Lenvatinib in Combination with Ifosfamide and Etoposide in Patients with Refractory or Relapsed Osteosarcoma (ITCC-050): a Phase 1/2 Study

Nathalie Gaspar, Rajkumar Venkatramani, Stefanie Hecker-Nolting, Soledad Gallego Melcon, Franco Locatelli, Francisco Bautista, Alessandra Longhi, Cyril Lervat, Natacha Entz-Werle, Michela Casanova, Isabelle Aerts, Sandra J. Strauss, Estelle Thebaud, Bruce Morland, Adela Cañete Nieto, Perrine Marec-Berard, Marion Gambart, Claudia Rossig, Chinyere E. Okpara, Cixin He, Lea Dutta, Quentin Campbell-Hewson

Department of Oncology for Child and Adolescent, Gustave Roussy Cancer Campus, Villejuif, France (N Gaspar MD); **Texas Children's Cancer Center, Baylor College of Medicine, Houston, TX, USA** (R Venkatramani MD); **Klinikum Stuttgart - Olgahospital, Stuttgart, Germany** (S Hecker-Nolting MD); **University Hospital Vall d'Hebron, Barcelona, Spain** (Prof S Gallego Melcon MD); **Ospedale Pediatrico Bambino Gesù, Sapienza, University of Rome, Rome, Italy** (Prof F Locatelli MD); **Hospital Infantil Universitario Niño Jesus, Madrid, Spain** (F Bautista MD); **Istituto Ortopedico Rizzoli IRCCS, Bologna, Italy** (A Longhi MD); **Pediatric and AYA Oncology Unit, Centre Oscar Lambret Lille, Lille, France** (C Lervat MD); **Chu Strasbourg-Hôpital Hautepierre, Strasbourg, France** (Prof N Entz-Werle MD); **Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy** (M Casanova MD); **Institut Curie, PSL Research University, Oncology Center SIREDO, Paris, France** (I Aerts MD); **University College London Hospital, London, UK** (S Strauss MD); **CHU Nantes - Hôpital Mère-Enfant, Nantes, France** (E Thebaud MD); **Birmingham Children's Hospital, Birmingham, UK** (Prof B Morland MD); **Hospital Universitario y Politecnico La Fe, Valencia, Spain** (A Cañete Nieto MD); **Centre Léon Bérard, Lyon, France** (P Marec-Berard MD); **CHU de Toulouse, Hôpital des Enfants, URCP, Toulouse, France** (M Gambart MD); **University Children's Hospital Muenster, Pediatric Hematology and Oncology, Muenster, Germany** (Prof C Rossig MD); **Eisai Ltd., Hatfield, UK** (C Okpara PhD); **Eisai Inc., Woodcliff Lake, NJ, USA** (C He PhD, L Dutta PharmD); **The Great North Children's Hospital, Royal Victoria Infirmary, Newcastle Upon Tyne, UK** (Q Campbell-Hewson MBchB).

Corresponding Author: Dr Nathalie Gaspar

Department of Oncology for Child and Adolescent,

Gustave Roussy Cancer Campus

114 Rue Edouard Vaillant 94800, Villejuif, France

Telephone: 00 33 (0) 1 42 11 41 73

Email: nathalie.gaspar@gustaveroussy.fr

ClinicalTrials.gov identifier: NCT02432274

Congresses where data has previously been published in part as a poster/abstract: Gaspar N et al., Poster Presented at SIOP 2018; Gaspar N et al., Poster Presented at ESMO 2019; Gaspar N et al., Poster Presented at SIOP 2019 (encore); Gaspar N et al., Poster Presented at CTOS 2019 (encore)

Word Count (body of ms only): 4015/3500

Figures and Tables: Figures (2) + Tables (2)/no limit

References: 27/30

Abstract/Summary (311/300 words):

Background: Tyrosine kinase inhibitors have demonstrated activity in osteosarcoma and may enhance the efficacy of chemotherapy. We aimed to determine the recommended phase 2 dose (RP2D) and antitumor activity of lenvatinib in combination with etoposide + ifosfamide.

Methods: This ongoing open-label, 17-site, phase 1/2 study (NCT02432274) includes the combination-dose-finding phase (n=22) and the single-arm phase 2 combination-expansion (n=20) of oral lenvatinib at a starting dose of 11 mg/m^2/day (capped at 24 mg/day) with intravenous etoposide 100 mg/m^2/day + ifosfamide 3000 mg/m^2/day (EI) on days 1-3 of each 21-day cycle. After five cycles, patients received lenvatinib monotherapy. Patients were aged 2-25 years with relapsed/refractory osteosarcoma, progression on standard therapy, and a ≥50% Lansky play score (<16 years old) or Karnofsky Performance Status (others). The phase 1 primary endpoint was RP2D of lenvatinib+EI (assessed by evaluating dose-limiting toxicities). The phase 2 primary endpoint was progression-free survival (PFS) rate at 4 months (PFS-4; percentage of patients without progressive disease or new anticancer therapy ≤18 weeks after first dose of study drug) per RECIST v1·1. Efficacy/safety were determined in all patients who received the RP2D.

Findings: The RP2D was lenvatinib 14 mg/m^2/day + EI. 35 Patients (aged 5-25 years) were treated at the RP2D from May 9, 2016 to July 18, 2019, the median follow-up was 9·6 months (IQR 7·5, 18·6). PFS-4 rate was 51% (18/35; 95% CI 34-69) per binomial estimate and 80% (95% CI 60-90) per Kaplan-Meier method. The most common grade 3-4 treatment-emergent adverse events (TEAEs) were neutropenia (77%; 27/35) and thrombocytopenia (71%; 25/35). 74% (26/35) had serious TEAEs, no treatment-related deaths occurred.

Interpretation: Lenvatinib+EI demonstrated promising antitumor activity with no new safety signals in refractory/relapsed osteosarcoma; this warrants further investigation in an ongoing randomized phase 2 study (NCT04154189).

Funding: Eisai Inc., Woodcliff Lake, NJ, USA, and Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA.

Keywords: Osteosarcoma, Lenvatinib, Etoposide, Ifosfamide

Research in Context

Evidence before this study:

We searched PubMed on November 16, 2020 using the terms “osteosarcoma” [Title/abstract] AND “Tyrosine kinase inhibitor” OR “TKI” [Title/abstract] AND “chemotherapy” [Title/abstract] for reports published over the past 10 years, with no restriction on language. The search was restricted to clinical studies, yielding 1 result: a phase 2 study involving tyrosine kinase inhibitor monotherapy in patients with advanced osteosarcoma who experienced disease progression with prior chemotherapy. Once the restriction to clinical studies was removed, the search yielded 12 results. We manually excluded 4 articles, primarily due to discussion and inclusion of other cancer types. Of the remaining 8 reports, 6 were focused on tyrosine kinase inhibitor monotherapies in osteosarcoma, 1 was a review article, and 1 report was a case study of 1 patient with relapsed osteosarcoma who was treated with a tyrosine kinase inhibitor in combination with a monoclonal antibody.

Added value of this study:

To our knowledge, this is the first study of a combination regimen consisting solely of a tyrosine kinase inhibitor and conventional cytotoxic chemotherapy for the treatment of osteosarcoma. Lenvatinib in combination with chemotherapy (etoposide + ifosfamide) resulted in a progression-free survival rate at four months which compared favorably to other studies in patients with relapsed osteosarcoma. The most common grade ≥3 adverse events observed with this combination included hematological and gastrointestinal toxicities. Overall, no new safety signals were identified.

Implications of all available evidence:

The results of this phase 1/2 study provide evidence of the antitumor activity of lenvatinib in combination with etoposide and ifosfamide in patients with refractory or relapsed osteosarcoma. This combination is being further evaluated in osteosarcoma in an ongoing randomized phase 2 study (NCT04154189).

INTRODUCTION

Patients with refractory or relapsed osteosarcoma have a poor prognosis and currently, there is no established standard of care for these patients.[1,2] Complete surgical resection has been associated with longer overall survival (OS) in patients with relapsed osteosarcoma and was found to be imperative for curative treatment.[3] In the second-line setting, systemic therapies have provided limited survival benefit.[3] According to the European Society for Medical Oncology (ESMO) guidelines,[4] systemic treatment options include chemotherapy regimens (ifosfamide or cyclophosphamide possibly in combination with etoposide and/or carboplatin; etoposide + carboplatin; gemcitabine + docetaxel), samarium-153-ethylene diamine tetramethylene phosphonic acid (Sm-153-EDTMP), and tyrosine kinase inhibitor monotherapies (sorafenib; regorafenib). Additionally, the National Comprehensive Center Network guidelines[5] recommend etoposide + high-dose ifosfamide, regorafenib, sorafenib, or sorafenib +/− the mTOR pathway inhibitor, everolimus.

Alterations in tyrosine kinase receptor pathways, including vascular endothelial growth factor (VEGF), fibroblast growth factor (FGF), and platelet-derived growth factor (PDGF) have been implicated in osteosarcoma growth, invasion, and metastasis.[6] Moreover, VEGF pathway genes are amplified in osteosarcoma,[7] and VEGF expression in sarcomas is correlated with poor long-term outcomes.[8] FGF/FGF receptor (FGFR)-signaling pathways have been found to play a role in the development of resistance to chemotherapy, radiotherapy, and molecularly targeted therapy in various cancer types including osteosarcoma.[9] Notably, tyrosine kinase inhibitor (TKI) monotherapies have demonstrated promising antitumor activity in osteosarcoma.[10,11] Additionally, research suggests that antiangiogenic agents may normalize the tumor vasculature,[12] which has resulted in enhanced delivery of chemotherapy in preclinical studies.[13]

Thus, TKIs warrant further investigation in combination with chemotherapy, and as a monotherapy, for patients with osteosarcoma.

Lenvatinib is an oral TKI that targets VEGF receptor (VEGFR) 1–3, FGFR1–4, platelet-derived growth factor receptors-α, RET, and KIT.[14] Unlike most TKIs, lenvatinib has a novel type V binding mode to VEGFR-2 and this allows for more potent VEGFR inhibition.[15] Lenvatinib has demonstrated preclinical antitumor activity in combination with etoposide + ifosfamide (EI) in osteosarcoma models—enhanced antitumor activity was observed in three of five human pediatric osteosarcoma cell line xenografts in mice (143B, G-292, and HOS) compared with lenvatinib alone or the combination of ifosfamide + etoposide.[16]

This study aimed to identify the recommended phase 2 dose (RP2D) of lenvatinib in combination with EI in patients with refractory or relapsed osteosarcoma and to evaluate the antitumor activity of this combination.

METHODS

Study Design and Patients

This is a phase 1/2, multicohort, international, open-label study (NCT02432274) conducted at 17 study centers. The study consisted of a single-agent (lenvatinib) dose-finding phase in children and adolescents (Cohort 1), a phase 2 single-agent expansion in patients with differentiated thyroid cancer (Cohort 2A), a single-agent expansion phase in patients with osteosarcoma (Cohort 2B), a combination-dose-finding phase in patients with osteosarcoma (Cohort 3A), and a phase 2 combination expansion in patients with osteosarcoma (Cohort 3B) (**appendix p8**).

Additional detail regarding the study design as well as the protocol can be found in the **appendix** (**p1,13-177**). Here, we report results from the combination cohorts 3A and 3B.

Eligible patients were two to ≤25 years old, had relapsed or refractory osteosarcoma, measurable or evaluable disease per Response Evaluation Criteria In Solid Tumors version 1·1 (RECIST v1·1), Lansky play score (patients <16 years old) or Karnofsky performance status score (patients ≥16 years old) of ≥50%, ≤ one prior VEGF/VEGFR-targeted therapy, and a life expectancy of at least three months. There was no limit on the number of prior lines of therapy patients could have received for the treatment of osteosarcoma. Patients were required to have adequately controlled blood pressure and adequate bone marrow and organ function. Patients with prior EI treatment were eligible unless they had experienced grade ≥3 nephrotoxicity or encephalopathy with ifosfamide treatment; prior lenvatinib was not allowed. Additional inclusion/exclusion factors are listed in the **appendix (p1)**.

The study was conducted in accordance with the International Conference on Harmonization, Good Clinical Practice (GCP) guidelines and all applicable local GCP guidelines and regulations. The study protocol, informed consent form, and any related documents were approved by Institutional Review Boards or Ethics Committees (**appendix p12**). All patients and legal guardians of patients under 18 years of age provided written informed consent and/or assent when applicable. A Protocol Steering Committee provided study oversight after all approvals were obtained.

Procedures

Lenvatinib was administered orally once daily based on body surface area with a dose cap of 24 mg/day. The starting dose was 11 mg/m^2/day, additional details on dosing ranges are available in the **appendix (p1,8)**. Etoposide 100 mg/m^2/day + ifosfamide 3000 mg/m^2/day (EI) was administered intravenously on days one to three of each 21-day cycle for a maximum of five cycles; lenvatinib monotherapy continued following these five cycles until disease progression, toxicity, or patient choice. Dose adjustments were made by grade of treatment-related toxicity; investigators could withdraw patients from the study for safety or administration reasons (**appendix p2**). Radiological tumor response assessments were performed per RECIST v1·1 by investigator assessment; scans were performed at baseline and every 6 weeks or sooner if clinically indicated until documentation of disease progression. Safety was assessed throughout the study, characterized by the incidence of treatment-emergent adverse events (TEAEs), and graded according to Common Terminology Criteria for Adverse Events v4·03. Clinical chemistry and hematology was evaluated every two weeks, urinary dipstick testing was performed weekly for patients with proteinuria.

Outcomes

The primary endpoint for phase 1 was to determine the RP2D of lenvatinib in combination with EI by evaluating dose-limiting toxicities (DLTs) during cycle 1. Additional detail regarding DLT evaluation is provided in the **appendix (p1)**.

The primary endpoint for phase 2 was progression-free survival at 4 months (PFS-4; defined as the percentage of patients who were alive and free of disease progression at 4 months) per RECIST v1·1 by investigator assessment. PFS-4 binomial estimate was based on adequate tumor assessments up to Week 18. Patients without data supporting that they were progression free at Week 18 were included in denominator but not the numerator of the binomial estimate.

These patients initiated new anticancer therapy, had no progression at treatment discontinuation, or did not have adequate tumor assessments, prior to Week 18, and their data were censored in the Kaplan-Meier estimate of PFS-4. Phase 2 secondary endpoints included PFS, time-to-progression (TTP), and tumor response (best overall response (BOR), objective response rate (ORR), disease control rate (DCR), duration of response (DOR), clinical benefit rate (CBR), and safety. Additional secondary analyses included population-based pharmacokinetic parameters, blood and tumor biomarkers, and acceptability of lenvatinib oral suspension, which will be explored later. Overall survival (OS) was changed from an exploratory objective to a secondary objective per a protocol amendment on November 22, 2019.

Statistical Analysis

Cohort 3A aimed to enroll 12-24 patients; Cohort 3B planned to enroll 18 lenvatinib-naïve patients as a sample size of 15 would provide a statistical power of 80% (**appendix p2**). The full analysis set (FAS) includes all patients enrolled for efficacy outcomes; safety was addressed in all patients enrolled through the Safety Analysis Set. The null hypothesis that the PFS-4 rate was ≤25% was tested using the one-sample exact test of a single proportion, at the one-sided 0·1 level. PFS-4 rate was calculated using binomial estimate in the FAS. PFS-4 rate is presented with corresponding two-sided, exact binomial 95% confidence intervals (CIs). PFS-4 rate was also calculated by Kaplan–Meier estimate in the FAS at the 4-month timepoint from the Kaplan-Meier curve. PFS-4, PFS, ORR, OS, and TTP were analyzed by pooling patients treated at the RP2D in Cohorts 3A and 3B. Patients with no PFS or OS events were censored at the time of data cutoff; censoring rules are available in the **appendix (p3)**. Additionally, median PFS and PFS-4 rate were evaluated post-hoc per the following subgroups: number of prior anticancer

regimens (one versus ≥ two) and prior ifosfamide therapy. Data was analyzed with Statistical Analysis Software version 9·4 TS Level 1M4.

The secondary endpoints PFS and TTP were analyzed by the Kaplan–Meier method. ORR, DCR, and CBR were calculated along with corresponding exact binomial 95% CIs.

Role of Funding Source

This work was supported by Eisai Inc., (Woodcliff Lake, NJ, USA) and Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., (Kenilworth, NJ, USA). Some of the authors of this study are employees of the sponsor, Eisai Inc., and, as such, took part in the study design, data handling, writing the manuscript, and the decision to submit; but all authors had access to the data and vouched for the accuracy and completeness of the data, analyses and the fidelity of the study to the protocol. All authors drafted and revised the manuscript, and the lead author made the final decision to submit on behalf of the author group.

RESULTS

From first enrollment to data cutoff, cohort 3A ran from May 9, 2016 to June 3, 2019, and cohort 3B ran from September 13, 2018 to July 18, 2019. Seven patients in cohort 3A were included in the lenvatinib 11 mg/m^2/day + EI group; all received this treatment (**Figure 1**). Two of these patients were over 18 years old; the other five were between six and 18 years old (**Table 1**). Thirty-five patients were included in the lenvatinib 14 mg/m^2/day + EI group pooled from cohort 3A and cohort 3B (cohort 3A, n=15; cohort 3B, n =20); eight were over 18 years old; one was below the age of six. Of these 35 patients, eight patients received a lower dose due to dose

capping. Three of these patients were from cohort 3A and so for dose-finding purposes, were assigned to the 11 mg/m^2 dose level. At the data cutoff dates, no patients from phase 1 had treatment ongoing and seven (35%) patients from phase 2 were still on treatment. The results presented herein include data from phase 1 for the planned lenvatinib 11 mg/m^2/day + EI group, and pooled phase 1 and phase 2 data for the planned lenvatinib 14 mg/m^2/day + EI group.

All patients had received at least one prior anticancer regimen and over 50% (lenvatinib 11 mg/m^2/day + EI:4/7; lenvatinib 14 mg/m^2/day + EI: 21/35) of patients in both groups had ≥ two lines of prior anticancer medications, only one in the 14 mg/m^2 group was previously treated with anti-VEGF therapy (**Table 1**). There were two patients (29%) and 12 (34%) patients who had been previously treated with EI in the lenvatinib 11 mg/m^2/day + EI and lenvatinib 14 mg/m^2/day + EI groups, respectively. At baseline, most patients had either lung metastases or lung and bone metastases (lenvatinib 11 mg/m^2/day + EI: 86%, 6/7; lenvatinib 14 mg/m^2/day + EI: 89%, 31/35). During survival follow-up, two patients in the lenvatinib 11 mg/m^2/day + EI group received an anticancer medication and one had an anti-cancer procedure. In the lenvatinib 14 mg/m^2/day + EI group, eight patients received anticancer medications, three had an anticancer procedure, and eight received an anticancer medication and had an anticancer procedure during survival follow-up. Censoring reasons for PFS and OS analyses in the 14 mg/m^2/day + EI group are shown in the **appendix (p9)**.

Seven patients in the lenvatinib 11 mg/m^2/day + EI group and 15 patients in the lenvatinib 14 mg/m^2/day + EI group were assessed for DLTs (phase 1). There were six DLTs observed in three patients. One patient at the 11 mg/m^2/day dose level experienced grade 3 thrombocytopenia. One

patient at the 14 mg/m^2/day dose level experienced grade 2 oral dysesthesia, grade 2 lower back pain, and grade 3 muscle spasms; the other patient with a DLT at this dose level experienced grade 2 thrombocytopenia and grade 3 epistaxis. The RP2D determined in phase 1 was lenvatinib 14 mg/m^2/day (with daily dose cap of 24 mg) + EI.

An overview of study-drug exposure and TEAEs is shown in the **appendix** (**p4**) (lenvatinib 11 mg/m^2/day + EI, phase 1; lenvatinib 14 mg/m^2/day + EI, pooled phase 1/2). The median duration of lenvatinib treatment was 7·10 (interquartile range [IQR] 2·73, 21·91) and 4·96 (IQR 2·69, 9·46) months in the lenvatinib 11 mg/m^2/day + EI (phase 1) and lenvatinib 14 mg/m^2/day + EI groups (phase 1/2), respectively. Of note, there were four patients in the lenvatinib 14 mg/m^2/day + EI group who remained on treatment for over a year.

In the lenvatinib 11 mg/m^2/day + EI group, TEAEs led to lenvatinib dose reduction in six patients (86%), and interruption in five patients (71%). In the lenvatinib 14 mg/m^2/day + EI group, TEAEs led to lenvatinib dose reduction in 21 patients (60%), and interruption in 19 patients (54%) (**appendix p4**). The median durations of lenvatinib treatment interruption due to local therapy were eight (IQR eight, 11) and 17 (IQR 15, 20) days in the lenvatinib 11 mg/m^2/day + EI and lenvatinib 14 mg/m^2/day + EI groups, respectively. There were two (29%) patients who withdrew from lenvatinib treatment in the lenvatinib 11 mg/m^2/day + EI group because of TEAEs related to disease progression (grade 4 malignant pleural effusion, n=1) or study drug (grade 3 pleural effusion, n=1). There were three patients (9%) who withdrew from lenvatinib treatment in the lenvatinib 14 mg/m^2/day + EI group because of TEAEs; of the three patients, one experienced eyelid edema related to study drug that started as grade 2 and worsened

to grade 3, one had grade 1 hypothyroidism and grade 1 increased blood lactate dehydrogenase both unrelated to study drug, and the remaining patient experienced grade 2 pneumothorax related to study drug. TEAEs led to withdrawal from all three study drugs in one patient (14%) in the lenvatinib 11 mg/m^2/day + EI group (grade 4 malignant pleural effusion due to disease progression, n=1), and two patients (6%) in the lenvatinib 14 mg/m^2/day + EI group (grade 1 blood lactate dehydrogenase increased and grade 1 hypothyroidism, n=1, both due to disease progression; grade 2 pneumothorax due to study drug, n=1). TEAEs led to discontinuation of EI in one patient (14%; grade 4 malignant pleural effusion due to disease progression) in the lenvatinib 11 mg/m^2/day + EI group, and three patients (9%; grade 3 eyelid edema related to study drug n=1, grade 1 hypothyroidism and increased blood lactate dehydrogenase not related to study drug, n=1, grade 2 pneumothorax related to study drug and grade 1 increased blood lactate dehydrogenase unrelated to study drug, n=1) in the lenvatinib 14 mg/m^2/day + EI group. The median number of chemotherapy cycles with EI administered was 5·0 in the lenvatinib 14 mg/m^2/day + EI group (etoposide, IQR 4·0, 5·0; ifosfamide, IQR 4·0, 5·0) (**appendix p4**).

All patients experienced TEAEs, irrespective of lenvatinib dose group. There were seven patients (100%) and 34 patients (97%) who experienced treatment-related AEs in the lenvatinib 11 mg/m^2/day + EI and lenvatinib 14 mg/m^2/day + EI groups, respectively (**appendix p4**). Most patients experienced grade ≥3 TEAEs (86% [6/7] in the lenvatinib 11 mg/m^2/day + EI group; 100% [35/35] in the lenvatinib 14 mg/m^2/day + EI group). The most common grade 3-4 TEAEs were anemia (71%, 5/7), thrombocytopenia (71%, 5/7), febrile neutropenia (57%, 4/7), and neutropenia (57%, 4/7) in the lenvatinib 11 mg/m^2/day + EI group, and were neutropenia (77% 27/35), thrombocytopenia (71%, 25/35), and anemia (54%, 19/35) in the lenvatinib 14

mg/m^2/day + EI group. More than half of all patients experienced serious TEAEs (71% [5/7] in the lenvatinib 11 mg/m^2/day + EI group; 74% [26/35] in the lenvatinib 14 mg/m^2/day + EI group). Serious TEAES were related to study drug in four patients in the lenvatinib 11 mg/m^2/day + EI group, (most commonly grade 3 febrile neutropenia [57%, 4/7]) and 20 patients in the lenvatinib 14 mg/m^2/day + EI group (most commonly febrile neutropenia and decreased white blood cell (WBC) count [both 31%, 11/35]). Fifteen deaths occurred during study or follow-up; 11 occurred >30 days after the last dose and four were considered treatment-emergent. Grade 5 TEAEs occurred in two patients in the lenvatinib 11 mg/m^2/day + EI group (dyspnea and hypoxic brain injury) and two patients in the lenvatinib 14 mg/m^2/day + EI group (dyspnea and malignant neoplasm progression); all were determined by the investigator as associated with progressive disease, and not treatment related (**appendix p4**).

The most common any grade TEAEs associated with 14 mg/m^2 lenvatinib + EI treatment were: neutropenia (77%, 27/35), thrombocytopenia (74%, 26/35), anemia (69%, 24/35), nausea (69%, 24/35), vomiting (69%, 24/35), diarrhea (57%, 20/35), and decreased WBC count (54%, 19/35). The most common grade 3–4 TEAEs were neutropenia (77%, 27/35), thrombocytopenia (71%, 25/35), anemia (54%, 19/35), and decreased WBC count (54%, 19/35) (**Table 2**). Two patients had an important protocol deviation: accidental overdose of etoposide and lenvatinib, respectively. These deviations were not considered to have significantly affected the results of the study and neither of the subjects discontinued study treatment because of the deviation. Pneumothorax occurred in 17% of patients in the study (7/42; six in the lenvatinib 14 mg/m^2/day + EI group) and led to discontinuation of study treatment in one patient (2%).Three of these cases of pneumothorax were grade 2 AEs (occurring on days 4, 70, and 319, respectively in each

of the three patients), two cases were grade 3 AEs (occurring on day 95 in one patient and both days 358 and 490 for the other patient), and the remaining case was a grade 1 AE (occurring on day 125 in one patient). Of the three patients who experienced grade 2 pneumothorax, two had prior resection of lung metastases, and the remaining patient had a prior history of thoracotomy. There was one patient with two occurrences of pneumothorax in the lenvatinib 11 mg/m^2/day + EI group (grade 1 on day 464 and grade 3 on day 838).

The PFS-4 rate was 50% (10/20; 95% CI 27–73) in the FAS per binomial estimate among the patients from cohort 3B (unpooled) who received the RP2D.

The efficacy results presented herein include the pooled outcomes from phase 1 and phase 2 per the planned dose level of lenvatinib 14 mg/m^2/day + EI, which are summarized in the **appendix (p5)**. The following results are presented per the FAS; the median follow-up time for survival was 9·6 months (IQR 7·5, 18·6)].

For the patients who received the 14 mg/m^2/day dose of lenvatinib + EI, PFS-4 rate was 51% (18/35, 95% CI 34–69) per binomial estimate (**appendix p5**). The Kaplan–Meier estimate of PFS-4 rate in all 35 patients was 80% (95% CI 60–90) (**appendix p5**). Median PFS was 8·7 months (95% CI 4·5–12·0 months) (**appendix p5**), corresponding to 15 events of disease progression, and the median follow-up time for PFS was 5·8 months (IQR 4·1, 9·7). As no PFS events were due to deaths, TTP was the same as PFS Additional post-hoc subgroup analyses demonstrated consistent efficacy as the PFS-4 rate in the FAS per binomial estimate ranged from 43% (6/14) to 57% (12/21) across all subgroups (**appendix p6**). The PFS-4 rates were similar

among patients who received one prior anticancer regimen (43% [6/14]; 95% CI 18–71), and ≥ two prior anticancer regimens including previous treatment with ifosfamide (50% [9/18]; 95% CI 26–74). The PFS-4 rate was 52% (11/21; 95% CI 30–74) in patients previously treated with ifosfamide and 50% (7/14; 95% CI 23–77) in patients not previously treated with ifosfamide (**appendix p6**). A list of patients censored for the PFS analysis is available as **appendix p7.**

The ORR, BOR, DOR, DCR, and CBR for phase 1b/2 are presented in the **appendix** (**p5**)**.** The duration of treatment, BOR, and change of response over time for phase 2 are presented in the **appendix (p9)**. The maximum percentage changes in the sums of diameters of target lesions at the data cutoff date and Kaplan–Meier plot of OS are shown in the **appendix (p10)**, 9 patients had OS events.

From Cohorts 3A and 3B, nine patients experienced relapse with the occurrence of new lung lesions between weeks 10–114, of which, two experienced pneumothorax: one at Week 13 before the new lung lesion appeared at Week 18 (n=1), and one at Week 119 after a new lung lesion appeared at Week 114 (n=1).

DISCUSSION

The identified RP2D of lenvatinib in combination with EI (14 mg/m^2/day dose) in this study was equivalent to the RP2D for lenvatinib monotherapy from the single-agent phase of this study[17] and consistent with the monotherapy dosing range approved in adults for other indications.[14] Adverse events that are commonly associated with lenvatinib include hypothyroidism, proteinuria, and hypertension and were observed in 51·4%, 40·0%, and

28·6% of patients who received lenvatinib 14 mg/m^2/day + EI, respectively. Generally, patients with hypothyroidism remained asymptomatic and were managed with hormone substitution. AEs were mostly manageable with dose interruptions and/or reductions, or additional per-protocol measures, and TEAEs led to withdrawal of lenvatinib, and withdrawal of all three study drugs, in a small percentage of patients across treatment groups.

The most frequent grade ≥3 AEs were cytopenias, which are typical AEs associated with ifosfamide and/or etoposide treatment.[18] Specifically, grade 3 and 4 thrombocytopenia and neutropenia events are common AEs associated with ifosfamide and etoposide.[18] Of the seven patients who experienced pneumothorax, two patients had prior resection of lung metastases which is thought to be an underlying risk factor for pneumothorax. Pneumothorax has been known to occur spontaneously in patients with osteosarcoma who have lung metastases and have received chemotherapy.[19] Additionally, pneumothorax has also been observed in patients following TKI monotherapy.[20] The incidence rate of pneumothorax (17%) in our study was similar to that observed in previous studies of TKI monotherapies (apatinib [32%];[20] lenvatinib [16%][21]). A previous phase 1 study in 44 patients with refractory or recurrent solid tumors also reported a comparable incidence of pneumothorax (25%) when evaluating triple therapy with a TKI (sorafenib), chemotherapy (low-dose cyclophosphamide), and bevacizumab.[22]

The combination of lenvatinib + EI demonstrated promising antitumor activity as the PFS-4 rate was 51% per binomial estimate in the lenvatinib 14 mg/m^2/day + EI group, higher than the PFS-4 rate (32%) previously observed with lenvatinib 14 mg/m^2/day in the single-agent

cohort of this study.[21] The majority of patients in the group receiving the combination of lenvatinib 14 mg/m^2/day + EI (RP2D) achieved PFS-4 per Kaplan–Meier estimate (80%; 95% CI 60–90). Although cross-study comparisons have limitations, it is notable that the PFS-4 rate in this study compared favorably to other studies in the same population (relapsed osteosarcoma), as PFS-4 rates around 45% were observed: cyclophosphamide + etoposide, PFS-4 of 42%;[23] gemcitabine + sirolimus, PFS-4 of 44% (95% CI 27–61),[24] sorafenib monotherapy, PFS-4 of 46% (95% CI 28–63).[10]

In this study, three patients in the lenvatinib 14 mg/m^2/day + EI group had partial responses for an ORR of 9% (95% CI 2–25); two of the three responders had received prior treatment with ifosfamide. However, ORR is not considered the most accurate measure of treatment response in osteosarcoma as calcification of lesions may impair tumor lesion shrinkage[25] and thus, DOR could only be measured in a minority of patients with noticeable shrinkage. As such, PFS-4 rate per binomial estimate is the recommended primary endpoint to determine antitumor activity in single-arm phase 2 studies.[25]

This study was limited by its single-arm nature and the small sample size. The use of RECIST v1.1 for the assessment of radiological progression is widely accepted, however, randomized controlled trials are often required to validate treatment effects based on single-arm assessment of PFS; therefore, further investigation is warranted. In randomized controlled trials, PFS is typically assessed per Kaplan-Meier method. However, it was noted that PFS rate at a particular timepoint per binomial estimate in a single-arm study may be more appropriate than PFS rate at that timepoint using the Kaplan-Meier method, due to censoring data and timing of tumor scans;

whereas this could be minimized in randomized controlled trials. Overall, the safety profile aligned with the safety profiles of each study drug,[14,26,27] and no unexpected toxicities were observed. The manageable safety profile, along with the promising efficacy results, suggests that TKIs may be combined with chemotherapy to potentially treat patients with relapsed or refractory osteosarcoma, however direct comparison with chemotherapy is not currently available. A randomized phase 2 study of EI ± lenvatinib in patients up to 25 years old with refractory or relapsed (first or subsequent relapse) osteosarcoma is underway (NCT04154189).

Author Contributions Statement:

NG, CEO, and CH contributed to the conception/study design. NG, RV, SHN, SGM, FL, FB, AL, CL, NEW, MC, IA, SJS, ET, BM, ACN, PMB, MG, CR, CEO, CH, LD, and QCH contributed to acquisition/analysis/or interpretation of data, drafting/editing, and take accountability for the work; similarly, all authors had full access to all the data in the study and had final responsibility for the decision to submit for publication. NG, CEO and CH accessed and verified the data.

ACKNOWLEDGEMENTS

This study was funded by Eisai Inc., Woodcliff Lake, NJ, USA, and Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA. Michael Venditto, PharmD, of Oxford PharmaGenesis Inc, Newtown, PA, USA, provided medical writing support. This support was funded by Eisai Inc., Woodcliff Lake, NJ, USA, and Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA.

This study was conducted in collaboration with the Innovative Therapies for Children with Cancer Consortium (ITCC; Study number ITCC-050).

The authors would like to thank Dr Pablo Berlanga of Gustave Roussy Cancer Campus for his contributions to this work.

Support was provided to SJS by the National Institute for Health Research, the University College London Hospitals Biomedical Research Centre, and the Cancer Research UK University College London Experimental Cancer Medicine Centre.

This study was not NIH funded, either fully or in part, and no authors are employed by NIH, or in receipt of an NIH grant. Further, no employees were employed by the WHO, IARC, or PAHO.

Declaration of Interests:

Nathalie Gaspar: reports fees from Eisai for presenting study results at a meeting.
Rajkumar Venkatramani: nothing to disclose.
Stefanie Hecker-Nolting: reports institutional study & grant funding from Eisai and an unpaid leadership role as Co-Chair of the Pediatric Cancer Data Commons, HIBiSCus, University of Chicago.
Soledad Gallego Melcon: reports personal fees from Bayer for an educational event and personal fees from Loxo Oncology, Bayer, and Eusa Pharma for participating on an advisory board.
Franco Locatelli: nothing to disclose.
Francisco Bautista: nothing to disclose.
Alessandra Longhi: nothing to disclose.
Cyril Lervat: nothing to disclose.
Natacha Entz-Werle: nothing to disclose.
Michela Casanova: nothing to disclose.
Isabelle Aerts: nothing to disclose.
Sandra J Strauss: reports personal consulting fees from GSK for participating on an advisory board.
Estelle Thebaud: nothing to disclose.
Bruce Morland: nothing to disclose.
Adela Cañete Nieto: nothing to disclose.
Perrine Marec-Berard: nothing to disclose.
Marion Gambart: nothing to disclose.
Claudia Rossig: nothing to disclose.
Chinyere E Okpara: employee of Eisai Ltd.
Cixin He: employee of Eisai Inc.
Lea Dutta: employee of Eisai Inc.
Quentin Campbell-Hewson: nothing to disclose.

Data-sharing 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.

REFERENCES

1. Zhang Y, Yang J, Zhao N, et al. Progress in the chemotherapeutic treatment of osteosarcoma. *Oncol Lett* 2018; **16**: 6228-37.
2. Omer N, Le Deley MC, Piperno-Neumann S, et al. Phase-II trials in osteosarcoma recurrences: A systematic review of past experience. *Eur J Cancer* 2017; **75**: 98-108.
3. Bielack SS, Kempf-Bielack B, Branscheid D, et al. Second and subsequent recurrences of osteosarcoma: presentation, treatment, and outcomes of 249 consecutive cooperative osteosarcoma study group patients. *J Clin Oncol* 2009; **27**: 557-65.
4. Casali PG, Bielack S, Abecassis N, et al. Bone sarcomas: ESMO-PaedCan-EURACAN Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2018; **29**: iv79-iv95.
5. National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology (NCCN Guidelines®). Bone Cancer. Version 1.2020. https://www.nccn.org/professionals/physician_gls/PDF/bone.pdf (accessed 20 Nov 2020).
6. Xie L, Ji T, Guo W. Anti-angiogenesis target therapy for advanced osteosarcoma (Review). *Oncol Rep* 2017; **38**: 625-36.
7. Yang J, Yang D, Sun Y, et al. Genetic amplification of the vascular endothelial growth factor (VEGF) pathway genes, including VEGFA, in human osteosarcoma. *Cancer* 2011; **117**: 4925-38.
8. Kaya M, Wada T, Akatsuka T, et al. Vascular endothelial growth factor expression in untreated osteosarcoma is predictive of pulmonary metastasis and poor prognosis. *Clin Cancer Res* 2000; **6**: 572-7.

9. Zhou Y, Wu C, Lu G, Hu Z, Chen Q, Du X. FGF/FGFR signaling pathway involved resistance in various cancer types. *J Cancer* 2020; **11**: 2000-7.

10. Grignani G, Palmerini E, Dileo P, et al. A phase II trial of sorafenib in relapsed and unresectable high-grade osteosarcoma after failure of standard multimodal therapy: an Italian Sarcoma Group study. *Ann Oncol* 2012; **23**: 508-16.

11. Davis LE, Bolejack V, Ryan CW, et al. Randomized double-blind phase II study of regorafenib in patients with metastatic osteosarcoma. *J Clin Oncol* 2019; **37**: 1424-31.

12. Goel S, Wong AH, Jain RK. Vascular normalization as a therapeutic strategy for malignant and nonmalignant disease. *Cold Spring Harb Perspect Med* 2012; **2**: a006486.

13. Yonucu S, Yiotalmaz D, Phipps C, Unlu MB, Kohandel M. Quantifying the effects of antiangiogenic and chemotherapy drug combinations on drug delivery and treatment efficacy. *PLoS Comput Biol* 2017; **13**: e1005724.

14. Lenvima (lenvatinib) [prescribing information]. Woodcliff Lake, NJ, USA: Eisai Inc.; 2020.

15. Okamoto K, Ikemori-Kawada M, Jestel A, et al. Distinct binding mode of multikinase inhibitor lenvatinib revealed by biochemical characterization. *ACS Med Chem Lett* 2015; **6**: 89-94.

16. Matsuki M, Okamoto K, Dezso Z, Agoulnik SI, Funahashi Y, Matsui J. Antitumor activity of a combination of lenvatinib mesilate, ifosfamide, and etoposide against human pediatric osteosarcoma cell lines [abstract]. *Cancer Res* 2016; **76(14 Suppl)**: Abstract 3266.

17. Gaspar N, Gallego S, Venkatramani R, et al. Single-agent dose-finding cohort of a phase 1/2 study of lenvatinib in children and adolescents with refractory or relapsed solid

tumors (ITCC-50 Study). Poster presented at: American Society of Clinical Oncology Annual Meeting; June 2–6, 2017; Chicago, IL.

18. Goorin AM, Harris MB, Bernstein M, et al. Phase II/III trial of etoposide and high-dose ifosfamide in newly diagnosed metastatic osteosarcoma: a pediatric oncology group trial. *J Clin Oncol* 2002; **20**: 426-33.

19. Gan Z, Lin S, Han K, Shen Z, Yao Y, Min D. Bilateral spontaneous pneumothorax in an osteosarcoma patient with pulmonary metastases: A case report. *Oncol Lett* 2016; **11**: 1179-80.

20. Xie L, Xu J, Sun X, et al. Apatinib for advanced osteosarcoma after failure of standard multimodal therapy: an open label phase II clinical trial. *Oncologist* 2019; **24**: e542-50.

21. Gaspar N, Casanova M, Bautista Sirvent FJ, et al. Single-agent expansion cohort of lenvatinib (LEN) and combination dose-finding cohort of LEN + etoposide (ETP) + ifosfamide (IFM) in patients (pts) aged 2 to ≤ 25 years with relapsed/refractory osteosarcoma (OS). Poster presented at: International Society for Paediatric Oncology; November 16–19, 2018; Kyoto, Japan.

22. Interiano RB, McCarville MB, Wu J, Davidoff AM, Sandoval J, Navid F. Pneumothorax as a complication of combination antiangiogenic therapy in children and young adults with refractory/recurrent solid tumors. *J Pediatr Surg* 2015; **50**: 1484-9.

23. Berger M, Grignani G, Ferrari S, et al. Phase 2 trial of two courses of cyclophosphamide and etoposide for relapsed high-risk osteosarcoma patients. *Cancer* 2009; **115**: 2980-7.

24. Martin-Broto J, Redondo A, Valverde C, et al. Gemcitabine plus sirolimus for relapsed and progressing osteosarcoma patients after standard chemotherapy: a multicenter,

single-arm phase II trial of Spanish Group for Research on Sarcoma (GEIS). *Ann Oncol* 2017; **28**: 2994-9.

25. Lagmay JP, Krailo MD, Dang H, et al. Outcome of patients with recurrent osteosarcoma enrolled in seven phase II trials through Children's Cancer Group, Pediatric Oncology Group, and Children's Oncology Group: learning from the past to move forward. *J Clin Oncol* 2016; **34**: 3031-8.

26. Etopophos (etoposide phosphate) [prescribing information]. Deerfield, IL, USA: Baxter Healthcare Corporation; 2019.

27. Ifex (ifosfamide) [prescribing information]. Deerfield, IL, USA: Baxter Healthcare Corporation; 2018.

Tables

Table 1. Baseline Characteristics

	Phase 1[a] Lenvatinib 11 mg/m^2/day + EI[c] (n = 7)	**Phase 1/2[a,b] Lenvatinib 14 mg/m^2/day + EI[c] (n = 35)**
Median age, years (IQR)	15·0 (12, 19)	15·0 (13, 17)
Age group, n (%)		
≥2 to <6 years	0	1 (3)
≥6 to <18 years	5 (71)	26 (74)
≥6 to <12 years	1 (14)	4 (11)
≥12 to <16 years	3 (43)	16 (46)
≥16 to <18 years	1 (14)	6 (17)
≥18 to ≤25 years	2 (29)	8 (23)
Sex, n (%)		
Male	5 (71)	23 (66)
Female	2 (29)	12 (34)
Median body surface area, m^2 (IQR)	1·6 (1·3, 1·8)	1·6 (1·4, 1·7)
Karnofsky/Lansky performance status[d], n (%)		
70	0	5 (14)
80	2 (29)	6 (17)
90	1 (14)	6 (17)
100	4 (57)	15 (43)
Not available	0	3 (9)
Number of prior anticancer therapy regimen(s)[e], n (%)		
1	3 (43)	14 (40)
2	2 (29)	12 (34)
≥3	2 (29)	9 (26)
Median number of prior anticancer therapy regimen(s) (IQR)	2 (1, 3)	2 (1, 3)
Prior anticancer therapy, n (%)		
Anthracyclines	7 (100)	34 (97)
Ifosfamide monotherapy	1 (14)	9 (26)
Ifosfamide + etoposide	2[f] (29)	12[f] (34)
Other[g]	7 (100)	35 (100)
Best overall response to prior ifosfamide treatment[h], n (%)		
Partial response	1 (33)[i]	2 (10)[i]
Median duration of last medication, months (IQR)	2·1 (1·5, 6·9)	5·3 (2·4, 8·5)
Best response to last anticancer medication, n (%)		

Complete response	0	1 (3)
Partial response	2 (29)	4 (11)
Stable disease	0	10 (29)
Progressive disease	3 (43)	15 (43)
NE/NA/unknown	2 (29)	5 (14)
Prior surgery, n (%)	7 (100)	16 (46)
Median duration of time between prior surgery and initiation of lenvatinib, months (IQR)	2·5 (1·1, 3·6)	6·5 (3·2, 8·9)
Prior radiation therapy, n (%)	0	3 (9)
Metastatic sites, n (%)		
0	1 (14)	1 (3)
1	5 (71)	22 (63)
2	1 (14)	11 (31)
≥3	0	1 (3)
Site of lesion, n (%)		
Lung	4 (57)	24 (69)
Bone	1 (14)	2 (6)
Lung and bone	2 (29)	7 (20)
Brain	0	1 (3)
Liver	0	1 (3)
Lymph	1 (14)	6 (17)
Other	0	9 (26)

[a]Chemotherapy administered intravenously once daily for days 1–3 of each 21-day cycle for five cycles.
[b]Includes eight patients who were planned to receive lenvatinib 14 mg/m^2 but did not because of dose capping.
[c]EI = etoposide 100 mg/m^2/day + ifosfamide 3000 mg/m^2/day.
[d]For patients aged <16 years, Lansky play-performance status score; for patients aged ≥16 years, Karnofsky performance status score.
[e]One (5%) patient in the lenvatinib 14 mg/m^2 + EI group underwent prior vascular endothelial growth factor-targeted therapy (bevacizumab
[f]One patient received ifosfamide + etoposide as first-line therapy.
[g]No patients had received prior tyrosine kinase inhibitor therapy.
[h]There were no complete responses.
[i]Percentage refers to the proportion of patients who received prior ifosfamide therapy.

NA, not applicable; NE, not evaluable.

584 **Table 2.** Most Common TEAEs Occurring in Patients (≥10% of Patients for Grade 1–2 TEAEs,
585 All Grade 3–5 TEAEs) by Planned Dose Level (Safety Analysis Set; Pooled Lenvatinib 14
586 mg/m^2/day + EI[a])

TEAE, n (%)	Phase 1/2[b,c] Lenvatinib 14 mg/m^2/day + EI[a] (n = 35)			
	Grade 1–2	Grade 3	Grade 4	Grade 5
Nausea	22 (63)	2 (6)	0	0
Vomiting	21 (60)	3 (9)	0	0
Hypothyroidism[d]	18 (51)	0	0	0
Diarrhea	16 (46)	4 (11)	0	0
Pyrexia	15 (43)	0	0	0
Abdominal pain	14 (40)	1 (3)	0	0
Headache	14 (40)	0	0	0
Proteinuria[d]	13 (37)	1 (3)	0	0
Arthralgia	12 (34)	0	0	0
Constipation	12 (34)	0	0	0
Decreased appetite	12 (34)	0	0	0
Fatigue	12 (34)	0	0	0
Asthenia	10 (29)	1 (3)	0	0
Back pain	10 (29)	1 (3)	0	0
Cough	10 (29)	1 (3)	0	0
Epistaxis	10 (29)	4 (11)	0	0
Hypertension[d]	9 (26)	1 (3)	0	0
Oropharyngeal pain	8 (23)	0	0	0
Weight decreased	8 (23)	1 (3)	0	0
Hematuria	7 (20)	0	0	0
Pain in extremity	7 (20)	2 (6)	0	0
Stomatitis	7 (20)	3 (9)	0	0
Alanine aminotransferase increased	6 (17)	1 (3)	0	0
Dizziness	6 (17)	0	0	0
Rash	6 (17)	0	0	0
Abdominal pain upper	5 (14)	0	0	0
Anemia	5 (14)	17 (49)	2 (6)	0
Aspartate aminotransferase increased	5 (14)	0	0	0
Blood thyroid stimulating hormone increased	5 (14)	0	0	0
Alopecia	4 (11)	0	0	0
Anal fissure	4 (11)	0	0	0
Dry skin	4 (11)	0	0	0
Dysphonia	4 (11)	0	0	0
Hematochezia	4 (11)	0	0	0

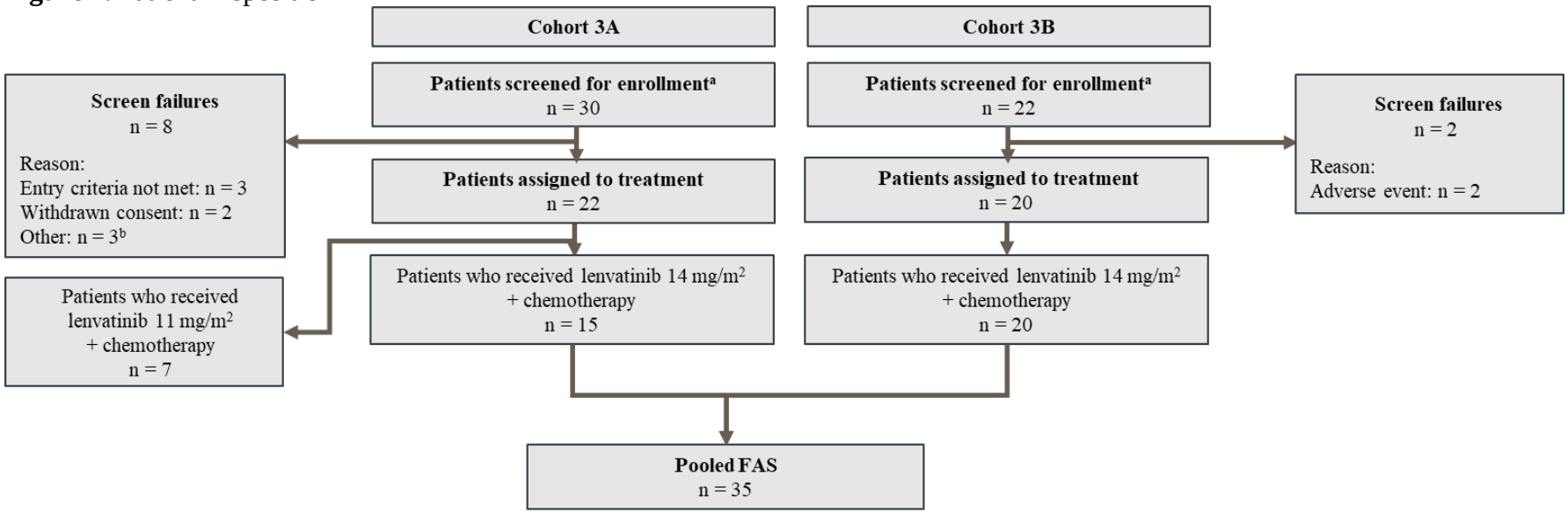
Myalgia	4 (11)	0	0	0
Oral pain	4 (11)	0	0	0
Palmar-plantar erythrodysesthesia syndrome	4 (11)	0	0	0
Pneumothorax	4 (11)	2 (6)	0	0
Procedural pain	4 (11)	0	0	0
Proctalgia	4 (11)	0	0	0
Sinus bradycardia	4 (11)	0	0	0
Tachycardia	4 (11)	0	0	0
Anxiety	3 (9)	1 (3)	0	0
Bone pain	3 (9)	1 (3)	0	0
Musculoskeletal pain	3 (9)	1 (3)	0	0
Anal inflammation	2 (6)	1 (3)	0	0
Blood bilirubin increased	2 (6)	1 (3)	0	0
Dehydration	2 (6)	3 (9)	0	0
Dyspnea	2 (6)	1 (3)	0	1 (3)
Hypophosphatemia	2 (6)	3 (9)	1 (3)	0
Lipase increased	2 (6)	0	1 (3)	0
Non-cardiac chest pain	2 (6)	2 (6)	0	0
Blood potassium decreased	1 (3)	1 (3)	0	0
Gastroenteritis	1 (3)	1 (3)	0	0
Hyperkalemia	1 (3)	1 (3)	0	0
Hypokalemia	1 (3)	3 (9)	0	0
Muscle spasms	1 (3)	1 (3)	0	0
Neuralgia	1 (3)	1 (3)	0	0
Pneumonia	1 (3)	1 (3)	0	0
Rectal hemorrhage	1 (3)	1 (3)	0	0
Thrombocytopenia	1 (3)	5 (14)	20 (57)	0
Toxic encephalopathy	1 (3)	1 (3)	0	0
Accidental overdose	0	2 (6)	0	0
Blood magnesium decreased	0	1 (3)	0	0
Diarrhea hemorrhagic	0	1 (3)	0	0
Electrolyte imbalance	0	1 (3)	0	0
Eyelid oedema	0	1 (3)	0	0
Febrile neutropenia	0	6 (17)	1 (3)	0
Full blood count decreased	0	1 (3)	0	0
Generalized tonic-clonic seizure	0	1 (3)	0	0
Hypotension	0	1 (3)	0	0
Leukopenia	0	1 (3)	4 (11)	0
Lower respiratory tract infection	0	1 (3)	0	0
Lymphocyte count decreased	0	4 (11)	5 (14)	0
Lymphopenia	0	1 (3)	1 (3)	0

Malignant neoplasm progression	0	0	0	1 (3)
Neutropenia	0	4 (11)	23 (66)	0
Esophageal candidiasis	0	1 (3)	0	0
Pancytopenia	0	0	1 (3)	0
Phantom pain	0	1 (3)	0	0
Renal failure	0	1 (3)	0	0
Spinal cord compression	0	1 (3)	0	0
Syncope	0	1 (3)	0	0
Tumor pain	0	1 (3)	0	0
Urticaria	0	1 (3)	0	0
Vascular device infection	0	1 (3)	0	0
Venoocclusive disease	0	1 (3)	0	0
Ventricular dysfunction	0	1 (3)	0	0
Vulvitis	0	0	1 (3)	0
White blood cell count decreased	0	3 (9)	16 (46)	0

[a]EI = etoposide 100 mg/m^2/day + ifosfamide 3000 mg/m^2/day.
[b]Chemotherapy administered intravenously once daily for days 1–3 of each 21-day cycle for 5 cycles.
[c]Includes eight patients who were planned to receive lenvatinib 14 mg/m^2 but did not because of dose capping.
[d]Adverse events commonly associated with lenvatinib.
Percentages are based on the total number of patients within the relevant treatment group in the safety analysis set.
Adverse events were graded using Medical Dictionary for Regulatory Activities version 21·1.
TEAE, treatment-emergent adverse event.

Figures

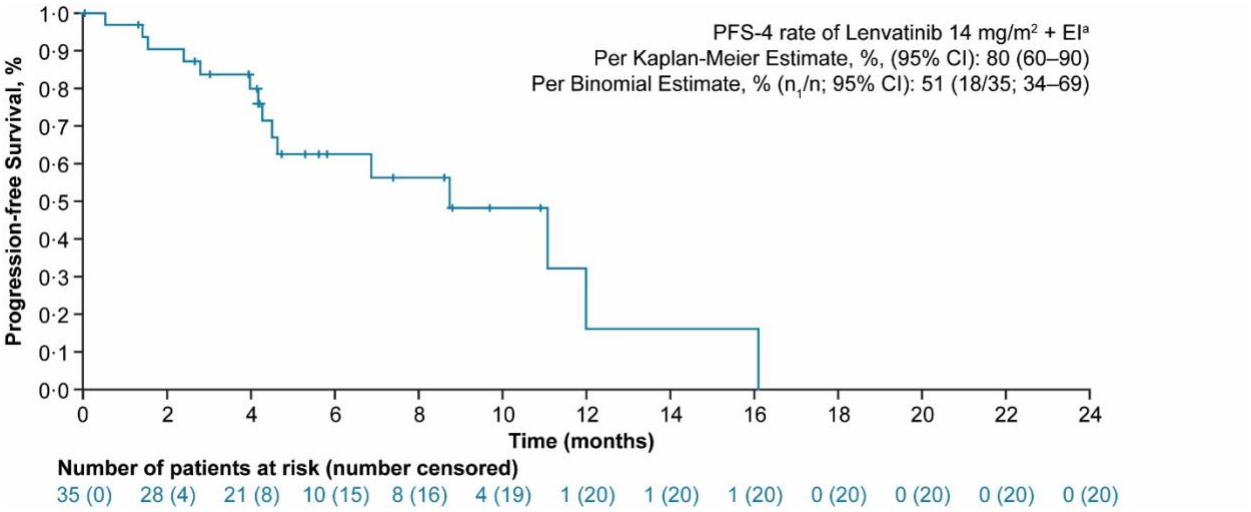
Figure 1. Patient Disposition



[a]Includes patients who provided written consent and were confirmed to have met eligibility criteria.
[b]Patient died (n=1), sponsor decision (n=1), etoposide unavailable (n=1).

FAS, full analysis set.

Figure 2. Phase 1b/2 Pooled Lenvatinib 14 mg/m^2 + EI[a] (FAS): Kaplan–Meier Plot of Progression-free Survival per Investigator Assessment per RECIST v1·1



[a]EI = etoposide 100 mg/m^2/day + ifosfamide 3000 mg/m^2/day.

CI, confidence interval; FAS, full analysis set; n_1, number of patients with specified outcome; PFS, progression-free survival; PFS-4, progression-free survival rate at four months; RECIST v1·1, Response Evaluation Criteria In Solid Tumors version 1·1.

Supplemental Methods

Study Design and Patients

The recommended phase 2 dose (RP2D) was defined as the dose of lenvatinib in combination with ifosfamide and etoposide that resulted in no more than one dose-limiting toxicity (DLT) per six patients, or hematologic DLT in one patient and nonhematologic DLT in another patient, per six patients, upon repeating the same dose level. In this study, 11 mg/m^2/day was chosen as the starting dose.

Once the recommended dose of lenvatinib in combination with chemotherapy was determined, patients with osteosarcoma were assigned to either Cohort 2B (phase 2 single agent expansion) or Cohort 3B (phase 2 combination expansion) depending on whether they were a candidate for ifosfamide and etoposide; patients from Cohort 2B who experienced disease progression could enroll into Cohort 3B. Patients who had received prior treatment with lenvatinib were not eligible to enroll with the exception of patients who were previously enrolled in Cohorts 1 or 2B of this study.

Cohort 3A first enrolled six lenvatinib-naïve patients to receive the starting dose of lenvatinib (20% lower than the recommended dose from the single-agent Cohort 1) and chemotherapy (etoposide 100 mg/m^2/day IV + ifosfamide 3000 mg/m^2/day IV on days 1–3 of each 21-day cycle). Lenvatinib doses were capped after body surface area adjustment and did not exceed 24 mg/day. Since patients with dose capping received a lower dose, patients who were dose capped and did not experience a DLT were replaced. However, DLTs experienced by patients who were dose capped on lenvatinib were counted to determine the RP2D. Doses were escalated or de-escalated based on the prespecified protocol rules. The RP2D was finalized upon occurrence of ≤1 DLT per six patients or when only two patients experienced a hematologic and nonhematologic DLT, respectively, upon repetition of the same dose level. Hematologic DLTs included: grade 4 neutropenia for ≥10 days, grade ≥3 thrombocytopenia with bleeding or lasting ≥10 days, grade ≥3 febrile neutropenia lasting ≥7 days, and delay in next chemotherapy ≥7 days. DLTs also included any grade ≥3 nonhematologic toxicity lasting ≥7 days, grade 4 hypertension, grade 3 proteinuria, and any recurrent grade 2 nonhematological toxicity requiring ≥2 dose interruptions and dose reductions.

Serious adverse events were defined as any untoward medical occurrence that at any dose: (1) results in death; (2) is life-threatening (ie, the patient was at immediate risk of death from the adverse event as it occurred; this does not include an event that, had it occurred in a more severe form or was allowed to continue, might have caused death); (3) requires inpatient hospitalization or prolongation of existing hospitalization; (4) results in persistent or significant disability/incapacity; (5) is a congenital anomaly/birth defect (in the child of a patient who was exposed to the study drug).

Inclusion and Exclusion Criteria

Patients were required to have adequate cardiac function as evidenced by a left ventricular ejection fraction of ≥50% determined by echocardiography, as well as adequate bone marrow function as evidenced by absolute neutrophil count (ANC) of ≥1·0 × 10^9/L and leukocyte count of ≥2 × 10^9/L (or ANC ≥ 0·8 × 10^9/L and leucocyte count ≥1 × 10^9/L, if bone marrow involvement. Adequate liver function was evidenced by bilirubin ≤1·5 times the upper limit of normal (ULN), alkaline phosphatase alanine aminotransferase, and aspartate aminotransferase ≤3 × ULN (≤5 in the case of liver metastases). Adequate renal function was determined by serum creatinine and urine dipstick for proteinuria. Patients were excluded if they had any active infection or infectious illness prior to dosing, or a clinically significant electrocardiogram abnormality, including a prolonged QTc interval (>480 msec), or gastrointestinal bleeding or active hemoptysis within 3 weeks of first dose of study drug, or any other condition that would preclude a patient's ability to participate, according to the investigators.

Patients were not allowed to receive anti-tumor therapy during the trial. A washout period of at least three weeks was required for prior chemotherapy, or at least six weeks if treatment included nitrosoureas.

Dose Reductions and Interruptions

Dose adjustments were made for patients who experience treatment-related toxicity according to the guidelines provided in the table below. Dose reductions were to occur in succession based on the previous dose level. Each dose level reduction is a 20% reduction from the previous dose. Once the dose had been reduced, it could not be increased at a later date.

Treatment-related toxicity[a,b] (including hepatic injury and thromboembolic events)	**Management**	**Dose adjustment[c]**
Grade 1	Continue treatment	No change
Intolerable grade 2[d] or grade 3[e]		
First occurrence	Interrupt until resolved to grade 0–1 or baseline	8·8 mg/m^2 (or 20% reduction of the starting dose) orally once daily (one-level reduction)
Second occurrence (same or new toxicity)	Interrupt until resolved to grade 0–1 or baseline	7·0 mg/m^2 (or 20% reduction of the previous dose) orally once daily (one-level reduction)
Third occurrence	Interrupt until resolved to grade 0–1 or baseline	5·6 mg/m^2 (or 20% reduction of the previous dose) orally once daily (one-level reduction)
Fourth occurrence	Interrupt until resolved to grade 0 –1 or baseline	Discuss with sponsor
Grade 4[f]	Discontinue study treatment	N/A

[a]Interruption of lenvatinib treatment for more than 28 days (due to lenvatinib-related toxicities) will require a discussion with the sponsor before treatment can be resumed.

[b]Initiate optimal medical management for nausea, vomiting, and/or diarrhea prior to any study treatment, interruption, or dose reduction.

[c]Based on a presumed starting dose of 11 mg/m^2.

[d]Applicable only to grade 2 toxicities judged by the patient and/or physician to be intolerable. Not applicable to abnormal clinical laboratory values that are not clinically relevant based on the judgment of the investigator.

[e]Obese patients with weight loss do not need to return to baseline or grade 1 weight loss to restart lenvatinib. There should be no weight loss for at least one week, and patients should be started at the lower dose and normal Body Mass Index (BMI) should be used for future dose reductions.

[f]Excluding laboratory abnormalities judged to be non-life-threatening, in which case manage as grade 3.

Patient Removal from Study

The investigator could discontinue treating a patient with study drug or withdraw the patient from the study at any time for safety or administrative reasons. The patient could decide to discontinue study drug or withdraw from the study at any time for any reason. The reason for discontinuation was documented. If a patient discontinued study drug(s), the patient entered the Posttreatment Follow-up Period and completed protocol-specified off-treatment visits, procedures, and survival follow-up unless the patient withdrew consent. During follow-up, patients who discontinued study drug without progressive disease (PD) had tumor assessments every six or eight weeks (per the appropriate tumor assessment schedule) for up to one year or sooner if clinically indicated, until PD was documented or until another anticancer therapy was initiated. All patients were followed for survival for one year or until death, unless the patient withdrew consent.

Statistical Analysis

Cohort 3A aimed to enroll 12–24 patients and Cohort 3B planned to enroll 18 lenvatinib-naïve patients. With the assumptions p0 = 25%, p1 = 50%, 1-sided α = 10%, and β = 20%, it was determined that a sample size of 15 patients would provide a statistical power of 80% for Cohort 3B. Among patients who discontinued study treatment, those who received subsequent anticancer therapy were censored for analysis of best overall response and progression-free survival at four months (PFS-4) upon receiving therapy.

685 **Rules for Censoring: PFS**

No	Situation	Date of Progression or Censoring	Outcome
1	No baseline tumor assessments	Date of first dose	Censored
2	No postbaseline tumor assessments	Date of first dose	Censored
3	Progression documented between scheduled visits	Date of first radiologic progressive disease assessment	Progressed
4	More than 1 not evaluable tumor timepoint assessment	Date of last adequate radiologic assessment before not evaluable tumor assessments	Censored
5	No progression at time of data cutoff	Date of last adequate radiologic assessment	Censored
6	New anticancer treatment started	Date of last adequate radiologic assessment prior to or on date of new anticancer treatment	Censored
7	Death before first tumor assessment	Date of death	Progressed
8	Death between adequate assessment visits	Date of death	Progressed
9	Death or progression after more than one missed visit/tumor assessment	Date of last adequate radiologic assessment before missed tumor assessments	Censored
10	Treatment discontinuation for reasons other than progressive disease	Date of last radiologic assessment before treatment discontinuation	Censored

686 **Rules for Censoring: Overall Survival**

Situation	End Date	Outcome
Death during study	Date of death	Death
Death after data cut-off	Date of data cut-off	Censored event
Patient still alive at data cut-off	Date of data cut-off	Censored event
Patient lost to follow-up before data cut-off	Date last known to be alive	Censored event

687

Supplemental Tables/Figures

Supplemental Tables

Supplemental Table 1. Safety Summary by Planned Dose Level (Safety Analysis Set; Pooled Lenvatinib 14 mg/m^2/day + EI[a])

	Phase 1[b] Lenvatinib 11 mg/m^2/d + EI[a] (n = 7)	**Phase 1/2[b,c] Lenvatinib 14 mg/m^2/d + EI[a] (N = 35)**
Study-drug exposure		
Treatment duration of lenvatinib, months median (IQR)	7·10 (2·73, 21·91)	4·96 (2·69, 9·46)
Percent of intended dose of lenvatinib, median (IQR)	77·1 (72·0, 86·6)	87·1 (63·1, 100)
Number of cycles received, median (IQR)		
Lenvatinib	10·0 (4·0, 29·0)	7·0 (4·0, 13·0)
Ifosfamide	4·0 (3·0, 5·0)	5·0 (4·0, 5·0)
Etoposide	4·0 (4·0, 5·0)	5·0 (4·0, 5·0)
Summary of adverse events		
TEAEs, n (%)[d]	7 (100)	35 (100)
≥3	6 (86)	35 (100)
TRAEs, n (%)	7 (100)	34 (97)
≥3	6 (86)	32 (91)
Serious TEAEs	5 (71)	26 (74)
Dose Modifications		
TEAEs leading to drug[e]:		
Withdrawal	1 (14)	2 (6)
Dose reduction	1 (14)	3 (9)
Interruption	0	1 (3)
TEAEs leading to lenvatinib:		
Withdrawal	2 (29)	3 (9)
Dose reduction	6 (86)	21 (60)
Interruption	5 (71)	19 (54)
TEAEs leading to chemotherapy[f]:		
Withdrawal	1 (14)	3 (9)
Dose reduction	1 (14)	7 (20)
Interruption	0	1 (3)

[a]Chemotherapy administered intravenously once daily for days 1–3 of each 21-day cycle for 5 cycles.
[b]Includes eight patients who were planned to receive lenvatinib 14 mg/m^2 but did not because of dose capping.
[c]EI = etoposide 100 mg/m^2/day + ifosfamide 3000 mg/m^2/d.
[d]All grade 5 adverse events were associated with disease progression, which included dyspnea in two patients, hypoxic brain injury in one patient, and malignant neoplasm progression in one patient.
[e]Applies to all three study medications.
[f]Applies to both ifosfamide and etoposide.

TEAE, treatment-emergent adverse event; TRAE, treatment-related adverse event.

Supplemental Table 2. Phase 1b and Phase 2 Summary of Tumor Responses (RECIST v1·1 by Investigator Assessment; FAS)

	Phase 1 **Lenvatinib 11 mg/m^2/day + EI[a]**	**Phase 1/2[b,c]** **Lenvatinib 14 mg/m^2/day + EI[a]**
Patients in FAS, n	7	35
PFS-4 rate per binomial estimate, n_1/n (%)	4/7 (57)	18/35 (51)
(95% CI[d])	(18–90)	(34–69)
Kaplan–Meier estimate of PFS rate at 4 months, % (95% CI)[e]	71 (26─92)	80 (60–90)
Median PFS, months (95% CI)	7·1 (2·1–Not estimable)	8·7 (4·5–12·0)
Median follow-up time for PFS, months (!QR)	7·7 (6·9–17·9)	5·8 (4·1–9·7)
Patients with measurable disease[f], n	7	32
ORR, n_1/n (%)	2/7 (29)	3/32 (9)
(95% CI[d])	(4–71)	(2–25)
BOR, n_1/n (%)		
CR	0	0
PR	2/7 (29)	3/32 (9)
SD	3/7 (43)	19/32 (59)
PD	2/7 (29)	6/32 (19)
NE	0	4/32 (13)
Median DOR, months[g]	Not estimable	Not estimable
Patients with measurable disease and evaluable disease, n	7	35
DCR[h], n (%)	5 (71)	25 (71)
(95% CI[d])	(29–96)	(54–85)
CBR[i], n (%)	4 (57)	13 (37)
(95% CI[d])	(18–90)	(21–55)

[a]EI = etoposide 100 mg/m^2/day + ifosfamide 3000 mg/m^2/day.
[b]Includes eight patients who were planned to receive lenvatinib 14 mg/m^2 but did not due to dose capping.
[c]There were no patients who crossed over from Cohort 2B to Cohort 3B. Therefore, all patients enrolled in Cohort 3B (phase 2) were lenvatinib treatment-naïve.
[d]95% CI based on Clopper and Pearson methodology.
[e]Four patients who had disease progression at 4·2, 4·3, 4·5 and 4·6 months were regarded as progression-free at Month 4 per the Kaplan–Meier plot.
[f]Measurable disease was defined as target lesions ± nontarget lesions at baseline. BOR and ORR are based on the number of patients with measurable disease.
[g]DOR reported for responders only, which included two patients in the lenvatinib 11 mg/m^2 group (6·1 and 6·9 months respectively and was censored for both after surgical resection of target lesions) and three in the 14 mg/m^2 group (DOR: 1·5, 4·6, and 6·2 months respectively and was censored for the three at the data cutoff date).
[h]Defined as CR + PR + SD ≥7 weeks for patients with measurable disease or CR + non-CR/non-PD ≥7 weeks for patients with evaluable disease.
[i]Defined as CR + PR + durable SD ≥23 weeks for patients with measurable disease or CR + non-CR/non-PD ≥23 weeks for patients with evaluable disease.

BOR, best overall response; CBR, clinical benefit rate; CI, confidence interval; CR, complete response; DCR, disease control rate; DOR, duration of response; FAS, full analysis set; IQR, interquartile range; n_1, number of patients with specified outcome; NE, not evaluable; ORR, objective response rate; PD, progressive disease; PR, partial response; PFS, progression-free survival; PFS-4, progression-free survival rate at four months; SD, stable disease.

Supplemental Table 3. Subgroup Analysis of Median PFS and PFS-4 Rate per Binomial and Kaplan–Meier Estimates in the Lenvatinib 14 mg/m2/day + EI Group (FAS and RECIST v1·1 by Investigator Assessment)

	Phase 1/2[a] Lenvatinib 14 mg/m^2/day + EI[b] (n = 35)				
	1 Prior anticancer regimen	**≥2 Prior anticancer regimens**	**Previously treated with ifosfamide**	**Not previously treated with ifosfamide**	**≥2 Prior anticancer regimens and previously treated with ifosfamide**
Patients in FAS, n	14	21	21	14	18
Median PFS, months	11·1	8·7	6·9	12·0	4·6
(95% CI)	1·4–11·1	4·3–16·1	4·3–16·1	1·4–12·0	4·0–16·1
Kaplan–Meier estimate of PFS-4 rate, %	83	79	78	83	74
(95 % CI)	48–96	52–91	51–91	48–96	45–90
PFS-4 rate per binomial estimate, n_1/n (%)	6/14 (43)	12/21 (57)	11/21 (52)	7/14 (50)	9/18 (50)
(95% CI)	18–71	34–78	30–74	23–77	26–74

[a]There were no patients who crossed over from Cohort 2B to Cohort 3B. Therefore, all patients enrolled in Cohort 3B (phase 2) were lenvatinib treatment-naïve.

[b]EI = etoposide 100 mg/m^2/day + ifosfamide 3000 mg/m^2/day.

CI, confidence interval; FAS, full analysis set; n_1, number of patients with specified outcome; PFS, progression-free survival; PFS-4, progression-free survival at four months.

Supplemental Table 4. Patients Who Were Had PD or were Censored for PFS Analysis

Patient #	PFS duration, months	PD/Censoring reason for PFS	Progression-free at Week 18? (Binomial Estimate of PFS-4)
1	4·7	New anti-cancer treatment started	Yes
2	3·0	New anti-cancer treatment started	No
3	2·7	New anti-cancer treatment started	No
4	4·2	New anti-cancer treatment started	Yes
5	5·8	No progression at time of treatment discontinuation	Yes
6	1·5	PD	No
7	4·0	PD	No
8[a]	4·5	PD	No[a]
9	6·9	PD	Yes
10	2·8	PD	No
11	2·7	Missing two or more consecutive tumor assessments[b]	No
12	1·3	No progression at time of treatment discontinuation	No
13	4·3	PD	No[c]
14	0·0	No post-baseline tumor assessments	No
15	4·2	PD	No[c]
16	8·8	No progression at time of data cutoff date	Yes
17	8·6	No progression at time of data cutoff date	Yes
18	5·3	New anti-cancer treatment started	Yes
19	2·4	PD	No
20	8·7	PD	Yes
21	11·1	PD	Yes
22	5·6	New anti-cancer treatment started	Yes
23	4·1	No progression at time of data cutoff date	Yes
24	3·9	No progression at time of data cutoff date	Yes
25	10·9	No progression at time of treatment discontinuation	Yes
26	9·7	New anti-cancer treatment started	Yes
27	4·2	New anti-cancer treatment started	Yes
28	12·0	PD	Yes
29	1·4	PD	No
30	7·4	No progression at time of data cutoff date	Yes
31	0·5	PD	No
32	16·1	PD	Yes
33	4·6	PD	No[c]
34	0·0	New anti-cancer treatment started	No
35	0·0	No post-baseline tumor assessments[b]	No

[a]This patient had SD, SD, and PR at Week 6, 12, and 18, respectively, with PD in an unscheduled Week 19 visit due to a new lesion. This patient was deemed to have disease progression at four months.

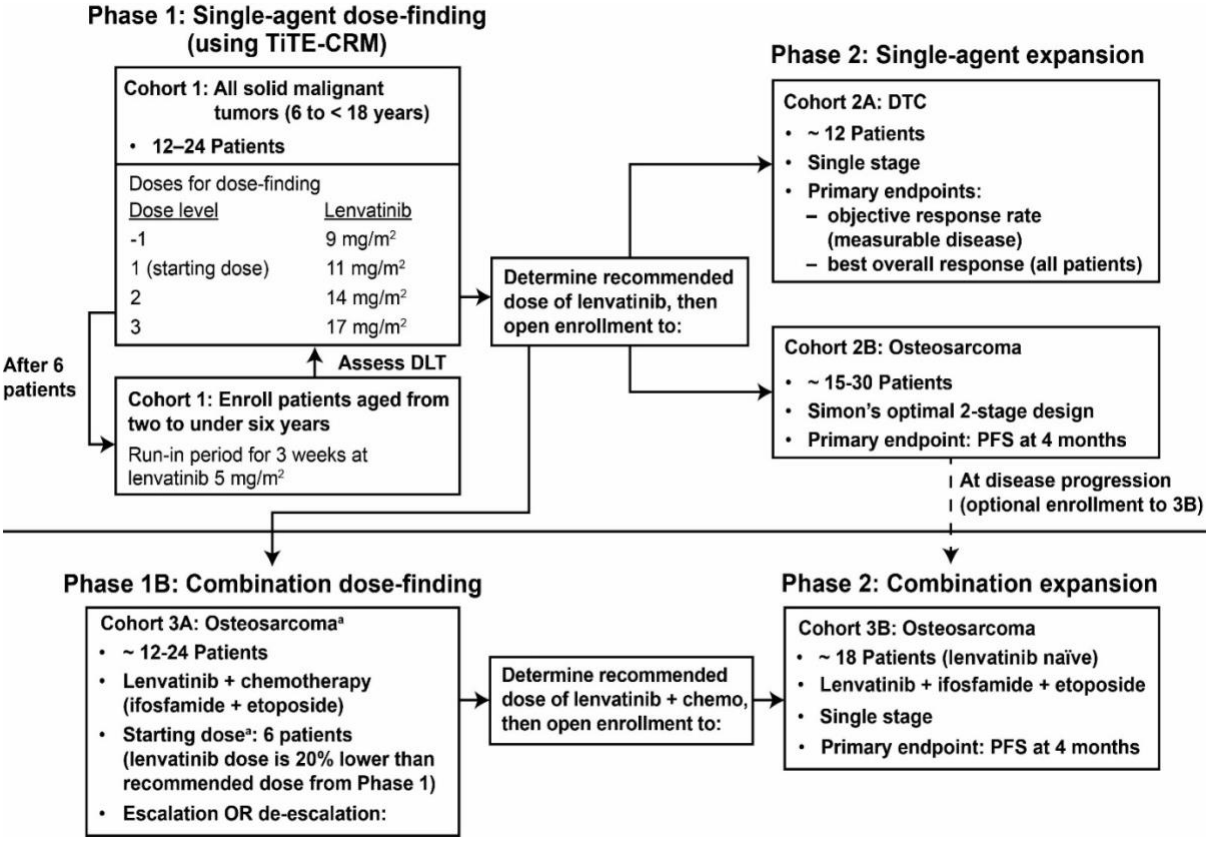
[b]These patients were considered as not having adequate tumor assessments and thus were censored.

[c]These patients had PD at Week 18 tumor assessment scheduled at 4·3, 4·2, and 4·6 months, respectively. They were deemed to have disease progression at four months.

PD, progressive disease; PFS, progression-free survival; PR, partial response; SD, stable disease.

Supplemental Figures

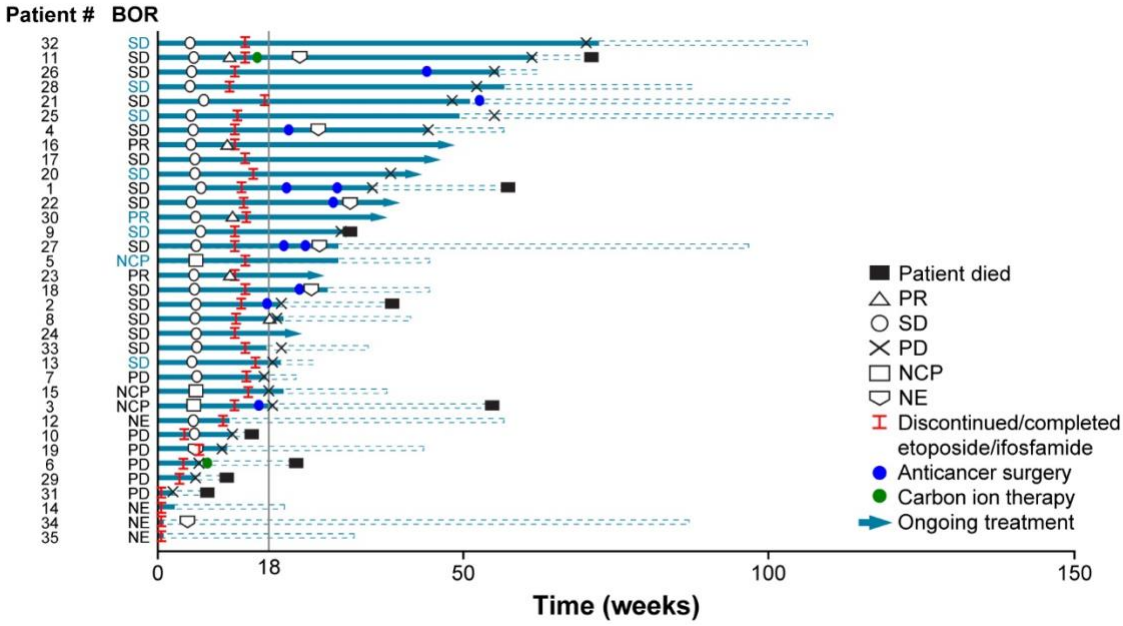
Supplemental Figure 1. Study Design



[a]Lower doses of lenvatinib will be explored.

DLT, dose-limiting toxicity; DTC, differentiated thyroid cancer; PFS, progression-free survival; TiTE-CRM, time-to-event continual-reassessment method.

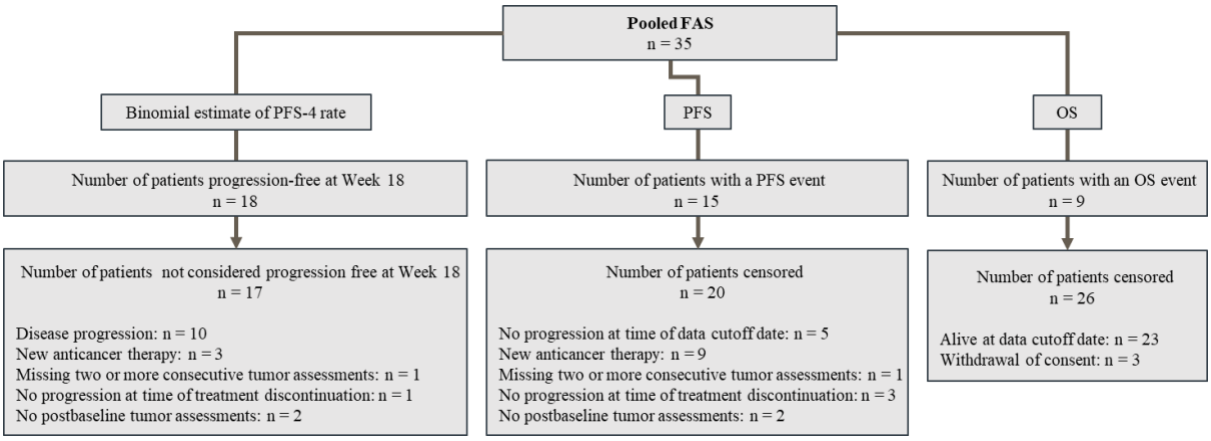
Supplemental Figure 2. Duration of Treatment, Best Overall Response, and Change of Response Over Time (FAS; Lenvatinib [14 mg/m^2/day] + EI[a]) for Phase 1/2[b,c,d]



[a]EI = etoposide 100 mg/m^2/day + ifosfamide 3000 mg/m^2/day.
[b]Each bar with solid line represents treatment duration, while the extended bars with the dashed lines represent the duration that the patient remained on the study after treatment discontinuation.
[c]Patients were planned with the dose level 14 mg/m² of lenvatinib and are ordered by treatment duration.
[d]Patients with dose capping (maximum dose of lenvatinib 24 mg) are indicated in blue text (eg. SD, PR, NCP).

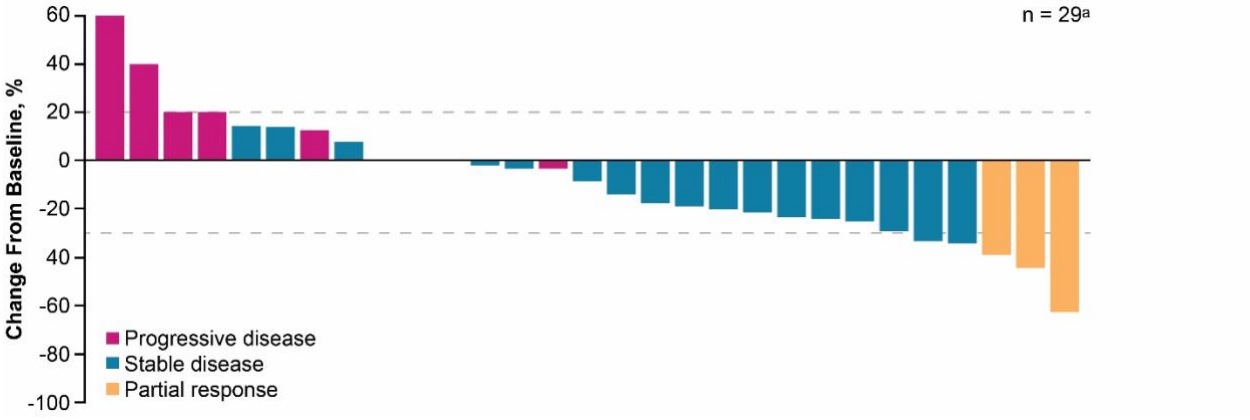
BOR, best overall response; NCP, noncomplete response or progressive disease; FAS, full analysis set; NE, not evaluable; PD, progressive disease; PR, partial response; SD, stable disease.

Supplemental Figure 3. Reasons for Censoring from Pooled FAS



FAS, full analysis set; OS, overall survival; PFS, progression-free survival; PFS-4, progression-free survival at four months.

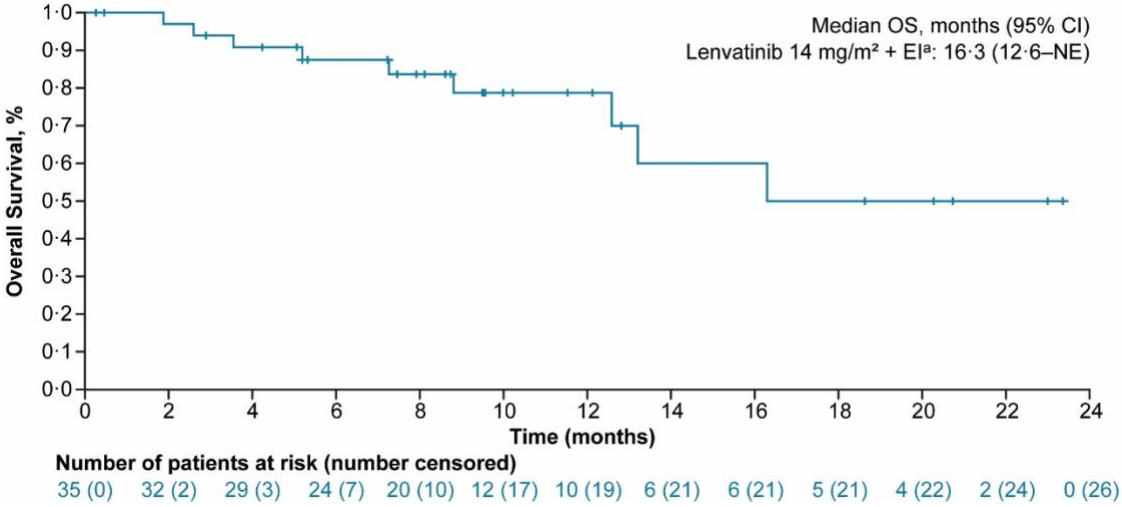
Supplemental Figure 4. Phase 1b/2 Pooled Lenvatinib 14 mg/m^2 + EI[a] (FAS): Maximum Percentage Change in Sum of Diameters of Target Lesions at Data Cutoff Date, Investigator Assessment Based on RECIST v1·1



[a]Three patients with nontarget lesions-only had no sum-of-diameter data available; three patients did not have adequate baseline tumor assessments.

CI, confidence interval; FAS, full analysis set; RECIST v1·1, Response Evaluation Criteria In Solid Tumors version 1·1.

Supplemental Figure 5. Phase 1b/2 Pooled Lenvatinib 14 mg/m^2 + EI[a] (FAS): Kaplan–Meier Plot of Overall Survival



[a]EI = etoposide 100 mg/m^2/day + ifosfamide 3000 mg/m^2/day.

CI, confidence interval; FAS, full analysis set; NE, not evaluable; OS, overall survival.

List of Investigators and Sites

Investigator Name	Site Name	Number of Patients Treated
Quentin Campbell-Hewson	The Great North Children's Hospital, Royal Victoria Infirmary, Newcastle Upon Tyne, UK	9
Francisco Bautista	Hospital Infantil Universitario Niño Jesus, Madrid, Spain	5
Rajkumar Venkatramani	Texas Children's Cancer Center, Baylor College of Medicine, Houston, TX, USA	5
Cyril Lervat	Pediatric and AYA Oncology Unit, Centre Oscar Lambret Lille, Lille, France	3
Alessandra Longhi	Istituto Ortopedico Rizzoli, Bologna, Italy	3
Isabelle Aerts	Institut Curie, PSL Research University, Oncology Center SIREDO, Paris, France	2
Natacha Entz-Werle	CHU Strasbourg - Hôpital Hautepierre, Strasbourg, France	2
Michela Casanova	Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy	2
Sandra J. Strauss	University College London Hospital, London, UK	2
Stefan Bielack	Klinikum Stuttgart – Olgahospital, Stuttgart, Germany	2
Estelle Thebaud	CHU Nantes - Hôpital Mère-Enfant, Nantes, France	1
Nathalie Gaspar	Department of Oncology for Child and Adolescent, Gustave Roussy Cancer Campus, Villejuif, France	1
Perrine Marec-Berard	Centre Léon Bérard, Lyon, France	1
Franco Locatelli	Ospedale Pediatrico Bambino Gesù, Sapienza, University of Rome, Rome, Italy	1
Soledad Gallego Melcon	University Hospital Vall d'Hebron, Barcelona, Spain	1
Adela Cañete Nieto	Hospital Universitario y Politecnico La Fe, Valencia, Spain	1
Bruce Morland	Birmingham Children's Hospital, Birmingham, UK	1
Marion Gambart	CHU de Toulouse, Hôpital des Enfants, URCP, Toulouse, France	0
Claudia Rossig	University Children's Hospital Muenster, Pediatric Hematology and Oncology, Muenster, Germany	0

770 List of Central and Local Ethics Committees for All Study Sites

Site Name	Central Ethics Committee	Local Ethics Committee
Texas Children's Cancer Center, Baylor College of Medicine, Houston, TX, USA	N/A	Institutional Review Board for Human Subject Research, Baylor College of Medicine and Affiliated Hospitals, Houston, TX, USA
CHU Nantes - Hôpital Mère-Enfant, Nantes, France	Comite de Protection des Personnes Ile de France V Hopital Saint Antonie, Paris, France	N/A
Institut Curie, PSL Research University, Oncology Center SIREDO, Paris, France	Comite de Protection des Personnes Ile de France V Hopital Saint Antonie, Paris, France	N/A
CHU de Toulouse, Hôpital des Enfants, URCP, Toulouse, France	Comite de Protection des Personnes Ile de France V Hopital Saint Antonie Paris, France	N/A
Department of Oncology for Child and Adolescent, Gustave Roussy Cancer Campus, Villejuif, France	Comite de Protection des Personnes Ile de France V Hopital Saint Antonie, Paris, France	N/A
CHU Strasbourg - Hôpital Hautepierre, Strasbourg, France	Comite de Protection des Personnes Ile de France V Hopital Saint Antonie, Paris, France	N/A
Centre Léon Bérard, Lyon, France	Comite de Protection des Personnes Ile de France V Hopital Saint Antonie, Paris, France	N/A
Pediatric and AYA Oncology Unit, Centre Oscar Lambret Lille, Lille, France	Comite de Protection des Personnes Ile de France V Hopital Saint Antonie, Paris, France	N/A
Ospedale Pediatrico Bambino Gesù, Sapienza, University of Rome, Rome, Italy	Comitato Etico Sperimentazione Clinica IRCCS Ospedale Pediatrico Bambino Gesù di Roma, Rome, Italy	N/A
Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy	Comitato Etico Sperimentazione Clinica IRCCS Ospedale Pediatrico Bambino Gesù di Roma, Rome, Italy	Comitato Etico Indipendente della Fondazione IRCCS Istituto Nazionale dei Tumori di Milano, Milan, Italy
Istituto Ortopedico Rizzoli, Bologna, Italy	Comitato Etico Sperimentazione Clinica IRCCS Ospedale Pediatrico Bambino Gesù di Roma, Rome, Italy	Comitato Etico Instituto Ortopedico Rizzoli, Bologna, Italy
Hospital Infantil Universitario Niño Jesus, Madrid, Spain	CEIC Hospital Infantil Universitario Niño Jesús, Madrid, Spain	N/A
University Hospital Vall d'Hebron, Barcelona, Spain	CEIC Hospital Infantil Universitario Niño Jesús, Madrid, Spain	CEIC Hospital Universitari Vall d'Hebron Barcelona, Spain
Hospital Universitario y Politecnico La Fe, Valencia, Spain	CEIC Hospital Infantil Universitario Niño Jesús, Madrid, Spain	N/A
The Great North Children's Hospital, Royal Victoria Infirmary, Newcastle Upon Tyne, UK	NRES Committee North East – Newcastle and North Tyneside 2, Jarrow, UK	N/A
Birmingham Children's Hospital, Birmingham, UK	NRES Committee North East – Newcastle and North Tyneside 2, Jarrow, UK	N/A
University College London Hospital, London, UK	NRES Committee North East – Newcastle and North Tyneside 2, Jarrow, UK	N/A
Klinikum Stuttgart – Olgahospital, Stuttgart, Germany	Landesarztekammer Baden-Wurttemberg Ethik Kommission, Stuttgart, Germany	N/A
University Children's Hospital Muenster, Pediatric Hematology and Oncology, Münster, Germany	Landesarztekammer Baden-Wurttemberg Ethik Kommission, Stuttgart, Germany	Ethik-Kommission der Ärztekammer Westfalen-Lippe und der Westfälischen Wilhelms-Universität Münster, Münster, Germany

771