Lenvatinib plus pembrolizumab in patients with advanced endometrial cancer: an interim analysis of a multicentre, open-label, single-arm, phase 2 trial

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Summary

Background Lenvatinib is a multikinase inhibitor of VEGFR1, VEGFR2, and VEGFR3, and other receptor tyrosine kinases. Pembrolizumab, an antibody targeting PD-1, has moderate efficacy in biomarker-unselected endometrial cancer. We aimed to assess the combination of lenvatinib plus pembrolizumab in patients with advanced endometrial carcinoma, after establishing the maximum tolerated dose in a phase 1b study.

Methods In this open-label, single-arm, phase 2 study done at 11 centres in the USA, eligible patients were aged 18 years or older and had metastatic endometrial cancer (unselected for microsatellite instability or PD-L1), had an Eastern Cooperative Oncology Group performance status of 0 or 1, had received no more than two previous systemic therapies, had measurable disease according to the immune-related Response Evaluation Criteria In Solid Tumors (irRECIST), and had a life expectancy of 12 weeks or longer. Patients received 20 mg oral lenvatinib daily plus 200 mg intravenous pembrolizumab every 3 weeks. Treatment continued until disease progression, development of unacceptable toxic effects, or withdrawal of consent. The primary endpoint of this interim analysis was the proportion of patients with an objective response at week 24 as assessed by investigators according to irRECIST in the per-protocol population. This trial is registered with ClinicalTrials.gov, number NCT02501096.

Findings Between Sept 10, 2015, and July 24, 2017, 54 patients were enrolled, 53 of whom were included in the analysis. At the cutoff date for anti-tumour activity data (Dec 15, 2017), median study follow-up was 13·3 months (IQR 6·7–20·1). 21 (39·6% [95% CI 26·5–54·0]) patients had an objective response at week 24. Serious treatment-related adverse events occurred in 16 (30%) patients, and one treatment-related death was reported (intracranial haemorrhage). The most frequently reported any-grade treatment-related adverse events were hypertension (31 [58%]), fatigue (29 [55%]), diarrhoea (27 [51%]), and hypothyroidism (25 [47%]). The most common grade 3 treatment-related adverse events were hypertension (18 [34%]) and diarrhoea (four [8%]). No grade 4 treatment-related adverse events were reported. Five (9%) patients discontinued study treatment because of treatment-related adverse events.

Interpretation Lenvatinib plus pembrolizumab showed anti-tumour activity in patients with advanced recurrent endometrial cancer with a safety profile that was similar to those previously reported for lenvatinib and pembrolizumab monotherapies, apart from an increased frequency of hypothyroidism. Lenvatinib plus pembrolizumab could represent a new potential treatment option for this patient population, and is being investigated in a randomised phase 3 study.

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Introduction

Endometrial cancer is the most common gynaecological malignancy in the USA, and accounts for approximately 11 000 deaths annually.[1] Whereas nearly 30% of primary surgical cases of endometrial carcinoma have high microsatellite instability or mismatch repair deficiency, 70% of recurrent cases are microsatellite stable.[2] Standard initial adjuvant therapy for advanced or recurrent endometrial cancer is paclitaxel plus carboplatin.[3] Treatment options for advanced disease after initial platinum–taxane therapy are scarce.[4]

VEGF activation induces angiogenesis, a process that is crucial to the growth and metastasis of endometrial cancer.[5] Furthermore, high VEGF expression is linked to poor prognosis.[6] Lenvatinib is an oral multikinase inhibitor that targets VEGFR1–3, FGFR1–4, PDGFRα, and the oncogenes *RET* and *KIT*.[7,8] In a phase 2 study[9] of lenvatinib monotherapy in patients with advanced, previously treated endometrial cancer, 19 (14%) of 133 patients had an objective response, and median progression-free survival was 5·4 months (95% CI 8·8–21·4). Pembrolizumab is a monoclonal antibody targeting PD-1 that has efficacy across various types of tumours that are mismatch-repair deficient.[10] In a subset of ten patients with colorectal cancer characterised by high microsatellite instability or mismatch repair

Research in context

Evidence before this study

We searched PubMed with the terms "endometrial carcinoma" [medical subject heading terms] AND "advanced" [title/abstract] for phase 2–3 trials published in any language between Sept 18, 2008, and Sept 18, 2018. We identified 46 reports, 17 of which we excluded because they were about other cancer types or non-systemic treatments. Of the remaining 29 reports, most were about chemotherapy regimens. Seven included hormone therapies, and 11 included targeted therapies. Eight of the articles we identified were about combination therapies, and eight were trials done in biomarker-preselected patients. The proportion of patients who achieved objective responses varied greatly across the reports, but the highest proportions were associated with chemotherapy-containing regimens in first-line and second-line settings.

Added value of this study

To our knowledge, this interim analysis is the first report of a combination regimen consisting of targeted therapy plus immunotherapy to treat advanced endometrial carcinoma. The combination of lenvatinib plus pembrolizumab in biomarker-unselected patients with advanced or recurrent endometrial carcinoma produced an objective response in a proportion of patients that compared favourably with results for standard chemotherapy regimens. Aside from an increased frequency of hypothyroidism, the safety profile of this combination was consistent with the safety profiles of the individual monotherapies.

Implications of all the available evidence

The interim results of this phase 2 study provide initial evidence of anti-tumour activity and safety of the lenvatinib plus pembrolizumab combination regimen for biomarker-unselected patients with advanced or recurrent endometrial carcinoma. Further study of lenvatinib plus pembrolizumab in this disease setting is underway.

	Lenvatinib plus pembrolizumab group (n=53)
Mean age, years (SD)	64 (8)
Race	
White	44 (83%)
Black	2 (4%)
Other	7 (13%)
ECOG performance status	
0	20 (38%)
1	33 (62%)
Histological subtypes	
Endometrioid adenocarcinoma	
FIGO grade 1	5 (9%)
FIGO grade 2	11 (21%)
FIGO grade 3	6 (11%)
Serous adenocarcinoma	20 (38%)
Clear cell adenocarcinoma	2 (4%)
Other adenocarcinomas or adenocarcinoma not otherwise specified	9 (17%)
Previous surgical tumour debulking	53 (100%)
Number of previous systemic therapies	
One	23 (43%)
Two	23 (43%)
Three or more	7 (13%)
Previous chemotherapy	
Platinum-based doublet therapy	52 (98%)
Platinum monotherapy	1 (2%)
Taxane monotherapy	1 (2%)
Doxorubicin or liposomal doxorubicin	12 (23%)
Other cytotoxic chemotherapy	4 (8%)
Previous hormonal therapy	6 (11%)
Previous bevacizumab	3 (6%)

(Table 1 continues on next page)

deficiency, pembrolizumab was associated with an objective response in four (40%) patients.[10,11] In another study,[12] in which 18 (95%) of the 19 patients with PD-L1-positive endometrial cancer had microsatellite-stable disease, pembrolizumab treatment resulted in an objective response in only three (13%) of 23 patients (efficacy analysis set). This objective response is similar to the modest efficacy reported with palliative chemotherapy and other anti-angiogenic therapies in similar settings (objective responses in 14–16% of patients; progression-free survival 3·4–4·2 months).[13,14] Therefore, there is an unmet therapeutic need for patients with recurrent microsatellite-stable endometrial cancer.

Co-inhibition of VEGF and PD-1 signalling—eg, the combination of an immune checkpoint inhibitor (pembrolizumab) and simultaneous inhibition of angiogenesis and VEGF-mediated immune suppression (lenvatinib)—could be an efficacious anti-tumour strategy.[15] In a mouse model, lenvatinib substantially decreased the population of tumour-associated macrophages and increased proportions of CD8-positive T cells, which led to increased anti-tumour activity by PD-1 inhibitors.[16–18] Whether co-inhibition of VEGF and PD-1 activity can effectively treat patients with advanced endometrial cancer, including those with microsatellite-stable tumours, is unknown. In this interim report of a phase 2 study, we assessed the activity and safety of lenvatinib plus pembrolizumab in patients with biomarker-unselected advanced endometrial carcinoma.

Methods

Study design and participants

This study is an open-label, single-arm, phase 2 trial of lenvatinib plus pembrolizumab at 11 cancer centres in

the USA. In this interim analysis, the cutoff date for activity data was Dec 15, 2017, and the cutoff date for safety data was Nov 1, 2017. Eligible patients were aged 18 years or older and had pathologically confirmed metastatic endometrial carcinoma, had received no more than two previous systemic therapies, had measurable disease according to the immune-related Response Evaluation Criteria In Solid Tumors (irRECIST),[19] had an Eastern Cooperative Oncology Group performance status score of 0 or 1, and had life expectancy of 12 weeks or longer. We previously did a phase 1b dose-finding study,[20] which included patients whose disease had progressed after approved therapies or for whom no standard effective therapies were available. Patients from that study could be carried over into the phase 2 trial. Patients enrolled specifically for the phase 2 trial could have received up to two previous lines of systemic therapy and had to have at least one lesion that was serially measurable according to irRECIST. All patients had to have adequately controlled blood pressure (with or without antihypertensive drugs) and adequate renal, bone marrow, blood coagulation, cardiac, and liver function (appendix pp 1–3). Patients previously treated with lenvatinib or any anti-PD-1 or anti-PD-L1 drugs were excluded from this study. A full list of inclusion and exclusion criteria is in the appendix (pp 1–3).

All patients provided written informed consent before enrolment. The trial protocol was compliant with Good Clinical Practice guidelines (as defined by the International Council on Harmonisation) and the principles of the Declaration of Helsinki, and was approved by the institutional review board or ethics committee at each participating centre.

Procedures

All patients received 20 mg oral lenvatinib daily and 200 mg intravenous pembrolizumab every 3 weeks. This dose was chosen on the basis of results from a dose-finding phase 1b study.[20] Toxicity was managed with supportive care, prespecified reductions in lenvatinib dose, and interruptions of study drug doses until adverse events became tolerable. If the lenvatinib dose was reduced or interrupted, the dose could not be increased at a later date. If adverse events were worse than grade 3, treatment was discontinued. Treatment continued until disease progression, development of unacceptable toxicity, or withdrawal of consent. All patients were followed-up every 12 weeks after their last dose of study drug to monitor survival and subsequent use of other anti-cancer drugs.

Tumour response was defined according to irRECIST, and was first assessed by investigators and then by independent review with CT or MRI of the chest, abdomen, and pelvis. Tumour assessments were done at baseline, every 6 weeks during the first 24 weeks, and every 9 weeks thereafter. Central testing of tumour microsatellite status was done with the MSI Analysis System (Promega, Madison, WI, USA).[11] Any previously available data for patients' microsatellite status, based on local testing done as per institutional guidelines, were also collected. PD-L1 status was measured with an investigational version of the PD-L1 immunohistochemistry 22C3 pharmDx (Agilent, Santa Clara, CA, USA). A provisional 1% combined positive cutoff score (which was defined as the number of staining tumour and immune cells relative to the total number of tumour cells) was used.

All adverse events were monitored and recorded. Their relationship to the study drug was assessed by investigators and classified by severity grade according to the Common Terminology Criteria for Adverse Events (version 4.03). Adverse events were described by preferred terms, which were defined with the Medical Dictionary for Regulatory Activities (version 20.1).

	Lenvatinib plus pembrolizumab group (n=53)
(Table 1 continued from previous page)	
Previous radiotherapy	30 (57%)
PD-L1 status	
Positive	13 (25%)
Negative	11 (21%)
Unknown	29 (55%)
Microsatellite status	
High microsatellite instability	4 (8%)
Microsatellite stable	45 (85%)
Unknown	4 (8%)

Data are n (%), unless otherwise specified. ECOG=Eastern Cooperative Oncology Group. FIGO=International Federation of Gynecology and Obstetrics.

Table 1: **Baseline characteristics of the per-protocol population**

	Investigator review (n=53)	Independent review (n=53)
Objective response at week 24	21 (39·6%; 26·5–54·0)	24 (45·3%; 31·6–59·6)
Objective response at data cutoff	21 (39·6%; 26·5–54·0)	25 (47·2%; 33·3–61·4)
Best overall response		
Complete response	1 (1·9%)	3 (5·7%)
Partial response	20 (37·7%)	22 (41·5%)
Stable disease	25 (47·2%)	19 (35·8%)
Progressive disease	4 (7·5%)	5 (9·4%)
Unknown or not assessable	3 (5·7%)	4 (7·5%)
Median duration of response, months		
Median (95% CI)	NE (7·4–NE)	NE (5·8–NE)
Range*	1·2–23·4	1·2–23·4
IQR	7·4–NE	NE–NE
Proportion with responses ≥6 months	12 (83·0%; 55·9–94·2)	11 (79·3%; 48·5–92·9)
Proportion with responses ≥12 months	7 (64·5%; 32·8–84·2)	8 (79·3%; 48·5–92·9)
Median time to response, months (95% CI; IQR)	2·7 (1·3–2·8; 1·3–2·8)	2·6 (1·4–2·8; 1·4–3·7)

Data are n (%; 95% CI) or n (%), unless otherwise specified. NE=not estimable (because of an insufficient number of events at the data cutoff to estimate the median or upper limits of the 95% CI).*Some patients had ongoing responses.

Table 2: **Tumour responses as assessed by investigators or independent reviewers**

See Online for appendix

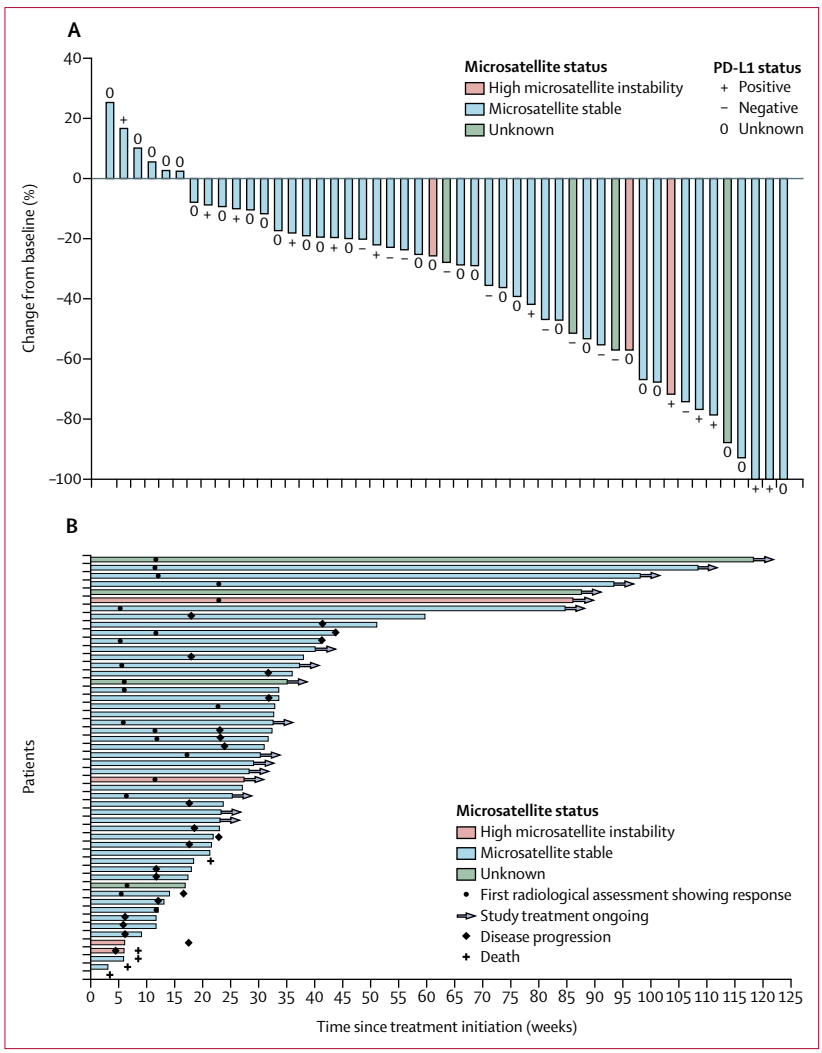

Figure 1: **Maximum percentage change in sum of diameters of target lesions from baseline (A), and time on treatment (B)**

In (A), only patients with available tumour assessments at data cutoff are shown. Changes in tumour size were judged by investigators according to the immune-related Response Evaluation Criteria In Solid Tumors. In (B), all patients in the per-protocol population (n=53) are shown.

Outcomes

The primary endpoint was the proportion of patients with an objective response (complete or partial response) at the week 24 tumour assessment as assessed by investigators according to irRECIST.[20] All responses were confirmed by a second assessment. Secondary activity endpoints, as assessed by the investigator with irRECIST as appropriate and reported here, were the proportion of patients who achieved an objective response overall (defined as best overall response of immune-related complete response or immune-related partial response at time of data cutoff), duration of response (defined as the time from immune-related complete response or immune-related partial response, whichever was recorded first, to the date of disease progression), and progression-free survival (defined as the time from first study dose to date of first documented disease progression or death, whichever occurred first). As part of the protocol, all outcomes were assessed first by investigators. Images were then sent to a central laboratory, where they were assessed by independent review. In this interim analysis we focus on objective response and secondary endpoints directly related to objective response. Secondary endpoints that include patients with stable disease (disease control, durable stable disease, clinical benefit, and overall survival) are not reported here, but will be reported in the final analysis at study completion. Prespecified exploratory endpoints were independent imaging review of tumour responses with modified RECIST criteria, and analysis of anti-tumour activity according to PD-L1 status (ie, positive *vs* negative).

Statistical analysis

There was no formal sample size calculation for this study. We planned to enrol up to 120 patients with endometrial carcinoma. However, because of the initial results noted in this open-label study, and because the patient population included has few treatment options, we decided to publish the data before study completion. As of the data cutoff, there were 54 patients who had at least 24 weeks of follow-up, or who had discontinued before week 24. One patient did not have endometrial carcinoma (histology of the primary tumour was uterine leiomyosarcoma), which was a major protocol violation. Therefore, activity outcomes were analysed for 53 patients (ie, per-protocol analysis set). Per the prespecified protocol, only patients with endometrial carcinoma were analysed. We calculated 95% CIs for the proportion of patients with objective responses with the Clopper-Pearson method. We estimated progression-free survival and the proportion of patients with durations of response of at least 6 months or 12 months with the Kaplan-Meier method, and calculated 95% CIs on the basis of the Greenwood formula with log–log transformation. Activity by microsatellite status was analysed as a post-hoc exploratory endpoint. All outcomes were analysed in the per-protocol population. This study is registered with ClinicalTrials.gov, number NCT02501096.

Role of the funding source

The funders of the study had roles in study design, data collection, data analysis, data interpretation, and writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Between Sept 10, 2015, and July 24, 2017, 54 patients who had at least 24 weeks' follow-up, or who had discontinued before week 24, were enrolled in the study. One patient was excluded because of a major protocol violation

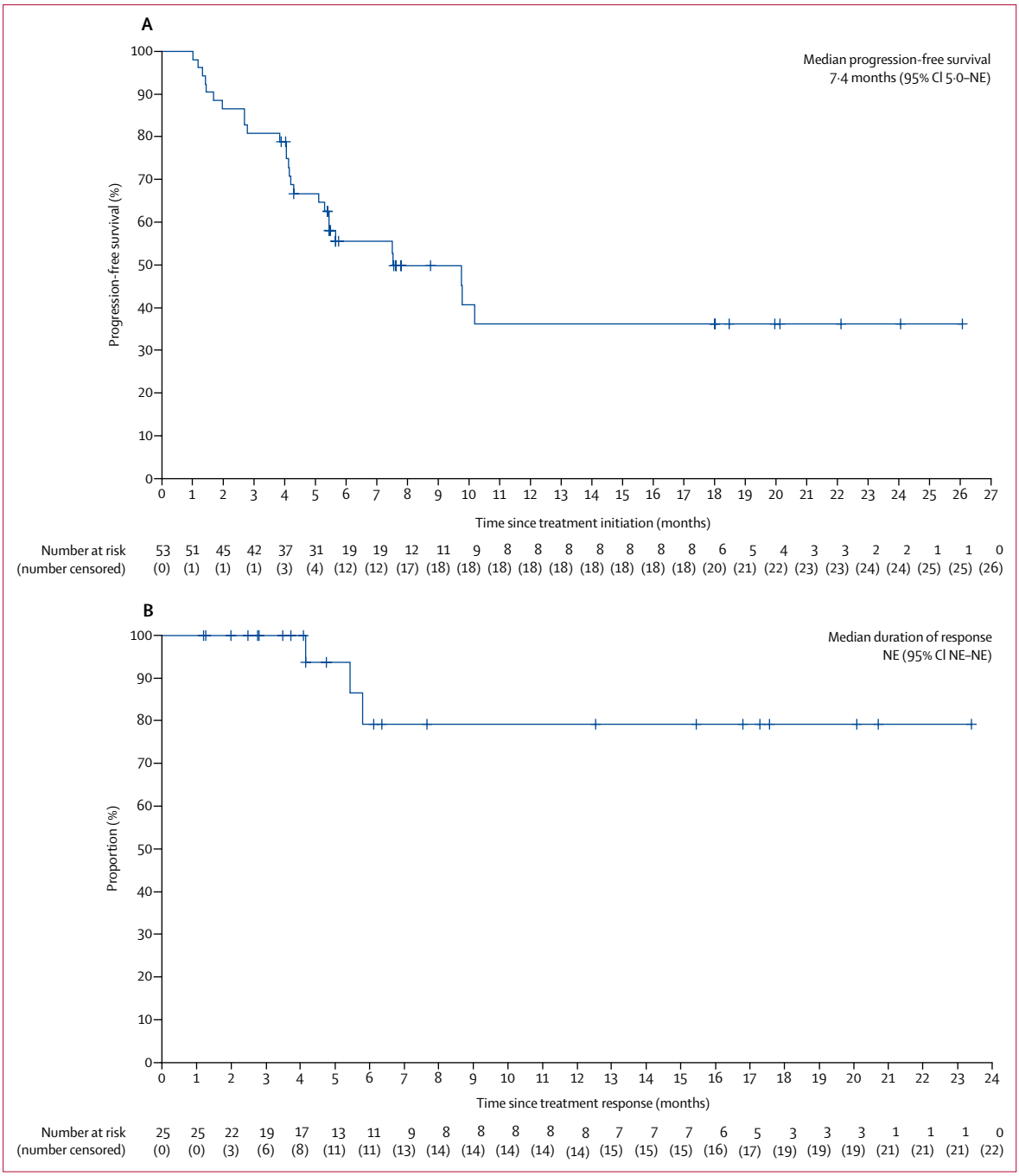

Figure 2: **Progression-free survival (A) and duration of response (B)**
In (A), progression-free survival was assessed by investigators in the per-protocol population (n=53), whereas in (B), duration of response was assessed by independent reviewers in responders only (n=25). Both investigators and independent reviewers used the immune-related Response Evaluation Criteria In Solid Tumors in their assessments. NE=not estimable.

(the primary tumour was uterine leiomyosarcoma and not endometrial carcinoma). Therefore, activity outcomes were analysed in 53 patients (ie, the per-protocol population). At the activity analysis cutoff (median follow-up 13·3 months [IQR 6·7–20·1]), 18 (34%) were receiving ongoing study treatment and 35 (66%) had discontinued study drug treatment. The most common histological subtypes of disease were endometrioid adenocarcinoma and serous carcinoma (table 1). 45 (85%) patients had microsatellite-stable tumours and four (8%) had tumours with high microsatellite instability (table 1).

	Grade 1–2	Grade 3*
Any treatment-related adverse event	13 (25%)	36 (68%)
Serious treatment-related adverse events	2 (4%)	13 (25%)
Fatigue	26 (49%)	3 (6%)
Hypothyroidism	25 (47%)	0
Diarrhoea	23 (43%)	4 (8%)
Decreased appetite	21 (40%)	0
Nausea	20 (38%)	0
Stomatitis	18 (34%)	0
Weight loss	15 (28%)	0
Arthralgia	14 (26%)	0
Palmar–plantar erythrodysesthesia syndrome	14 (26%)	3 (6%)
Hypertension	13 (25%)	18 (34%)
Vomiting	13 (25%)	0
Headache	12 (23%)	0
Proteinuria	12 (23%)	1 (2%)
Dysphonia	10 (19%)	0
Dry mouth	9 (17%)	0
Dry skin	7 (13%)	0
Abdominal pain	6 (11%)	0
Constipation	6 (11%)	0
Hypomagnesaemia	6 (11%)	0
Oral pain	6 (11%)	1 (2%)
Dehydration	5 (9%)	1 (2%)
Increased aspartate aminotransferase	4 (8%)	1 (2%)
Anaemia	3 (6%)	1 (2%)
Hyponatraemia	2 (4%)	2 (4%)
Increased lipase	2 (4%)	1 (2%)
Increased alanine aminotransferase	2 (4%)	1 (2%)
Prolonged electrocardiogram QT interval	2 (4%)	1 (2%)
Hypokalaemia	1 (2%)	1 (2%)
Acute kidney injury	0	2 (4%)
Pulmonary embolism	0	2 (4%)
Syncope	0	2 (4%)
Adrenal insufficiency	0	1 (2%)
Cardiac failure	0	1 (2%)
Colitis	0	1 (2%)
Dysarthria	0	1 (2%)
Hypertensive encephalopathy	0	1 (2%)
Ischaemic colitis	0	1 (2%)
Neutropenia	0	1 (2%)
Pancreatitis	0	1 (2%)
Retinal vein occlusion	0	1 (2%)
Small intestinal obstruction	0	1 (2%)
Upper abdominal pain	0	1 (2%)

Data are n (%). Overall n=53. Grade 1 or 2 treatment-related adverse events occurring in at least 10% of the population and all grade 3 treatment-related adverse events are shown. Adverse events were graded according to the CommonTerminology Criteria for Adverse Events (version 4.03). *No grade 4 treatment-related adverse events were reported, and one grade 5 event (intracranial haemorrhage) was reported.

Table 3: **Treatment-related adverse events in the per-protocol population**

At 24 weeks, 21 (39·6% [95% CI 26·5–54·0]) participants had an objective response to lenvatinib plus pembrolizumab according to investigator assessments (table 2). Similar tumour responses were recorded by independent reviewers (table 2). Five (38·5% [95% CI 13·9–68·4]) of 13 patients with PD-L1-positive tumours, six (54·5% [23·4–83·3]) of 11 with PD-L1-negative tumours, and ten (34·5% [17·9–54·3]) of 29 with unknown PD-L1 status had objective responses.

49 patients had evaluable tumour assessments at the time of data cutoff, 43 (88%) of whom had a decrease in tumour size from baseline (figure 1A). Time on treatment for all patients is shown in figure 1B. 21 (39·6%; 26·5–54·0) patients had an objective response overall (table 2). With a median follow-up for progression-free survival of 7·7 months (IQR 5·6–19·9), by which time 27 (51%) patients had disease progression or had died, median progression-free survival was 7·4 months (95% CI 5·0 to not estimable; figure 2A). The Kaplan-Meier estimate for median duration of response was not reached (95% CI 7·4 to not estimable). A similar duration of response was noted in independent review (figure 2B). As assessed by investigators, 83·0% (95% CI 55·9–94·2) had a duration of response of at least 6 months and 64·5% (32·8–84·2) had a response of at least 12 months' duration (table 2).

Any-grade treatment-related adverse events occurred in 50 (94%) patients, and grade 3 treatment-related adverse events occurred in 36 (68%). No grade 4 treatment-related adverse events were reported. Five (9%) patients discontinued the study because of treatment-related adverse events (one patient with grade 2 ischaemic colitis and grade 3 acute kidney injury, then one each with grade 3 acute kidney injury, grade 3 increased alanine aminotransferase concentrations, grade 2 adrenal insufficiency, and grade 5 intracranial haemorrhage). Treatment-related adverse events led to dose interruptions in 39 (74%) patients and dose reductions in 28 (53%) patients. Overall, the most frequently reported any-grade treatment-related adverse events were hypertension, fatigue, diarrhoea, and hypothyroidism (table 3). 16 (30%) patients had a serious treatment-related adverse event (two [4%] grade 2, 13 [25%] grade 3, and one [2%] grade 5). Of the five deaths that occurred in this study, one (caused by intracranial haemorrhage) was judged to be treatment related. The other four deaths were attributed to progressive disease (n=2); *Escherichia* sepsis infection (n=1), and gastrointestinal perforation (n=1). 30 patients had treatment-related, immune-mediated prespecified adverse events known to be associated with immunotherapy (including skin, endocrine, gastrointestinal, pulmonary, hepatic, and renal adverse events), three (10%) of whom received high-dose glucocorticoids (≥40 mg of prednisone or equivalent per day) as treatment.

In a post-hoc analysis, we noted objective responses in two (50% [95% CI 6·8–93·2]) of the four patients

with tumours with high microsatellite instability, and 16 (35·6% [21·9–51·2]) of the 45 patients with microsatellite-stable tumours.

Discussion

In this interim report of a multicentre, open-label, single-arm, phase 2 study, lenvatinib plus pembrolizumab was associated with anti-tumour activity in patients with previously treated and advanced endometrial carcinoma, irrespective of microsatellite instability or PD-L1 expression status. Most adverse events were manageable with dose modifications or interruptions, or with supportive care.

At present, the only approved treatment strategies for advanced endometrial carcinomas are megestrol[21] (for palliative treatment of advanced endometrial carcinomas) and pembrolizumab monotherapy[10] (for endometrial carcinoma with high microsatellite instability). The proportion of patients with an objective response at week 24 in our interim analysis compares favourably with previously reported activity data for chemotherapy and other anticancer drugs that are either approved or under investigation in patients with similarly treated recurrent endometrial cancer.[9,12–14] Furthermore, hormonal therapies, such as megestrol, medroxyprogesterone, tamoxifen, and aromatase inhibitors, are associated with similarly short progression-free survival of 1·0–3·2 months in patients with advanced or recurrent endometrial carcinoma.[21–26] Notably, in our study, objective responses were recorded in 16 of 45 patients with microsatellite-stable tumours (the predominant subtype of endometrial cancer)—a higher proportion than was reported in other studies[13,14] of advanced endometrial cancer. Only four patients had tumours with high microsatellite instability in our study, which precludes a comparison of objective response between groups based on microsatellite stability or instability.

Most toxicities reported in the study were manageable with dose reductions, dose interruptions, and supportive care. 9% of patients discontinued treatment because of treatment-related adverse events. Serious treatment-related adverse events were reported for 30% of patients, and one patient had a fatal treatment-related adverse event (intracranial haemorrhage). One patient had a fatal gastrointestinal perforation that was judged to be unrelated to study treatment by the investigator. However, we note that gastrointestinal perforation is a known adverse effect of anti-angiogenic therapies.[27] The safety profile of the lenvatinib plus pembrolizumab combination was broadly similar to previously reported safety profiles for lenvatinib monotherapy and pembrolizumab monotherapy,[9,12,28–30] but the frequency of hypothyroidism in our cohort (47%) was higher than that in previous reports (10–25%[9,28,29]).

This interim analysis has several limitations. As is typical of early-phase clinical trials,[9,11,12] the patient population was small and the study was not randomised. The heterogeneity of the study population in terms of tumour histology could be perceived to be a limitation. However, we think it is a strength that the study population was not restricted to a single histology, but rather reflects the true burden and diversity of metastatic endometrial cancer in the recurrent disease setting. Another limitation of this report, as expected of an interim report, is that the data are not completely mature. However, in view of the anti-tumour activity shown in this patient group, who have few treatment options, we chose to report the interim data. The final results will be presented when the data fully mature. As a result of the interim findings of this study, a randomised phase 3 trial of lenvatinib plus pembrolizumab versus doxorubicin or paclitaxel in patients with advanced endometrial cancer is recruiting (NCT03517449).

Contributors

VM, DR, NJV, MSB, ALC, JM, CDS, DMH, CA, and MT gathered patient data. MG did the statistical analyses. VM wrote the first draft of the Article. All authors contributed to study design, data interpretation, critical review of Article drafts, and approval of the final version for submission.

Declaration of interests

VM reports grant support from Astra Zeneca, personal fees, study fees, and travel expenses from Eisai, Merck, and Karyopharm, and study funding from Lilly, Takeda, and Genentech. DR has received research funding from Eisai. NJV has received consultation fees from Merck about pembrolizumab and lenvatinib, and personal fees from Caris and Merck, and has done paid consultancy work for Pfizer, Genentech, Bristol-Myers Squibb, and Astra Zeneca, which have drugs similar to pembrolizumab. MSB has received grants and personal fees from Eisai. DMH reports personal fees from Atara, Chugai, Boehringer Ingelheim, AstraZeneca, Pfizer, Bayer, and Genentech, and grants from AstraZeneca, Puma Biotechnology, Bayer, and Loxo Oncology. DES, CED, MG, PS, and RS are employees of Eisai. CED also reports personal fees from Eisai, and is the lenvatinib team leader at Eisai. EVS reports non-financial support and stock incentives from, and is an employee of, Merck Research Labs. CA reports personal fees from Tesaro, Immunogen, Clovis, Mateon, and Cerulean. MT reports consulting fees from Bristol-Myers Squibb, Eisai, Blueprint Medicines, Loxo Oncology, Novartis, Array Biopharma, Trillium, and Arqule. ALC, JM, and CDS declare no competing interests

Data sharing

Because this report is an interim analysis, the data mentioned herein, including individual participant data, are not generally available. Requests can be made to the corresponding author.

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