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Second-line lenvatinib in patients with recurrent endometrial cancer☆,☆☆

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ABSTRACT

Objective. This study assessed the efficacy of lenvatinib, a multitargeted tyrosine kinase inhibitor, as second-line therapy in patients with unresectable endometrial cancer. The primary end point was the objective response rate (ORR) as assessed by independent radiologic review (IRR). Secondary end points included median progression-free survival (PFS), overall survival (OS), and clinical benefit rate. Exploratory end points examined the association of baseline levels of plasma biomarkers (50 circulating cytokine and/or angiogenic factors measured by immunoassays) with efficacy outcomes.

Methods. An international, open-label, single-arm, multicenter, phase 2 trial was conducted. Eligible patients had histologically confirmed unresectable endometrial cancer that relapsed after 1 prior systemic platinum-based chemotherapy. Patients received once-daily oral lenvatinib 24 mg in a 28-day dosing cycle.

Results. There were 133 patients in the study. By IRR, 19 patients had a confirmed objective response for an ORR of 14.3% (95% CI: 8.8–21.4). Durable stable disease (≥23 weeks) was observed in 31 patients (23.3%) and the clinical benefit rate was 37.6% (95% CI: 29.3–46.4). Median PFS was 5.6 months (95% CI: 3.7–6.3), and median OS was 10.6 months (95% CI: 8.9–14.9). The most common (any grade) treatment-related adverse events were fatigue/asthenia (48%), hypertension (49%), nausea/vomiting (32%), decreased appetite (32%), and diarrhea (31%). Lower baseline levels of angiopoietin-2 were associated with longer PFS, OS, and a higher ORR.

Conclusions. Patients with recurrent endometrial cancer treated with second-line lenvatinib experienced modest antitumor activity and treatment was generally well tolerated, with a safety profile consistent with previous studies.

1. Introduction

Endometrial cancer primarily afflicts older women. The highest incidence is in women aged 45 to 74 years, with a median age at diagnosis of 62 years [1–3]. If diagnosed early, patients have a 5-year relative survival rate of 95% [1,4].

Endometrial cancer is difficult to treat in the second-line setting. A phase 3 study of ixabepilone versus paclitaxel or doxorubicin for second-line treatment of patients with advanced endometrial cancer was discontinued for futility [5]. Moreover, a phase 3 trial comparing

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zoptarelin to doxorubicin also failed to improve the overall survival (OS) of patients with advanced endometrial cancer [6]. Several other clinical trials of both targeted therapies and chemotherapeutic regimens have also demonstrated disappointing outcomes in advanced and recurrent endometrial carcinoma, underscoring the challenging nature of this disease [7–11].

Though some combination chemotherapies can be associated with improved objective response rates (ORR), progression-free survival (PFS), and OS [12,13], their use may result in an increased risk for serious adverse events [12,13]. Regardless of the treatment received, the clinical prognosis of patients with recurrent or advanced endometrial cancer remains poor, with a 5-year survival rate of approximately 17%, a median OS of <12 months [13], and a median PFS of about 4 months after second-line treatment [5,6]. There is a substantial unmet need for second-line therapies, including molecularly targeted agents, to treat and improve the prognosis of patients with recurrent or advanced endometrial cancer. Some recent trials of immuno-oncology therapies are promising. The addition of bevacizumab to carboplatin and paclitaxel improved PFS in a phase 2 trial for patients with advanced or recurrent endometrial cancer [14], and a phase 2 trial using selinexor to treat patients with gynecological cancers showed promising disease control [15]. Additional trials combining atezolizumab (NCT03603184) or dostarlimab (NCT03981796) with carboplatin and paclitaxel are underway.

Vascular endothelial growth factor (VEGF) stimulates angiogenesis, promotes tumor growth, and facilitates metastasis in various solid cell tumors, including endometrial cancer [16]. Moreover, VEGF expression is associated with unfavorable histopathological features and poor prognosis in endometrial cancer [16]. Several VEGF-targeted therapies exist; however, patients treated with therapies that only target the VEGF-signaling pathway may eventually develop resistance due to alternate proangiogenic mechanisms, including activation of the fibroblast growth factor (FGF)-signaling pathway [17], which is known to facilitate angiogenesis. Approximately 12% of patients with endometrial cancer have somatic mutations in FGF receptor-2 [18], further supporting a role for FGF as a mediator of cancer progression in these patients.

Lenvatinib is an oral multityrosine kinase inhibitor that targets VEGF receptors 1–3, FGF receptors 1–4, platelet-derived growth factor receptor alpha, RET, and KIT [19–21]. Lenvatinib monotherapy is approved for the treatment of radioactive iodine-refractory differentiated thyroid cancer and unresectable hepatocellular carcinoma [22]. Lenvatinib showed promising antitumor activity in a phase 1 dose-escalation study in 77 patients with advanced solid tumors, which included 4 patients with endometrial cancer [23]. Currently, 2 ongoing phase 3 trials of lenvatinib plus pembrolizumab in patients with advanced endometrial cancer are underway (ClinicalTrials.gov: NCT03517449 and NCT03884101). Our phase 2 study evaluated the efficacy and safety of single-agent lenvatinib in patients with recurrent or advanced endometrial cancer after failure of 1 prior platinum-based therapy.

2. Methods

2.1. Study design

In this open-label, single-arm, phase 2 study, patients with advanced or recurrent endometrial cancer received 24 mg oral lenvatinib once-daily in a 28-day dosing cycle (ClinicalTrials.gov identifier: NCT01111461). Patients were enrolled across 69 sites in Belgium, Bulgaria, Hungary, Poland, Romania, Russia, Ukraine, and the United States. The study was conducted in accordance with the International Conference on Harmonisation Good Clinical Practice guidelines, and local institutional review board or independent ethics committee standards of practice. All patients provided written informed consent prior to study enrollment.

2.2. Patients

Eligible patients (aged ≥18 years) had histologically confirmed diagnosis of endometrial cancer and had disease progression after 1 prior, platinum-based, systemic chemotherapy for metastatic or primary unresectable endometrial cancer. Patients who received platinum-based chemotherapy in the (neo)adjuvant setting and had disease progression within 1 year were eligible; those who progressed after 1 year must have received 1 additional chemotherapy to be eligible. Other key inclusion criteria included the presence of measurable disease per Response Evaluation Criteria In Solid Tumors version 1.1 (RECIST v1.1) and an Eastern Cooperative Oncology Group performance status ≤2. Patients were excluded if they had received prior VEGF-inhibitors or >1 prior systemic chemotherapy for metastatic or primary unresectable endometrial carcinoma. Patients were excluded if they were not fully recovered from prior radiotherapy; had an antitumor therapy or major surgery within 3 weeks of enrollment; received any investigational drug <30 days prior to treatment initiation; had a malignancy within the past 2 years; or had a condition that could interfere with the study.

2.3. Study end points and assessments

The primary end point was the ORR defined as the percentage of patients with a best overall response (BOR) of complete response (CR) or partial response (PR) based on RECIST v1.1, as determined by independent radiologic review (IRR). A BOR of CR was confirmed by a subsequent CR assessment at least 4 weeks later. A BOR of PR was confirmed by a subsequent CR or PR assessment at least 4 weeks later.

Secondary efficacy end points were PFS, OS, stable disease (SD; lasting ≥7 weeks), clinical benefit rate, and disease control rate (as assessed by IRR and RECIST v1.1). The clinical benefit rate was defined as the percentage of patients with a CR or PR, or durable SD (≥23 weeks). The disease control rate was defined as the percentage of patients with a CR, PR, or SD. Efficacy was also assessed by the investigator (secondary method) using RECIST v1.1. Tumors were evaluated using computed tomography or magnetic resonance imaging every 8 weeks.

The safety end point consisted of monitoring and recording all adverse events. Treatment-emergent adverse events (TEAEs) were coded using the Medical Dictionary for Regulatory Affairs (version 15.0) and graded for severity using the National Cancer Institute Common Terminology Criteria for Adverse Event (version 4.0). The relationship of a TEAE to the study drug was determined by the investigator.

Exploratory analyses to identify biomarkers potentially predictive of PFS, OS, BOR, or maximum tumor shrinkage were conducted. Plasma samples were collected at baseline, day 1 of dosing cycle 2, and post-treatment. Plasma samples were evaluated using an enzyme-linked immunosorbent assay or multiplex bead-based immunoassay that was comprised of a panel of 50 circulating cytokines and/or angiogenic factors. These circulating factors were selected based on known lenvatinib targets, key factors involved in angiogenesis and endothelial cell function, and previous studies [24,25].

2.4. Statistical analyses

A sample size of 130 patients was planned, based on Simon's optimal 2-stage design [26], and a null hypothesis rate of ≤10% against an alternative response rate of ≥20%. According to this design, if <6 responses were observed based on investigator assessment among the first 47 patients, then the treatment would be rejected, and the study discontinued. At the end of the study, if ≥19 responses were observed among 130 patients who met the intent-to-treat (ITT) criteria (as patients who received ≥1 dose of lenvatinib), the treatment would be considered active in this population.

Efficacy analyses were performed in the ITT population. Safety analyses were performed on the safety populations, defined as patients who

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received any dose of lenvatinib and had ≥1 postbaseline safety evaluation. PFS and OS were estimated using Kaplan–Meier statistics. Safety results and biomarker analyses were summarized using descriptive statistics. *P*-values for correlations between cytokines and/or angiogenic factors and OS or PFS were calculated using a univariate Cox proportional hazard model. The exact Wilcoxon test was used for BORs and Spearman's rank correlation test was used for maximum tumor shrinkage.

3. Results

3.1. Patients

Between March 3, 2010 and May 21, 2012 (data cutoff date), 133 patients received lenvatinib, 82 (62%) of whom completed the treatment phase (Fig. S1). Patient demographics and baseline characteristics are listed in Table 1.

3.2. Efficacy

The primary end point of ORR was 14.3% (n = 19/133; 95% CI: 8.8–21.4) as assessed by IRR, and 21.1% (n = 28/133; 95% CI: 14.5–29.0) as assessed by the clinical trial investigators (Table 2). There appeared to be a greater ORR in patients without baseline liver lesions (26% [n = 23/90]; 95% CI: 16.9–35.8) versus those with liver metastases (12% [n = 5/43]; 95% CI: 3.9–25.1) as assessed by investigator. The ORR did not vary greatly across histologic subtype (15% vs 14% for endometrioid and non-endometrioid cancers, respectively). The median duration of response was 7.2 months (95% CI: 4.5–not estimable) and 8.0 months (95% CI: 3.8–11.3) by IRR and investigator assessment, respectively (Table 2). Most patients showed a decrease in tumor size based on both IRR and investigator assessment (Fig. 1A and B) with a median maximum tumor shrinkage of −20.3% by IRR and −21.0% by investigator assessment (range: −100 to 25.8% and −100 to 57.0%, respectively; Table 2). Median PFS was 5.6 months (95% CI: 3.7–6.3) and 5.4 months (95% CI: 3.7–6.7), as assessed by IRR and investigator, respectively (Fig. 2A). The 6-month PFS rate was 41% (95% CI: 32% to 51%), by both investigator and independent assessment. In an updated analysis (November 2012), 79 deaths had occurred. The median OS was 10.6 months (95% CI: 8.9–14.9; Fig. 2B), with a survival rate of 74% (95% CI: 66.0–81.2) at 6 months and 45% (95% CI: 36.5–54.0) at 1 year (Fig. 2B).

3.3. Safety

Patients were exposed to lenvatinib for a median duration of 3.7 months (range: 0.2 to 15.5 months; Table S1). TEAEs occurred in 95% of patients; the most frequently occurring (>5% of patients) ≥ grade 3 TEAEs were hypertension (33%), fatigue (12%), asthenia (10%), abdominal pain (6%), proteinuria (8%), and dehydration (6%). Of these, hypertension, proteinuria, fatigue, and diarrhea were predefined TEAEs of special interest. TEAEs led to study-drug interruptions in 59% (n = 78/133) of patients and 30% (n = 40/133) required a dose reduction. Treatment discontinuation due to a TEAE was reported for 31% (n = 41/133) of patients.

Treatment-related TEAEs were reported in 87% (n = 116/133) of patients (Table 3). The 5 most frequently reported treatment-related TEAEs were fatigue/asthenia (48%; n = 64/133), hypertension (49%; n = 65/133), nausea/vomiting (32%; n = 42/133), decreased appetite (32%; n = 43/133), and diarrhea (31%; n = 41/133; Table 3). Treatment-related TEAEs with grade ≥ 3 were reported in 59% (n = 78/133) of patients, of which hypertension occurred most frequently (31%; n = 41/133; Table 3). Treatment-related fistulas occurred in 2 patients: gastrointestinal fistula (n = 1) and genital tract fistula (n = 1). Treatment-related TEAEs leading to discontinuation were reported for 18% (n = 24/133) of patients. Treatment-related TEAEs leading to discontinuation are summarized in Table S2. Three deaths were considered probably related to the study drug (Table 3): one due to asthenia, one due to deterioration of general physical health, and one due to renal failure.

Table 1
Patient demographic and baseline characteristics (ITT population).

Parameter	Lenvatinib 24 mg/day (N = 133)
Median age (range), years	62.0 (38–80)
Race, n (%)	
White	112 (84)
Black	10 (8)
Other	11 (8)
ECOG performance status score, n (%)	
0	50 (38)
1	71 (53)
2	12 (9)
Histology, n (%)	
Endometrioid	89 (67)
Papillary Serous	24 (18)
Clear cell	10 (8)
Other	10 (8)
Adenocarcinoma	5 (4)
Adenocarcinoma, poorly differentiated	1 (1)
Endometrial adenocarcinoma	1 (1)
Papillary adenocarcinoma	1 (1)
Polypoid adenocarcinoma	1 (1)
Poorly differentiated adenocarcinoma	1 (1)
Locally advanced lesions, n (%)[a]	13 (10)
Metastatic lesions, n (%)	119 (89)
Liver	43 (32)
Bone	8 (6)
Pelvis	1 (1)
Other	106 (80)
Lung	63 (47)
Lymph node	66 (50)
Spleen	9 (7)
Number of prior chemotherapy regimens, n (%)[b]	
1	132 (99)
2	1 (1)
Type of prior therapy[c], n (%)	
Adjuvant	26 (20)
Therapeutic	118 (89)
Neoadjuvant	8 (6)
Maintenance	2 (2)
Unknown	3 (2)
Median time (range)	
Since first diagnosis, years	1.7 (0−12)
Duration of prior therapy, months	3.7 (0.1–16.1)
Median time from end of last therapy to first dose (range)	
Anticancer treatment	23.6 (2.7–444.6) weeks
Radiotherapy treatment	15.7 (1.2–138.7) months
Prior chemotherapies, n (%)	
Carboplatin	80 (60)
Paclitaxel	64 (48)
Cisplatin	47 (35)
Doxorubicin	43 (32)
Carboplatin + paclitaxel	10 (8)
Epirubicin	6 (5)
Cisplatin + doxorubicin	4 (3)
Docetaxel	3 (2)
Best response with prior therapy, n (%)	
Complete response	18 (14)
Partial response	21 (16)
Stable disease	36 (27)
Progressive disease	37 (28)
Unknown/not evaluable/not applicable	21 (16)

ECOG, Eastern Cooperative Oncology Group; ITT, intent-to-treat.
[a] Patients who had locally advanced regions exclusively at baseline.
[b] Patient received 2 prior systemic chemotherapy regimens: a platinum-based regimen in the adjuvant setting for unresectable disease and systemic topotecan therapy before enrollment.
[c] Numbers are not additive; some patients may have had >1 type of prior therapy (e.g., adjuvant/neoadjuvant only, therapeutic only, adjuvant/neoadjuvant + therapeutic only, therapeutic + maintenance only, or unknown).

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Table 2
Summary of tumor responses as assessed by IRR or investigator using RECIST v1.1 (ITT population).

Response category	Lenvatinib 24 mg/day (N = 133)	
	IRR	Investigator
Objective response rate, n (%)	19 (14.3)	28 (21.1)
95% CI	8.8–21.4	14.5–29.0
Best overall response, n (%)		
Complete response	1 (0.8)	2 (1.5)
95% CI	0–4.1	0.2–5.3
Partial response	18 (13.5)	26 (19.5)
95% CI	8.2–20.5	13.2–27.3
Progressive disease	24.0 (18.0)	16 (12.0)
95% CI	11.9–25.6	7.0–18.8
Stable disease (≥7 weeks)	62 (46.6)	60 (45.1)
95% CI	37.9–55.5	36.5–54.0
Durable stable disease (≥23 weeks)	31 (23.3)	31 (23.3)
95% CI	16.4–31.4	16.4–31.4
Clinical benefit rate[a], n (%)	50 (37.6)	59 (44.4)
95% CI	29.3–46.4	35.8–53.2
Disease control rate[b], n (%)	81 (60.9)	88 (66.2)
95% CI	52.1–69.2	57.5–74.1
Median duration of response, months[c]	7.2	8.0
95% CI	4.5–NE	3.8–11.3
Median time to response, months[d]	1.8	1.9
95% CI	1.7–3.2	1.7–2.3
Median maximum tumor shrinkage (range), %	−20.3 (−100, 25.8)	−21.0 (−100, 57.0)

CI, confidence interval; IRR, independent radiologic review; ITT, intent-to-treat; NE, not estimable; RECIST v1.1, Response Evaluation Criteria In Solid Tumors version 1.1.
[a] Clinical benefit rate is defined as the proportion of patients who achieved complete response, partial response, or durable stable disease lasting ≥23 weeks.
[b] Disease control rate is defined at the proportion of patients who achieved complete response, partial response, or stable disease lasting at least 7 weeks.
[c] Among responders.
[d] Best overall response, by Investigator assessment, N = 28; by IRR, N = 19.

3.4. Biomarkers

After 1 cycle of lenvatinib treatment, a change from baseline levels was observed in 18 of the 50 circulating cytokine and/or angiogenic factors (CAFs) tested (Fig. S2). Among the 18 CAFs that changed from baseline to cycle 2, day 1, angiopoietin-2 (Ang-2 and ANG2[90] are the same analyte measured using different assay platforms) was the only serum biomarker where baseline plasma levels correlated with 4 clinical outcome measurements of PFS, OS, BOR, and maximum tumor shrinkage (Table S3). Quartile analysis demonstrated an improvement in median PFS (Fig. 3A) and OS (Fig. 3B) in patients with lower baseline angiopoietin-2 levels Fig. 3. Notably, the ORR for patients with lower baseline angiopoietin-2 levels was 26.9% (95% CI: 15.6–41.0). In contrast, ORR was 5.7% (95% CI: 1.6–14.0) for patients with higher angiopoietin-2 levels (using a simulated cutoff value of 2082.5 pg/mL based on receiver operating characteristics analysis) (Table S4).

4. Discussion

This phase 2 study confirmed that lenvatinib has demonstrated antitumor activity as a second-line treatment for patients with recurrent or advanced endometrial cancer. Lenvatinib was generally well tolerated in this patient population and had a safety profile consistent with previous trials using lenvatinib monotherapy for various solid tumor types [27,28]. As expected with VEGF-inhibitor therapies, hypertension was the most frequently reported treatment-related TEAE with grade ≥ 3 severity [29]. Treatment-related TEAEs led to study discontinuation in 24 patients (18%), with hypertension being the most common reason for discontinuation (n = 5; Table S2), followed by grade 4 pulmonary embolism (n = 3; Table S2). Most toxicities were manageable with study-drug dose adjustments.

Treatment with lenvatinib was associated with a 21% (n = 28/133) ORR by investigator assessment and an ORR of 14% (n = 19/133) by IRR; these responses were durable, lasting a median of 7.2–8 months. In addition, the median PFS was 5.6 months and the median OS was 10.6 months. Among the 19 patients who were classified by IRR as having an objective response of either PR or CR in this study, 3 had a previous PR to first-line therapy. In response to lenvatinib treatment in this study, 62 patients (46.6%) achieved stable disease (≥7 weeks); 12 of these patients had a prior CR and 9 had a prior PR to first-line therapy. Acknowledging the limitations of cross-study comparisons, our findings are similar to those observed with other VEGF-targeted therapies in clinical trials for endometrial cancer conducted at the time of this study [30]. For example, in patients with recurrent or persistent endometrial cancer, bevacizumab treatment resulted in an ORR of 14%, a median PFS of 4.2 months, and a median OS of 10.5 months [30]. A phase 2 trial of bevacizumab in combination with carboplatin and paclitaxel for patients with advanced or recurrent endometrial cancer found that the addition of bevacizumab led to a PFS of 13.0 months and an ORR of 72.7% [14]. Thus, there remained an unmet need for effective therapies for patients with advanced or recurrent endometrial cancer.

Although single-agent therapy trials, including this one, have shown only modest anticancer benefits, recent trials using a combination regimen of lenvatinib and pembrolizumab are more promising [31]. An ongoing phase 1b/2 study (NCT02501096) of lenvatinib plus pembrolizumab, an anti-PD-1 antibody, has demonstrated promising antitumor activity in patients with previously treated advanced endometrial cancer. The study reported that among patients who were not microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR), there was an ORR of 37.2% (95% CI: 27.5–47.8) [31]. In addition, a phase 1 study evaluating the safety and efficacy of lenvatinib plus paclitaxel in patients with recurrent gynecological cancers, including endometrial cancer, is currently underway (NCT02788708). There is evidence that lenvatinib may have some immunological activity, which may be contributing to its activity in this combination therapy. Treatment with lenvatinib significantly increased the percentage of IFN-γ-secreting $CD8^+$ T cells and decreased the percentage of tumor-associated macrophages in the CT26 model [32]. In the Hepa1-6 model, treatment with lenvatinib decreased the population of monocytes and macrophages and increased the population of $CD8^+$ T cells [32,33].

In conclusion, in patients with recurrent or advanced endometrial cancer, lenvatinib treatment following platinum-based therapy demonstrated antitumor activity comparable with other agents in its class and had a manageable safety profile. Our results suggest that future efforts should focus on combination therapies, including use of lenvatinib, in patients with recurrent or advanced endometrial cancer. This recommendation is supported further by the recent accelerated approval of the combination of lenvatinib plus pembrolizumab by the United States Food and Drug Administration for the treatment of patients with advanced endometrial cancer that is not MSI-H or dMMR who have progressed following 1 prior systemic therapy and are not eligible for curative surgery or radiation [22]. Additionally, 2 randomized phase 3 trials of lenvatinib combined with pembrolizumab are currently ongoing in patients with advanced endometrial carcinoma (NCT03517449 and NCT03884101).

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ygyno.2019.12.039.

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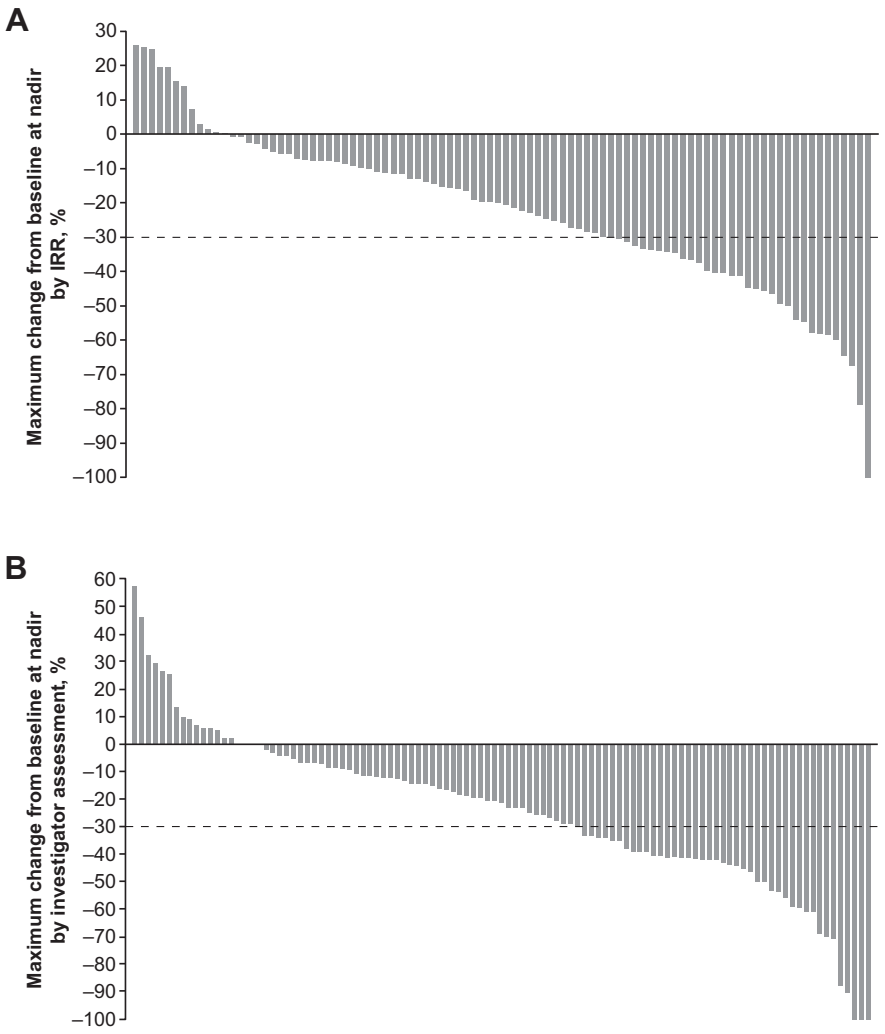

Fig. 1. Maximum percentage change[a] from baseline to nadir in sum diameter of target lesions in the ITT population after treatment with lenvatinib as assessed by IRR (A) and investigator assessment (B). [a]RECIST version 1.1 used longest diameter for non-nodal lesions and short-axis diameter for nodal lesions in calculating the sum of diameters for tumor response. Each bar represents 1 patient. CR, complete response; IRR, independent radiologic review; ITT, intent-to-treat; NE, not estimable; PD, progressive disease; PR, partial response; RECIST, Response Evaluation Criteria In Solid Tumors; SD, stable disease lasting ≥7 weeks.

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Data statement

The data will not be available for sharing at this time as the data are commercially confidential. However, Eisai will consider written requests to share the data on a case-by-case basis.

Role of the funding source

This study was sponsored by Eisai Inc., Woodcliff Lake, NJ, USA. Employees of the study sponsor were involved in the study design; in the collection, analysis, and interpretation of data; and in the writing of the report. The corresponding author (Ignace Vergote) had final responsibility for the decision to submit the paper for publication. Medical writing support was provided by Tarah M. Connolly, Ph.D. of Oxford PharmaGenesis Inc., Newtown, PA, with funding provided by Eisai Inc., Woodcliff Lake, NJ, USA and Eisai Inc., and Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA.

Author contribution statement (all authors)

Ignace Vergote: Conceptualization, data curation, formal analysis, investigation (conduct of the research), methodology, project administration, resources for the study, supervision of the study, validation, visualization of data, and writing, review, and editing of the manuscript.

Matthew A. Powell: Investigation, project administration, supervision of the study, visualization, and writing, review, and editing of the manuscript.

Michael G. Teneriello: Investigation, project administration, resources for the study, supervision of the study, visualization, and writing, review, and editing of the manuscript.

David S. Miller: Conceptualization, investigation, resources for the study, and writing, review, and editing of the manuscript.

Agustin A. Garcia: Investigation and writing, review, and editing of the manuscript.

Olga N. Mikheeva: Investigation and writing, review, and editing of the manuscript.

Mariusz Bidzinski: Supervision of the study and writing, review, and editing of the manuscript.

Cristina Ligia Cebotaru: Investigation, resources for the study, supervision of the study, and writing, review, and editing of the manuscript.

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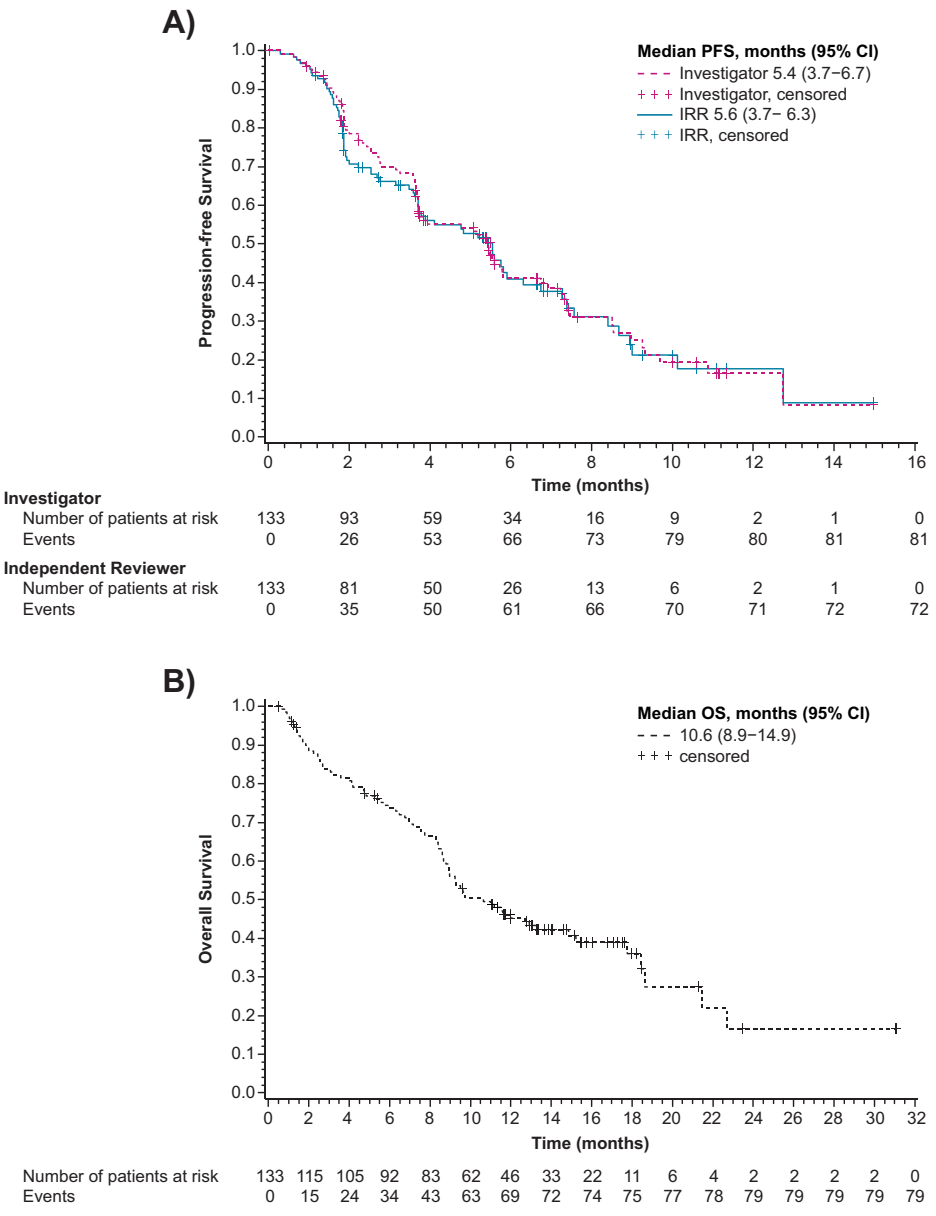

Fig. 2. Kaplan–Meier estimate of progression-free survival (A), and overall survival (B) in the ITT population. IRR, independent radiologic review; ITT, intent-to-treat.

Corina E. Dutcus: Project administration, supervision of the study, and writing, review, and editing of the manuscript.

Min Ren: Formal analysis and methodology, writing, review, and editing of the manuscript.

Tadashi Kadowaki: Formal analysis, methodology, software development/support and writing, review, and editing of the manuscript.

Yasuhiro Funahashi: Conceptualization, funding acquisition, investigation, project administration, supervision of the study, visualization, and writing, review, and editing of the manuscript.

Richard T. Penson: Conceptualization, funding acquisition, investigation, provision of resources, and writing, review, and editing of the manuscript.

Declaration of competing interest

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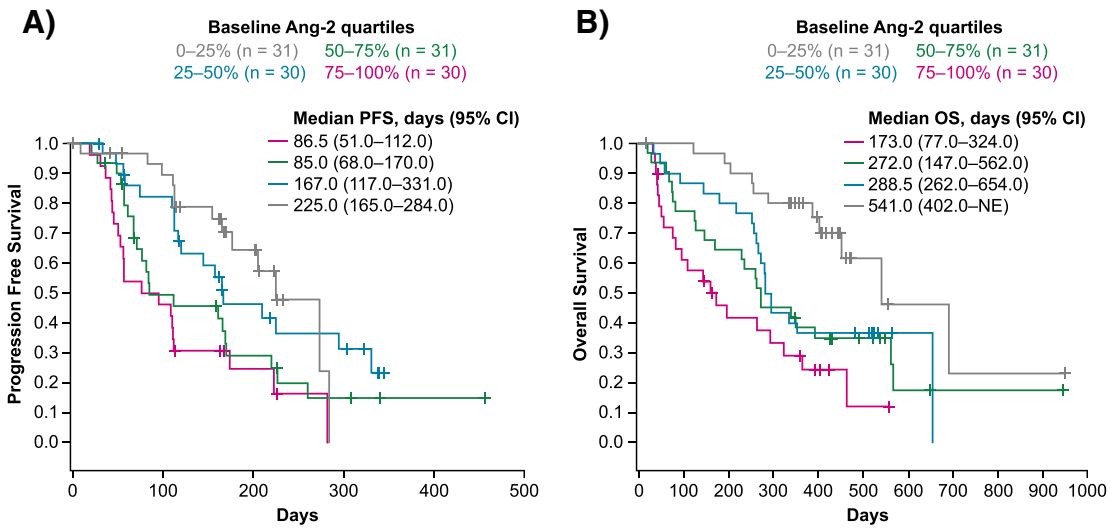

Fig. 3. Kaplan–Meier estimates of PFS (A) or OS (B) by angiopoietin-2 levels (Ang-2)[a] at baseline, as assessed by the investigator (ITT population). Ang-2, angiopoietin-2; CI, confidence interval; ITT, intent-to-treat; NE, not estimable; OS, overall survival; PFS, progression-free survival. [a] As assessed by enzyme-linked immunosorbent assay.

Min Ren: Employee of Eisai during the conduct of the study.

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Table 3
Summary of treatment-related adverse events (by preferred term for any grade occurring in ≥5% of the population; safety analysis set).

Parameter, n (%)	Lenvatinib (N = 133)	
Treatment-related TEAEs	116 (87)	
Grade ≥ 3	78 (59)	
Serious adverse events	36 (27)	
Deaths[a]	3 (2)	
Treatment-related TEAEs leading to:		
Dose interruption	71 (53)	
Dose reduction	38 (29)	
Treatment discontinuation	24 (18)	
Treatment-related TEAEs by preferred term	**Any grade**	**Grade ≥ 3**
Fatigue/asthenia[b]	64 (48)	21 (16)
Hypertension	65 (49)	41 (31)
Nausea/vomiting	42 (32)	5 (4)
Decreased appetite	43 (32)	2 (2)
Diarrhea	41 (31)	5 (4)
Abdominal/upper abdominal pain[c]	33 (25)	4 (3)
Headache	29 (22)	2 (2)
Proteinuria	28 (21)	9 (7)
Stomatitis	27 (20)	4 (3)
Dysphonia	22 (17)	0
Decreased weight	21 (16)	3 (2)
Hypothyroidism	21 (16)	1 (1)
Dry mouth	15 (11)	0
Dizziness	15 (11)	0
Dysgeusia	15 (11)	0
Constipation	13 (10)	0
Palmar-plantar erythrodysesthesia syndrome	10 (8)	3 (2)
Thrombocytopenia	10 (8)	2 (2)
Epistaxis	9 (7)	0
Peripheral edema	8 (6)	0
Dehydration	8 (6)	5 (4)
Increased blood thyroid-stimulating hormone	8 (6)	1 (1)

TEAE, treatment-emergent adverse event.

[a] Deaths were considered related to adverse events of asthenia, deterioration in general physical health, and renal failure, respectively. Upon review of the available information for these patients, it was determined that advanced disease and disease progression may also have contributed to the events.

[b] Pooled asthenia/fatigue includes the following preferred terms: asthenia, fatigue, and lethargy.

[c] Pooled abdominal/upper abdominal pain includes the following preferred terms: abdominal pain, upper abdominal pain, and gastrointestinal pain.

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