3)
Pruritus	5 (16)	0
Stomatitis	5 (16)	0
Asthenia	4 (13)	1 (3)
Increased blood alkaline phosphatase	4 (13)	1 (3)
Hypomagnesemia	4 (13)	1 (3)
Rash	4 (13)	0
Decreased weight	4 (13)	1 (3)
Patients with any immune-mediated AE or infusion reaction[c]	16 (52)	3 (10)
Hypothyroidism	14 (45)	0
Hyperthyroidism	2 (6)	0
Colitis	1 (3)	0
Infusion reaction	1 (3)	1 (3)
Pancreatitis	1 (3)	1 (3)
Severe skin reactions	1 (3)	1 (3)
Thyroiditis	1 (3)	0
Clinically significant AEs for lenvatinib[c]	29 (94)	17 (55)
Hypertension	21 (68)	9 (29)
Hypothyroidism	14 (45)	0
Proteinuria	13 (42)	3 (10)
Hepatotoxicity	11 (35)	5 (16)
Hemorrhage	6 (19)	1 (3)
Palmar-plantar erythrodysesthesia syndrome	6 (19)	1 (3)
Arterial thromboembolic events	1 (3)	1 (3)
QT prolongation	1 (3)	1 (3)
Renal events	1 (3)	1 (3)
Fistula formation	1 (3)	0

AE, adverse event.
All data are n (%).
[a] Determined by the investigator to be related to study drug.
[b] One patient experienced a grade 5 event of hypovolemic shock that was considered by the investigator to be treatment related.
[c] Events were based on a list of terms (including related terms) specified by the sponsors and considered regardless of attribution by investigators.

The most frequently occurring grade 3 or 4 treatment-related AEs were hypertension (29%), fatigue (13%), diarrhea (10%), and increased alanine aminotransferase (10%). One patient (3%) died due to a treatment-related AE of hypovolemic shock, which occurred on treatment day 135, during treatment cycle 6. This was preceded by gastrointestinal symptoms of nausea and coffee ground emesis; subsequently, the patient went into renal failure with lactic acidosis and died from multiorgan failure. Seven patients (23%) discontinued study drug due to treatment-related AEs of increased alanine aminotransferase and aspartate aminotransferase ($n = 2$ each), increased blood alkaline phosphatase, cholecystitis, diarrhea, headache, hypovolemic shock, pulmonary embolism, maculopapular rash, and vomiting ($n = 1$ each); some patients experienced ≥1 AE that led to discontinuation.

Immune-mediated AEs and infusion reactions occurred in 16 patients (52%). The most common immune-mediated AEs were hypothyroidism (45%) and hyperthyroidism (6%). Grade 3 immune-mediated AEs occurred in 2 patients (6%; pancreatitis and severe skin reaction, n = 1 each). A grade 3 infusion reaction was reported for 1 patient (3%).

Clinically significant AEs for lenvatinib occurred in 29 patients (94%). Of these, 17 patients (55%) experienced grade 3 or 4 AEs (no grade 5). The most frequently occurring clinically significant AE for lenvatinib was hypertension (68%; grade 3, 29%).

4. Discussion

The current study provides evidence of antitumor activity with no new safety signals identified for lenvatinib plus pembrolizumab in patients with advanced and heavily pretreated ovarian cancer (patients were required to have received 3 prior lines of therapy, 77% were platinum resistant or refractory, and 61% had received prior bevacizumab). The ORR by BICR was 35%, and 38% of patients had an estimated response duration of at least 1 year. Median PFS and OS were 6.2 and 21.3 months, respectively. Notably, responses occurred irrespective of tumor PD-L1 status. There was a slight discordance between investigator and BICR assessment (ORR 26% vs 35%, respectively). A variety of factors could have contributed to this, including the transcoelomic spread of ovarian cancer. For a small study, this level of discrepancy was considered to be within acceptable bounds as it represents a small absolute difference (8 vs 11 responders). Adverse events were as anticipated given the previously established safety profiles for lenvatinib and pembrolizumab. Since the LEAP-005 multicohort study was designed, the treatment landscape for ovarian cancer has changed radically. There has been increasing use of both bevacizumab and PARP inhibitors as maintenance therapy [3,20–23] and re-exposure to bevacizumab has become a treatment option [3]. Moreover, new treatments have become available in the advanced ovarian cancer setting, including in the fourth-line setting. As a fourth-line or later therapy, niraparib (PARP inhibitor) demonstrated an overall response rate of 28% in patients with HRD-positive ovarian cancers that were platinum sensitive and PARP inhibitor naive [24]. Mirvetuximab soravtansine demonstrated an ORR of 32.4% and median duration of response of 6.9 months in patients with folate receptor alpha–positive, platinum-resistant advanced ovarian cancer [25]. Because these studies enrolled patient populations with different characteristics to those enrolled in the current study, any cross-trial comparisons should be approached with caution. Together, the sum of these changes means that it is difficult to define a valid and representative fourth-line ovarian cancer population.

This was a small, single-arm study and the results must therefore be interpreted with caution. However, comparison with data from studies evaluating pembrolizumab monotherapy in patients with advanced ovarian cancer suggests the potential for improvements in ORR and PFS with the combination of lenvatinib with pembrolizumab over pembrolizumab monotherapy. For example, in the phase 1b KEYNOTE-028 study, 12% of patients with previously treated, PD-L1–positive advanced metastatic ovarian cancer responded to pembrolizumab monotherapy and 27% achieved stable disease. In the phase 2 KEYNOTE-100 study of pembrolizumab monotherapy for patients with advanced ovarian cancer after frontline platinum, the ORR was 8% in patients who received ≤2 prior lines of therapy and 10% in patients who received 3 to 5 prior lines of therapy. At present, there are no studies that have evaluated lenvatinib monotherapy in patients with ovarian cancer.

In our study, we found that median OS was longer among patients with tumor PD-L1 CPS ≥ 1 (26.6 months) than among those with tumor PD-L1 CPS < 1 (13.0 months). PD-L1 expression has been shown to be positively associated with survival in patients with ovarian cancer in a real-world data set, suggesting PD-L1 expression may have prognostic value in ovarian cancer [26]. Consequently, it is not possible

to determine whether the observed difference in OS for patients with PD-L1 CPS ≥ 1 disease compared with those with PD-L1 CPS < 1 disease is a treatment effect associated with lenvatinib plus pembrolizumab treatment or a prognostic effect associated with tumor PD-L1 expression, or even whether it occurred by chance given the small number of patients with PD-L1 CPS < 1 disease in our study. Given that responses were observed irrespective of PD-L1 expression, the ORR data suggest that a prognostic effect might be the greater contributor to the difference in OS. Additional genetic and molecular characteristics were not evaluated during the study, and as such, data are not available to evaluate potential biomarkers for response to lenvatinib plus pembrolizumab.

Other studies have evaluated combination therapies incorporating lenvatinib or pembrolizumab in patients with advanced ovarian cancer. In a phase 1b study, treatment with lenvatinib plus paclitaxel demonstrated an ORR of 71% and median PFS of 7.2 months in patients with platinum-resistant ovarian cancer [16]. Several small phase 1 and 2 studies have evaluated combinations of pembrolizumab with bevacizumab and cyclophosphamide [27], pegylated liposomal doxorubicin [28], and PARP inhibitors [29] in patients with recurrent ovarian cancer. These studies have reported response rates between 18% and 48%. Given the differences in treatment regimens, study design, and patient populations among these studies, cross-trial comparisons with outcomes among patients enrolled in the LEAP-005 ovarian cohort are challenging.

Results from phase 3 studies have provided limited support for immunotherapy alone or immunotherapy plus standard chemotherapy among patients with ovarian cancer, suggesting that the approach employed in LEAP-005 of combining immunotherapy (pembrolizumab) with a targeted agent with activity against multiple VEGF receptors (lenvatinib) was appropriate and may have provided a potential chemotherapy-sparing option. Results from the phase 3 JAVELIN Ovarian 200 study showed that neither avelumab alone nor avelumab plus pegylated liposomal doxorubicin improved PFS or OS versus pegylated liposomal doxorubicin alone in patients with platinum-resistant or platinum-refractory ovarian cancer [30]. In the phase 3 ATALANTE study of platinum-based chemotherapy plus bevacizumab with or without atezolizumab, the coprimary endpoint of PFS was not met (hazard ratio, 0.83; 95% CI, 0.69–0.99; $P = 0.041$) [31]. Ongoing phase 3 studies are currently evaluating pembrolizumab or placebo plus paclitaxel with/without bevacizumab for recurrent ovarian cancer (ClinicalTrials.gov, NCT05116189 [ENGOT-ov65/KEYNOTE-B96]) and pembrolizumab or placebo plus chemotherapy with maintenance olaparib for first-line treatment of *BRCA* nonmutated ovarian cancer (NCT03740165 [ENGOT-ov43/KEYLYNK-001]).

The safety findings from the LEAP-005 ovarian cohort were consistent with the known safety profiles for lenvatinib and pembrolizumab as monotherapy and in combination with one another [7,32]. Safety findings from the ovarian cohort of LEAP-005 were generally similar with those from other cohorts of LEAP-005, although the rates of grade 3 to 5 treatment-related AEs were marginally higher in the ovarian cohort than the other cohorts [33]. Seven patients discontinued treatment due to treatment-related AEs. The most frequent grade 3 or 4 treatment-related AEs, such as hypertension, fatigue, diarrhea, proteinuria, vomiting, and abdominal pain, are known AEs for lenvatinib; fatigue and abdominal pain are known AEs for pembrolizumab. One patient died due to hypovolemic shock that was considered by the investigator to be treatment related. This was preceded by gastrointestinal symptoms of nausea and coffee ground emesis; following this, the patient went into renal failure with lactic acidosis and died from multiorgan failure.

In conclusion, this study showed that lenvatinib plus pembrolizumab has clinical activity as fourth-line therapy in patients with recurrent advanced ovarian cancer, and no new safety signals were observed relative to the individual monotherapies. The findings from this study will add to the available evidence regarding immunotherapy for patients with advanced ovarian cancer.

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CRediT authorship contribution statement

Antonio González-Martín: Writing – review & editing, Writing – original draft, Formal analysis, Conceptualization. **Hyun Cheol Chung:** Writing – review & editing, Methodology, Formal analysis. **Esma Saada-Bouzid:** Writing – review & editing, Methodology, Formal analysis. **Eduardo Yanez:** Writing – review & editing, Methodology, Formal analysis. **Helene Senellart:** Writing – review & editing, Methodology, Formal analysis. **Philippe A. Cassier:** Writing – review & editing, Formal analysis. **Bristi Basu:** Writing – review & editing, Methodology, Formal analysis. **Bradley R. Corr:** Writing – review & editing, Methodology, Formal analysis. **Eugenia Girda:** Writing – review & editing, Writing – original draft, Methodology, Formal analysis, Conceptualization. **Corina Dutcus:** Writing – review & editing, Formal analysis, Conceptualization. **Chinyere E. Okpara:** Writing – review & editing, Writing – original draft, Formal analysis. **Razi Ghori:** Writing – review & editing, Formal analysis, Data curation, Conceptualization. **Fan Jin:** Writing – review & editing, Formal analysis. **Roman Groisberg:** Writing – review & editing, Writing – original draft, Formal analysis, Conceptualization. **Zarnie Lwin:** Writing – review & editing, Writing – original draft, Formal analysis, Conceptualization.

Data availability

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 promptly assessed 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 US 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 will construct biomarker covariates and add them to a file with clinical data that is uploaded to an analysis portal so that the requestor can perform the proposed analyses.

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