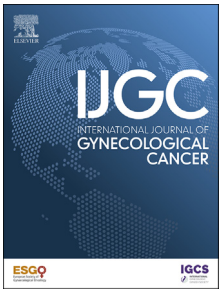
CLINICAL TRIALS

Randomized study evaluating optimal dose, efficacy, and safety of E7386 plus lenvatinib versus treatment of physician's choice in advanced/recurrent endometrial carcinoma previously treated with platinum-based chemotherapy and immune checkpoint inhibitors



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ABSTRACT

Background: Randomized controlled trial data for patients with endometrial cancer who experience disease progression after anti-programmed cell death [ligand] 1 (PD-[L]1) therapy are lacking. E7386, a novel small-molecule inhibitor, has been shown to enhance anti-angiogenesis when combined with lenvatinib. The escalation and expansion parts of Study 102 showed preliminary anti-tumor activity and manageable safety of E7386 plus lenvatinib in patients with advanced, un-resectable, or recurrent endometrial cancer previously treated with anti-PD-(L)1.

Primary Objective: This study aimed to determine the optimal dose of E7386 in combination with lenvatinib.

Study Hypothesis: E7386 plus lenvatinib will show a manageable safety profile and clinically meaningful anti-tumor activity in patients with advanced, un-resectable, or recurrent endometrial carcinoma previously treated with chemotherapy and anti-PD-(L)1 therapy.

Trial Design: Study 102 is an open-label, global, phase 1b/2 trial. Patients with endometrial carcinoma will be randomized 1:1:1:1 to E7386 120 mg twice daily plus lenvatinib 14 mg once daily, E7386 60 mg twice daily plus lenvatinib 14 mg once daily, lenvatinib 24 mg once daily monotherapy, or treatment of physician's choice (doxorubicin 60 mg/m^2 once every 3 weeks or paclitaxel 80 mg/m^2 once weekly [3 weeks on/1 week off]).

Major Inclusion/Exclusion Criteria: Eligible patients are aged $\geq$18 years with Eastern Cooperative Oncology Group performance status of 0 to 1 and must have advanced, un-resectable, or recurrent endometrial carcinoma that has progressed on/after prior platinum-based chemotherapy and PD-(L)1-directed therapy. Up to 3 previous lines of therapy are permitted. Individuals with prior treatment with lenvatinib or E7386 or known intolerance and/or known hypersensitivity to E7386, lenvatinib, doxorubicin, or paclitaxel, or any of their excipients, are not eligible to participate.

Primary End points: The primary end points are safety and the objective response rate per Response Evaluation Criteria in Solid Tumors version 1.1 by investigator assessment at week 24.

Sample Size: The study aims to include 120 patients across approximately 80 investigational sites in North America, Europe, and Asia-Pacific regions.

Estimated Dates for Completing Accrual and Presenting Results: Enrollment is expected to take approximately 9 months, with presentation of results in 2026.

Trial Registration: The trial is registered at ClinicalTrials.gov, NCT04008797.

Keywords:
Endometrial Carcinoma; E7386; Lenvatinib; Dose Optimization

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INTRODUCTION

Endometrial cancer is the most common gynecologic cancer worldwide, with an 18% 5-year survival rate for patients with distant stage disease (per Surveillance, Epidemiology, and End Results staging).[1] Treatment of advanced stage/recurrent disease includes chemotherapy and anti-programmed cell death [ligand] 1 (PD-[L]1) therapy[2]; after anti-PD-(L)1 therapy, chemotherapy agents such as paclitaxel or doxorubicin are used[2] but with limited efficacy, and there is a lack of prospective, randomized controlled trial data for patients with endometrial cancer who experience disease progression after anti-PD-(L)1 therapy. Given the lack of prospective clinical trial data, studies are urgently needed to identify novel treatments to improve outcomes in patients with endometrial cancer that progresses after chemotherapy and anti-PD-(L)1 therapy.

Vascular endothelial growth factor (VEGF) expression, which promotes angiogenesis and tumor growth, is associated with poor outcomes in endometrial cancer[3]; thus, therapies targeting VEGF have been tested.[4-7] Lenvatinib, a multiple receptor tyrosine kinase inhibitor of VEGF receptors 1 to 3, fibroblast growth factor receptors 1 to 4, platelet-derived growth factor receptor α, RET, and KIT, has shown anti-tumor activity (objective response rate, 14.3%; clinical benefit rate, 37.6%) and manageable safety (grade $\geq$3 treatment-related adverse events, 59%; treatment-related adverse events leading to discontinuation, 18%) as a monotherapy in patients with un-resectable endometrial cancer after 1 prior systemic platinum-based chemotherapy.[4] Moreover, lenvatinib is approved in combination with pembrolizumab for the treatment of patients with advanced endometrial cancer after previous systemic therapy in any setting on the basis of results from the phase 3 randomized Study 309/KEYNOTE-775, conducted in patients naïve to programmed cell death 1-targeting regimens.[8]

E7386, a novel small-molecule inhibitor, has been reported to inhibit the interaction between β-catenin and CREB-binding protein.[9] The molecular structure of E7386 is shown in Figure 1. In several preclinical solid tumor models, E7386 in combination with lenvatinib caused increased tumor sensitivity to lenvatinib by enhancing anti-angiogenesis through the inhibition of pericyte-covered vessels and hypoxia response.[10-12] On the basis of this hypothesis, the open-label, global, phase 1b/2 Study 102 (NCT04008797) was initiated to investigate E7386 in combination with lenvatinib. The dose-escalation part of Study 102 (the study design presented in Fig. S), which investigated E7386 plus lenvatinib in 2 cohorts of patients (with hepatocellular carcinoma and solid tumors), has been completed. The recommended dose in the solid tumors cohort was determined to be E7386 120 mg twice daily in combination with lenvatinib 20 mg once daily.[13]

The dose-expansion part of Study 102 further investigated E7386 plus lenvatinib in 3 tumor types (hepatocellular carcinoma, colorectal cancer, and endometrial cancer)[14] (Fig. S). During the dose-expansion part, patients with endometrial cancer who had received prior treatment with lenvatinib were eligible. Partway through enrollment to the endometrial cancer cohort, the starting dose of lenvatinib was modified to 14 mg once daily with consideration of non-clinical data suggesting enhanced anti-tumor activity of the combination, even with a reduced dose level of lenvatinib.[15] In a preliminary analysis in patients with endometrial cancer (n = 16), E7386 plus lenvatinib showed an objective response rate of 43.8% (95% CI 19.8 to 70.1). Any grade and grade 3 treatment-related adverse events were observed in 93.8% and 50.0% of patients, respectively, with no grade 4 or 5 events observed, and a low rate of study drug discontinuations due to treatment-emergent adverse events (6.3%). Any grade treatment-emergent adverse events observed in $\geq$50% of patients were vomiting (68.8%), nausea (62.5%), and diarrhea (56.3%).[16] On the basis of the promising preliminary anti-tumor activity and manageable safety observed in the dose-expansion phase, we present the design of the phase 2 dose-optimization part of Study 102 in patients with endometrial carcinoma. The objectives of the Study 102 dose-optimization part include determination of the optimal dose of E7386 in combination with lenvatinib, assessment of the contribution of E7386 to the overall treatment effect of E7386 plus lenvatinib, and assessment of E7386 plus lenvatinib efficacy relative to currently used chemotherapy options (ie, treatment of physician's choice [TPC]; doxorubicin or paclitaxel) for patients with endometrial carcinoma that has progressed after prior platinum-based chemotherapy and PD-(L)1—directed therapy (Fig. 2).

METHODS

Trial Design

Study 102 is an open-label, global, phase 1b/2 trial. The dose-optimization part of this study is actively recruiting and aims to enroll 120 patients across approximately 80 investigational sites in North America, Europe, and Asia-Pacific regions. The study protocol and amendments are to be approved by institutional review boards or independent ethics committees at each study site. All patients are required to provide written informed consent to the study investigator before they undergo any protocol-specific procedure.

The dose-optimization part of Study 102 will assess 2 different doses of E7386 plus lenvatinib: the recommended dose of 120 mg twice daily when used in combination with lenvatinib, and a lower dose level of 60 mg twice daily. Lenvatinib monotherapy (starting dose of 24 mg once daily), which has shown anti-tumor activity in patients with endometrial cancer who were previously treated,[4] will also be included as the third treatment arm to assess the contribution of E7386 to the overall treatment effect. To assess the anti-tumor activity of E7386 plus lenvatinib relative to commonly used chemotherapeutic agents, TPC (doxorubicin or paclitaxel) will be included as the fourth treatment arm (Fig. 2). Patients with endometrial carcinoma will be randomly assigned in a 1:1:1:1 ratio to receive 1 of the following treatments: E7386 120 mg twice daily in combination with lenvatinib 14 mg once daily (n = 30), E7386 60 mg twice daily in combination with lenvatinib 14 mg once daily (n = 30), lenvatinib 24 mg once daily monotherapy (n = 30), or TPC (doxorubicin 60 mg/m^2 once every 3 weeks or paclitaxel 80 mg/m^2 once weekly [3 weeks on/1 week off]; n = 30 in total) (Fig. 2).

Patients in the lenvatinib monotherapy and TPC arms who experience disease progression per Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1) may be eligible to cross over to receive E7386 120 mg twice daily in combination with lenvatinib 14 mg once daily, after discussion with the sponsor. For patients in the lenvatinib monotherapy arm receiving <14 mg once

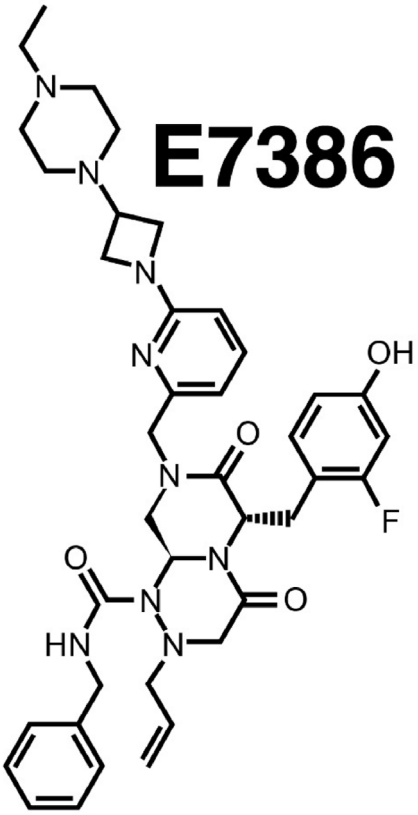

Figure 1 Molecular structure of E7386.

daily lenvatinib for the management of lenvatinib-related toxicity, the lenvatinib starting dose in the optional crossover will be the dose the patient was receiving at the time of disease progression. The optional crossover treatment must be initiated within 2 months of documented disease progression. Patients who receive new systemic anti-cancer treatment after administration of the last dose of lenvatinib or TPC will not be eligible.

Participants

The key inclusion/exclusion criteria are listed in Table 1. The eligible patients are aged $\geq$18 years at the time of informed consent, and must have advanced, un-resectable, or recurrent endometrial carcinoma that has progressed on/after prior platinum-based chemotherapy and a PD-(L)1-directed therapy for endometrial carcinoma. Up to 3 prior lines of therapy (regardless of setting)

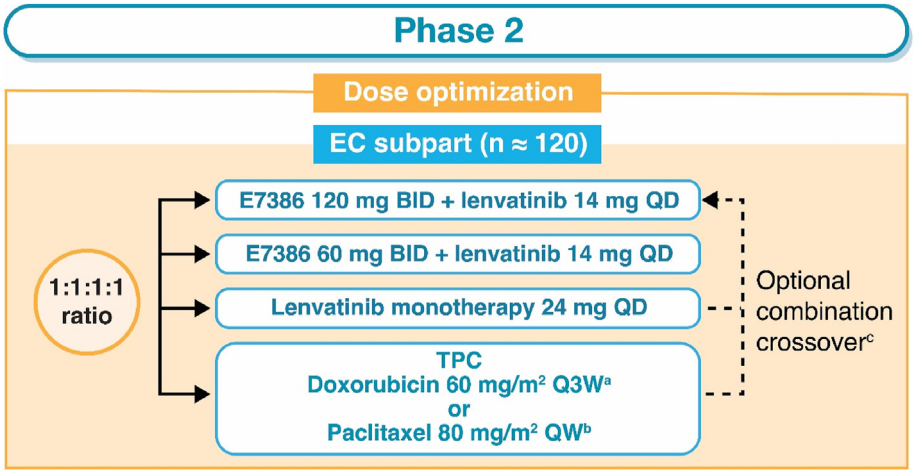

Figure 2 Study schema of phase 1b/2 Study 102 phase 2: EC dose-optimization part. [a]Maximum cumulative dose will be 500 mg/m^2; [b]paclitaxel will be administered QW, on a 3 weeks on/1week off schedule; [c]patients in the lenvatinib monotherapy and TPC arms who experience disease progression per RECIST v1.1 may be eligible to receive E7386 in combination with lenvatinib. For patients in the lenvatinib monotherapy arm receiving $<$14 mg QD lenvatinib for the management of lenvatinib-related toxicity, the lenvatinib starting dose in the optional crossover will be the dose the patient was receiving at the time of PD. BID, twice daily; EC, endometrial carcinoma; PD, progressive disease; Q3W, once every 3 weeks; QD, once daily; QW, once weekly; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1; TPC, treatment of physician's choice.

Table 1 Key Inclusion and Exclusion Criteria of Participants in the Study

Key inclusion criteria
• Aged ≥18 y at the time of informed consent.
• ≥1 measurable lesion based on RECIST v1.1.
• ECOG performance status of 0-1.
• A confirmed diagnosis of advanced, unresectable, or recurrent solid tumor and consent to biopsy before enrollment (archival tumor samples may be submitted instead if performing biopsy causes safety concerns or if patient has no accessible non-target lesions).
• Adequate organ function (liver, kidney, bone marrow) and serum mineral levels.
• Adequately controlled BP with or without anti-hypertensive medications, defined as BP ≤150/90 mm Hg at screening and no change in anti-hypertensive medications within 1 week before starting treatment in this study.
• **Must have EC that has progressed after prior platinum-based chemotherapy and a PD-(L)1–directed therapy for EC.**
○ **≤3 lines of prior therapy, regardless of setting, are allowed.**
○ **Prior hormonal therapy and radiation are allowed and do not count as prior lines of therapy.**
Key exclusion criteria
• **Prior treatment with E7386, or lenvatinib.**
• Known intolerance and/or known hypersensitivity to E7386, lenvatinib, and both doxorubicin and paclitaxel, or any of their excipients.
• History of other malignancy (except for definitively treated melanoma *in situ*, basal or squamous cell carcinoma of the skin, carcinoma *in situ* [eg, bladder or cervix]) within the past 24 months before the first dose of study drug.
• **Patients with carcinosarcoma (malignant mixed Müllerian tumor), leiomyosarcoma, and endometrial stromal sarcomas.**
• Patients having radiographic evidence of major blood vessel invasion/infiltration. The degree of tumor invasion/infiltration of major blood vessels should be considered because of the potential risk of severe hemorrhage associated with tumor shrinkage/necrosis after lenvatinib therapy.
• Patients with pre-existing ≥grade 3 gastrointestinal or non-gastrointestinal fistula.

Abbreviations: BP, blood pressure; EC, endometrial carcinoma; ECOG, Eastern Cooperative Oncology Group; PD-(L)1, programmed cell death (ligand) 1; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1.

are permitted; prior hormonal therapy and radiation are permitted and do not count as prior lines of therapy. Eligible patients must also have ≥1 measurable lesion based on RECIST v1.1, Eastern Cooperative Oncology Group performance status of 0 to 1, adequate organ (liver, kidney, and bone marrow) function, and adequate serum mineral levels.

Individuals with prior treatment with lenvatinib or E7386 or known intolerance and/or known hypersensitivity to E7386, lenvatinib, doxorubicin, or paclitaxel, or any of their excipients, are not eligible to participate. Patients with carcinosarcoma (malignant mixed Müllerian tumor), leiomyosarcoma, and endometrial stromal sarcomas are not eligible. Patients with any history of other malignancy (except for definitively treated melanoma *in situ*, basal or squamous cell carcinoma of the skin, carcinoma *in situ* [eg, bladder or cervix]) within the past 24 months before the first dose of study drug will be excluded.

Study Assessments and End points

Study end points are listed in Table 2. Each patient will be observed for evaluation of safety and anti-tumor activity. Safety end points will include summaries of the number of participants with adverse events and serious adverse events for each treatment arm. All adverse events will be monitored and recorded, including all Common Terminology Criteria for Adverse Events version 5.0 grades (for both increasing and decreasing severity). Adverse events will be recorded from the time of informed consent until 30 days after the last dose of study drug(s) or until a new anti-cancer therapy is initiated in the patient. Key efficacy end points will include objective response rate at week 24 (primary end point), duration of response, best overall response, disease control rate, clinical benefit rate, progression-free survival, and overall survival. These end points are further defined in Table 2. Tumors will be assessed by the investigator using RECIST v1.1. Patients who discontinue the study drug without disease progression will continue to undergo tumor assessments until disease progression is documented, another anti-cancer therapy is initiated, or consent is withdrawn. Key exploratory end points will include biomarkers (based on tissue availability) and patient-reported outcomes. The optimal dose of E7386 in combination with lenvatinib will be determined on the basis of the totality of data in Study 102 (including efficacy, safety, pharmacokinetics, biomarkers, and patient-reported outcomes) and available data from other clinical studies with E7386.

Sample Size

Approximately 30 patients per treatment arm are generally deemed sufficient for dose optimization.[17] With a sample size of 30 patients per arm, there is an 80%-to-90% probability of selecting the optimal dose using the "pick the winner" method,[18] assuming the difference in tumor responses between higher and lower dose levels is ≥10% apart.

Randomization and Blinding

Patients will be randomly assigned 1:1:1:1 to each of the 4 treatment arms. Randomization will be stratified by geographic region: Asia versus North America versus Rest of the World. Because Study 102 is an open-label study, no blinding will be performed.

Table 2 Study 102: Objectives and End Points for the EC Dose-Optimization Part

Objectives	End points
Primary	**Primary**
• To determine the optimal dose of E7386 in combination with lenvatinib in EC.[a]	• Safety-related end points, including summaries of adverse events and serious adverse events. • ORR per RECIST v1.1 by investigator assessment at wk 24.
Secondary	**Secondary**
• To assess the contribution of E7386 to the overall treatment effect of E7386 in combination with lenvatinib. • To assess the efficacy of E7386 in combination with lenvatinib relative to TPC in EC.[b]	• PK profile of study drug(s). • Efficacy-related end points, including the following: ○ BOR. ○ DCR (proportion of patients who have a BOR of CR or PR, or SD [duration of SD ≥7 wk from the first dose]). ○ CBR (proportion of patients who have a BOR of CR or PR, or durable SD [duration of SD ≥23 wk]). ○ Progression-free survival (time from the first dose of study drug to the first documentation of PD or death from any cause, whichever occurs first). ○ Overall survival (time from the first dose of study drug to death from any cause). ○ DOR (time from first documentation of CR or PR to the first documentation of PD or death from any cause, whichever occurs first).
	Key exploratory
	• Biomarkers (based on tissue availability). • Patient-reported outcomes.

Abbreviations: BOR, best overall response; CBR, clinical benefit rate; CR, complete response; DCR, disease control rate; DOR, duration of response; EC, endometrial carcinoma; ORR, objective response rate; PD, progressive disease; PK, pharmacokinetic; PR, partial response; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1; RP2D, recommended phase 2 dose; SD, stable disease; TPC, treatment of physician's choice.

[a]Based on totality of the data (primary, secondary, and exploratory end points);

[b]based on ORR at week 24 and secondary efficacy-related end points.

Statistical Methods

Statistical analyses will include descriptive statistics for numerical comparisons of the 2 E7386 combination arms and inferential statistics for comparisons of the TPC and lenvatinib monotherapy arms. The 4 treatment arms will be summarized descriptively for objective response rate. The point estimate of objective response rate will be provided by treatment group, together with 95% CI using the Clopper-Pearson exact binomial method. Progression-free survival will be estimated and plotted over time using the Kaplan-Meier method. Median progression-free survival will be provided with 95% CI. Overall survival and duration of response will be analyzed in the same way as progression-free survival. The number and percentage of patients with all treatment-emergent adverse events and serious adverse events will be summarized descriptively.

DISCUSSION

Several phase 3 randomized clinical trials have revealed the benefit of anti-PD-(L)1 therapy in combination with platinum-based chemotherapy over platinum-based chemotherapy alone in the first-line setting for patients with endometrial cancer.[19-22] These results led to treatment guideline modifications,[2] and to the adoption of immunotherapy plus chemotherapy in clinical practice for the first-line treatment of patients with endometrial cancer, including approvals of pembrolizumab plus carboplatin and paclitaxel[23,24] and dostarlimab plus carboplatin and paclitaxel.[25,26] Although these new approaches have led to improved outcomes in the first-line setting, there is a paucity of prospective data for available treatments after progression on anti-PD-(L)1 therapy. Thus, clinical trials and novel treatment options are urgently needed to improve outcomes in patients with endometrial carcinoma that progresses on or after platinum- and anti-PD-(L)1-based treatment regimens across molecular sub-types.

E7386 plus lenvatinib shows promise as a combination therapy in the previously mentioned setting given the emerging clinical data for this combination, and the clinical activity of lenvatinib as monotherapy[4] and in combination with pembrolizumab[27] reported in previous endometrial cancer trials. Furthermore, extant nonclinical data have shown enhanced anti-tumor activity with the combination of E7386 and lenvatinib.[10-12] These data, along with observed preliminary anti-tumor activity and manageable safety profile of E7386 plus lenvatinib in patients with advanced endometrial cancer previously treated with anti-PD-(L)1,[13,16] warrant further evaluation to determine the optimal dose of the combination in these patients.

The dose-optimization part of Study 102 (NCT04008797) is currently active and will help address the unmet need for novel treatment options for patients with endometrial carcinoma that has progressed after platinum- and anti-PD-(L)1-based therapy.

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Patient Consent for Publication Not applicable.

Ethics Approval This study involves human participants and will be conducted in accordance with the ethical principles that originate from the Declaration of Helsinki and that are consistent with International Council for Harmonisation guidelines on Good Clinical Practice and regulatory requirements, as applicable.

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H.M.: advisory board of Eisai.

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

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