Amsterdam, 27 June 2024
EMA/330823/2024
Committee for Medicinal Products for Human Use (CHMP)

Assessment report for paediatric studies submitted according to Article 46 of the Regulation (EC) No 1901/2006

Kisplyx

Lenvatinib

Procedure no: EMEA/H/C/004224/P46/020

Lenvima

Lenvatinib

Procedure no: EMA/H/C/003727/P46/023

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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1. Introduction

On 16 February 2024, the MAH submitted the final Clinical Study Report for Study E7080-G000-230 (hereafter referred to as Study 230), in accordance with Article 46 of Regulation (EC) No1901/2006, as amended. Study 230 is part of the clinical development program for Lenvatinib in the approved Paediatric Investigation Plan (EMEA-001119-PIP02-12-M08). The study was completed on 29 September 2023, which was the final database lock for the Study 230.

2. Scientific discussion

2.1. Information on the development program

Lenvatinib is a receptor tyrosine kinase (RTK) inhibitor that selectively inhibits the kinase activities of vascular endothelial growth factor (VEGF) receptors VEGFR1 (FLT1), VEGFR2 (KDR), and VEGFR3 (FLT4), in addition to other proangiogenic and oncogenic pathway-related RTKs including fibroblast growth factor (FGF) receptors FGFR1, 2, 3, and 4, the platelet derived growth factor (PDGF) receptor PDGFRα, KIT, and RET.

The marketing authorisations for Lenvima (EMEA/H/C/003727) and Kisplyx (EMEA/H/C/004224) were granted renewal on 20 May 2020 and 17 June 2021, respectively, including the indications for **Lenvima** of *Differentiated Thyroid Carcinoma (DTC), Hepatocellular Carcinoma (HCC), Endometrial Carcinoma (EC) and the advanced renal cell carcinoma (RCC)* for **Kisplyx.**

The MAH stated that Study E7080-G000-230 (hereafter referred to as "Study 230") falls within the scope of the Paediatric Regulation; it is identified as Study 8 in the lenvatinib paediatric investigation plan (PIP 2: EMEA-001119-PIP02-12). Study 230 was a multicenter, open-label, randomized, controlled, Phase 2 study in children, adolescents, and young adults (≤25 years) with relapsed or refractory osteosarcoma. This study was completed on 29 September 2023, which was the final database lock for the study.

Within the clinical development scope of Lenvima /Kisplyx in paediatric setting, Study 230 and Study E7080-G000-207, (hereafter referred to as Study 207) are the main two clinical studies in EMEA-001119-PIP02-12-M08. A Type II variation was submitted to the Lenvima license on 16 June 2023 (EMEA/H/C/003727/II/0050) to update sections 4.2, 4.8, 5.1 and 5.2 of the SmPC with paediatric information based on the results from Studies 207 and 230. CHMP gave the positive opinion on November 2023. Another Type II variation was submitted on November 2023 ((EMEA/H/C/003727/II/0055), also including the partial results from Study E7080-G000-207 (hereafter referred to as Study 207) and Study E7080-G000-230 (hereafter referred to as Study 230), as the part of the lenvatinib PIP (EMEA-001119-PIP02-12-M08).

The second PIP EMEA001119-PIP03-19-M03 (condition: solid tumours) was approved on December 2023 and an additional Type II variation (variation category C.I.4) is submitted for both Lenvima and Kisplyx licenses to include the final results of the paediatric Study 230.

There are no plans to submit any extension of indications within the paediatric setting for lenvatinib as a single agent or in combination with chemotherapy (ifosfamide and etoposide) for paediatric patients with relapsed or refractory DTC or osteosarcoma based on the submitted final CRS of Study 230 and thus no changes to the SmPC are proposed in this procedure.

The summary of the Study 230 is provided in the Table 1 below.

Table 1 The summary of the main clinical study 230

Study Number	Objectives of the Study	Study Design and Type of Control	Dosage Regimen; Route of Administration	Number of Subjects (Planned/ Actual)	Healthy Subjects or Diagnosis of Patients	Duration of Treatment
E7080-G000-230	**Primary Objective** To evaluate whether lenvatinib in combination with chemotherapy (ifosfamide and etoposide [**Arm A**; the "triplet" regimen]) is superior to chemotherapy alone (ifosfamide and etoposide [**Arm B**; the "doublet" regimen]) in improving progression-free survival (PFS) based on independent imaging review (IIR) assessments (hereafter referred to as "per IIR") using Response Evaluation Criteria in Solid Tumors (RECIST 1.1), in children, adolescents, and young adults with relapsed or refractory osteosarcoma	Phase 2, multicenter, open label, randomized study of lenvatinib in combination with ifosfamide and etoposide versus ifosfamide and etoposide in children, adolescents and young adults with relapsed or refractory osteosarcoma	**Arm A**: LENV: 14 mg/m^2 IFOS: 3000 mg/m^2 ETOP: 100 mg/m^2 **Arm B**: IFOS: 3000 mg/m^2 ETOP: 100 mg/m^2 **Route/regimen** LENV: PO Once daily, in 21-day cycles IFOS and ETOP: IV, Days 1 to 3 of each 21-day cycle (up to 5 cycles)	Planned: 72 subjects: 36 subjects/arm **Arm A** 40 randomized (39 treated) **Arm B** 41 randomized (39 treated)	Subjects (aged ≥2 to ≤25 years at time of informed consent) with histologically or cytologically confirmed diagnosis of high-grade osteosarcoma that was refractory or relapsed after 1 - 2 prior lines of systemic treatment and no history of Grade ≥3 ifosfamide-related nephrotoxicity or encephalopathy.	Subjects in both treatment arms received chemotherapy (ifosfamide + etoposide) for a maximum of 5 cycles. Subjects in **Arm A** (and eligible subjects in **Arm B**) received lenvatinib QD, which could be continued as a single agent after the following: completion/dis-continuation of chemotherapy, until PD (confirmed per IIR in Randomization Phase), development of unacceptable toxicity, investigator or subject request, initiation of a new anticancer therapy, withdrawal of consent, or sponsor's termination of the study, whichever occurred first. **Subjects in Arm B** who had PD per RECIST 1.1 were eligible for optional treatment with lenvatinib (indefinitely) ± chemotherapy (maximum of 5 cycles)

CSR = clinical study report, DTC = differentiated thyroid cancer, ETOP = etoposide, IFOS = ifosfamide, IV = intravenous(ly), LENV = lenvatinib, PD = progressive disease, PO = oral(ly), RD = recommended dose, RR-DTC = refractory differentiated thyroid cancer, QD = once daily.

2.2. Clinical aspects

2.2.1. Introduction

This report includes the final CRS of study 230 for Lenvima and Kisplyx in accordance with Article 46 of Regulation (EC) No1901/2006. No extension of the indication is applied for and no modifications are proposed to the SmPC.

The MAH has submitted previously the reports for:

- E7080-G000-230: Phase 2 Study to Compare the Efficacy and Safety of Lenvatinib in Combination with Ifosfamide and Etoposide versus Ifosfamide and Etoposide in Children, Adolescents and Young Adults with Relapsed or Refractory Osteosarcoma (OLIE): the primary CSR dated on 24 Jan 2023 and Revision 1 dated on 08 Jun 2023.

  An integrated population PK analysis of lenvatinib was performed using pooled data from several studies including 4 studies in paediatric subjects: Study 207, Study E7080-G000-216, Study 230, and Study E7080-G000-231, and the PK report (CPMS-E7080-017R-v1) for details of the analysis and results was submitted in 2023.

- The biomarker analysis report for the Study 230 submitted in the type II variation (EMEA/H/C/003727/II/0050) with entitled TSBM-E7080-230-ANA-1R "Biomarker Analysis of Lenvatinib (E7080) in a Multicenter, Open-label, Randomized Phase 2 Study to Compare the Efficacy and Safety of Lenvatinib in Combination With Ifosfamide and Etoposide Versus Ifosfamide and Etoposide in Children, Adolescents, and Young Adults With Relapsed or Refractory Osteosarcoma (OLIE)"

2.2.2. Methods

A Multicenter, Open-label, Randomized Phase 2 Study to Compare the Efficacy and Safety of Lenvatinib in Combination with Ifosfamide and Etoposide versus Ifosfamide and Etoposide in Children, Adolescents and Young Adults with Relapsed or Refractory Osteosarcoma (OLIE)

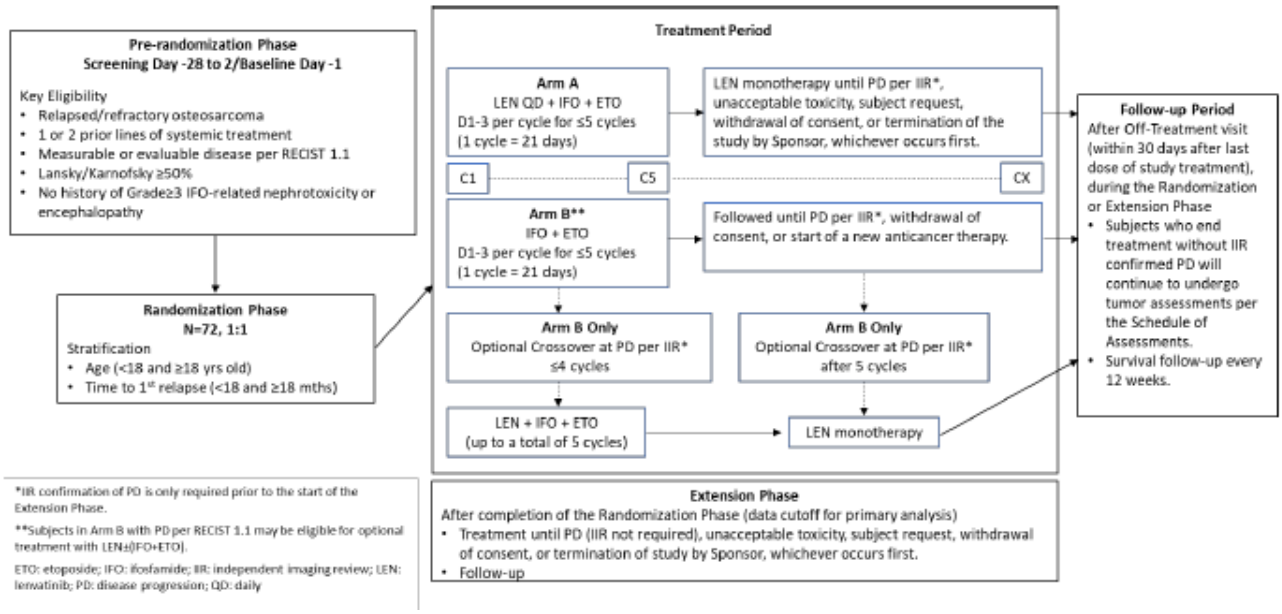

Figure 1 Study 230 design

Arm A = lenvatinib (LEN) + ifosfamide (IFO) + etoposide (ETO), Arm B = IFO + ETO (maximum of 5 cycles)

Subjects in Arm B with PD per Response Evaluation for Solid Tumors (RECIST) 1.1 were eligible for optional treatment with lenvatinib ±chemotherapy. See Section 9.1.4 for further details. Follow-up occurred during the Randomization Phase (if subject discontinued treatment during the Randomization Phase), or during the Extension Phase, after termination of study treatment. Confirmation of PD by IIR was only required at the start of the Extension Phase.

C1 = Cycle 1, C5 = Cycle 5, Cx = nth cycle, D1 = Day 1, IIR = independent imaging review, PD = disease progression.

Study participants

Key inclusion Criteria

- Male or female, at least 2 years and no more than 25 years of age at the time of informed consent
- Histologically or cytologically confirmed diagnosis of high-grade refractory or relapsed osteosarcoma
- One or 2 prior lines of systemic treatment
- Measurable or evaluable disease per RECIST 1.1
- Adequate bone marrow function, blood coagulation function, liver function, renal function, cardiac function, and blood pressure control
- Lansky play score or KPS score of at least 50.

Key exclusion Criteria

- Prior treatment with lenvatinib
- Clinically significant ECG abnormalities
- History of Grade 3 or higher ifosfamide-related nephrotoxicity or encephalopathy
- Any serious concomitant illness that in the opinion of the investigator(s) could have affected the subject's safety or interfered with the study assessments.

Treatments

Arm A: lenvatinib 14 mg/m2 (orally, once daily, in 21-day continuous cycles) plus ifosfamide 3000 mg/m2/day (intravenously [IV], Day 1 to Day 3 of each cycle for a total of up to 5 cycles) and etoposide 100 mg/m2/day (IV, Day 1 to Day 3 of each cycle for a total of up to 5 cycles)

Arm B: ifosfamide 3000 mg/m2/day (IV, Day 1 to Day 3 of each cycle for a total of up to 5 cycles) and etoposide 100 mg/m2/day (IV, Day 1 to Day 3 of each cycle for a total of up to 5 cycles)

After adjustment for BSA, the dose of lenvatinib could not exceed 24 mg QD. An extemporaneous suspension of lenvatinib capsules was used for subjects unable to swallow capsules. After completion or discontinuation of ifosfamide and etoposide, treatment with lenvatinib could be continued as a single agent until PD or until another protocol-specified event occurred.

Optional Lenvatinib Crossover (Subjects in Arm B Only):

Subjects in Arm B with PD based on RECIST 1.1 (per IIR in the Randomization Phase and per investigator assessment in the Extension Phase) were eligible for optional treatment with lenvatinib (± chemotherapy [maximum 5 cycles]), which could continue until subsequent PD (per investigator assessment using RECIST 1.1) or until another protocol-specified withdrawal criterion was met.

Objectives and endpoints

Objectives	Endpoints
Primary	
To evaluate whether lenvatinib in combination with ifosfamide and etoposide is superior to ifosfamide and etoposide alone in improving progression-free survival (PFS) in children, adolescents, and young adults with relapsed or refractory osteosarcoma.	PFS assessed by IIR, defined as the time from the date of randomization to the date of the first documentation of PD or death (whichever occurred first) as determined using RECIST 1.1.
Secondary	
Compare the difference in PFS at 4 months (PFS-4m) and at 1 year (PFS-1y) between the 2 treatment arms per IIR	PFS, defined as the time from the date of randomization to the date of first documentation of disease progression or death (whichever occurred first)
Compare the difference in overall survival (OS) and OS rate at 1 year (OS-1y) between the 2 treatment arms	OS, defined as the time from the date of randomization to the date of death from any cause
Compare the difference in overall objective response rate (ORR) and ORR at 4 months (ORR-4m) between the 2 treatment arms	Objective response rate (ORR), defined as the proportion of subjects who had a best overall response (BOR) of CR or PR
Compare the difference in safety and tolerability between the 2 treatment arms	Adverse events (AE), serious AEs (SAE), clinical laboratory values, ECG parameters, vital sign measurements, and performance status
Characterize the pharmacokinetics (PK) of lenvatinib, when administered in combination with ifosfamide and etoposide	Population-based PK parameters of lenvatinib
Compare difference HRQoL assessed using the PedsQL Generic Core Scales and Cancer Module between the 2 treatment arms	Changes in score from Baseline for all PedsQL scales, including Generic Core Scales and Cancer Module; time to first deterioration which is defined as the number of months between randomization and the first deterioration event; time to definitive deterioration which is defined as the number of months between randomization and the earliest deterioration event with no subsequent recovery above the deterioration threshold.
Assess the palatability and acceptability of the suspension formulation of lenvatinib.	Palatability and acceptability of the lenvatinib suspension formulation assessed using the Palatability Questionnaire.
Exploratory	
Explore the difference in DOR, DCR, and CBR between the 2 treatment arms per IIR and investigator assessment	DOR by IIR and investigator assessment, defined as the time from the date a response was first documented until the date of the first documentation of PD or

	date of death from any cause
Explore the differences in PFS, PFS-4m, PFS-1y, ORR-4m, and ORR between the 2 treatment arms based on investigator assessment	DCR by IIR and investigator assessment, defined as the proportion of subjects who had a BOR of CR, PR or stable disease (SD). In this context, SD was defined as duration of at least 5 weeks after randomization
Compare between the 2 treatment arms: The proportion of subjects who achieved complete removal of baseline lesion(s) The proportion of subjects with unresectable baseline lesion(s) that were converted to resectable	CBR by IIR and investigator assessment, defined as the proportion of subjects who had a BOR of CR, PR, or durable SD (duration of at least 23 weeks after randomization) Efficacy endpoints (PFS, PFS-4m, PFS-1y, ORR-4m, and ORR) evaluated based on investigator assessment Proportion of subjects who achieved complete removal of baseline lesions and the proportion of subjects with unresectable baseline lesions(s) that were converted to resectable
Investigate the relationship between subject tumor biomarkers and clinical response and toxicity of lenvatinib in combination with ifosfamide and etoposide.	Blood and tumor biomarker samples may be used for exploratory analysis for evaluation of response- or safety-related outcomes as well as for potential use in diagnostic development.

For the secondary endpoints, PFS rate at 4 months (PFS-4m) and at 1 year (PFS-1y) were defined as the percentage of subjects who were alive and without PD at 4 months and at 1 year, respectively, from the randomization date. The PFS rates were estimated using the KM method.

Randomisation and blinding (masking)

The study is open-label. However, Eisai's biostatistics and programming team, as well as the IIR reviewers of tumour assessments, were blinded.

Subjects were randomized to 1 of 2 treatment arms in a 1:1 ratio stratified by time to first relapse/refractory disease (early [<18 months] or late [≥18 months]) and age (<18 years and ≥18 years).

Statistical Methods

Full Analysis Set (FAS, intent-to-treat analysis) includes all subjects who were enrolled and randomly assigned to study treatment. Safety Analysis Set includes those subjects who received at least 1 dose of any study drug.

For this final synoptic CSR, cumulative disposition, exposure, and OS data are presented for the FAS as of the end of study (EOS; final database lock). Cumulative data for treatment-emergent AEs (TEAEs), including SAEs, as of the EOS are summarized for the Safety Analysis Set and for subjects from Arm B who crossed over to optional treatment with lenvatinib. The tables present cumulative data for the study (from the start of study treatment) while the listings present individual subject data from the

time of data cutoff for the primary analysis until the EOS. The data are final as of the database lock date (29 Sep 2023).

Results

The primary analysis was conducted at the primary data cutoff date (22 June 2022). The primary analysis sets for efficacy and safety were as follows:

- The Full Analysis Set (FAS) was defined as all subjects assigned to treatment regardless of the treatment actually received.
- The Safety Analysis Set was defined as subjects who received at least 1 dose of any study drug.

The FAS was the primary analysis set for the efficacy analyses and the Safety Analysis Set was the primary analysis set used for the safety analyses.
For the end of study (EOS) final analysis (database lock date: 29 Sep 2023), cumulative disposition, exposure, and OS data are presented for the FAS as of the end of study. Cumulative data for treatment-emergent adverse events (TEAEs), including serious adverse events (SAEs), as of the EOS are summarized for the Safety Analysis Set and for subjects from Arm B who crossed over to optional treatment with lenvatinib.

Participant flow

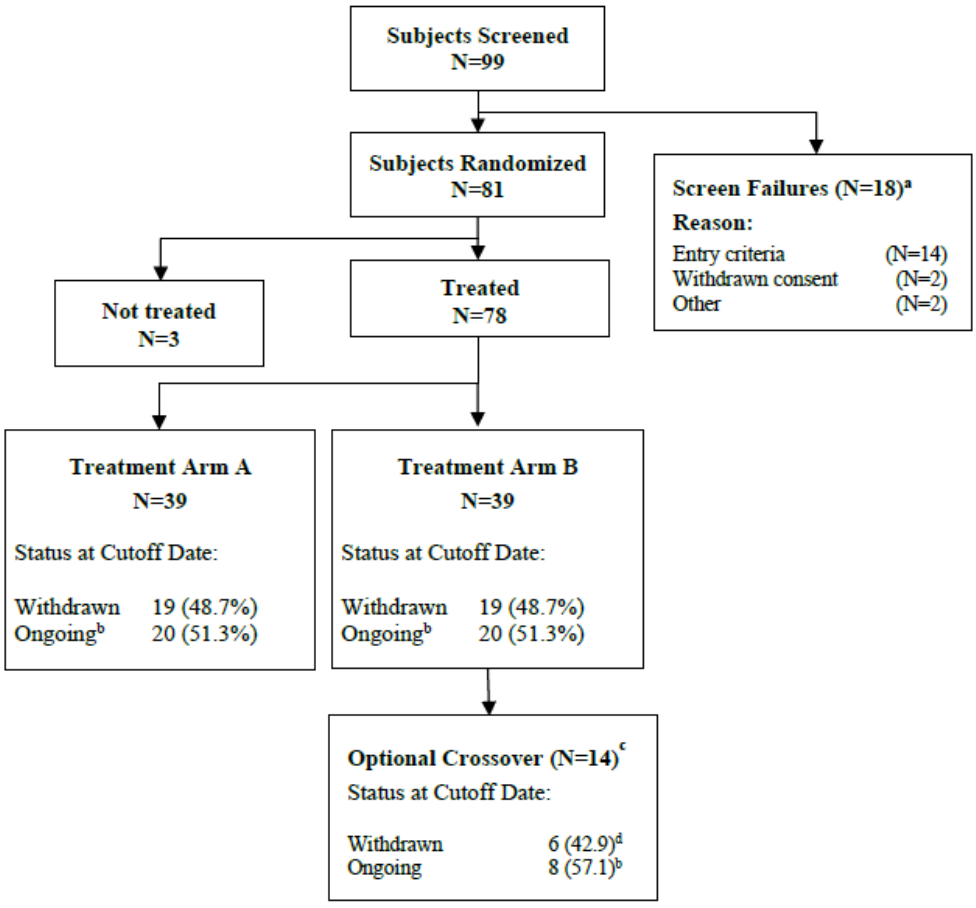

Figure 2 Subject Disposition and primary reason for withdrawal from the study

Data cutoff date: 22 Jun 2022. Arm A: Lenv + IFOS +ETOP; Arm B: IFOS +ETOP. eCRF = electronic case report form, ETOP = etoposide, IFOS = ifosfamide, Lenv = lenvatinib. a: Based on primary reason reported on the Screening Disposition eCRF. b: Includes subjects who were still receiving study treatment as well as those in survival follow-up as of the cutoff date. c: Crossover to treatment with lenvatinib ± chemotherapy after disease progression. d: Subject no longer in survival follow-up as of the cutoff date.

Source: Tables 14.1.1.1, 14.1.1.3, and 14.1.1.9.

Recruitment

Study 230 was conducted between 22 Mar 2020 (first subject signed ICF) and 22 Jun 2022 (data cutoff date for primary analysis). The data are final as of the database lock date (29 Sep 2023). Subjects were enrolled at 44 study sites in 18 countries (3 regions).

In this study, 81 subjects (40 in Arm A, 41 in Arm B) were assigned to treatment and included in the FAS; 3 subjects (1 in Arm A and 2 in Arm B) did not receive any study drug and were excluded from the FAS. 78 treated subjects (39 in each arm) were included in the Safety Analysis Set.

As of the EOS, all 78 treated subjects had discontinued study treatment; ongoing subjects were transitioned to commercial lenvatinib (recorded on the case report form as "treatment discontinued: reason, other").

As of the EOS, all 81 subjects in the FAS had withdrawn from the study. Fifty (61.7%) of the 81 subjects, 25 in Arm A and 25 in Arm B, had died and 10 subjects (12.3%), 4 in Arm A and 6 in Arm B, withdrew consent. For 18 subjects, survival follow-up ended when the sponsor terminated the study; the remaining 3 subjects transitioned to an access program using commercial lenvatinib. No subjects were lost to follow-up.

Table 2 Subject Disposition and Reasons for Discontinuation of Treatment at End of Study – Full Analysis Set

Category	Arm A LENV + IFOS + ETOP (N=40) n (%)	Arm B IFOS + ETOP (N=41) n (%)	Total (N=81) n (%)
Randomized	40 (100)	41 (100)	81 (100)
Not Treated	1 (2.5)	2 (4.9)	3 (3.7)
Treated	39 (97.5)	39 (95.1)	78 (96.3)
Treatment Completed per Protocol	1 (2.5)	22 (53.7)	23 (28.4)
Discontinued Treatment	38 (95.0)	17 (41.5)	55 (67.9)
Primary Reason for Discontinuation of Study Treatment			
Disease Progression	26 (65.0)	13 (31.7)	39 (48.1)
Radiological Disease Progression	25 (62.5)	12 (29.3)	37 (45.7)
Clinical Disease Progression	1 (2.5)	1 (2.4)	2 (2.5)
Adverse Event	3 (7.5)	0 (0.0)	3 (3.7)
Subject Choice	1 (2.5)	1 (2.4)	2 (2.5)
Withdrawal of Consent[a]	2 (5.0)	2 (4.9)	4 (4.9)
Physician Decision	3 (7.5)	1 (2.4)	4 (4.9)
Other	3 (7.5)	0 (0.0)	3 (3.7)
Subject transitioned to MAP	2 (5.0)	0 (0.0)	2 (2.5)
Subject transitioned to PAP	1 (2.5)	0 (0.0)	1 (1.2)

Database lock date: 29 Sep 2023.
Table contains cumulative data from start of treatment through the end of study.
Percentages are based on the number of subjects randomized in the relevant treatment groups.
Rows containing only zeroes have been omitted from the in-text table.
For subjects in both Arm A and Arm B, completed/discontinued treatment refers to completion/ discontinuation of all study drugs.
ETOP = etoposide 100 mg/m², IFOS = ifosfamide 3000 mg/m², LENV = lenvatinib 14 mg/m²,
MAP = managed access program, PAP = patient access program.
a: 'Withdrawal of Consent' combines reasons of 'Withdrawal of consent from study' and 'Withdrawal by parent/guardian.'
Source: Table 14.1.1.2.

The study was conducted in 3 phases:

- Pre-randomization Phase (≤28 days' duration for each subject): Consisted of Screening and Baseline periods, and established protocol eligibility.
- *Randomization Phase*: Consisted of Treatment and Follow-up periods. The Randomization Phase began at the time that the first subject was randomly assigned to treatment and ended on the data cutoff date for the primary analysis (22 Jun 2022).
- *Extension Phase*: After the data cutoff date for the primary analysis had occurred, all subjects still receiving study treatment entered the Extension Phase, which consisted of a Treatment and Follow-up period.
- The *Follow-up Period* (for both the Randomization and Extension Phases) began the day after the subject's Off-Treatment visit and lasted for up to 2 years after the subject's end of treatment, unless the subject met a protocol-specified withdrawal criterion.

Optional Lenvatinib Crossover Treatment (Arm B Subjects)

Sixteen subjects in Arm B crossed over to optional lenvatinib treatment; 2 subjects did so after data cutoff for the primary analysis.

Eleven subjects crossed over after completing all 5 cycles of chemotherapy. The remaining 5 subjects crossed over during the chemotherapy period: 1 subject received no cycles of IFOS+ETOP with

lenvatinib, 1 subject received 1 cycle of IFOS+ETOP with lenvatinib, and 3 subjects received 2 cycles of IFOS+ETOP with Lenvatinib. All 16 subjects discontinued optional lenvatinib treatment as of the EOS; 11 of the 16 subjects (68.8%) due to PD. Of the 5 remaining subjects, 2 discontinued for an AE, and 1 each discontinued for subject choice, physician's decision, and transition to a managed access program for commercial Lenvatinib.

Table 3 Anticancer Medications During Survival Follow-up (Full Analysis Set)

Anatomical Class (ATC Level 1) Pharmacological Class (ATC Level 3) WHO Drug Name (Preferred Term)	Len + Ifo + Eto (N=40) n (%)	Ifo + Eto (N=41) n (%)	Total (N=81) n (%)
Subjects with Any Anticancer Medications During Survival Follow-up	20 (50.0)	26 (63.4)	46 (56.8)
ANTINEOPLASTIC AND IMMUNOMODULATING AGENTS	20 (50.0)	26 (63.4)	46 (56.8)
ALKYLATING AGENTS	6 (15.0)	9 (22.0)	15 (18.5)
CYCLOPHOSPHAMIDE	3 (7.5)	2 (4.9)	5 (6.2)
IFOSFAMIDE	3 (7.5)	6 (14.6)	9 (11.1)
TROFOSFAMIDE	0 (0.0)	1 (2.4)	1 (1.2)
ANTIMETABOLITES	9 (22.5)	12 (29.3)	21 (25.9)
FLUDARABINE	0 (0.0)	1 (2.4)	1 (1.2)
GEMCITABINE	9 (22.5)	12 (29.3)	21 (25.9)
MONOCLONAL ANTIBODIES AND ANTIBODY DRUG CONJUGATES	3 (7.5)	3 (7.3)	6 (7.4)
DOSTARLIMAB	2 (5.0)	3 (7.3)	5 (6.2)
DURVALUMAB	1 (2.5)	0 (0.0)	1 (1.2)
TREMELIMUMAB	1 (2.5)	0 (0.0)	1 (1.2)
OTHER ANTINEOPLASTIC AGENTS	7 (17.5)	4 (9.8)	11 (13.6)
CARBOPLATIN	1 (2.5)	0 (0.0)	1 (1.2)
CELECOXIB	1 (2.5)	0 (0.0)	1 (1.2)
ENTINOSTAT	1 (2.5)	0 (0.0)	1 (1.2)
NIRAPARIB	2 (5.0)	3 (7.3)	5 (6.2)
OXALIPLATIN	2 (5.0)	1 (2.4)	3 (3.7)
RETINOIDS FOR CANCER TREATMENT	1 (2.5)	0 (0.0)	1 (1.2)
THALIDOMIDE	1 (2.5)	0 (0.0)	1 (1.2)
PLANT ALKALOIDS AND OTHER NATURAL PRODUCTS	16 (40.0)	20 (48.8)	36 (44.4)
DOCETAXEL	9 (22.5)	10 (24.4)	19 (23.5)
ETOPOSIDE	9 (22.5)	10 (24.4)	19 (23.5)
IRINOTECAN	2 (5.0)	1 (2.4)	3 (3.7)
TOPOTECAN	0 (0.0)	1 (2.4)	1 (1.2)
PROTEIN KINASE INHIBITORS	10 (25.0)	12 (29.3)	22 (27.2)
CABOZANTINIB	2 (5.0)	6 (14.6)	8 (9.9)
EVEROLIMUS	1 (2.5)	0 (0.0)	1 (1.2)
LENVATINIB	1 (2.5)	1 (2.4)	2 (2.5)
PAZOPANIB	1 (2.5)	1 (2.4)	2 (2.5)
REGORAFENIB	3 (7.5)	4 (9.8)	7 (8.6)
RIVOCERANIB	1 (2.5)	0 (0.0)	1 (1.2)
SORAFENIB	3 (7.5)	1 (2.4)	4 (4.9)
CARDIOVASCULAR SYSTEM	1 (2.5)	0 (0.0)	1 (1.2)
LIPID MODIFYING AGENTS, PLAIN	1 (2.5)	0 (0.0)	1 (1.2)
FENOFIBRATE	1 (2.5)	0 (0.0)	1 (1.2)

Percentages are based on the total number of subjects within the relevant treatment group for the Full Analysis Set.
Subjects with 2 or more medications within an ATC level (or drug name) are counted only once within that ATC level (or drug name).
Medications are coded using WHO Drug Dictionary Version WHODDMAR21B3G.
Source: Dataset ADANCAM

Final Database Lock Date: 29SEP2023
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Table 4 Anticancer Procedures During Survival Follow-up (Full Analysis Set)

MedDRA System Organ Class Preferred Term	Len + Ifo + Eto (N=40) n (%)	Ifo + Eto (N=41) n (%)	Total (N=81) n (%)
Subjects with Any Anticancer Procedures During Survival Follow-up	12 (30.0)	14 (34.1)	26 (32.1)
Bone and joint therapeutic procedures	5 (12.5)	9 (22.0)	14 (17.3)
Finger amputation	0 (0.0)	1 (2.4)	1 (1.2)
Leg amputation	1 (2.5)	1 (2.4)	2 (2.5)
Radiotherapy to bone	3 (7.5)	6 (14.6)	9 (11.1)
Radiotherapy to joint	2 (5.0)	0 (0.0)	2 (2.5)
Rotationplasty	0 (0.0)	1 (2.4)	1 (1.2)
Toe amputation	0 (0.0)	1 (2.4)	1 (1.2)
Cardiac therapeutic procedures	0 (0.0)	1 (2.4)	1 (1.2)
Pericardial excision	0 (0.0)	1 (2.4)	1 (1.2)
Gastrointestinal therapeutic procedures	1 (2.5)	0 (0.0)	1 (1.2)
Radiotherapy to pancreas	1 (2.5)	0 (0.0)	1 (1.2)
Investigations, imaging and histopathology procedures NEC	0 (0.0)	1 (2.4)	1 (1.2)
Biopsy	0 (0.0)	1 (2.4)	1 (1.2)
Nervous system, skull and spine therapeutic procedures	0 (0.0)	1 (2.4)	1 (1.2)
Brain tumour operation	0 (0.0)	1 (2.4)	1 (1.2)
Respiratory tract therapeutic procedures	5 (12.5)	5 (12.2)	10 (12.3)
Diaphragmatic operation	0 (0.0)	1 (2.4)	1 (1.2)
Pulmonary resection	0 (0.0)	3 (7.3)	3 (3.7)
Radiotherapy to lung	4 (10.0)	2 (4.9)	6 (7.4)
Thoracic cavity drainage	1 (2.5)	0 (0.0)	1 (1.2)
Skin investigations	0 (0.0)	1 (2.4)	1 (1.2)
Biopsy skin	0 (0.0)	1 (2.4)	1 (1.2)
Therapeutic procedures and supportive care NEC	5 (12.5)	4 (9.8)	9 (11.1)
Cancer surgery	0 (0.0)	1 (2.4)	1 (1.2)
Radiotherapy	5 (12.5)	2 (4.9)	7 (8.6)
Tumour excision	0 (0.0)	1 (2.4)	1 (1.2)

Percentages are based on the total number of subjects within the relevant treatment group for the Full Analysis Set.
Subjects with two or more preferred terms in the same system organ class (or with the same preferred term) are counted only once for that system organ class (or preferred term).
Procedures were coded using MedDRA version 25.0.
Source: Dataset ADPR

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Baseline data

Demographics and Disease characteristics

Demographics, baseline characteristics, and prior anticancer therapies are described in Study 230 primary CSR.

Protocol Deviations

No major protocol deviations occurred between the cutoff date for the primary analysis and the EOS.

Results

The median age of all subjects enrolled was 15.0 years, with 56 subjects (69.1%) aged less than 17 years. The median age of subjects at the time of first osteosarcoma diagnosis was 13.5 years and

12.0 years for Arm A and Arm B, respectively. Most subjects were white (n=50, 61.7%); 20 subjects (24.7%) were Asian, and 2 subjects (2.5%) were black. Most subjects had a Karnovsky Performance Status (KPS) or Lansky play score of 80 or above. Consistent with the known prevalence of osteosarcoma, there were more males (M) than females (F) (46M/35F) enrolled in the study; the proportion of males to females was greater in Arm A (25M/15F) than in Arm B (21M/20F). There were no other clinically relevant differences in baseline demographics between the treatment arms.

All subjects enrolled had relapsed or refractory osteosarcoma, 80 (98.8%) of which were high- grade (ie, Grade 3 or Grade 4). At Baseline, 64 subjects (79.0%) had lung lesions and 27 subjects (33.3%) had bone lesions per IIR.

Time to first relapse was less than 18 months for 70 subjects (86.4%), 35 in each arm. The median time from diagnosis of metastatic disease to randomization was 9.5 months in Arm A and 6.0 months in Arm B.

All 81 subjects in the FAS had received at least 1 prior anticancer medication. The most frequently used prior anticancer medications were cisplatin, doxorubicin, and methotrexate. A total of 38 subjects (20 in Arm A, 18 in Arm B) had received prior ifosfamide and 22 (14 in Arm A, 8 in Arm B) had received prior etoposide; 14 subjects in Arm A and 7 subjects in Arm B had previously received both agents. Two subjects, both in Arm A, had received prior therapy with a receptor tyrosine kinase inhibitor.

Efficacy results

All efficacy analyses were based on the FAS, which consisted of all subjects who were randomly assigned to treatment. The analyses of PFS and other secondary endpoints were performed at the primary DCO date of 22 Jun 2022. The analysis of the key secondary endpoint, OS, was also performed at EOS, final database lock date 29 Sep 2023.

9 subjects (22.5%) in Arm A and 18 subjects (43.9%) in Arm B had 1 or more baseline lesion(s) resected, including target and nontarget lesions. In the post hoc analysis excluding subjects who underwent lesion removal during the study (ie, those subjects who had been censored in the primary PFS analysis) from the analysis, median PFS was 6.3 months in Arm A and 2.9 months in Arm B (HR=0.42).

Six subjects in Arm A and 4 subjects in Arm B had a best overall response (BOR) of partial response (PR) (assessed by IIR in the FAS), for an ORR of 15.0% and 9.8%, respectively.

Overall Survival at End of Study (EOS)

As of the EOS, there were 15 additional months of OS follow-up data after the primary analysis cutoff date. Median (95% CI) OS was 12.4 months (10.4, 19.8) in Arm A and 17.2 months (11.1, 22.3) in Arm B (stratified HR=0.93 [95% CI: 0.53, 1.62]; nominal P=0.3924).

Median follow-up time for the final OS analysis was 24.1 months (95% CI: 23.4, 27.5) for Arm A and 29.5 months (95% CI: 24.5, 32.3) for Arm B.

Table 5. Overall Survival (FAS)

Category	Len + Ifo + Eto (N=40)	Ifo + Eto (N=41)
Deaths, n (%)	25 (62.5)	25 (61.0)
Censored, n (%)	15 (37.5)	16 (39.0)
Withdrawal of Consent	4 (10.0)	6 (14.6)
Alive	11 (27.5)	10 (24.4)
Overall Survival (months)[a]		
Median (95% CI)	12.4 (10.4, 19.8)	17.2 (11.1, 22.3)
Q1 (95% CI)	8.9 (4.4, 11.3)	6.1 (3.3, 14.3)
Q3 (95% CI)	NE (17.3, NE)	NE (20.0, NE)
Len + Ifo + Eto vs Ifo + Eto		
Stratified Hazard Ratio (95% CI)[b,c]	0.93 (0.53, 1.62)	
Stratified Log-rank One-sided Test P value[c]	0.3924	
Overall Survival Rate (%) (95% CI)[d] at		
4 months	89.9 (75.2, 96.1)	89.4 (74.1, 95.9)
6 months	84.7 (69.1, 92.8)	77.8 (60.5, 88.3)
9 months	74.0 (57.0, 85.1)	72.1 (54.2, 83.9)
12 months	51.3 (34.1, 66.0)	66.3 (48.3, 79.3)
18 months	39.9 (24.1, 55.2)	46.1 (29.2, 61.4)
24 months	31.3 (17.1, 46.6)	28.8 (15.1, 44.2)
Duration of Survival Follow-up (months)[a,e]		
Median (95% CI)	24.1 (23.4, 27.5)	29.5 (24.5, 32.3)
Q1 (95% CI)	23.4 (8.3, 24.1)	24.5 (3.1, 27.4)
Q3 (95% CI)	27.5 (24.1, NE)	32.3 (27.4, NE)

Percentages are based on the total number of subjects within the relevant treatment group for the Full Analysis Set.
NE = not estimable; IRT = Interactive Response Technology.
a: Quartiles are estimated by Kaplan-Meier method, and the 2-sided 95% CIs are estimated with a generalized Brookmeyer and Crowley method.
b: Hazard ratio is based on a Cox Proportional Hazard Model including treatment group as a factor; Efron method is used for ties.
c: Stratified by Age (<18 years, ≥18 years) in IRT.
d: Overall survival rate and 2-sided 95% CIs are calculated using Kaplan-Meier product-limit method and Greenwood Formula.
e: Estimates for survival follow-up time are calculated in the same way as the Kaplan-Meier estimate of overall survival but with the meaning of 'censor' and 'event' status indicator reversed.
Source: Dataset ADEF

Final Database Lock Date: 29SEP2023
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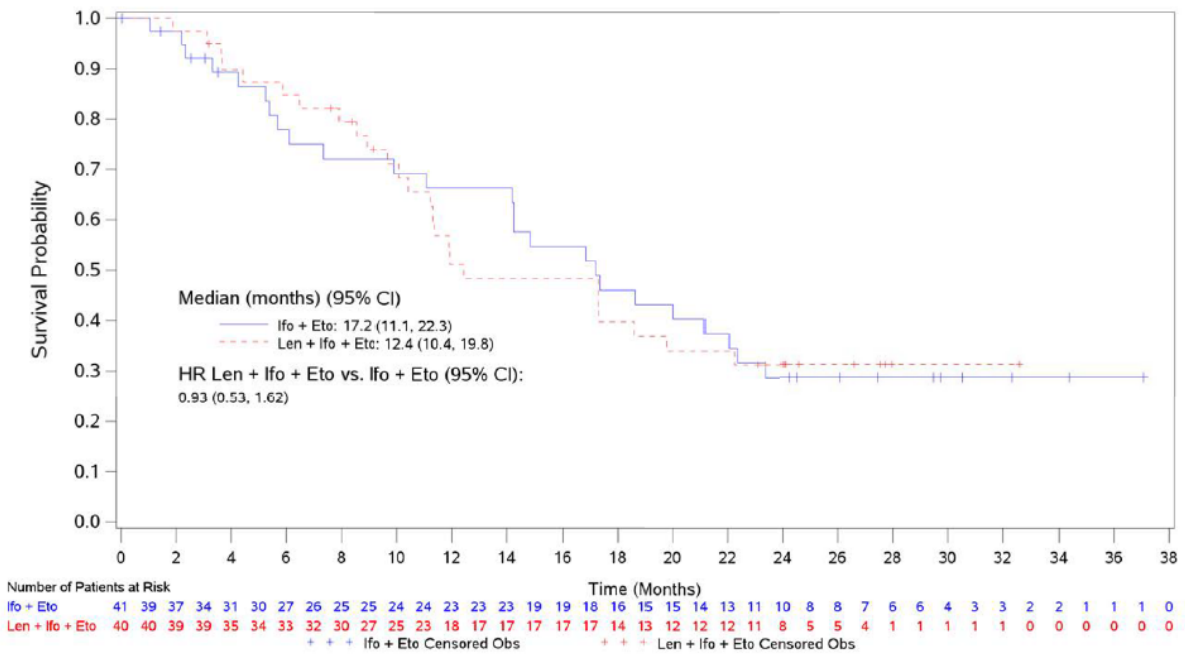

Median is estimated by Kaplan-Meier method, and the 95% confidence interval is estimated with a generalized Brookmeyer and Crowley method. Hazard ratio is expressed as Len + Ifo + Eto/Ifo + Eto and was estimated from Cox Proportional Hazard Model stratified by Age (<18 years, 18 years) in IRT. The treatment group is used as a covariate in the model; and Efron method is used for ties.
Len + Ifo + Eto = Lenvatinib 14 mg/m² + Ifosfamide 3000 mg/m² +Etoposide 100 mg/m²; Ifo + Eto = Ifosfamide 3000 mg/m² +Etoposide 100 mg/m².
Source: ADTTE

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Figure 3 Kaplan-Meier Plot of Overall Survival (FAS)

Health-Related Quality of Life

The quality of life analysis set included 81 participants (41 participants randomized to Len+Ifo+Eto and 40 randomized to Ifo+Eto).The completion rates (at least 1 complete score) at the Off-Treatment Visit were 48.0% for Len+Ifo+Eto and 44.7% for Ifo+Eto.

Subjects in Arm A and Arm B had similar HRQoL scores. For the generic questionnaire and cancer module, the total score did not differ significantly for Arm A and Arm B and did not reach the minimal threshold for clinically important differences.

The overall mean difference in HRQoL was not significant for any of the scales on the generic and cancer modules from Baseline to Week 18 using ANCOVA modelling. Hazard ratios (HR) for time to first deterioration were not significant for any of the subscales of the generic and cancer modules. A significant HR favoring Arm A over Arm B was observed for time to definitive deterioration for the communication scale of the cancer module (HR 0.15; 95% CI: 0.03, 0.78). Hazard ratios for all other scales for both the generic and cancer modules were not significant for time to definitive deterioration (Module 5.3.5.1 Study 230 CSR Section 11.3.1.4.1).

Palatability of Lenvatinib Suspension

Five subjects received lenvatinib as an oral suspension and completed the Palatability and Acceptability Questionnaire. The overall acceptability of the lenvatinib suspension was rated as "may be good or may be bad" by 2 subjects, "good" by 2 subjects, and "super good" by 1 subject (Module 5.3.5.1 Study 230 CSR Table 14.2.3.4.2).

The details are referred to the stand-alone Study 230 HRQoL report.

Pharmacokinetic (PK)/Pharmacodynamic (PD) Results

An integrated population PK analysis of lenvatinib was performed using pooled data from several studies including 4 studies in paediatric subjects: Study 207, Study E7080-G000-216, Study 230, and Study E7080-G000-231 (CPMS-E7080-017R-v1).

Conclusions from the population PK analysis are:

- Lenvatinib oral clearance (CL/F) was affected by body weight.
- In the presence of body weight effect, lenvatinib CL/F was not affected by age for subjects

aged 2 years or older.

- Dosing lenvatinib per BSA in children and adolescents resulted in a similar exposure to that in adults dosed at a fixed dose of 24 mg.
- Predicted exposure levels normalized by dose level were generally comparable between tumour types.

Biomarker Analysis

No conclusive associations were observed between biomarkers and PFS or adverse events (AEs) in subjects treated with lenvatinib in combination with ifosfamide and etoposide. The pharmacodynamic changes observed in serum biomarkers (increased VEGF, FGF-19, and FGF-23, and decreased ANG-2) indicated that lenvatinib in combination with ifosfamide and etoposide had an inhibitory effect on the FGFR and VEGFR signaling pathways, consistent with the mechanism of action for lenvatinib and results of previous lenvatinib single agent clinical studies in adults and the paediatric population (Study 207) and in combination with ifosfamide and etoposide in osteosarcoma (Study 207). (Refer to TSBM-E7080-207-ANA-1R).

Safety results

Safety Results (Safety Analysis Set)

Extent of Exposure

As of the EOS, 78 subjects (39 subjects in each arm) had received at least 1 dose of study drug and were included in the Safety Analysis Set. The median (minimum [min], maximum [max]) duration of treatment in Arm A was 35.71 weeks (5.9, 115.3), versus 33.14 weeks (5.9, 55.1) in the primary analysis.

Optional lenvatinib crossover (Arm B subjects only): Median (min, max) duration of lenvatinib treatment for the 16 subjects who crossed over to optional lenvatinib treatment was 51.8 weeks (11, 106).

Ifosfamide and Etoposide Exposure

The exposure to ifosfamide or etoposide as of the EOS was unchanged relative to exposure as described in the Study 230 primary CSR.

Lenvatinib Exposure

In general, the overall extent of exposure as of the EOS was longer relative to that described in Study 230 primary CSR. As of the EOS, median (min, max) duration of treatment in Arm A was 35.71 weeks (5.9, 115.3). *Optional lenvatinib crossover (Arm B subjects only).* Median (min, max) duration of

lenvatinib treatment for the 16 subjects who crossed over to optional lenvatinib treatment was 51.8 weeks (11, 106) .

Ifosfamide and Etoposide Exposure

The exposure to IFOS and ETOP as of the EOS was unchanged relative to exposure as described in Study 230 primary CSR.

Adverse Events

Overview of Adverse Events

As of the EOS, 77 subjects (98.7%) experienced TEAEs. The most commonly reported TEAEs (incidence ≥40%) in Arm A as of the EOS were hypothyroidism (89.7%), anaemia (71.8%), nausea (59.0%), platelet count decreased (59.0%), proteinuria (59.0%), vomiting (48.7%), and hypertension (43.6%).

The most commonly reported TEAEs (incidence ≥30%) in Arm B as of the EOS were anaemia (69.2%), platelet count decreased (43.6%), nausea (41.0%), neutrophil count decreased (33.3%), and white blood cell count decreased (33.3%).

Adverse events reported for the 16 subjects in Arm B during optional lenvatinib crossover: As of the EOS, the most commonly reported TEAEs (incidence ≥35%) in these 16 subjects were hypothyroidism (50.0%), hypertension (43.8%), pain in extremity (37.5%), and proteinuria (37.5%).

Table 6. Overview of Treatment-Emergent Adverse Events at End of Study – Safety Analysis Set

Category	Arm A LENV + IFOS + ETOP (N=39) n (%)	Arm B IFOS + ETOP (N=39) n (%)	Total (N=78) n (%)
Subjects with Any TEAEs	38 (97.4)	39 (100)	77 (98.7)
Subjects with Any TEAE Worst CTCAE Grade of:			
≥3	37 (94.9)	32 (82.1)	69 (88.5)
3	10 (25.6)	11 (28.2)	21 (26.9)
4	22 (56.4)	20 (51.3)	42 (53.8)
5	5 (12.8)	1 (2.6)	6 (7.7)
Subjects with Any TE SAEs[a]:	30 (76.9)	20 (51.3)	50 (64.1)
Any Fatal TEAEs	5 (12.8)	1 (2.6)	6 (7.7)
Any Nonfatal TE SAEs	30 (76.9)	20 (51.3)	50 (64.1)
Subjects with Study Drug Dose Adjustment[a]	35 (89.7)	11 (28.2)	46 (59.0)
TEAEs Leading to Study Drug Discontinuation of:	10 (25.6)	3 (7.7)	13 (16.7)
Lenv & Both Chemo Agents[b]	1 (2.6)	NA	NA
Lenvatinib[c]	6 (15.4)	NA	NA
Both Chemo Agents[b,d]	6 (15.4)	0 (0.0)	6 (7.7)
Etoposide[d]	6 (15.4)	2 (5.1)	8 (10.3)
Ifosfamide[d]	6 (15.4)	1 (2.6)	7 (9.0)
TEAEs Leading to Dose Reduction or Drug Interruption of:	35 (89.7)	9 (23.1)	44 (56.4)
Lenv & Both Chemo Agents[b]	9 (23.1)	NA	NA
Lenvatinib[c]	33 (84.6)	NA	NA
Both Chemo Agents[b,d]	14 (35.9)	6 (15.4)	20 (25.6)
Etoposide[d]	14 (35.9)	7 (17.9)	21 (26.9)
Ifosfamide[d]	16 (41.0)	8 (20.5)	24 (30.8)
TEAEs Leading to Drug Interruption of:	27 (69.2)	5 (12.8)	32 (41.0)
Lenv & Both Chemo Agents[b]	2 (5.1)	NA	NA
Lenvatinib[c]	27 (69.2)	NA	NA
Both Chemo Agents[b,d]	5 (12.8)	2 (5.1)	7 (9.0)
Etoposide[d]	5 (12.8)	3 (7.7)	8 (10.3)
Ifosfamide[d]	6 (15.4)	4 (10.3)	10 (12.8)
TEAEs Leading to Dose Reduction of:	30 (76.9)	6 (15.4)	36 (46.2)
Lenv & Both Chemo Agents[b]	2 (5.1)	NA	NA
Lenvatinib[c]	26 (66.7)	NA	NA
Both Chemo Agents[b,d]	10 (25.6)	5 (12.8)	15 (19.2)
Etoposide[d]	10 (25.6)	5 (12.8)	15 (19.2)
Ifosfamide[d]	11 (28.2)	6 (15.4)	17 (21.8)

Database lock date: 29 Sep 2023.
Table includes events that occurred from the start of treatment through the end of study.
Data records occurring on or after the first dose date of the crossover are excluded from this table for subjects in Arm B (IFOS 3000 mg/m² + ETOP 100 mg/m²) who crossed over to optional treatment with LENV +/- chemotherapy.
MedDRA preferred terms of "neoplasm progression," "malignant neoplasm progression" and "disease progression" not related to the study drug are excluded.
For each row category, subjects with 2 or more AEs in that category are counted only once.
AEs were coded using MedDRA version 25.0 and graded using Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.
AE = adverse event, chemo = chemotherapy (ETOP, IFOS), ETOP = etoposide, IFOS = ifosfamide, LENV = lenvatinib, MedDRA = Medical Dictionary for Regulatory Activities, NA = not applicable, SAE = serious AE, TE = treatment emergent, TEAE = treatment-emergent AE.
a: Each subject may be counted in multiple categories. Dose adjustment includes study drug discontinuation, dose reduction, and/or drug interruption.
b: Due to the same AE.
c: Regardless of action taken for ETOP or IFOS.
d: Regardless of action taken for other study drug(s).
Source: Table 14.3.1.2.1.

Table 7. Treatment-Emergent Adverse Events with CTCAE Grade 3 or Higher by Preferred Term in Decreasing Incidence (Safety Analysis Set)

Preferred Term	Len + Ifo + Eto (N=39) n (%)	Ifo + Eto (N=39) n (%)	Total (N=78) n (%)
Subjects with Any TEAEs of Grade 3 or Higher	37 (94.9)	32 (82.1)	69 (88.5)
Anaemia	26 (66.7)	19 (48.7)	45 (57.7)
Platelet count decreased	20 (51.3)	9 (23.1)	29 (37.2)
Febrile neutropenia	15 (38.5)	8 (20.5)	23 (29.5)
Neutrophil count decreased	13 (33.3)	13 (33.3)	26 (33.3)
Neutropenia	10 (25.6)	7 (17.9)	17 (21.8)
Proteinuria	10 (25.6)	1 (2.6)	11 (14.1)
Hypertension	7 (17.9)	0 (0.0)	7 (9.0)
Thrombocytopenia	7 (17.9)	3 (7.7)	10 (12.8)
Leukopenia	5 (12.8)	4 (10.3)	9 (11.5)
Aspartate aminotransferase increased	4 (10.3)	2 (5.1)	6 (7.7)
Lymphocyte count decreased	4 (10.3)	6 (15.4)	10 (12.8)
Pneumothorax	4 (10.3)	0 (0.0)	4 (5.1)
Alanine aminotransferase increased	3 (7.7)	2 (5.1)	5 (6.4)
Decreased appetite	3 (7.7)	0 (0.0)	3 (3.8)
Hypokalaemia	3 (7.7)	5 (12.8)	8 (10.3)
Hypophosphataemia	3 (7.7)	2 (5.1)	5 (6.4)
Malignant pleural effusion	3 (7.7)	1 (2.6)	4 (5.1)
Stomatitis	3 (7.7)	0 (0.0)	3 (3.8)
Toxic encephalopathy	3 (7.7)	0 (0.0)	3 (3.8)
White blood cell count decreased	3 (7.7)	12 (30.8)	15 (19.2)
Abdominal pain	2 (5.1)	0 (0.0)	2 (2.6)
Allergic transfusion reaction	2 (5.1)	0 (0.0)	2 (2.6)
Arthralgia	2 (5.1)	1 (2.6)	3 (3.8)
Back pain	2 (5.1)	0 (0.0)	2 (2.6)
Fatigue	2 (5.1)	0 (0.0)	2 (2.6)
Myalgia	2 (5.1)	0 (0.0)	2 (2.6)
Pneumonia	2 (5.1)	0 (0.0)	2 (2.6)
Amylase increased	1 (2.6)	0 (0.0)	1 (1.3)
Anal fistula	1 (2.6)	0 (0.0)	1 (1.3)

Preferred Term	Len + Ifo + Eto (N=39) n (%)	Ifo + Eto (N=39) n (%)	Total (N=78) n (%)
Subjects with Any TEAEs of Grade 3 or Higher	37 (94.9)	32 (82.1)	69 (88.5)
Anaemia	26 (66.7)	19 (48.7)	45 (57.7)
Platelet count decreased	20 (51.3)	9 (23.1)	29 (37.2)
Febrile neutropenia	15 (38.5)	8 (20.5)	23 (29.5)
Neutrophil count decreased	13 (33.3)	13 (33.3)	26 (33.3)
Neutropenia	10 (25.6)	7 (17.9)	17 (21.8)
Proteinuria	10 (25.6)	1 (2.6)	11 (14.1)
Hypertension	7 (17.9)	0 (0.0)	7 (9.0)
Thrombocytopenia	7 (17.9)	3 (7.7)	10 (12.8)
Leukopenia	5 (12.8)	4 (10.3)	9 (11.5)
Aspartate aminotransferase increased	4 (10.3)	2 (5.1)	6 (7.7)
Lymphocyte count decreased	4 (10.3)	6 (15.4)	10 (12.8)
Pneumothorax	4 (10.3)	0 (0.0)	4 (5.1)
Alanine aminotransferase increased	3 (7.7)	2 (5.1)	5 (6.4)
Decreased appetite	3 (7.7)	0 (0.0)	3 (3.8)
Hypokalaemia	3 (7.7)	5 (12.8)	8 (10.3)
Hypophosphataemia	3 (7.7)	2 (5.1)	5 (6.4)
Malignant pleural effusion	3 (7.7)	1 (2.6)	4 (5.1)
Stomatitis	3 (7.7)	0 (0.0)	3 (3.8)
Toxic encephalopathy	3 (7.7)	0 (0.0)	3 (3.8)
White blood cell count decreased	3 (7.7)	12 (30.8)	15 (19.2)
Abdominal pain	2 (5.1)	0 (0.0)	2 (2.6)
Allergic transfusion reaction	2 (5.1)	0 (0.0)	2 (2.6)
Arthralgia	2 (5.1)	1 (2.6)	3 (3.8)
Back pain	2 (5.1)	0 (0.0)	2 (2.6)
Fatigue	2 (5.1)	0 (0.0)	2 (2.6)
Myalgia	2 (5.1)	0 (0.0)	2 (2.6)
Pneumonia	2 (5.1)	0 (0.0)	2 (2.6)
Amylase increased	1 (2.6)	0 (0.0)	1 (1.3)
Anal fistula	1 (2.6)	0 (0.0)	1 (1.3)

Preferred Term	Len + Ifo + Eto (N=39) n (%)	Ifo + Eto (N=39) n (%)	Total (N=78) n (%)
Metastases to heart	1 (2.6)	0 (0.0)	1 (1.3)
Muscular weakness	1 (2.6)	0 (0.0)	1 (1.3)
Musculoskeletal chest pain	1 (2.6)	0 (0.0)	1 (1.3)
Nausea	1 (2.6)	0 (0.0)	1 (1.3)
Osteomyelitis	1 (2.6)	0 (0.0)	1 (1.3)
Palmar-plantar erythrodysaesthesia syndrome	1 (2.6)	0 (0.0)	1 (1.3)
Pleural effusion	1 (2.6)	1 (2.6)	2 (2.6)
Pneumonia fungal	1 (2.6)	0 (0.0)	1 (1.3)
Post procedural cellulitis	1 (2.6)	0 (0.0)	1 (1.3)
Post procedural haemorrhage	1 (2.6)	0 (0.0)	1 (1.3)
Posterior reversible encephalopathy syndrome	1 (2.6)	0 (0.0)	1 (1.3)
Postoperative wound complication	1 (2.6)	0 (0.0)	1 (1.3)
Proctitis	1 (2.6)	0 (0.0)	1 (1.3)
Renal tubular dysfunction	1 (2.6)	0 (0.0)	1 (1.3)
Respiratory failure	1 (2.6)	1 (2.6)	2 (2.6)
Sepsis	1 (2.6)	2 (5.1)	3 (3.8)
Syncope	1 (2.6)	0 (0.0)	1 (1.3)
Transaminases increased	1 (2.6)	0 (0.0)	1 (1.3)
Activated partial thromboplastin time prolonged	0 (0.0)	1 (2.6)	1 (1.3)
Anaphylactic reaction	0 (0.0)	1 (2.6)	1 (1.3)
Cancer pain	0 (0.0)	1 (2.6)	1 (1.3)
Device breakage	0 (0.0)	2 (5.1)	2 (2.6)
Device related infection	0 (0.0)	1 (2.6)	1 (1.3)
Glycosuria	0 (0.0)	1 (2.6)	1 (1.3)
Haemoglobin decreased	0 (0.0)	1 (2.6)	1 (1.3)
Hypoalbuminaemia	0 (0.0)	1 (2.6)	1 (1.3)
Hypocalcaemia	0 (0.0)	1 (2.6)	1 (1.3)
Leukocytosis	0 (0.0)	1 (2.6)	1 (1.3)
Pyrexia	0 (0.0)	1 (2.6)	1 (1.3)
Renal tubular injury	0 (0.0)	1 (2.6)	1 (1.3)

Preferred Term	Len + Ifo + Eto (N=39) n (%)	Ifo + Eto (N=39) n (%)	Total (N=78) n (%)
Blood alkaline phosphatase increased	1 (2.6)	1 (2.6)	2 (2.6)
Blood bilirubin increased	1 (2.6)	0 (0.0)	1 (1.3)
Blood phosphorus decreased	1 (2.6)	0 (0.0)	1 (1.3)
Bone pain	1 (2.6)	0 (0.0)	1 (1.3)
COVID-19	1 (2.6)	0 (0.0)	1 (1.3)
Cardiac failure	1 (2.6)	0 (0.0)	1 (1.3)
Catheter site ulcer	1 (2.6)	0 (0.0)	1 (1.3)
Cholestasis	1 (2.6)	0 (0.0)	1 (1.3)
Deep vein thrombosis	1 (2.6)	0 (0.0)	1 (1.3)
Dehydration	1 (2.6)	1 (2.6)	2 (2.6)
Dizziness	1 (2.6)	0 (0.0)	1 (1.3)
Drug hypersensitivity	1 (2.6)	1 (2.6)	2 (2.6)
Dysphagia	1 (2.6)	0 (0.0)	1 (1.3)
Dyspnoea	1 (2.6)	2 (5.1)	3 (3.8)
Escherichia sepsis	1 (2.6)	0 (0.0)	1 (1.3)
Gallbladder obstruction	1 (2.6)	0 (0.0)	1 (1.3)
Gamma-glutamyltransferase increased	1 (2.6)	1 (2.6)	2 (2.6)
Gastroenteritis	1 (2.6)	0 (0.0)	1 (1.3)
Haematuria	1 (2.6)	0 (0.0)	1 (1.3)
Headache	1 (2.6)	0 (0.0)	1 (1.3)
Hepatitis acute	1 (2.6)	0 (0.0)	1 (1.3)
Hyperbilirubinaemia	1 (2.6)	0 (0.0)	1 (1.3)
Hyperkalaemia	1 (2.6)	0 (0.0)	1 (1.3)
Hypertransaminasaemia	1 (2.6)	0 (0.0)	1 (1.3)
Hyponatraemia	1 (2.6)	0 (0.0)	1 (1.3)
Hypoxia	1 (2.6)	1 (2.6)	2 (2.6)
Infectious pleural effusion	1 (2.6)	0 (0.0)	1 (1.3)
Lymphopenia	1 (2.6)	3 (7.7)	4 (5.1)
Malignant spinal cord compression	1 (2.6)	0 (0.0)	1 (1.3)
Metabolic encephalopathy	1 (2.6)	0 (0.0)	1 (1.3)
Skin infection	0 (0.0)	1 (2.6)	1 (1.3)
Spinal cord compression	0 (0.0)	1 (2.6)	1 (1.3)
Staphylococcal sepsis	0 (0.0)	1 (2.6)	1 (1.3)
Tumour pain	0 (0.0)	1 (2.6)	1 (1.3)
Urine output decreased	0 (0.0)	1 (2.6)	1 (1.3)
Vascular device infection	0 (0.0)	1 (2.6)	1 (1.3)
Vomiting	0 (0.0)	1 (2.6)	1 (1.3)
Wound infection staphylococcal	0 (0.0)	1 (2.6)	1 (1.3)

Data records occurring on or after the first dose date of the crossover are excluded from this table for subjects in Arm B (Ifosfamide 3000 mg/m² + Etoposide 100 mg/m²) who crossed over to optional treatment with lenvatinib +/- chemotherapy.
MedDRA preferred terms "Neoplasm progression", "Malignant neoplasm progression" and "Disease progression" not related to the study drug are excluded. Subjects with 2 or more TEAEs reported in the same PT are counted only once.
Adverse event terms are coded using Medical Dictionary for Regulatory Activities (MedDRA) version 25.0.
Adverse events are graded using Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.
TEAE = treatment-emergent adverse event; PT = preferred term.
Source: Dataset ADAE

Final Database Lock Date: 29SEP2023
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Deaths

As of the EOS, 49 subjects (62.8%; 24 in Arm A and 25 in Arm B) had died. Of these 49 deaths, 19 (9 in Arm A and 10 in Arm B) occurred after the cutoff for the primary analysis: 17 attributed to PD and 2 (both in Arm A) attributed to an AE.

The two Grade 5 AEs in Arm A were treatment-emergent pleural effusion and dyspnea in one and non-treatment-emergent cardiac metastasis in one patient.

One subject had a Grade 5 treatment-related TEAE, pneumonia, which occurred before the cutoff for the primary analysis.

Table 8. Summary of Deaths (Safety Analysis Set)

Category	Len + Ifo + Eto (N=39) n (%)	Ifo + Eto (N=39) n (%)	Total (N=78) n (%)
All Deaths	24 (61.5)	25 (64.1)	49 (62.8)
TEAEs with Fatal Outcome[a]	6 (15.4)	2 (5.1)	8 (10.3)
Malignant Neoplasm Progression	1 (2.6)	1 (2.6)	2 (2.6)
Other Fatal Events	5 (12.8)	1 (2.6)	6 (7.7)
Other Deaths During Survival Follow-up	18 (46.2)	23 (59.0)	41 (52.6)

Data records occurring on or after the first dose date of the crossover are excluded from this table for subjects in Arm B (Ifosfamide 3000 mg/m² + Etoposide 100 mg/m²) who crossed over to optional treatment with lenvatinib +/- chemotherapy.
a: Includes MedDRA preferred terms "Neoplasm progression", "Malignant neoplasm progression" and "Disease progression"
Source: Dataset ADAE

Final Database Lock Date: 29SEP2023
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Nonfatal Serious Adverse Events

As of the EOS, nonfatal treatment-emergent SAEs occurred in 50 subjects (64.1%), 30 in Arm A and 20 in Arm B. A total of 35 subjects (44.9%), 23 in Arm A and 12 in Arm B, had an SAE assessed as treatment-related by the investigator. Seven subjects (2 in Arm A and 5 in Arm B) had nonfatal SAEs after data cutoff for the primary analysis.

Table 9. Treatment-Emergent Serious Adverse Events by Preferred Term in Decreasing Incidence (Safety Analysis Set)

MedDRA Preferred Term	Len + Ifo + Eto (N=39) n (%)	Ifo + Eto (N=39) n (%)	Total (N=78) n (%)
Subjects with Any Treatment-Emergent SAEs	30 (76.9)	20 (51.3)	50 (64.1)
Febrile neutropenia	15 (38.5)	7 (17.9)	22 (28.2)
Pneumothorax	7 (17.9)	1 (2.6)	8 (10.3)
Pyrexia	6 (15.4)	2 (5.1)	8 (10.3)
Malignant pleural effusion	4 (10.3)	1 (2.6)	5 (6.4)
Platelet count decreased	3 (7.7)	0 (0.0)	3 (3.8)
Toxic encephalopathy	3 (7.7)	0 (0.0)	3 (3.8)
Abdominal pain	2 (5.1)	0 (0.0)	2 (2.6)
COVID-19	2 (5.1)	0 (0.0)	2 (2.6)
Pneumonia	2 (5.1)	0 (0.0)	2 (2.6)
Proteinuria	2 (5.1)	0 (0.0)	2 (2.6)
Seizure	2 (5.1)	1 (2.6)	3 (3.8)
Wound dehiscence	2 (5.1)	1 (2.6)	3 (3.8)
Anaemia	1 (2.6)	0 (0.0)	1 (1.3)
Anal fistula	1 (2.6)	0 (0.0)	1 (1.3)
Bone pain	1 (2.6)	0 (0.0)	1 (1.3)
Cardiac failure	1 (2.6)	0 (0.0)	1 (1.3)
Catheter site ulcer	1 (2.6)	0 (0.0)	1 (1.3)
Cholecystitis	1 (2.6)	0 (0.0)	1 (1.3)
Cystitis haemorrhagic	1 (2.6)	0 (0.0)	1 (1.3)
Decreased appetite	1 (2.6)	0 (0.0)	1 (1.3)
Deep vein thrombosis	1 (2.6)	1 (2.6)	2 (2.6)
Dehydration	1 (2.6)	0 (0.0)	1 (1.3)
Device extrusion	1 (2.6)	0 (0.0)	1 (1.3)
Diarrhoea	1 (2.6)	0 (0.0)	1 (1.3)
Dyspnoea	1 (2.6)	1 (2.6)	2 (2.6)
Escherichia sepsis	1 (2.6)	0 (0.0)	1 (1.3)
Gallbladder obstruction	1 (2.6)	0 (0.0)	1 (1.3)
Gastroenteritis	1 (2.6)	0 (0.0)	1 (1.3)
Haematuria	1 (2.6)	0 (0.0)	1 (1.3)
Hepatitis acute	1 (2.6)	0 (0.0)	1 (1.3)
Hypertension	1 (2.6)	0 (0.0)	1 (1.3)

MedDRA Preferred Term	Len + Ifo + Eto (N=39) n (%)	Ifo + Eto (N=39) n (%)	Total (N=78) n (%)
Hypertensive urgency	1 (2.6)	0 (0.0)	1 (1.3)
Hypokalaemia	1 (2.6)	0 (0.0)	1 (1.3)
Hypophosphataemia	1 (2.6)	0 (0.0)	1 (1.3)
Infectious pleural effusion	1 (2.6)	0 (0.0)	1 (1.3)
Malignant spinal cord compression	1 (2.6)	0 (0.0)	1 (1.3)
Metabolic encephalopathy	1 (2.6)	0 (0.0)	1 (1.3)
Metastases to central nervous system	1 (2.6)	0 (0.0)	1 (1.3)
Metastases to heart	1 (2.6)	0 (0.0)	1 (1.3)
Neutropenia	1 (2.6)	0 (0.0)	1 (1.3)
Neutrophil count decreased	1 (2.6)	1 (2.6)	2 (2.6)
Osteomyelitis	1 (2.6)	0 (0.0)	1 (1.3)
Pleural effusion	1 (2.6)	1 (2.6)	2 (2.6)
Pleural infection	1 (2.6)	0 (0.0)	1 (1.3)
Pneumonia fungal	1 (2.6)	0 (0.0)	1 (1.3)
Post procedural cellulitis	1 (2.6)	0 (0.0)	1 (1.3)
Post procedural haemorrhage	1 (2.6)	0 (0.0)	1 (1.3)
Posterior reversible encephalopathy syndrome	1 (2.6)	0 (0.0)	1 (1.3)
Postoperative wound complication	1 (2.6)	0 (0.0)	1 (1.3)
Respiratory failure	1 (2.6)	1 (2.6)	2 (2.6)
Respiratory syncytial virus infection	1 (2.6)	0 (0.0)	1 (1.3)
Stomatitis	1 (2.6)	0 (0.0)	1 (1.3)
Syncope	1 (2.6)	0 (0.0)	1 (1.3)
Thrombocytopenia	1 (2.6)	0 (0.0)	1 (1.3)
Transaminases increased	1 (2.6)	0 (0.0)	1 (1.3)
Anaphylactic reaction	0 (0.0)	1 (2.6)	1 (1.3)
Bacteraemia	0 (0.0)	1 (2.6)	1 (1.3)
Cancer pain	0 (0.0)	1 (2.6)	1 (1.3)
Device breakage	0 (0.0)	2 (5.1)	2 (2.6)
Device related infection	0 (0.0)	1 (2.6)	1 (1.3)
Drug hypersensitivity	0 (0.0)	1 (2.6)	1 (1.3)
Haemoglobin decreased	0 (0.0)	1 (2.6)	1 (1.3)
Hypoxia	0 (0.0)	1 (2.6)	1 (1.3)

MedDRA Preferred Term	Len + Ifo + Eto (N=39) n (%)	Ifo + Eto (N=39) n (%)	Total (N=78) n (%)
Infection	0 (0.0)	1 (2.6)	1 (1.3)
Nausea	0 (0.0)	1 (2.6)	1 (1.3)
Renal tubular injury	0 (0.0)	1 (2.6)	1 (1.3)
Sepsis	0 (0.0)	2 (5.1)	2 (2.6)
Skin infection	0 (0.0)	1 (2.6)	1 (1.3)
Staphylococcal sepsis	0 (0.0)	1 (2.6)	1 (1.3)
Tumour pain	0 (0.0)	1 (2.6)	1 (1.3)
Vascular device infection	0 (0.0)	2 (5.1)	2 (2.6)
Vomiting	0 (0.0)	1 (2.6)	1 (1.3)
Wound infection staphylococcal	0 (0.0)	1 (2.6)	1 (1.3)

Data records occurring on or after the first dose date of the crossover are excluded from this table for subjects in Arm B (Ifosfamide 3000 mg/m² + Etoposide 100 mg/m²) who crossed over to optional treatment with lenvatinib +/- chemotherapy.
MedDRA preferred terms "Neoplasm progression", "Malignant neoplasm progression" and "Disease progression" not related to the study drug are excluded.
Subjects with 2 or more treatment-emergent SAEs reported in the same PT are counted only once within that PT.
Adverse event terms are coded using Medical Dictionary for Regulatory Activities (MedDRA) version 25.0.
SAE = serious adverse event; PT = preferred term.
Source: Dataset ADAE

Final Database Lock Date: 29SEP2023
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Other Significant Adverse Events

Adverse Events Resulting in Treatment Discontinuation

As of the EOS, 13 subjects (16.7%; 10 in Arm A and 3 in Arm B) had a TEAE leading to discontinuation of any study drug; 6 subjects in Arm A discontinued lenvatinib. One subject in Arm A experienced a

TEAE leading to discontinuation after the data cutoff for the primary analysis. One additional subject, in Arm B, experienced an AE leading to treatment discontinuation after data cutoff for the primary analysis, namely serious Grade 3 pulmonary embolism.

Clinically Significant Adverse Events

As of the EOS, 54 subjects (69.2%) had a clinically significant event (CSE); 37 (94.9%) in Arm A and 17 (43.6%) in Arm B. A total of 22 subjects (56.4%) in Arm A and 4 subjects (10.3%) in Arm B had a CSE that was Grade ≥3; CSEs led to treatment discontinuation in 4 subjects, all in Arm A.

Pneumothorax is a known risk for lenvatinib in other tumour types; however, the observed incidence is numerically higher in patients with relapsed/refractory osteosarcoma treated with lenvatinib (see Study E7080-G000-207 [Single Agent] CSR and Study 230 primary CSR).

As of the EOS, 14 subjects (17.9%) had pneumothorax, 11 subjects in Arm A and 3 subjects in Arm B.

Table 10. Overview of Clinically Significant Treatment-Emergent Adverse Events for Lenvatinib (Safety Analysis Set)

	Len + Ifo + Eto (N=39) n (%)	Ifo + Eto (N=39) n (%)	Total (N=78) n (%)
Overall			
Subjects with Any Clinically Significant Treatment-Emergent Adverse Events for Lenvatinib, n (%)	37 (94.9)	17 (43.6)	54 (69.2)
Worst CTCAE Grade, n (%)			
1	0 (0.0)	11 (28.2)	11 (14.1)
2	15 (38.5)	2 (5.1)	17 (21.8)
>=3	22 (56.4)	4 (10.3)	26 (33.3)
3	18 (46.2)	4 (10.3)	22 (28.2)
4	3 (7.7)	0 (0.0)	3 (3.8)
5	1 (2.6)	0 (0.0)	1 (1.3)
Time to First Onset of Any Clinically Significant Treatment-Emergent Adverse Events for Lenvatinib (weeks)			
n	37	17	54
Mean (SD)	3.54 (3.856)	8.53 (14.668)	5.11 (8.973)
Median	2.29	2.14	2.29
Q1, Q3	1.14, 5.86	1.71, 6.00	1.14, 6.00
Min, Max	0.1, 21.4	0.1, 50.3	0.1, 50.3
Subjects with Any Clinically Significant Treatment-Emergent Adverse Events for Lenvatinib Leading to[a]			
Drug Discontinuation	4 (10.3)	0 (0.0)	4 (5.1)
Dose Reduction	19 (48.7)	1 (2.6)	20 (25.6)
Drug Interruption	16 (41.0)	0 (0.0)	16 (20.5)
Cardiac Dysfunction			
Subjects with Any Cardiac Dysfunction, n (%)	6 (15.4)	0 (0.0)	6 (7.7)
Worst CTCAE Grade, n (%)			
1	1 (2.6)	0 (0.0)	1 (1.3)
2	4 (10.3)	0 (0.0)	4 (5.1)
>=3	1 (2.6)	0 (0.0)	1 (1.3)
5	1 (2.6)	0 (0.0)	1 (1.3)

	Len + Ifo + Eto (N=39) n (%)	Ifo + Eto (N=39) n (%)	Total (N=78) n (%)
Time to First Onset of Cardiac Dysfunction (weeks)			
n	6		6
Mean (SD)	27.40 (9.886)		27.40 (9.886)
Median	30.50		30.50
Q1, Q3	29.86, 33.00		29.86, 33.00
Min, Max	7.4, 33.1		7.4, 33.1
Subjects with Any Cardiac Dysfunction Leading to[a]			
Drug Discontinuation	1 (2.6)	0 (0.0)	1 (1.3)
Dose Reduction	1 (2.6)	0 (0.0)	1 (1.3)
Drug Interruption	1 (2.6)	0 (0.0)	1 (1.3)
Fistula Formation			
Subjects with Any Fistula Formation, n (%)	1 (2.6)	0 (0.0)	1 (1.3)
Worst CTCAE Grade, n (%)			
>=3	1 (2.6)	0 (0.0)	1 (1.3)
3	1 (2.6)	0 (0.0)	1 (1.3)
Time to First Onset of Fistula Formation (weeks)			
n	1		1
Mean (SD)	5.00 (NA)		5.00 (NA)
Median	5.00		5.00
Q1, Q3	5.00, 5.00		5.00, 5.00
Min, Max	5.0, 5.0		5.0, 5.0
Subjects with Any Fistula Formation Leading to[a]			
Drug Discontinuation	0 (0.0)	0 (0.0)	0 (0.0)
Dose Reduction	0 (0.0)	0 (0.0)	0 (0.0)
Drug Interruption	1 (2.6)	0 (0.0)	1 (1.3)

	Len + Ifo + Eto (N=39) n (%)	Ifo + Eto (N=39) n (%)	Total (N=78) n (%)
Haemorrhage terms (excl laboratory terms)			
Subjects with Any Haemorrhage terms (excl laboratory terms), n (%)	16 (41.0)	8 (20.5)	24 (30.8)
Worst CTCAE Grade, n (%)			
1	10 (25.6)	7 (17.9)	17 (21.8)
2	4 (10.3)	1 (2.6)	5 (6.4)
>=3	2 (5.1)	0 (0.0)	2 (2.6)
3	2 (5.1)	0 (0.0)	2 (2.6)
Time to First Onset of Haemorrhage terms (excl laboratory terms) (weeks)			
n	16	8	24
Mean (SD)	8.99 (9.133)	8.43 (17.128)	8.80 (11.990)
Median	5.71	1.86	4.43
Q1, Q3	2.50, 13.00	1.14, 5.50	1.71, 9.71
Min, Max	0.1, 32.3	0.1, 50.3	0.1, 50.3
Subjects with Any Haemorrhage terms (excl laboratory terms) Leading to[a]			
Drug Discontinuation	0 (0.0)	0 (0.0)	0 (0.0)
Dose Reduction	1 (2.6)	0 (0.0)	1 (1.3)
Drug Interruption	2 (5.1)	0 (0.0)	2 (2.6)
Hepatotoxicity			
Subjects with Any Hepatotoxicity, n (%)	15 (38.5)	5 (12.8)	20 (25.6)
Worst CTCAE Grade, n (%)			
1	7 (17.9)	3 (7.7)	10 (12.8)
2	1 (2.6)	0 (0.0)	1 (1.3)
>=3	7 (17.9)	2 (5.1)	9 (11.5)
3	4 (10.3)	2 (5.1)	6 (7.7)
4	3 (7.7)	0 (0.0)	3 (3.8)

	Len + Ifo + Eto (N=39) n (%)	Ifo + Eto (N=39) n (%)	Total (N=78) n (%)
Time to First Onset of Hepatotoxicity (weeks)			
n	15	5	20
Mean (SD)	11.76 (12.490)	6.57 (6.144)	10.46 (11.323)
Median	9.14	6.29	7.57
Q1, Q3	1.71, 19.14	1.00, 8.86	1.64, 14.14
Min, Max	0.3, 41.9	1.0, 15.7	0.3, 41.9
Subjects with Any Hepatotoxicity Leading to[a]			
Drug Discontinuation	0 (0.0)	0 (0.0)	0 (0.0)
Dose Reduction	4 (10.3)	0 (0.0)	4 (5.1)
Drug Interruption	2 (5.1)	0 (0.0)	2 (2.6)
Hypertension			
Subjects with Any Hypertension, n (%)	18 (46.2)	0 (0.0)	18 (23.1)
Worst CTCAE Grade, n (%)			
1	4 (10.3)	0 (0.0)	4 (5.1)
2	7 (17.9)	0 (0.0)	7 (9.0)
>=3	7 (17.9)	0 (0.0)	7 (9.0)
3	7 (17.9)	0 (0.0)	7 (9.0)
Time to First Onset of Hypertension (weeks)			
n	18		18
Mean (SD)	10.35 (10.328)		10.35 (10.328)
Median	6.43		6.43
Q1, Q3	3.29, 13.14		3.29, 13.14
Min, Max	0.1, 34.3		0.1, 34.3
Subjects with Any Hypertension Leading to[a]			
Drug Discontinuation	0 (0.0)	0 (0.0)	0 (0.0)
Dose Reduction	3 (7.7)	0 (0.0)	3 (3.8)
Drug Interruption	2 (5.1)	0 (0.0)	2 (2.6)

	Len + Ifo + Eto (N=39) n (%)	Ifo + Eto (N=39) n (%)	Total (N=78) n (%)
Hypocalcemia			
Subjects with Any Hypocalcemia, n (%)	2 (5.1)	4 (10.3)	6 (7.7)
Worst CTCAE Grade, n (%)			
1	0 (0.0)	3 (7.7)	3 (3.8)
2	2 (5.1)	0 (0.0)	2 (2.6)
>=3	0 (0.0)	1 (2.6)	1 (1.3)
3	0 (0.0)	1 (2.6)	1 (1.3)
Time to First Onset of Hypocalcemia (weeks)			
n	2	4	6
Mean (SD)	6.21 (8.384)	4.82 (5.433)	5.29 (5.682)
Median	6.21	3.14	3.14
Q1, Q3	0.29, 12.14	1.64, 8.00	0.29, 12.14
Min, Max	0.3, 12.1	0.3, 12.7	0.3, 12.7
Subjects with Any Hypocalcemia Leading to[a]			
Drug Discontinuation	0 (0.0)	0 (0.0)	0 (0.0)
Dose Reduction	0 (0.0)	0 (0.0)	0 (0.0)
Drug Interruption	0 (0.0)	0 (0.0)	0 (0.0)
Hypothyroidism			
Subjects with Any Hypothyroidism, n (%)	35 (89.7)	0 (0.0)	35 (44.9)
Worst CTCAE Grade, n (%)			
1	2 (5.1)	0 (0.0)	2 (2.6)
2	33 (84.6)	0 (0.0)	33 (42.3)
Time to First Onset of Hypothyroidism (weeks)			
n	35		35
Mean (SD)	9.35 (10.283)		9.35 (10.283)
Median	6.14		6.14
Q1, Q3	2.29, 10.00		2.29, 10.00
Min, Max	1.4, 37.6		1.4, 37.6

	Len + Ifo + Eto (N=39) n (%)	Ifo + Eto (N=39) n (%)	Total (N=78) n (%)
Subjects with Any Hypothyroidism Leading to[a]			
Drug Discontinuation	0 (0.0)	0 (0.0)	0 (0.0)
Dose Reduction	1 (2.6)	0 (0.0)	1 (1.3)
Drug Interruption	0 (0.0)	0 (0.0)	0 (0.0)
Palmar-plantar Erythrodysesthesia Syndrome			
Subjects with Any Palmar-plantar Erythrodysesthesia Syndrome, n (%)	5 (12.8)	0 (0.0)	5 (6.4)
Worst CTCAE Grade, n (%)			
1	1 (2.6)	0 (0.0)	1 (1.3)
2	3 (7.7)	0 (0.0)	3 (3.8)
>=3	1 (2.6)	0 (0.0)	1 (1.3)
3	1 (2.6)	0 (0.0)	1 (1.3)
Time to First Onset of Palmar-plantar Erythrodysesthesia Syndrome (weeks)			
n	5		5
Mean (SD)	15.23 (7.520)		15.23 (7.520)
Median	13.57		13.57
Q1, Q3	10.57, 20.00		10.57, 20.00
Min, Max	6.6, 25.4		6.6, 25.4
Subjects with Any Palmar-plantar Erythrodysesthesia Syndrome Leading to[a]			
Drug Discontinuation	0 (0.0)	0 (0.0)	0 (0.0)
Dose Reduction	2 (5.1)	0 (0.0)	2 (2.6)
Drug Interruption	2 (5.1)	0 (0.0)	2 (2.6)
Pneumothorax			
Subjects with Any Pneumothorax, n (%)	11 (28.2)	1 (2.6)	12 (15.4)
Worst CTCAE Grade, n (%)			
1	3 (7.7)	0 (0.0)	3 (3.8)
2	4 (10.3)	1 (2.6)	5 (6.4)
>=3	4 (10.3)	0 (0.0)	4 (5.1)
3	4 (10.3)	0 (0.0)	4 (5.1)

	Len + Ifo + Eto (N=39) n (%)	Ifo + Eto (N=39) n (%)	Total (N=78) n (%)
Time to First Onset of Pneumothorax (weeks)			
n	11	1	12
Mean (SD)	21.18 (16.209)	1.57 (NA)	19.55 (16.459)
Median	25.29	1.57	15.79
Q1, Q3	5.86, 36.57	1.57, 1.57	5.86, 32.79
Min, Max	3.3, 45.1	1.6, 1.6	1.6, 45.1
Subjects with Any Pneumothorax Leading to[a]			
Drug Discontinuation	0 (0.0)	0 (0.0)	0 (0.0)
Dose Reduction	3 (7.7)	0 (0.0)	3 (3.8)
Drug Interruption	7 (17.9)	0 (0.0)	7 (9.0)
Posterior Reversible Encephalopathy Syndrome			
Subjects with Any Posterior Reversible Encephalopathy Syndrome, n (%)	1 (2.6)	0 (0.0)	1 (1.3)
Worst CTCAE Grade, n (%)			
>=3	1 (2.6)	0 (0.0)	1 (1.3)
3	1 (2.6)	0 (0.0)	1 (1.3)
Time to First Onset of Posterior Reversible Encephalopathy Syndrome (weeks)			
n	1		1
Mean (SD)	4.43 (NA)		4.43 (NA)
Median	4.43		4.43
Q1, Q3	4.43, 4.43		4.43, 4.43
Min, Max	4.4, 4.4		4.4, 4.4
Subjects with Any Posterior Reversible Encephalopathy Syndrome Leading to[a]			
Drug Discontinuation	0 (0.0)	0 (0.0)	0 (0.0)
Dose Reduction	1 (2.6)	0 (0.0)	1 (1.3)
Drug Interruption	0 (0.0)	0 (0.0)	0 (0.0)

	Len + Ifo + Eto (N=39) n (%)	Ifo + Eto (N=39) n (%)	Total (N=78) n (%)
Proteinuria			
Subjects with Any Proteinuria, n (%)	23 (59.0)	5 (12.8)	28 (35.9)
Worst CTCAE Grade, n (%)			
1	7 (17.9)	3 (7.7)	10 (12.8)
2	6 (15.4)	1 (2.6)	7 (9.0)
>=3	10 (25.6)	1 (2.6)	11 (14.1)
3	10 (25.6)	1 (2.6)	11 (14.1)
Time to First Onset of Proteinuria (weeks)			
n	23	5	28
Mean (SD)	13.68 (13.499)	10.80 (17.459)	13.17 (13.960)
Median	11.00	4.43	8.00
Q1, Q3	3.00, 17.86	2.00, 5.14	3.00, 17.21
Min, Max	1.1, 54.3	0.6, 41.9	0.6, 54.3
Subjects with Any Proteinuria Leading to[a]			
Drug Discontinuation	3 (7.7)	0 (0.0)	3 (3.8)
Dose Reduction	10 (25.6)	1 (2.6)	11 (14.1)
Drug Interruption	6 (15.4)	0 (0.0)	6 (7.7)
Renal Events			
Subjects with Any Renal Events, n (%)	1 (2.6)	1 (2.6)	2 (2.6)
Worst CTCAE Grade, n (%)			
1	1 (2.6)	0 (0.0)	1 (1.3)
2	0 (0.0)	1 (2.6)	1 (1.3)
Time to First Onset of Renal Events (weeks)			
n	1	1	2
Mean (SD)	4.14 (NA)	6.00 (NA)	5.07 (1.313)
Median	4.14	6.00	5.07
Q1, Q3	4.14, 4.14	6.00, 6.00	4.14, 6.00
Min, Max	4.1, 4.1	6.0, 6.0	4.1, 6.0

	Len + Ifo + Eto (N=39) n (%)	Ifo + Eto (N=39) n (%)	Total (N=78) n (%)
Subjects with Any Renal Events Leading to[a]			
Drug Discontinuation	0 (0.0)	0 (0.0)	0 (0.0)
Dose Reduction	0 (0.0)	0 (0.0)	0 (0.0)
Drug Interruption	1 (2.6)	0 (0.0)	1 (1.3)
Torsade de pointes/QT prolongation			
Subjects with Any Torsade de pointes/QT prolongation, n (%)	1 (2.6)	0 (0.0)	1 (1.3)
Worst CTCAE Grade, n (%)			
1	1 (2.6)	0 (0.0)	1 (1.3)
Time to First Onset of Torsade de pointes/QT prolongation (weeks)			
n	1		1
Mean (SD)	0.14 (NA)		0.14 (NA)
Median	0.14		0.14
Q1, Q3	0.14, 0.14		0.14, 0.14
Min, Max	0.1, 0.1		0.1, 0.1
Subjects with Any Torsade de pointes/QT prolongation Leading to[a]			
Drug Discontinuation	0 (0.0)	0 (0.0)	0 (0.0)
Dose Reduction	0 (0.0)	0 (0.0)	0 (0.0)
Drug Interruption	0 (0.0)	0 (0.0)	0 (0.0)

Data records occurring on or after the first dose date of the crossover are excluded from this table for subjects in Arm B (Ifosfamide 3000 mg/m² + Etoposide 100 mg/m²) who crossed over to optional treatment with lenvatinib +/- chemotherapy.
MedDRA preferred terms "Neoplasm progression", "Malignant neoplasm progression" and "Disease progression" not related to the study drug are excluded. Subject is counted only once in each category and may be counted in multiple categories.
Adverse events are graded using Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.
a: Leading to action taken for lenvatinib, regardless of any action taken for ifosfamide and etoposide.
Source: Dataset ADAE

Final Database Lock Date: 29SEP2023
Program:/sasdata/obg/development/e7080/g000-230/biostats/csradd/dev/pg/tables/t-ae-aecs.sas

Discussion

Study 230 is a multicenter, randomized, open-label, Phase 2 study of lenvatinib in combination with ifosfamide (IFOS) and etoposide (ETOP) (Arm A) versus IFOS plus ETOP (Arm B) in children, adolescents, and young adults with relapsed or refractory osteosarcoma. E7080-G000-230 primary CSRs dated 24 Jan 2023 (Primary CSR) and 22 Jun 2023 (Primary CSR Revision 1) have been submitted previously. The MAH has provided in this submission the final CSR with the final database lock date of 29 Sep 2023. There are no plans to submit any extension of indications within the paediatric setting based on the results of this study.

The aim of the study was to evaluate whether lenvatinib in combination with ifosfamide and etoposide (Arm A) was superior to ifosfamide and etoposide alone (Arm B) in improving progression-free survival (PFS) based on independent imaging review (IIR) assessments using Response Evaluation Criteria for Solid Tumors v1.1 (RECIST 1.1), in children, adolescents, and young adults with relapsed or refractory osteosarcoma. Secondary objectives included comparing the differences between the 2 treatment arms in PFS rate at 4 months and at 1 year per IIR, overall survival (OS) and OS rate at 1-year, objective response rate (ORR) and ORR at 4 months per IIR, and pharmacokinetics (PK) of lenvatinib when administered in combination with ifosfamide and etoposide. Subjects in Arm B (ifosfamide and etoposide), with PD per RECIST 1.1, had the option to crossover (within 30 days of documented disease progression) to treatment with lenvatinib (with or without ifosfamide and etoposide), which could continue until the next PD or until another protocol-specified withdrawal criterion was met.

In the primary CRS of Study 230, the primary efficacy endpoint, PFS based on IIR assessments of tumour response was met. The secondary efficacy endpoints included PFS per IIR at 4 months (PFS-4m) and at 1 year (PFS-1y), OS, and ORR assessed by IIR.

The primary endpoint, median PFS (per IIR) for the FAS, was 6.5 months (95% CI: 5.7, 8.2) in Arm A and 5.5 months (95% CI: 2.9, 6.5) in Arm B; hazard ratio (HR)=0.54 (95% CI: 0.27, 1.08), P=0.0396; the difference was not statistically significant (P value was predefined 1-sided type 1 error rate of 0.025).The Kaplan-Meier (KM) estimate of PFS-4m per IIR for the FAS was 76.3% for Arm A and 66.0% for Arm B, with a 1-sided P value of 0.168. The KM estimate of PFS-1y per IIR for the FAS (95% CI) was not estimable (NE) (NE, NE) in Arm A versus 14.9% (1.1, 44.5) in Arm B.

After discontinuing study treatment, 36 subjects (44.4%) received another anticancer medication, 15 (37.5%) in Arm A and 21 (51.2%) in Arm B. Of note, the higher use of posttreatment anticancer medications in Arm B probably had impact on the long-term clinical outcomes, such as OS.

At the time of the final OS analysis submitted with this application, no statistically significant difference between 2 arms indicated was observed. The OS was 12.4 months (10.4, 19.8) in Arm A and 17.2 months (11.1, 22.3) in Arm B (stratified HR=0.93 [95% CI: 0.53, 1.62]; nominal P=0.3924). The 95% CIs are overlapping. Median follow-up time for the final OS analysis was 24.1 months (95% CI: 23.4, 27.5) for Arm A and 29.5 months (95% CI: 24.5, 32.3) for Arm B. The OS curves do not show a clear trend and appear to cross at about 10 months. The subsequent anticancer treatment was a confounding factor for OS analysis during follow-up period. In addition, surgery was chosen as the subsequent treatment for 9 subjects (22.5%) in Arm A and 18 subjects (43.9%) in Arm B who had 1 or more baseline lesion(s) resected, including target and nontarget lesions. A post hoc analysis excluding subjects (ie, those subjects who had been censored in the primary PFS analysis) was performed: After excluding these patients who underwent lesion removal during the study from the analysis, median PFS was 6.3 months in Arm A and 2.9 months in Arm B (HR=0.42). Despite of 3.4 months benefit on median PFS in Arm A over Arm B, no statistical significant difference was confirmed. Therefore, the overall results for the add-on of lenvatinib are not supportive and there is no clear sign of benefit, without demonstrating statistically significant differences, favourable or not.

TEAEs were generally manageable. As of the EOS, 77 subjects (98.7%) experienced TEAEs. The most commonly reported TEAEs (incidence ≥40%) in Arm A as of the EOS were hypothyroidism (89.7%), anaemia (71.8%), nausea (59.0%), platelet count decreased (59.0%), proteinuria (59.0%), vomiting (48.7%), and hypertension (43.6%). A total of 67 (85.9%) subjects had the Treatment Related TEAEs of Grade 3 or Higher (36 (92.3%) subjects in Arm A and 31 (79.5%) subjects in Arm B). Nonfatal treatment-emergent SAEs occurred in 50 subjects (64.1%), 30 in Arm A and 20 in Arm B.

Overall, 49 subjects (62.8%; 24 in Arm A and 25 in Arm B) had died, and of 19 cases (9 in Arm A and 10 in Arm B) occurred after the cutoff for the primary analysis: 17 attributed to PD and 2 (both in Arm A) attributed to an AE. These two Grade 5 AEs were treatment-emergent pleural effusion, dyspnoea and non-treatment-emergent cardiac metastasis. One subject had a Grade 5 treatment-related TEAE, pneumonia, which occurred before the cutoff for the primary analysis. **Only the narrative of one fatal case (not related to the disease progression) after the cutoff for the primary analysis was provided, the MAH should provide the missing narratives.**

The MAH should include the final OS results for the Study 230 in the SmPC section 5.1.

Overall, 13 subjects (16.7%; 10 in Arm A and 3 in Arm B) had a TEAE leading to discontinuation of any study drug; 6 subjects in Arm A discontinued lenvatinib. Clinical laboratory data, vital sign and ECG data, physical examination findings, and other observations related to safety did not reveal any new safety signals. The safety profile of lenvatinib in combination with ifosfamide and etoposide remained unchanged at the EOS since the primary analysis.

Pneumothorax is a known complication of osteosarcoma, specifically in patients with pulmonary metastases and has been reported for tyrosine kinase inhibitors, including lenvatinib, and in patients receiving chemotherapy for osteosarcoma. As of the EOS, **14 subjects (17.9%)** had pneumothorax, **11 subjects in Arm A and 3 subjects in Arm B**. The observed incidence of pneumothorax is likely associated with the subjects' underlying osteosarcoma and presence of lung metastases. Most events of pneumothorax were managed by the medical support care, and/ or dose modifications of study agents. This ADR is reflected in the SmPC for paediatric population ("*In Study 230, pneumothorax was reported in* ***12 patients (11 patients [28.2%] treated with lenvatinib plus ifosfamide and etoposide, and 1 patient [2.6%]*** *treated with ifosfamide and etoposide"*), but the results should be updated with the final data cut-off.

Overall, the safety profile of lenvatinib plus chemotherapy in this study is consistent with the known toxicity profiles of the individual agents. The AE profile for lenvatinib was overall as expected for this class of compound and consistent with the current lenvatinib SmPC and the clinical program as a whole. Similarly, the AE profiles of ifosfamide and etoposide were consistent with their known safety profile.

3. First request for supplementary information

Based on the data submitted, the MAH should address the following questions (other concerns) as part of this procedure:

1) The MAH should include the final OS results for the Study 230 in the SmPC section 5.1.
2) The results for pneumothorax cases should be updated in the SmPC with the final data cut-off.
3) Only the narrative of one fatal case (not related to the disease progression) after the cutoff for the primary analysis was provided, the MAH should provide the missing narratives.

The timetable is a 30 day response timetable with clock stop.

4. MAH responses to First request for supplementary information

MAH responses to First request for supplementary information

Question 1

The MAH should include the final OS results for the Study 230 in the SmPC section 5.1.

Response

The MAH acknowledges the agency's request; however, proposes not to include the final OS results from Study 230 in Section 5.1 of the Lenvima SmPC given that the study was not designed or powered to test for a difference in OS between the 2 treatment arms. In addition, OS was impacted by the greater proportion of subjects who had baseline tumour lesions surgically resected during the study in Arm B (ifosfamide plus etoposide; 43.9%) versus Arm A (lenvatinib plus ifosfamide plus etoposide; 22.5%) and by the greater use of subsequent anticancer medications in Arm B (51.2%) versus Arm A (37.5%), and therefore would not be informative to the prescribers (please refer to Section 11.3.1.2.2 of the Study 230 Primary CSR, dated 08 June 2023; submitted under Procedure No. EMEA/H/C/003727/II/0050).

Furthermore, given that the study did not meet its primary endpoint of PFS, and no paediatric indication for lenvatinib was supported by the results of Study 230, the MAH considers that inclusion of the descriptive final OS results in the Lenvima SmPC is not warranted. Please note, clinical data from studies conducted in the paediatric population, including Study 230, have been included in Section 5.1 of the Lenvima SmPC, as part of the Type II variation (Procedure No. EMEA/H/C/003727/II/0050), which received positive CHMP opinion on 09 Nov 2023.

Assessment

The MAH does not to add the final OS data the of Study 230 in the section 5.1 of SmPC. Despite of several confounding factors, both the comprehensive efficacy and safety results are of relevance for inclusion in the SmPC.

The MAH should include the final OS results for the Study 230 in the SmPC section 5.1.

Conclusion

Issue was not resolved

The MAH should include the final OS results for the Study 230 in the SmPC section 5.1 and is requested to submit the proposal for the amended SmPC section 5.1 before implementation along with the agreed changes in the section 4.8 regarding the pneumothorax cases at the final data cut-off for Study 230 (see also Question 2).

Following the assessment report, the following statement was agreed for inclusion in the section 5.1:

"Study 230 was not powered to detect a statistically significant difference in OS. At the end of study analysis, the HR was 0.93 (95% CI: 0.53, 1.62) for the comparison of lenvatinib in combination with ifosfamide and etoposide versus ifosfamide and etoposide, with median OS 12.4 months (95%CI 10.4, 19.8) versus 17.2 months (95%CI 11.1, 22.3), respectively and median follow-up time 24.1 months and 29.5 months, respectively."

Conclusion

Issue resolved

Question 2

The results for pneumothorax cases should be updated in the SmPC with the final data cut-off.

Response

The MAH agrees to update the Lenvima SmPC Section 4.8 with the results for pneumothorax cases based on the final data cutoff for Study 230.

The MAH proposes the following updated text highlighted in red.

Present	Proposed
Section 4.8 In Study 230, pneumothorax was reported in 12 patients (11 patients [28.2%] treated with lenvatinib plus ifosfamide and etoposide, and 1 patient [2.6%] treated with ifosfamide and etoposide).	**Section 4.8** In Study 230, pneumothorax was reported in a total of 14 patients (11 patients [28.2%] treated with lenvatinib plus ifosfamide and etoposide, and 3 patients [7.7%] treated with ifosfamide and etoposide).

Assessment

The MAH proposes the update regarding the pneumothorax cases based on the final data cutoff for Study 230 in the section 4.8 of Lenvima SmPC as requested. However, the updated version of the SmPC has not been submitted.

Conclusion

Issue resolved

Question 3

Only the narrative of one fatal case (not related to the disease progression) after the cutoff for the primary analysis was provided, the MAH should provide the missing narratives.

Response

As discussed further with the EMA, it was clarified on 18 April 2024, that the missing narrative requested, relates to a Subject. The narrative for this subject, who had discontinued treatment due to disease progression, was provided in the primary clinical study report (CSR). This narrative has now been updated with information on the death due to metastases to heart (Day 527), which was not treatment emergent (see the last paragraph in the narrative).

Subject [redacted]

Subject Number	[redacted]
Study Name	E7080-G000-230
Manufacturer's Control Number	[redacted]
Assigned Treatment	Lenvatinib 14 mg/m^2 oral once daily Etoposide 100 mg/m^2/day intravenous (Day 1 to 3) every 21 days Ifosfamide 3000 mg/m^2/day intravenous (Day 1 to 3) every 21 days
Nonfatal SAE(s)	Dehydration, Cystitis haemorrhagic, Febrile neutropenia, Cholecystitis, Thrombocytopenia, Hypophosphataemia, Abdominal pain, Diarrhoea, Neutropenia, Syncope, Proteinuria, Infectious pleural effusion, COVID19, Decreased appetite, Metastases to heart, Pleural infection
AE(s) Leading to Lenvatinib Discontinuation	Metastases to heart
AE(s) Leading to Ifosfamide Discontinuation	Platelet count decreased
AE(s) Leading to Etoposide Discontinuation	Platelet count decreased
Other Significant Events	Cystitis haemorrhagic, Proteinuria, Alanine aminotransferase increased, Aspartate aminotransferase increased

A patient was diagnosed with high-grade osteoblastic and fibroblastic osteosarcoma of the right femur in 2018, metastatic disease in 2020, and the date of last disease progression was 2021. Medical history included cisplatin, doxorubicin, methotrexate, mifamurtide, lung lobectomy, and ostectomy. Prior and concomitant medication included alfacalcidol, aluminium hydroxide;magnesium hydroxide, amikacin, aprepitant, bisacodyl, carbohydrates NOS;electrolytes NOS;fatty acids NOS;minerals NOS;proteins NOS;vitamins NOS (Ensure Plus®), ceftriaxone, cefuroxime, clindamycin, dexamethasone, diazepam, diphenhydramine, enoxaparin, esomeprazole, fentanyl, filgrastim, furosemide, glucose;sodium chloride, granisetron, ibuprofen, levetiracetam, levofloxacin, levothyroxine, lidocaine, loratadine, lorazepam, macrogol 3350, magnesium, magnesium oxide, magnesium sulfate, mesna, metamizole, methylprednisolone, metoclopramide, metronidazole, morphine, naloxone;oxycodone, olanzapine, omeprazole, ondansetron, oxycodone, palonosetron, papaverine, paracetamol, phenazopyridine, phytomenadione, piperacillin;tazobactam, potassium, potassium phosphate dibasic, , potassium phosphate monobasic, sodium phosphate, promethazine, ropivacaine, sodium chloride, solutions for parenteral nutrition, sulfamethoxazole;trimethoprim, tramadol, triptorelin, tropicamide, ursodeoxycholic acid, and vancomycin. At Screening, tumor assessments of target/nontarget lesions via CT scan showed lung masses (right). The Karnofsky performance status was 100.

In 2021 (Day 1), treatment with lenvatinib was initiated at 21 mg, treatment with etoposide and ifosfamide was started at 152 mg and 4500 mg, respectively.

In 2021 (Day 4), the subject was hospitalized for haemorrhagic cystitis (Grade 2) and experienced hypokalaemia (Grade 3) and hypomagnesemia (Grade 2). Laboratory tests showed potassium 2.9 mmol/L (NR: not provided) and magnesium 0.4387 mmol/L (NR: 0.697 – 0.902). The subject was treated with magnesium sulfate, mesna, and potassium and recovered from hypokalaemia and hypomagnesemia on the same day (Day 4). In 2021 (Day 6), red blood cell in urine dipstick showed $\geq$ 200 erythrocytes/μL. The subject was also treated with aluminum hydroxide; magnesium hydroxide, phenazopyridine, and metamizole. In 2021 (Day 7), abdominal ultrasound was normal. The study drugs did not change. In 2021 (Day 8), the subject recovered from haemorrhagic cystitis.

The Investigator considered haemorrhagic cystitis serious and related to study drugs; hypomagnesemia nonserious and related to study drugs; hypokalaemia nonserious and not related to study drug.

In 2021 (Day 12), the subject was hospitalized for febrile neutropenia (Grade 3) and experienced decreased platelet count (Grade 4). Laboratory tests showed body temperature of 36.9 ºC, WBC 0.67 x109/L (NR: 4.5 – 11), ANC 0.10 x109/L (NR: 1.9 – 7.9), platelets 20 x109/L (NR: 150 – 450), and CRP 6.84 mg/dL (NR: not provided). The subject was treated with amikacin, filgrastim, piperacillin;taxobactam, sulfamethoxazole;trimethoprim, oxycodone, and paracetamol. The study drugs did not change. In 2021 (Day 15), decreased platelet count improved to Grade 3. In 2021 (Day 16), the subject recovered from febrile neutropenia. In 2021 (Day 22), the subject recovered from decreased platelet count. The Investigator considered febrile neutropenia serious and related to study drugs; decreased platelet count nonserious and related to study drugs.

In 2021 (Day 24), the subject was hospitalized for cholecystitis (Grade 2) confirmed by abdominal x-ray. In 2021 (Day 25), ultrasound of the abdomen showed inflammation/swelling of the gallbladder. Laboratory tests were within the normal range.

The subject was treated with cefuroxime, metronidazole, morphine, papaverine, ursodeoxycholic acid, oxycodone, and sodium chloride. In 2021 (Day 28), the subject recovered from the event. In 2021 (Day 29), the subject experienced renal impairment (renal function deterioration; Grade 1), BUN and creatinine was not provided and lenvatinib was interrupted due to cholecystitis and renal impairment; etoposide and ifosfamide did not change. In 2021 (Day 31), lenvatinib was resumed at a reduced dose of 11.2 mg/m2 (17 mg) due to cholecystitis and renal impairment. In 2021 (Day 34), the subject

recovered from renal impairment. The Investigator considered cholecystitis serious and related to study drugs; renal impairment nonserious and related to study drugs.

In 2021 (Day 34), the subject was hospitalized for thrombocytopenia (Grade 4) and hypophosphatemia (Grade 3). Laboratory tests showed platelets 6.10 x10^9/L (NR: 150 – 450) and phosphorus 1.2 mg/dL (NR: 2.5 – 5.0). The study drug administration did not change due to the events. The subject was treated with platelet transfusion and potassium phosphate monobasic; sodium phosphate. In 2021 (Day 35), the subject recovered from thrombocytopenia. Hypophosphatemia continued with severity changes between Grade 2 and Grade 3. In 2021 (Day 88), the subject recovered from hypophosphatemia. The Investigator considered thrombocytopenia and hypophosphatemia serious and related to the study drugs.

In 2021 (Day 54), the subject was hospitalized for febrile neutropenia (Grade 3) with ANC 0.1 x10^3/uL and body temperature of 38.3ºC. The study drug administration did not change due to the events. The subject was treated with piperacillin/tazobactam, amikacin, filgrastim, and potassium phosphate monobasic/sodium phosphate. The subject recovered from hypophosphatemia on the same day (Day 54). In 2021 (Day 57), the subject recovered from febrile neutropenia and was discharged from the hospital. The Investigator considered febrile neutropenia serious and related to study drugs; hypophosphatemia nonserious and related to study drugs.

In 2021 (Day 68), the subject experienced diarrhoea (Grade 1). In 2021 (Day 69), the subject was hospitalized for abdominal pain (Grade 1) and persistent diarrhoea (Grade 1). The subject was treated with sodium chloride, morphine, and oxycodone. The subject recovered from diarrhoea later that day (Day 69). In 2021 (Day 70), the subject recovered from abdominal pain with sequelae. In 2021 (Day 72), the subject experienced syncope for less than 1 minute and one episode of dizziness and remained in the hospital for syncope (Grade 3), dehydration (Grade 3), and neutropenia (Grade 4) with neutrophil 10.2 %. ECG was normal and QTcF interval was 424 msec. Laboratory tests showed potassium 3.0 mmol/L (NR: 3.5 – 5.1). The subject recovered from syncope the same day (Day 72). The subject was treated with glucose; sodium chloride and sodium chloride. In 2021 (Day 74) the subject remained hospitalized for febrile neutropenia (Grade 3) with ANC 0 x109/L and body temperature 37.3 ºC. On the same day (Day 74), the subject recovered from dehydration. The study drug administration did not change. The subject was treated with piperacillin, tazobactam, amikacin, filgrastim, and paracetamol. In 2021 (Day 80), the subject recovered from febrile neutropenia and neutropenia. The Investigator considered these events serious and related to study drug.

In 2021 (Day 72), the subject experienced decreased platelet count (Grade 4) with platelets 7.10 x109/L (NR: 150 – 450). The subject was treated with platelet transfusion. In 2021 (Day 88), the subject experienced decreased platelet count (Grade 3) with platelets 26 x109/L. On the same day (Day 88), etoposide and ifosfamide planned doses were interrupted due to the event (last doses of etoposide and ifosfamide were In 2021 [Day 66]; lenvatinib did not change. On the same day (Day 88), the subject experienced proteinuria (Grade 3) with urine protein dipstick 3+ and increased aspartate aminotransferase (Grade 2) with AST 93.1 U/L (NR: ≤31). In 2021 (Day 92), decreased platelet count worsened to Grade 4 with platelets 20 x 109/L. In 2021 (Day 94), decreased platelet count improved to Grade 3 with platelets 30 x 109/L and etoposide and ifosfamide were withdrawn due to decreased platelet count. Laboratory tests showed CRP 0.90 mg/dL, 24 hr urine protein of 1.9 g, and BP 133/75 mmHg (99th/90th) (Baseline: 95/57 mmHg [50th/50th]).

Lenvatinib was interrupted due to proteinuria. The subject was treated with esomeprazole. In 2021 (Day 98), the subject recovered from decreased platelet count, and proteinuria improved to Grade 2. In 2021 (Day 101), the subject recovered from increased aspartate aminotransferase improved to Grade 1. In 2021 (Day 107), increased alanine aminotransferase worsened to Grade 3 with ALT 228.6 U/L (NR: ≤ 34). On the same day (Day 107), the subject recovered from proteinuria, and increased aspartate

aminotransferase worsened to Grade with AST 3 209.6 U/L. Lenvatinib remained interrupted due to increased aspartate aminotransferase and increased alanine aminotransferase. In 2021 (Day 112), the subject recovered from increased aspartate aminotransferase, and increased alanine aminotransferase improved to Grade 2 with ALT 146.2 U/L. In 2021 (Day 119), the subject recovered from increased alanine aminotransferase. On the same day (Day 119), lenvatinib was resumed at a reduced dose of 9.0 mg/m2 (14 mg) due to increased aspartate aminotransferase and increased alanine aminotransferase. The Investigator considered proteinuria serious (important medical event) and related to the study drug; increased aspartate aminotransferase and increased alanine aminotransferase nonserious and related to the study drugs.

In 2021 (Day 143), the subject was hospitalized for infectious pleural effusion (Grade 3) with intermittent fever 38 2 ºC following a pre-planned resection of lung metastases. Lenvatinib administration did not change due to the event. The subject was treated with clindamycin, metamizole, and piperacillin. In 2021 (Day 147), CT scan showed pleural effusion with suspicion of empyema. In 2021 (Day 154), the subject recovered from infectious pleural effusion. The Investigator considered infectious pleural effusion serious and not related to the study drugs.

In 2021 (Day 161), the subject experienced decreased appetite (Grade 3). In 2021 (Day 173), the subject developed COVID-19 (Grade 2). In 2021 (Day 175), the subject was hospitalized for COVID-19 (Grade 2), pleural infection (Grade 2), and decreased appetite (Grade 3), and experienced hypokalaemia (Grade 3). The subject's body temperature was 38.2 ºC and body weight kg. The subject was treated with paracetamol, morphine, levofloxacin, metamizole, Ensure Plus, and TPN solution. In 2021 (Day 177), the subject recovered from pyrexia, and hypokalaemia worsened to Grade 3. In 2021 (Day 178), the subject underwent pleural cavity aspiration. In 2021 (Day 179), hypokalaemia improved to Grade 2, and resolved In 2021 (Day 180). The subject was treated with solutions for parenteral nutrition. In 2021 (Day 191), the subject recovered from pleural infection. In 2021 (Day 195), the subject recovered from COVID-19. In 2021 (Day 198), lenvatinib was reduced to 13 mg due to change in body surface area.

In 2021 (Day 217), the subject recovered from decreased appetite. In 2021 (Day 249), the subject experienced abdominal pain (Grade 3). In 2021 (Day 250), lenvatinib was interrupted due to abdominal pain. In 2021 (Day 263), lenvatinib was resumed at a reduced dose of 7.2 mg/m2 (10 mg) due to abdominal pain.

Mycobacterium tuberculosis complex, fungal, and bacterial tests were all negative. The Investigator considered pleural infection, COVID-19, and decreased appetite serious and not related to study drugs; pyrexia and hypokalaemia nonserious and not related to the study drugs.

In 2021 (Day 326), the subject experienced metastases to heart (Grade 4) based on CT of chest. The subject was treated with enoxaparin, and lenvatinib was discontinued due to the event. The subject did not recover from the event. The Investigator considered the event serious (life threatening) and not related to study drug.

In 2022 (Day 329), tumour response assessment confirmed cardiac metastasis and disease progression. On the same day (Day 329), the subject was discontinued from the study treatment due to disease progression and received the last dose of lenvatinib in 2022 (Day 326); etoposide and ifosfamide, C4D3, In 2021 (Day 66). In 2022 (Day 346), the subject started on a new anticancer treatment, regorafenib.

In 2022 (Day 527, 199 days after the last dose of lenvatinib, 461 days after the last dose of etoposide and ifosfamide), the subject died due to metastases to heart. The Investigator considered the event serious and not related to the study drugs.

Assessment

The applicant provided the detailed information on the missing narrative of the fatal case as requested. This patient had discontinued treatment due to disease progression and the narrative has now been updated with information on the death due to metastases to heart at Day 527, 199 days after the last dose of lenvatinib, 461 days after the last dose of etoposide and ifosfamide. The Investigator considered the event serious and not related to the study drugs, the causality assessment has not been further discussed by the MAH.

Conclusion

Issue not pursued.

5. CHMP's overall conclusion and recommendation

The data from the final CRS of Study 230 further inform on the efficacy and safety of lenvatinib in combination with chemotherapy in osteosarcoma patients with longer follow-up. The MAH should include the final OS results for the Study 230 in the SmPC section 5.1. No extension of the indication is proposed in this procedure, this is supported.

Pneumothorax is noticeable as AE and has been reported for other tyrosine kinase inhibitors and in patients receiving chemotherapy for osteosarcoma, and appears to be mainly associated with pulmonary metastases and underlying osteosarcoma. The results for pneumothorax cases should be updated in the SmPC with the final data cut-off. The safety profile of lenvatinib in combination with ifosfamide and etoposide remained unchanged at the EOS since the primary analysis. It's notable that more toxicities were reported in Arm A probably due to the adding-on lenvatinib treatment, leading to uncertainty on its benefit risk profile.

☒ Fulfilled:

In view of the available data regarding Study 230, the MAH should either submit a variation in accordance with Articles 16 and 17 of Regulation (EC) No 726/2004 or provide a justification for not doing so. This should be provided without any delay and ***no later than 60 days after the receipt*** of these conclusions.

☐ Not fulfilled:

6. Conclusion

Based on the data submitted, the MAH should update the SmPC and implement the following changes in the coming type IB procedure:

1) Inclusion of the OS analysis results for the study 230 in the section 5.1:

   "Study 230 was not powered to detect a statistically significant difference in OS. At the end of study analysis, the HR was 0.93 (95% CI: 0.53, 1.62) for the comparison of lenvatinib in combination with ifosfamide and etoposide versus ifosfamide and etoposide, with median OS 12.4 months (95%CI 10.4, 19.8) versus 17.2 months (95%CI 11.1, 22.3), respectively and median follow-up time 24.1 months and 29.5 months, respectively."

2) Update the number of pneumothorax cases in the section 4.8:

"In Study 230, pneumothorax was reported in **a total of 14** patients (11 patients (28.2%) treated with lenvatinib plus ifosfamide and etoposide, and **3 patients (7.7%)** treated with ifosfamide and etoposide)."