Amsterdam, 25 May 2023
EMA/380284/2024
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/P46/017

Lenvima

Lenvatinib

Procedure no: EMA/H/C/003727/P46/020

Note

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

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000 An agency of the European Union

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1. Introduction

On 16 January 2023, the MAH submitted a completed paediatric study for lenvatinib, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

A short critical expert overview has been provided as synoptic clinical study report.

2. Scientific discussion

2.1. Information on the development program

The reports submitted by the MAH are related to the following PIP studies which were subject of the compliance check procedure with outcome on 26 March 2021:

- Study 5 (Study E7080-G000-207, (hereafter Study 207)) a Phase 1/2 Study of Lenvatinib in Children and Adolescents With Refractory or Relapsed Solid Malignancies and Young Adults with Osteosarcoma

- Study 7 Population PK analysis to establish the dose-response relationship of lenvatinib in paediatric patients with differentiated thyroid cancer (DTC) and support extrapolation of efficacy from adult patients to paediatric patients with DTC

The MAH stated that Study E7080-G000-207 is part of a clinical development program for lenvatinib and is listed as Study 5 in the approved Paediatric Investigation Plan (EMEA-001119-PIP02-12-M08). The study was completed on 20th July 2022 (last visit of the last subject).

The indications proposed in the PIP are:

-Treatment of paediatric patients with 131I-refractory follicular or papillary thyroid cancer

-Treatment of paediatric patients with refractory or relapsed osteosarcoma

The Applicant does not state in the submission cover letter whether extension of indication application is planned for a DTC indication in paediatric patients and no changes to the SmPC are currently proposed. The submitted Study 207 is the only study in which paediatric patients with DTC were eligible, but only 1 patient was enrolled. The majority is represented by osteosarcoma patients.

In osteosarcoma patients, another the Study 8 is ongoing (E7080-G000-230, added in procedure EMEA-001119-PIP02-12-M05), a multi-centre, randomized, controlled trial to evaluate the efficacy and safety of lenvatinib as add-on to ifosfamide and etoposide in children from 2 years to less than 18 years (and adults) with refractory or relapsed osteosarcoma. It includes subjects with histologically confirmed high-grade osteosarcoma, who have measurable or evaluable disease and who do not have a clinically significant ECG abnormality.

The Study 7 (M&S analyses, POPPK) added in procedure EMEA-001119-PIP02-12-M05 in 2018 aimed to remove requirements for including a certain number of DTC patients (12 patients planned) in Study 207. An extrapolation of efficacy from adult patients to paediatric patients with DTC was proposed due to a rarity of paediatric DTC patient population.

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, both for an unlimited period.

The approved indications for **Lenvima** are:

Differentiated Thyroid Carcinoma (DTC)

LENVIMA as monotherapy is indicated for the treatment of adult patients with progressive, locally advanced or metastatic, differentiated (papillary/follicular/Hürthle cell) thyroid carcinoma (DTC), refractory to radioactive iodine (RAI).

Hepatocellular Carcinoma (HCC)

LENVIMA as monotherapy is indicated for the treatment of adult patients with advanced or unresectable hepatocellular carcinoma (HCC) who have received no prior systemic therapy (see section 5.1).

Endometrial Carcinoma (EC)

LENVIMA in combination with pembrolizumab is indicated for the treatment of adult patients with advanced or recurrent endometrial carcinoma (EC) who have disease progression on or following prior treatment with a platinum-containing therapy in any setting and are not candidates for curative surgery or radiation.

The approved indications for **Kisplyx** are:

Kisplyx is indicated for the treatment of adults with advanced renal cell carcinoma (RCC):

• in combination with pembrolizumab, as first-line treatment (see section 5.1).

• in combination with everolimus, following one prior vascular endothelial growth factor (VEGF)-targeted therapy (see section 5.1).

Posology for Lenvima in adults for Differentiated thyroid cancer (DTC)

The recommended daily dose of lenvatinib is 24 mg (two 10-mg capsules and one 4-mg capsule) once daily. The daily dose is to be modified as needed according to the dose/toxicity management plan.

Dose adjustments and discontinuations for DTC

Management of adverse reactions may require dose interruption, adjustment, or discontinuation of lenvatinib therapy (see section 4.4). Mild to moderate adverse reactions (e.g., Grade 1 or 2) generally do not warrant interruption of lenvatinib, unless intolerable to the patient despite optimal management. Severe (e.g., Grade 3) or intolerable adverse reactions require interruption of lenvatinib until improvement of the reaction to Grade 0 to 1 or baseline. For lenvatinib-related toxicities (see Table 4), upon resolution/improvement of an adverse reaction to Grade 0 to 1 or baseline, treatment should be resumed at a reduced dose of lenvatinib as suggested in Table 1.

Table 1 Dose modifications from recommended lenvatinib daily dose in DTC patients[a]

Dose level	Daily dose	Number of capsules
Recommended daily dose	24 mg orally once daily	Two 10-mg capsules plus one 4-mg capsule
First dose reduction	20 mg orally once daily	Two 10-mg capsules
Second dose reduction	14 mg orally once daily	One 10-mg capsule plus one 4-mg capsule
Third dose reduction	10 mg orally once daily[a]	One 10-mg capsule

a. Further dose reductions should be considered on an individual patient basis as limited data are available for doses below 10 mg.

Treatment should be discontinued in case of life-threatening reactions (e.g., Grade 4) with the exception of laboratory abnormalities judged to be non-life-threatening, in which case they should be managed as severe reactions (e.g., Grade 3).

Method of administration

Lenvatinib is for oral use. The capsules should be taken at about the same time each day, with or without food (see section 5.2). The capsules should be swallowed whole with water. Caregivers should not open the capsule, in order to avoid repeated exposure to the contents of the capsule.

Alternatively, the lenvatinib capsules may be added without breaking or crushing them to a tablespoon of water or apple juice in a small glass to produce a suspension. The capsules must be left in the liquid for at least 10 minutes and stirred for at least 3 minutes to dissolve the capsule shells. The suspension is to be swallowed. After drinking, the same amount of water or apple juice (one tablespoon) must be added to the glass and swirled a few times. The additional liquid must be swallowed.

Limited information on paediatric use is included in the SmPC of Lenvima in

-Section 4.2:

Paediatric population

Lenvatinib should not be used in children younger than 2 years of age because of safety concerns identified in animal studies (see section 5.3). The safety and efficacy of lenvatinib in children aged 2 to <18 years have not yet been established (see section 5.1). No data are available.

-Section 4.8

Paediatric population

Clinical data are not available in this population (see section 4.2).

-Section 5.1

Paediatric population

The European Medicines Agency has deferred the obligation to submit the results of studies with lenvatinib in one or more subsets of the paediatric population in the treatment of radioiodine-refractory differentiated thyroid cancer, hepatocellular carcinoma (HCC) and endometrial carcinoma (EC).

-Section 5.2

Paediatric Population

Paediatric patients have not been studied.

-Section 5.3

Juvenile animal toxicity studies

Mortality was the dose-limiting toxicity in juvenile rats in which dosing was initiated on postnatal day (PND) 7 or PND21 and was observed at exposures that were respectively 125- or 12-fold lower compared with the exposure at which mortality was observed in adult rats, suggesting an increasing sensitivity to toxicity with decreasing age. Therefore, mortality may be attributed to complications related to primary duodenal lesions with possible contribution from additional toxicities in immature target organs.

The toxicity of lenvatinib was more prominent in younger rats (dosing initiated on PND7) compared with those with dosing initiated on PND21 and mortality and some toxicities were observed earlier in the juvenile rats at 10 mg/kg compared with adult rats administered the same dose level. Growth

retardation, secondary delay of physical development, and lesions attributable to pharmacologic effects (incisors, femur [epiphyseal growth plate], kidneys, adrenals, and duodenum) were also observed in juvenile rats.

Background information for paediatric DTC indication (Source: PIP summary, MAH)

Pathology

Differentiated thyroid cancer (DTC) is the term used to cover the two most common types of thyroid cancer, namely follicular and papillary thyroid cancer [Steliarova-Foucher et al. 2006; Waguespack et al. 2006]. These are both differentiated thyroid carcinomas arising from the follicular epithelium. The other two main types are medullary thyroid cancer (MTC), which arises from the parafollicular C-cells, and anaplastic (undifferentiated) thyroid cancer. These different types of thyroid cancer are recognised by the World Health Organization's International Classification of Diseases for Oncology (ICD-O).

Aetiology

The best known causal factor for DTC is ionizing radiation [Steliarova-Foucher et al. 2006; Jarzab and Handkiewicz-Junak 2007]. This is particularly notable in children, as demonstrated by the large increase in the incidence of DTC in Eastern European children following the nuclear accident at Chernobyl in the Ukraine in 1986 and due to an increased uptake of radioiodine. The increase was in both papillary and follicular carcinomas. Endemic iodine deficiency was thought to contribute to the effect, although the causal role of endemic iodine deficiency or dietary iodine supplementation in the absence of radiation exposure is unclear. Radiotherapy to the head and neck to treat malignancies (and historically for benign conditions) has also been associated with the development of DTC in children and young adults.

Differentiated thyroid cancer becomes more common in females after the age of 10 years and from the age of 13 years it is notably more common in females, suggesting a hormonal influence on its aetiology.

There is also some familial tendency with DTC, although the genetic mutations associated with this are poorly defined.

Epidemiology

Differentiated thyroid cancer accounts for about 90% of all thyroid cancers [Pacini et al. 2010] and approximately the same proportion applies to new cases of DTC occurring in European countries [Kilfoy et al. 2009]. The majority of cases of DTC are of the papillary type. Given that there were 32,898 new cases of thyroid cancer reported in the EU in 2008 for all age groups, equivalent to 4.9 cases per 100,000 population [Globocan 2008], this indicates that the annual incidence of DTC in the EU is approximately 29,600, amounting to approximately 44 cases per million population.

The annual incidence of thyroid cancers in paediatric populations in the EU has been calculated from extensive data collected from 61 European cancer registries by Steliarova-Foucher et al. (2006) under the Automated Childhood Cancer Information System project. These data can be used to estimate the annual EU incidence of DTC by paediatric age group.

The study pooled data on 1133 paediatric (≤19 years old) cases of childhood thyroid cancer covering the period 1978-1997 from Denmark, Estonia, Finland, France, Germany, Hungary, Iceland, Ireland, Italy, Malta, Netherlands, Norway, Slovakia, Slovenia, Spain, Switzerland, Turkey, and UK. This provides a good representation of EU countries. Data were also collected on 557 cases from Belarus. However, due to the much higher incidence of DTC in Belarus than the other countries studied (due to the Chernobyl accident), data from Belarus were not included in the pooled analysis.

Paediatric cancer registries only provided data from paediatric age groups up to 14 years old, while general cancer registries provided data from all age groups, including children up to 19 years old. Data

from both types of registries were used to create a 'combined' data-set for children in the age groups 0 to 4, 5 to 9 and 10 to 14 years old (with the paediatric registry data being used in the case of populations covered by both types of registry). The general registries were used alone to provide data for adolescents aged 15 to 19 years old and to provide alternative data for children up to 14 years (although data from age groups within this range are not provided in the paper).

The study found that the annual incidence of papillary carcinoma across the whole age group of 0 to 14 years, as calculated using the data from the combined data-set, was 0.72 per million, whereas the result calculated from the general registry data was significantly less at 0.44 per million. Similarly, the annual incidence of follicular carcinoma across the whole age group of 0 to 14 years, as calculated using the data from the combined data-set, was 0.10 per million, whereas the result calculated from the general registry data was significantly less at 0.06 per million. The reason for these differences is unclear. However, as shown in Table 1 presented in the article, in order to provide a liberal estimate of incidence in the three age groups up to 14 years, the results in these groups from the combined data-set have been corrected by the ratio of these different results, i.e., 1.64 and 1.67 for papillary and follicular cancer, respectively. The incidence for the age group 15 to 19 years has been taken from the general registry data. The results for the analysis are shown in Table 1.

The study also found that the incidence of DTC increased by approximately 3% per annum during the period studied, mostly due to increases in the incidence of papillary carcinoma. This could be due to factors such as greater disease awareness and earlier diagnosis (so moving cases into the paediatric from the adult population). Steliarova-Foucher and colleagues considered that this increase in incidence might continue so bringing the rates more in line with the higher rates found in the United States. These changes in incidence in Europe should be taken in account when estimating the EU incidence of paediatric DTC in 2008, to enable a comparison with rates in the whole EU population in the same year (discussed earlier). Assuming that the average results for the study period occurred approximately half way through this period and assuming a liberal 3% annual growth in incidence over the 20.5 years from then until the end of 2008, this applies a correction factor of $1.0320.5 = 1.83$ to all the incidence data.

The annual incidence of DTC in paediatric populations in the EU in 2008 was approximately 542, which is only about 2% of all the estimated 29,600 new cases of DTC presenting in all age groups that year. Therefore, DTC is rare in children, especially in those under the age of 10 years and only isolated cases are reported in children under the age of 5 years.

Presentation

Differentiated thyroid cancer presents quite differently in the paediatric population compared with adults, which has implications for its management:

The primary tumour is much larger at presentation in the paediatric population (especially in relation to the whole gland) [Jarzab et al. 2005]. For example, amongst 1039 consecutive patients with papillary carcinoma treated at the Mayo Clinic, Rochester, Minnesota in the United States [Zimmermann et al. 1988], newly diagnosed nodules were >4 cm in 36% of children (<17 years old) compared with 15% of adults and <1 cm in 9% of children compared with 22% of adults. In addition, multifocal disease is more common in children (at least a quarter of cases in patients presenting under 21 years of age) [Borson-Chazot et al. 2004; Welch Dinauer et al. 1997].

Cervical lymph node and distant metastases are more common at presentation in the paediatric population [Jarzab et al. 2005]. For example, in the Mayo Clinic series, cervical node and distal metastases were found, respectively, in 90% and 7% of children (<17 years old), but in only 35% and 2% of adults [Zimmermann et al. 1988]. The lungs are almost always the sole metastatic site in children and adolescents and these metastases are almost always functional (approximately 95%), unlike in adults [Jarzab and Handkiewicz-Junak 2007]. The latter finding appears to be related to a difference in

expression of the sodium iodide symporter (NIS), which is more common in tumours in children compared with those in adults [Jarzab et al. 2005].

Recurrence rates are higher in the paediatric population than adults. For example in a US study by Mazzaferri and Kloos (2001) in 1528 patients with DTC with a median follow-up of 16.6 years, recurrence rates reached approximately 50% in children up to 9 years old, compared with rates of approximately 20% to 25% in adults aged 20 to 60 years old; recurrence rates increased again to over 30% in adults over 60 years old.

Diagnosis

European guidelines recommend that the diagnostic work-up for a patient with a thyroid nodule includes a thyroid ultrasound and measurement of thyroid stimulating hormone (TSH) [Pacini et al. 2010; Pacini et al. 2006]. If the TSH is low, a radionuclide thyroid scan should be performed. Any hyperfunctioning nodules are unlikely to be malignant and so do not require fine-needle aspiration cytology (FNAC). The latter investigation should be performed in all other cases with nodules >1 cm in diameter or with nodules <1 cm in diameter when there are other indicators of risk, namely a history of head and neck radiotherapy, a family history of thyroid cancer, presence of cervical lymphadenopathy, or suspicious features on palpation or on ultrasound. Papillary carcinoma can be diagnosed cytologically, but follicular carcinoma cannot. In the latter case, some surgeons undertake a lobectomy and obtain a histological diagnosis before proceeding to definitive surgery, while others undertake the definitive surgery immediately following cytological detection of follicular neoplasia.

2.2. Information on the pharmaceutical formulation used in the study

Lenvatinib was administered in the Study E7080-G000-207 as #4 size (approximately 14.3 mm in length) hydroxypropyl methylcellulose (HPMC) capsules in 3 strengths differentiated by color (iron oxide red and iron oxide yellow):

- 1-mg capsule (yellowish red cap and white body, containing 1 mg E7080 anhydrous-free base),

- 4 mg capsule (yellowish-red cap and body, containing 4 mg E7080 anhydrous-free base),

- 10 mg capsule (yellowish-red cap with yellow body, containing 10 mg E7080 anhydrous-free base).

Excipients of the E7080 formulation will be calcium carbonate, mannitol, microcrystalline cellulose, hydroxypropylcellulose, low-substituted hydroxypropylcellulose, talc, hypromellose, titanium dioxide, iron oxide yellow, and iron oxide red. Lenvatinib capsules may be suspended in water or apple juice for children unable to swallow capsules. Instructions for the preparation of the lenvatinib suspension: prepare the suspension with water or apple juice. The suspension should be directly injected into the mouth of the subjects and should not be washed down with additional fluid. The suspension is stable for 24 hours after preparation and should be kept at or below 25 °C (77 °F).

As per the section 4.2 of the approved Lenvima and Kisplyx SmPCs, the lenvatinib capsules may be added without breaking or crushing them to a tablespoon of water or apple juice in a small glass to produce a suspension. The capsules must be left in the liquid for at least 10 minutes and stirred for at least 3 minutes to dissolve the capsule shells. The suspension is to be swallowed. After drinking, the same amount of water or apple juice (one tablespoon) must be added to the glass and swirled a few times. The additional liquid must be swallowed. One of the secondary objectives of the Study 207 was to assess the palatability and acceptability of the oral suspension formulation of lenvatinib.

2.3. Clinical aspects

2.3.1. Introduction

This report concerns the submission of study E7080-G000-207 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 of the SmPC are proposed.

The MAH submitted final reports for:

- E7080-G000-207: Phase 1/2 Study of Lenvatinib in Children and Adolescents With Refractory or Relapsed Solid Malignancies and Young Adults with Osteosarcoma: data for the single-agent lenvatinib therapy Cohorts 1 and 2 (10 Aug 2020);
- E7080-G000-207: Phase 1/2 Study of Lenvatinib in Children and Adolescents With Refractory or Relapsed Solid Malignancies and Young Adults with Osteosarcoma: data for the combination-therapy Cohorts 3A and 3B (01 Oct 2020).

In addition, the MAH submitted:

- Biomarker analysis report TSBM-E7080-207-ANA-1R "Correlation of Biomarkers With Clinical Outcomes of Lenvatinib in a Phase ½ Study of Lenvatinib in Children and Adolescents With Refractory or Relapsed Solid Malignancies and Young Adults With Osteosarcoma" (02 Sep 2020)
- Modeling and Simulation analysis summary report CPMS-E7080-014R-v1 "Population PK and PK/PD Analysis of Lenvatinib in Children and Adolescents With Refractory or Relapsed Solid Malignancies and Young Adults with Osteosarcoma" (3 February 2020)

2.3.2. Biomarkers analysis

Description

The submitted Biomarker Analysis Report, TSBM-E7080-207-ANA-1R, for Study E7080-G000-207 (Study 207) provided the results of the exploratory biomarker analyses of serum, tumor gene expression, and tumour gene alteration biomarkers and their correlation with PFS-4 status based on the Biomarker Analysis Plan (BAP), TSBM-E7080-207-ANA-1P-A1.

The biomarker analyses were carried out for the secondary objective listed in study E7080-G000-207 (Study 207) as follows: Examine blood and tumour biomarkers and correlate with clinical response to lenvatinib.

As per the Study 207 protocol, serum samples from study subjects were collected at Baseline, Day 8 of Cycle 1 (Combination-Agent Cohorts 3A and 3B), Day 15 of Cycle 1 (Single-Agent cohorts), Day 1 of all subsequent cycles, and at the Off-Treatment Visit. For subjects 2 to <6 years, blood serum samples were collected in Cohort 1 at Cycle 1 Day 1 (predose). An archival tumour sample from the most recent surgery or biopsy was collected at any time before and during the study, unless no such material was available.

Serum levels of ANG2, FGF19, FGF21, VEGF, and IFN-γ and IFN-γ -regulated chemokines (CXCL9, CXCL10, and CXCL11) at baseline and selected post-treatment visits were measured. Using the tumour tissues, gene expression levels and gene alteration status for the selected genes were measured.

In the submitted report, all planned analyses described in BAP except for the baseline tumour gene alteration correlation analysis are reported.

Methods

Study participants and treatments

Please refer to the study E7080-G000-207 below.

Objective

The objective of the biomarker analysis was to:

• Examine blood and tumour biomarkers and correlate with clinical response to lenvatinib.

Outcomes/endpoints

The biomarker endpoint was assessment of blood or tumour biomarkers that correlate with clinical response to lenvatinib treatment.

The following categories of biomarkers were explored: 1) Pharmacodynamic, 2) Predictive, and 3) Response. The predictive biomarker analyses included baseline serum biomarker analysis as well as tumour gene alteration biomarker analysis and tumour gene expression biomarker analysis of archival tumour tissue samples from each study cohort. Response biomarkers included post-treatment serum biomarker samples to identify those that could be used to monitor efficacy.

Statistical Methods

Definitions of Analysis Sets:

- Serum Biomarker Analysis Set: a subset of the Full Analysis Set, including subjects with at least 1 serum biomarker measurement.
- Gene Expression Analysis Set: a subset of the Full Analysis Set, including subjects with a baseline tumour gene expression biomarker measurement.
- Gene Alteration Analysis: a subset of the Full Analysis Set, including subjects with a baseline tumour gene alteration biomarker measurement.

Change-in-level of serum biomarkers (post-treatment versus baseline) were converted into percentage change over baseline for statistical analysis. For the tumour gene expression biomarker analysis, each expression value was converted into log2 scale for statistical analysis.

Baseline characteristics of the Serum Biomarker Analysis Set, Gene Expression Analysis Set, and Gene Alteration Analysis Set, such as age, sex, race, and ethnicity, were summarized by study cohort. The summarized characteristics were selected from the statistical analysis plan for Study E7080-G000-207.

Pharmacodynamic Biomarker Analysis

Change-in-level of serum biomarker from baseline was summarized per study cohort and analysed using the 1-sample Wilcoxon signed-rank test. The 1-sample t test was also used for the analysis. The time points to be summarized were as follows:

1. Cohort 1: Baseline, C1D1 (for 2 subjects who received run-in treatment only), C2D1, and C3D1

2. Cohorts 2A and 2B: Baseline, C2D1, and C3D1

3. Cohorts 3A and 3B: Baseline, C2D1, and C4D1

As only 2 subjects were evaluated at C1D1, results at this time point were not discussed.

Correlation Analysis

Correlation analyses were performed for Cohorts 2B and 3B separately. No correlation analyses were performed for the other study cohorts because there were no efficacy-related primary endpoints in Cohorts 1 and 3A, and only 1 subject was enrolled in Cohort 2A.

Baseline Serum Biomarker Correlation Analysis

Correlation analysis of baseline serum biomarker levels with PFS-4 status were performed using the 2-sample Wilcoxon rank-sum test between subject group with PFS equal to or longer than 4 months and subject group with PFS shorter than 4 months. The 2-sample t test was also used for the analysis.

Change-in-level of Serum Biomarker Correlation Analysis

Correlation analysis of change-in-level of serum biomarker from baseline to a selected time point with PFS-4 status was performed using the 2-sample Wilcoxon rank-sum test between subject group with PFS equal to or longer than 4 months and subject group with PFS shorter than 4 months. The 2-sample t test was also used for the analysis.

Baseline Tumor Gene Expression Biomarker Correlation Analysis

Thirty-six genes were defined as genes in the angiogenic and growth factor pathway: ANGPT1, ANGPT2, FGF1, FGF2, FGF3, FGF4, FGF5, FGF6, FGF7, FGF8, FGF9, FGF10, FGF11, FGF12, FGF13, FGF14, FGF16, FGF17, FGF18, FGF19, FGF20, FGF21, FGF22, FGF23, FGFR1, FGFR2, FGFR3, FGFR4, FIGF, FLT1, FLT4, KDR, PGF, TEK, VEGFA, and VEGFC.

Correlation analysis of baseline gene expression levels with PFS-4 status was performed for each of these genes using the 2-sample Wilcoxon rank-sum test between subject group with PFS equal to or longer than 4 months and subject group with PFS shorter than 4 months. The 2-sample t test was also used for the analysis.

Baseline Tumor Gene Alteration Biomarker Correlation Analysis

Correlation analysis was to be performed on genes with more than 20% or 30% alteration frequency in each study cohort. Correlation analysis of baseline gene alteration status (wild-type group versus gene-alteration group) with PFS-4 status was to be performed using the Fisher's exact test between subject group with PFS equal to or longer than 4 months and subject group with PFS shorter than 4 months. Due to the small sample size (12 subjects in Cohort 2B and 3 subjects in Cohort 3B), biomarker correlative analysis for gene alteration was not performed.

Clustering analysis

Clustering analyses with baseline tumour gene expression biomarkers were performed for Cohorts 2B and 3B separately. No clustering analyses were performed for the other study cohorts because there were no efficacy-related primary endpoints in Cohorts 1 and 3A, and only 1 subject was enrolled in Cohort 2A.

Subgroups were defined by clustering analysis using the baseline expression levels of 36 genes in the angiogenic and growth factor pathway. The distance matrix was calculated using the Manhattan method, and the dendrogram was generated using the Ward's method. Correlation analysis of PFS-4

status among defined subgroups was performed using the Fisher's exact test between subject group with PFS equal or longer than 4 months and subject group with PFS shorter than 4 months.

Results

Number analysed

Table 1 Analysis Sets

	Cohort 1 (N=23) n (%)	Cohort 2A (N=1) n (%)	Cohort 2B (N=31) n (%)	Cohort 3A (N=22) n (%)	Cohort 3B (N=20) n (%)
Subjects Treated	23	1	31	22	20
Serum Biomarker Analysis Set[a]	22 (95.7)	1 (100)	31 (100)	21 (95.5)	17 (85.0)
Gene Expression Analysis Set[b]	18 (78.3)	1 (100)	18 (58.1)	8 (36.4)	6 (30.0)
Gene Alteration Analysis Set[c]	13 (56.5)	1 (100)	12 (38.7)	2 (9.1)	3 (15.0)

a Includes all subjects in the Full Analysis Set with at least 1 serum biomarker measurement.

b Includes all subjects in the Full Analysis Set with a baseline tumor gene expression biomarker measurement.

c Includes all subjects in the Full Analysis Set with a baseline tumor gene alteration biomarker measurement.

Source: E7080-G000-207 Clinical Study Reports and Source Table 1.

Biomarker results

Pharmacodynamic Biomarkers

Median percentage changes in levels of serum biomarkers from baseline to C2D1, C3D1, and C4D1 are summarized by biomarker and cohort in Table 5 and discussed below. Significance was determined by p-values less than 0.05 based on 1-sample Wilcoxon signed-rank test.

• ANG2: ANG2 levels decreased significantly from baseline across all cohorts to all time points.

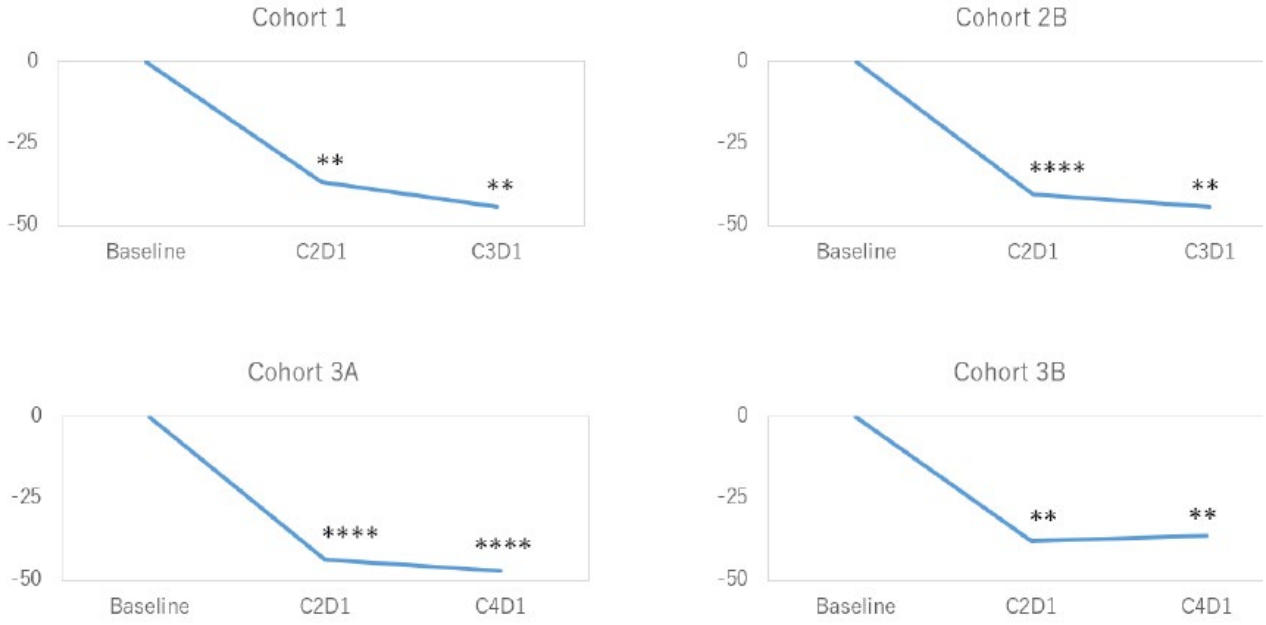


Figure 1 Study Percentage Changes in Serum ANG2 Levels From Baseline: Serum Biomarker Analysis Set

• FGF21: FGF21 levels in the lenvatinib monotherapy cohorts (Cohorts 1 and 2B) increased significantly from baseline to C2D1. FGF21 levels in the lenvatinib combination cohorts (Cohorts 3A and 3B) increased significantly from baseline to C2D1 (Cohort 3A only) and C4D1 (both cohorts).

• FGF19: FGF19 levels increased significantly across all cohorts from baseline to C2D1, and continued to increase in the osteosarcoma expansion cohorts (Cohorts 2B and 3B).

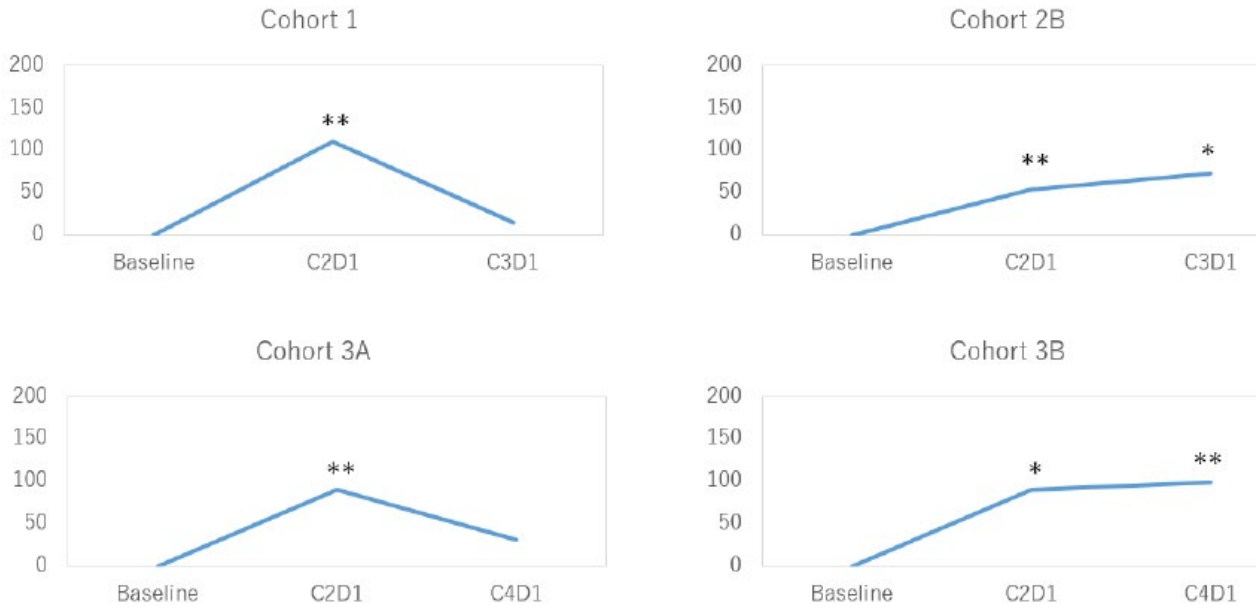


Figure 2 Study Percentage Changes in Serum FGF19 Levels From Baseline: Serum Biomarker Analysis Set

• VEGF: VEGF levels increased significantly across all cohorts from baseline to C2D1, and continued to increase significantly in the combination of lenvatinib with ifosfamide and etoposide cohorts (Cohorts 3A and 3B; ie, to C4D1), remained significantly higher in Cohort 1 (ie, to C3D1), and returned to near baseline levels at C3D1 in Cohort 2B.

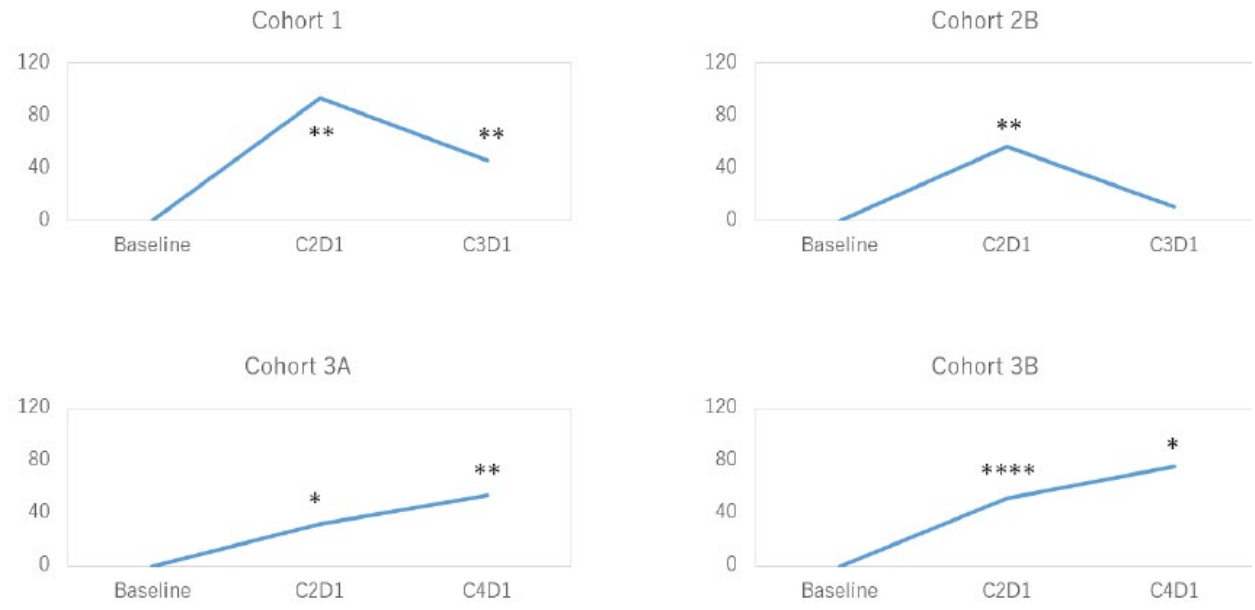


Figure 3 Study Percentage Changes in Serum VEGF Levels From Baseline: Serum Biomarker Analysis Set

• IFN-γ: Percentage changes in IFN-γ levels from baseline were not consistent across all cohorts.

• CXCL9: CXCL9 levels in the monotherapy cohort (Cohort 1) increased significantly from baseline to C3D1. Percentage changes in CXCL9 levels were not significant in other cohorts.

• CXCL10: CXCL10 levels increased significantly in the lenvatinib monotherapy cohorts (Cohorts 1 and 2B) from baseline to all time points, CXCL10 levels in Cohort 3A increased significantly from baseline to C2D1, and no statistically significant percentage changes were observed in Cohort 3B.

• CXCL11: CXCL11 levels significantly increased from baseline to C2D1 and C4D1 in the combination of lenvatinib with ifosfamide and etoposide cohorts (Cohorts 3A and 3B), respectively. No statistically significant percentage changes were observed in other cohorts.

In the combination arm of lenvatinib with ifosfamide and etoposide expansion cohorts (Cohorts 3A and 3B), in addition to increased percentage changes in levels of VEGF and FGF19 and decreased levels of ANG2, which are similar to those in the lenvatinib monotherapy expansion cohort, levels of CXCL11 increased, which was different from the lenvatinib monotherapy cohorts. In addition, CXCL10 levels increased after treatment in only lenvatinib monotherapy cohorts (Cohort 1 and 2B).

Correlation Analysis of Baseline Serum Biomarkers With PFS-4 Status

For the baseline level of each serum biomarker, correlation analysis with PFS-4 status (based on RECIST 1.1) was performed separately in Cohorts 2B and 3B. Correlative analyses for only these cohorts were presented, because there are no efficacy-related primary endpoints in Cohorts 1 and 3A.

No statistically significant difference in baseline serum levels of any of the biomarkers evaluated based on PFS-4 status was observed in Cohorts 2B and 3B.

Correlation Analysis of Percentage Changes in Levels of Serum Biomarkers From Baseline With PFS-4 Status

For percentage change in level of each serum biomarker from baseline, correlation analysis with PFS-4 status (based on RECIST 1.1) was performed separately in Cohorts 2B and 3B. Correlative analyses

only for these cohorts were presented because there are no efficacy-related primary endpoints in Cohorts 1 and 3A. The percentage changes in FGF21 levels from baseline to C2D1 in lenvatinib monotherapy osteosarcoma Cohort 2B were significantly different (P=0.04760 from Wilcoxon rank-sum test) between the subjects with PFS ≥4 months and those with PFS <4 months, with median percentage changes of -36.4% and 74.2%, respectively, but these associations were not detected at C3D1. No significant difference in percentage change from baseline serum levels based on PFS-4 status for any other biomarkers evaluated was observed.

Tumour Gene Alteration Profiles

In Cohorts 2B and 3B, tumor gene alteration analysis was performed on tumour tissue samples using the next-generation sequencing platform Ion S5 XL Sequencer (Thermo Fisher Scientific, Waltham, MA) with the Oncomine® Comprehensive Assay v3 (OCA v3). RET was among the OCA v3 targets (161 genes overall) implicated in cancer. No fusions or mutations were observed for RET. Because of the small sample size, the correlation of gene alteration status with PFS-4 status was not conducted.

In Cohort 2B, gene alterations in 12 genes were detected at 8% or greater frequency (which corresponds to gene alterations observed in 1 or more subjects). Notably, gene alterations in ATM (25%), TP53 (25%), CCND3 (17%), KIT (17%), and MYC (17%) were identified in more than 10% of samples.

In Cohort 3B, gene alterations in 8 genes (ATM, ATRX, CCND3, CDK4, MDM2, MYC, MYCL, and NF2) were detected in 1 subject each.

Correlation Analysis of Tumor Gene Expression Biomarkers With PFS-4 Status

In Cohorts 2B and 3B, the 770 genes of the gene panel and the custom-added additional 29 genes were tested by the nCounter® platform (NanoString Technologies, Seattle, WA) with the PanCancer Pathways Panel in collected tumor tissue samples.

Correlation analyses of baseline gene expression levels with PFS-4 status were performed by 2-sample Wilcoxon rank-sum test in Cohorts 2B and 3B.

Among 36 angiogenic and growth factor pathways genes, no significant difference in baseline gene expression levels was observed based on PFS-4 status when analyzed using the Wilcoxon rank-sum test in this small sample size.

Although not statistically significant and in this small sample size, baseline expression levels of FGFR4 in Cohort 2B were higher in subjects with PFS ≥4 months (n=5; median: 137.3; range: 108.5 to 154.6) compared to those with PFS <4 months (n=12; median: 13.9; range: 8.3 to 97.5)

Subgroup Identification by Gene Expression Profile

This analysis focused on 36 genes consisting of angiogenic and growth factor pathways from the point of view of the mechanism of action of the lenvatinib (see Section 6.2.4.2 for a complete list of additional genes).

Subjects were classified into 2 major groups (Groups 1 and 2) by clustering analysis based on the expression profile of 36 angiogenic and growth factor pathway genes in Cohorts 2B and 3B.

In Cohort 2B, Group 1 was characterized by relatively high expression levels of FGF ligands and relatively low expression levels of VEGFA, FGFR1, and FGFR3. Group 2 of Cohort 2B was characterized by relatively low expression levels of FGF ligands. In Cohort 3B, Group 1 was characterized by low expression levels of FGF ligands and Group 2 was characterized by high expression levels of FGF ligands.

Although not statistically significant in this small sample size, the PFS-4 rate with high FGF in Cohort 2B was 43% (3/7 subjects) compared to 20% (2/10 subjects) with low FGF.

Table 2 Baseline Tumor Gene Expression Biomarker Level With Clustering Group, Correlation Analysis: Gene Expression Analysis Set

Cohort	PFS-4 Eval Status[a] (N)	Clustering Group 1[b] N (%)	Clustering Group 2[b] N (%)	Fisher's Exact Test
2B	Yes (N=5)	3 (17.6)	2 (11.8)	0.5928
	No (N=12)	4 (23.5)	8 (47.1)	
3B	Yes (N=4)	3 (60.0)	1 (20.0)	0.4000
	No (N=1)	0	1 (20.0)	

Note: One subject in Cohort 2B Clustering Group 2 and 1 subject in Cohort 3B Clustering Group 1 were not evaluable for PFS-4 and therefore are not presented in this table.
PD = progressive disease, PFS-4 = progression-free survival at 4 months from the first dose, RECIST 1.1 = Response Evaluation Criteria in Solid Tumors version 1.1.
a Yes = evaluable for PFS-4 and alive and without PD at 4 months from the first dose based on RECIST 1.1 per the investigator.
No = evaluable for PFS-4 and not alive or with PD at 4 months from the first dose based on RECIST 1.1 per the investigator.
b Clustering group was derived from clustering analysis using the expression levels of 36 genes in angiogenic and growth factor pathway, in which the distance matrix was calculated using the Manhattan method, and the dendrogram was generated using the Ward's method.
Source: Source Table 9.

Discussion on biomarkers analyses

Although conducted in a relatively limited number of patients in the Study 207 (n=97, serum biomarkers investigated in 92 patients, tumour tissue samples in 51 and 31 patients for gene expression and gene alteration analyses of biomarkers, respectively), the obtained biomarker analyses results indicate the expected pharmacodynamic changes due to inhibition of VEGF and FGF signaling pathways, and are consistent with results in adult patients and with non-clinical findings (Ichikawa, et al., 2016; Tohyama, et al., 2014; Yamamoto, et al., 2014).

The limited sample size might have been one of the reasons for difficulties in identifying biomarkers that could be predictive for efficacy, in particular for the chosen primary endpoint for efficacy analyses (PFS-4) in patients with osteosarcoma treated either with lenvatinib monotherapy or its combination with chemotherapy. Baseline levels of CXCL10 tended to be higher for the subject group with PFS shorter than 4 months compared with the other group in Cohort 2B, in line with a suggested prognostic value of this biomarker in osteosarcoma patients (Niu et al, 2020). No association with PFS-4 status was observed for baseline serum levels of FGF21, therefore its prognostic role suggested in hepatocellular carcinoma is not evident for osteosarcoma.

Subgroup identification by gene expression profiles for 36 genes of relevance for angiogenic and growth factor pathways indicated that the high FGF group is associated with higher PFS-4 rates, similarly to results in other tumour types (e.g. renal cell carcinoma or hepatocellular carcinoma).

RET was among the Oncomine Comprehensive Assay v3 (OCA v3) targets (161 genes overall) implicated in cancer. No fusions or mutations were observed for RET.

2.3.3. Modeling and simulation analysis

Description

The MAH submitted Modeling and Simulation analysis summary report CPMS-E7080-014R-v1 "Population PK and PK/PD Analysis of Lenvatinib in Children and Adolescents With Refractory or Relapsed Solid Malignancies and Young Adults with Osteosarcoma" (3 February 2020).

This report describes the population PK analysis of lenvatinib on pooled data from several studies including Study 207, and the PK/PD analyses of safety and efficacy in children and adolescents with relapsed or refractory solid malignant tumors using data from study 207 only.

This analysis corresponds to a PIP Study 7 added in procedure EMEA-001119-PIP02-12-M04 as outlined below.

Table 3 PIP Study 7

Study identifier(s)	**Not yet available**
Study description	Population PK analysis to establish the dose-response relationship of lenvatinib in paediatric patients with differentiated thyroid cancer (DTC) and to support extrapolation of efficacy from adult patients to paediatric patients with DTC

Study objectives	• To describe lenvatinib PK in paediatric patients with refractory or relapsed solid malignancies in Study E7080-G000-207 (Study 207) using population PK modelling. • To support extrapolation of lenvatinib efficacy from adult patients to paediatric patients with DTC. Lenvatinib systemic exposures (AUC range at steady state) from paediatric patients, who participated in Studies 207 and E7080-A000-216 (Study 216), will be compared to exposures in adults with DTC who received once daily doses of 24 mg lenvatinib in Study E7080-G000-303 (Study 303).
Methodology	Lenvatinib systemic exposures (AUC range at steady state) from paediatric patients who participated in Studies 207 and 216 will be compared to exposures in adult patients with DTC who received once daily doses of 24 mg lenvatinib in Study 303. Population PK modelling: Paediatric and adult data will be used in building the PK model. Population PK analysis will be performed on data from Study 207, which is pooled with existing data from Phase 1 clinical pharmacology healthy volunteer studies (Studies 001-008), from Phase 1 studies in adult patients (Study E7080-E044-101, E7080-A001-102, E7080-J081-103 and E7080-J081-105), two Phase 2 (E7080-G000-201, E7080-J081-208) , Phase 3) study in adult patients with thyroid cancer (Study 303) and Phase 1/2 study in paediatric patients with recurrent and refractory solid tumours (Study 216), including central nervous system tumours, who received lenvatinib in combination with everolimus. For the Population PK analysis, a three compartment disposition model will be fitted to the data including that from the paediatric patients in Studies 207 and 216. Covariates to be included in the model: age, body weight on clearances and volume parameters, healthy subjects on CL/F, albumin < 30 g/L and alkaline phosphatase (ALP) > upper limit of normal (ULN) on CL/F, and capsule formulation on relative bioavailability. First Order Conditional Estimation with Interaction (FOCEI) in NONMEM will be used. Model qualification of population PK will be performed by visual predictive checks and goodness of fit plots and the model will be validated using bootstrap analysis

Study population and subset definition (incl. stratification)	The following study population will be fitted to the model: • Study 207: paediatric and adult patients with solid tumours; • Study 216: paediatric and adult patients with solid tumours; • Study 303: adult patients with DTC.
Number of study participants by paediatric subset (e.g., age, sex, stratum)	The PK model will be fitted to data from the following number of subjects: Number of adult subjects: • At least 230 healthy volunteers; • At least 140 adult patients with solid tumours; • At least 90 adult patients with thyroid cancer (Study 201); • At least 30 adult patients with thyroid cancer (Study 208); • At least 250 adult patients with DTC (Study 303). Number of paediatric subjects: • At least 66 paediatric patients with solid tumours (Study 207); • At least 6 paediatric patients with solid tumours (Study 216).
Date of initiation	Not specified by PDCO
Date of completion	By September 2020 The completion of this study is deferred.

The following justification was provided by the MAH at the time of the Study 7 proposal:

"To support identifying a dose which achieves comparable exposures in paediatric and adult subjects, the objectives of this population PK analysis are to describe lenvatinib PK in paediatric subjects and compare it to that in adults.

The additional objective is to extrapolate efficacy from adults to paediatric subjects with DTC, PK comparisons will be made by comparing lenvatinib systemic exposures (AUC range at steady state) in paediatric subjects receiving daily lenvatinib doses based on body surface area in Studies 207 and 216 and adult subjects with DTC who received fixed doses of lenvatinib (24 mg/day) in Study 303.

In Study 303 in adult patients with DTC, a dose of 24 mg lenvatinib once daily significantly prolonged progression-free survival (PFS) versus placebo (median: 18.3 vs 3.6 months, respectively; hazard ratio 0.21; 99% confidence interval, 0.14–0.31; P < 0.001) and was associated with a significantly better response rate (64.8% vs 1.5%, respectively). Evaluation of the relationship between PFS and lenvatinib exposure (AUC) was performed on the PFS data from the lenvatinib arm of Study 303 (Report CPMS-E7080-007R is provided in this response package). There was no exposure-response relationship in PFS: Kaplan–Meier plot and Cox regression analysis demonstrates that within the lenvatinib group, over a wide range of AUC (between 1410 to 10,700 ng•h/mL), PFS was similar.

The MAH proposes to highlight the International Council for Harmonisation (ICH) E11 recommendation for the use of extrapolation in paediatric drug development. ICH E11 defines extrapolation as an acceptable approach to providing evidence in support of the effective and safe use of drugs in the paediatric population when it can be assumed that the course of the disease and the expected response to a medicinal product would be sufficiently similar in both the paediatric and the reference (adult or other paediatric) populations.

Consistent with the extrapolation recommendation in E11, the safety and PK data obtained in the Phase 1 part of Study 207 (Draft Population PK analysis report for Study 207 provided in the initial PIP Mod04 submission) showed the following:

- Preliminary results showed that the recommended Phase 2 dose (RP2D) of 14 mg/m2/day in the paediatric population resulted in comparable exposure at steady-state to that in adults receiving a daily dose of 24 mg
- In the presence of a body weight effect lenvatinib PK was unaffected by age
- Body surface area (BSA)-based dosing in the paediatric population is adequate since exposure to lenvatinib was comparable to that in adults
- The safety profile for the proposed starting dose of 14 mg/m2/day in the paediatric population is similar to that observed in adults starting at 24 mg/day

In addition, although clinical differences in DTC appear in adult and paediatric subjects (with a higher rate of lymph node and distant metastases in paediatric subjects), there is no histological evidence at present to suggest that there would be a difference in the efficacy observed in adults and paediatric subjects with DTC.

Hence, the safety and PK data obtained in paediatric subjects from Study 207 receiving starting doses of 14 mg/m2/day support lenvatinib clinical administration in paediatric subjects with DTC, and a potential extrapolation of efficacy from adult to paediatric subjects could be made."

Clinical trial E7080-G000-207 (Study 5) and M&S study (Study 7) for paediatric DTC development were checked in procedure EMEA-C3-001119-PIP02-12-M07 and were considered to have been completed in compliance with the agreed PIP.

The compliance check was finalised on the 26th of March 2021.

As the reports of relevance for both PIP studies 5 and 7 have been submitted, the results are assessed from a perspective of a potential extrapolation of efficacy from adult to peadiatric patients with DTC, as was planned by the MAH and supported by the PDCO.

The clinical development in osteosarcoma indication is ongoing and the M&S analyses provided in this procedure are currently not discussed in the context of clinical development in osteosarcoma patients.

The M&S analyses are of descriptive nature for this indication. Clinical efficacy and safety data from an early study 207 (PIP Study 5) that recruited patients with osteosarcoma have been submitted within this procedure (please refer to the Study 207 assessment below). Another Study 8 is ongoing (E7080-G000-230, added in procedure EMEA-001119-PIP02-12-M05), a multi-centre, randomized, controlled trial to evaluate the efficacy and safety of lenvatinib as add-on to ifosfamide and etoposide in children from 2 years to less than 18 years (and adults) with refractory or relapsed osteosarcoma. It includes subjects with histologically confirmed high-grade osteosarcoma, who have measurable or evaluable disease and who do not have a clinically significant ECG abnormality.

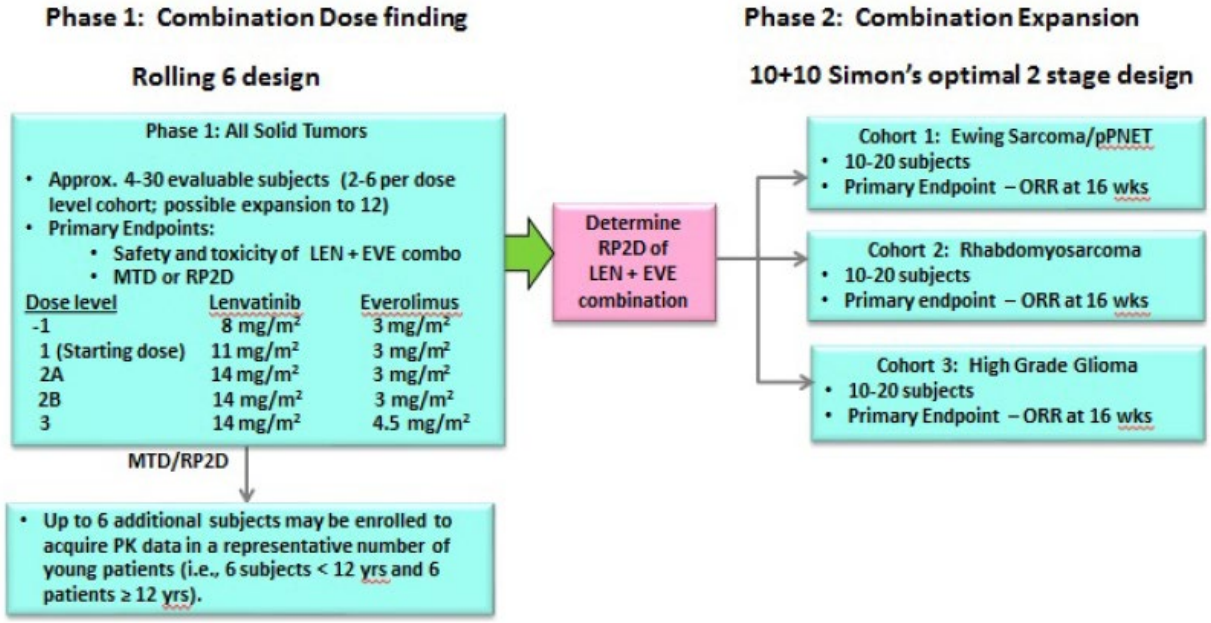
Therefore, M&S analyses are currently planned as descriptive and supportive for the osteosarcoma indication as clinical efficacy and safety data would become available to support benefit-risk.

Methods

Data sources and treatments

Study 207 is an ongoing multicenter, open-label, Phase 1/2 study of lenvatinib as a single agent or in combination with etoposide and ifosfamide in paediatric subjects, and consist of 2 phases, Phase 1 and Phase 2. Both phases of the study include a Pretreatment Phase, a Treatment Phase, and an Extension Phase. Please refer to the Study 207 design below.

Study 216 is an ongoing multicenter, open-label, Phase 1/2 study of lenvatinib in combination with everolimus in paediatric subjects with relapsed or refractory solid tumours. An overview of the study design is presented below. Interim lenvatinib PK data from Phase 1 component of the study was used in the current PK modeling.



Dose Level 2 includes 2 sub dose levels, 2A and 2B, depending on the maximum daily dose of lenvatinib allowed and body surface area of the subjects. At Dose Level 2A, the maximum daily dose of lenvatinib will not exceed 18 mg daily with a minimum body surface area (BSA) of 0.6 m^2. At Dose Level 2B, the maximum daily dose of lenvatinib allowed will not exceed 24 mg and requires a minimum BSA of 1.33 m^2.
EVE = everolimus, LEN = lenvatinib, MTD = maximum tolerated dose, ORR = objective response rate, PK = pharmacokinetic, pPNET = peripheral primitive neuroectodermal tumor, RP2D = recommended Phase 2 dose.

Figure 4 Study 216 design

Objectives of M&S analyses

The objectives of the population pharmacokinetics (PK) analysis of lenvatinib on pooled data from several studies, including study 207, are:

• Characterize the PK of lenvatinib in children and adolescents with refractory or relapsed solid malignancies and compare to that in adult subjects with solid tumors.

• Identify intrinsic and extrinsic covariates that explain between-subject variability in lenvatinib PK

The objectives of the PK/PD analysis for efficacy for study 207 are:

• Explore the relationship between lenvatinib exposure and tumor response in children and adolescents with osteosarcoma in study 207

The objectives of the PK/PD analysis for safety for study 207 are:

• Explore the relationship between lenvatinib exposure and occurrence of the following treatment-emergent adverse events (TEAEs) in children and adolescents with refractory or relapsed solid malignancies in study 207, which included: hypertension, proteinuria, decreased appetite, vomiting, hypothyroidism, diarrhea.

Covariate Data Collection

A Population PK model for lenvatinib was previously developed in adult subjects with DTC (CPMS-E7080-007R). PK model included the following covariates: body weight on clearances and volume parameters, healthy subjects on CL/F, albumin < 30 g/L and alkaline phosphatase (ALP) > upper limit of normal (ULN) on CL/F, and capsule formulation on relative bioavailability. In the current analysis, these effects were included in the PK model, and only age was tested as an additional covariate effect.

Pharmacokinetic Assessment

Blood samples (2 mL each) were collected from all subjects in Study 207 at the time points shown below.

Table 4 Lenvatinib Pharmacokinetic Sampling Time Points (Study 207)

Time Point[a]	Time (h)
Run-In Day 15	Predose[b]
Cycle 1 Day 1	Postdose: 0.5-4 and 6-10
Cycle 1 Day 15[c]	Predose Postdose: 0.5-4 and 6-10
Cycle 2 Day 1	Predose Postdose: 2-12

Note: PK blood samples should be drawn on day of tumor assessments (predose). If the tumor assessments fall on the same day as study treatment PK samples, they need not be collected again to avoid duplicate samples.
h = hour(s).
a. If dose interruption is necessary in these time points, only predose sample should be collected, if possible.
b. Sample to be collected during the Run-in Period (Cohort 1).
c. Samples not required for Cohorts 3A and 3B

For the PK evaluation data were pooled together with PK data from previous lenvatinib Phase 1 clinical pharmacology healthy volunteer studies (001-008), four Phase 1 studies in adult subjects with solid tumors (101,102, 103 and 105) and two Phase 2 (201, 208) and one Phase 3 (303) study in adult subjects with DTC.

Table below lists these 15 studies and shows the PK sampling schedule in these studies.

Table 5 Brief Description of Studies with PK Sampling to be Included in Population PK Analysis

Study	Dose Range and Regimen	N	Formulation	Subjects	Pharmacokinetic sampling
E7080-G000-303	24 mg QD continuous	256	Capsule	[a]DTC	Day 1 and 15 of Cycle 1: Pre-dose, and post-dose on 0.5-4 h and 6-10 h, Cycle 2 Day 1: Pre-dose and 2-12 h post dose Ctrough: Cycle 3-Cycle 6/Day1
E7080-G000-201	10 mg BID and 24 mg QD continuous	92	Tablet	[a]DTC and [b]MTC	Day 1 of Cycle 1 and Cycle 2: Pre-dose, 0.5and 2 h, Pre-dose on Cycle 1 Day 8 and Pre-dose and 2h post-dose on Cycle 3 Day1
E7080-J018-208	24 mg QD continuous	34	Capsule	DTC, MTC and [c]ATC	Day 1 of Cycle 1 and Cycle 2: Pre-dose, and post-dose on 0.5-4 h and 6-10 h, Cycle 1 Day 15: Pre-dose and 2-12 h post dose
E7080-E044-101	0.2 – 32 mg QD continuous	65	Tablet	Solid Tumors	Day 1 of Cycle 1 and Cycle 2: 0.25, 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, and 24 h post dose Ctrough: Days 1, 8, and 15 of Cycle 1
E7080-A001-102	Schedule 1: 0.1 – 3.2 mg BID x 7d/14d Schedule 2: 3.2 – 12 mg BID continuous 10 mg BID continuous	47	Tablet	Solid Tumors/ Melanoma	Day 1 of Cycle 1 and Cycle 2: 0.25, 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, and 24 h post dose Ctrough: Days 8, 15 and 22 of Cycle 1
E7080-J081-103	0.5 – 20 mg BID x 14d/21d	18	Tablet	Solid Tumors	1, 2, 3, 5, 6, 8, 12, 24, 48, 96, and 168 h post dose on Day1 of Cycle 0 and Day 14 of Cycle1 Ctrough: Days 5, 8 and 11 of Cycle 1, Day 8 of Cycle 2
E7080-J081-105	20 and 24 mg QD continuous	9	Capsule	Solid Tumors	Day 1 and 15 of Cycle 1: 1, 2, 4, 8, and 24 h post dose Ctrough: Days 8, 15 of Cycle 1, Day 15 of Cycle 2
E7080-A001-001	10 mg	20	Tablet/ capsule	Healthy volunteers	Pre-dose and at 1, 2, 3, 4, 8, 16, 24, 48, 72, 96, 120, 144, and 168 h post-dose
E7080-A001-002	32 mg	51	Capsule	Healthy volunteers	Pre-dose and at 0.5, 1, 2, 3, 4, 5, 6, 8, 12, 24, 48, 72, and 96 h post-dose
E7080-A001-003	10 mg	16	Capsule	Healthy volunteers	Pre-dose and at 1, 2, 3, 4, 8, 12, 16, 24, 48, 72, 96, 120, 144, and 168 h post-dose
E7080-A001-004	5 mg	17	Capsule	Healthy volunteers	Pre-dose and at 0.5, 1, 2, 3, 4, 8, 12, 16, 24, 48, 72, 96, 120, 144, 168, 240, 288, and 336 h post-dose
E7080-A001-005	24 mg	26	Capsule	Healthy volunteers and renal impairment	Pre-dose and at 0.5, 1, 2, 3, 4, 8, 12, 16, 24, 48, 72, 96, 120, 144, and 168 h post-dose
E7080-A001-006	5 and 10 mg	26	Capsule	Healthy volunteers and hepatic impairment	Pre-dose and at 0.5, 1, 2, 3, 4, 8, 12, 16, 24, 48, 72, 96, 120, 144, 168, 240, 288, and 336 h post-dose
E7080-A001-007	24 mg	15	Capsule	Healthy volunteers	Pre-dose and at 0.5, 1, 2, 3, 4, 8, 12, 16, 24, 48, 72, 96, 120, 144, and 168 h post-dose
E7080-A001-008	10 mg	60	Capsule	Healthy volunteers	Pre-dose and at 1, 2, 3, 4, 8, 12, 16, 24, 48, 72, 96, and 120 h post-dose

[a]Differentiated Thyroid Cancer
[b]Medullary Thyroid Cancer
[c]Anaplastic Thyroid Cancer

Efficacy Assessments

PK/PD analyses for efficacy (tumour response) were based on data from the lenvatinib arm in Study 207. Tumour assessment was performed based on RECIST 1.1. Investigator determined response assessments at each assessment time point were entered onto the appropriate CRF. Subjects must have evaluable disease or measurable disease based on RECIST 1.1.

Safety Assessments

PK/PD analyses for safety were based only on data for most frequent adverse event (AE) in Study 207. Other safety assessments consisted of monitoring and recording all AEs, including all Common Terminology Criteria for Adverse Events (CTCAE) v4.03 grades (for both increasing and decreasing severity), and serious adverse events (SAEs); regular laboratory evaluation of hematology, blood chemistry, and urine values; periodic measurement of vital signs and 12-lead ECGs; and echocardiograms, Lansky play score or Karnofsky performance status score, physical examinations, and height assessments.

Population PK model

Population PK analyses were performed using NONMEM software version 7.4 with the Windows front end PDx-Pop version 5.2.2, R version 3.0 or later and/or the SAS System for Windows version 9.3.

A Population PK model for lenvatinib was previously developed using pooled data from 8 Phase 1 clinical pharmacology healthy volunteer studies (001-008), four Phase 1 MTD determination studies in adult subjects with solid tumors (101,102, 103 and 105) and two Phase 2 (201, 208) and one Phase 3 (303) study in adult subjects with DTC (CPMS-E7080-007R).

Lenvatinib PK was best described by a 3-compartment model with simultaneous first and zero order absorption and linear elimination from the central compartment parameterized for apparent plasma clearance of drug after oral administration (CL/F), apparent volume of the central compartment (V1/F), apparent volume of peripheral compartments (V2/F and V3/F), inter-compartmental clearance between V1 and V2 and V1 and V3 (Q2/F and Q3/F), absorption rate constant (Ka), and duration of zero-order absorption (D1).

PK model included the following covariates: body weight on clearances and volume parameters, healthy subjects on CL/F, albumin < 30 g/L and alkaline phosphatase (ALP) > upper limit of normal (ULN) on CL/F, and capsule formulation on relative bioavailability. In the current analysis, these effects were included in the PK model, and only age was tested as an additional covariate effect. As data allow, estimation of model parameters was performed using first order conditional estimation method with interaction (FOCEI).

PK/PD analyses

Exposure-Response Analysis for Tumour Response (Study 207 Osteosarcoma)

Exposure-response analysis for tumour response was based on data from subjects with osteosarcoma in Study 207. Boxplot of lenvatinib AUC based on starting dose stratified by BOR was constructed.

Exposure-Response Analysis for Individual AE (Study 207)

Exposure-response analysis for adverse event was based on data from subjects in Study 207. Boxplot of lenvatinib AUC based on starting dose stratified by highest CTCAE grade was constructed. TEAEs explored were: hypertension, proteinuria, decreased appetite, vomiting, hypothyroidism, diarrhoea.

Results

Population PK model

PK profiles from the 86 paediatric subjects (59 adolescents and 27 children) from Studies 207 and 216 were pooled with data from 769 adult healthy subjects and patients with cancer from Phase 1, 2 and 3 studies.

Table 6. Summary Statistics of Age and Body Weight for Subjects in PK Dataset (Pediatric Subjects)

	Variable	N	Mean	SD	Median	Min	Max
Adolescents (12 – 17 years old)	Age (year)	59	14.6	1.7	15.0	12.0	17.0
	Weight (kg)	59	52.3	13.8	50.5	25.6	95.5
Children (< 12 years old)	Age (year)	27	8.3	2.2	8.0	3.0	11.0
	Weight (kg)	27	27.1	8.6	25.5	15.7	50.3

A 3-compartment model with simultaneous zero and first-order absorption and first-order elimination from the central compartment included the following covariates was fitted to the data using non-linear effect modelling: body weight on clearances and volume parameters, healthy subjects on CL/F, albumin < 30 g/L and alkaline phosphatase (ALP) > ULN on CL/F, and capsule formulation on relative bioavailability.

Population estimates of Ka, D1 and the effect of capsule formulation on relative bioavailability (F1) were fixed with those in the previous population PK analysis in adult subjects with thyroid cancer because data to estimate them was limited in Studies 207 and 216. The theoretical values of allometric exponents (0.75 for apparent clearance and intercompartment clearances and 1.0 for volumes of distribution) were considered to have physiological basis and used in the model.

The parameter estimates, precision of the estimate and 95% confidence intervals for the lenvatinib PK model are presented in Table below.

Table 7. Parameter Estimates of lenvatinib PopPK Model (Run 011)

Parameter	NONMEM Estimates		
	Point Estimate	%RSE	95% Confidence Interval
$CL/F\ [L/h] = \Theta_{CL}*(WGT/72.6)^{\Theta WGT}*\Theta_{ALB}^{ALB}*\Theta_{ALP}^{ALP}*\Theta_{HV}^{HV}$			
Basal CL/F in L/h [Θ_{CL}]	6.39	2.83	6.04 – 6.74
Effect of Weight on CL/F [Θ_{WGT}]	0.75 FIX		
Effect of ALB(<30) on CL/F [Θ_{ALB}]	0.880	2.98	0.829 – 0.931
Effect of ALP (>ULN) on CL/F [Θ_{ALP}]	0.893	1.22	0.872 – 0.914
Effect of Healthy population on CL/F [Θ_{HV}]	1.15 FIX		
$V1/F\ [L] = \Theta_{V1}*(WGT/72.6)^{\Theta WGT}$			
Basal V1/F in L [Θ_{V1}]	49.6	2.78	46.9 – 52.3
Effect of Weight on V1/F [Θ_{WGT}]	1.00 FIX		
$V2/F\ [L] = \Theta_{V2}*(WGT/72.6)^{\Theta WGT}$			
Basal V2/F in L [Θ_{V2}]	30.0	2.62	28.5 – 31.5

Parameter	NONMEM Estimates		
	Point Estimate	%RSE	95% Confidence Interval
Effect of Weight on V2/F [Θ_{WGT}]	1.00 FIX		
V3/F [L] = Θ_{V3}*(WGT/72.6) $^{\Theta WGT}$			
Basal V3/F in L [Θ_{V3}]	39.1	2.21	37.4 – 40.8
Effect of Weight on V3/F [Θ_{WGT}]	1.00 FIX		
Q1/F [L/h] = Θ_{Q1}*(WGT/72.6) $^{\Theta WGT}$			
Basal Q1/F in L/h [Θ_{Q1}]	3.28	4.18	3.01 – 3.55
Effect of Weight on Q1/F [Θ_{WGT}]	0.75 FIX		
Q2/F [L/h] = Θ_{Q2}*(WGT/72.6) $^{\Theta WGT}$			
Basal Q2/F in L/h [Θ_{Q2}]	0.775	3.03	0.729 – 0.821
Effect of Weight on Q2/F [Θ_{WGT}]	0.75 FIX		
Ka [1/h] = Θ_{Ka}			
Basal Ka in 1/h [Θ_{Ka}]	1.02 FIX		
D1 [h] = Θ_{D1}			
Basal D1 in h [Θ_{D1}]	1.22 FIX		
F1 = Θ_{F1}			
Relative bioavailability of capsule vs tablet formulation [Θ_{F1}]	0.9 FIX		
Inter-individual variability (%CV)			
CL/F	35.1	5.46	–
V1/F	31.8	12.3	–
Ka	58.8	11.2	–
D1	77.8	8.55	–
F1	36.6	6.70	–
Residual variability			
Proportional (%CV) (Clin pharm studies)	17.5	0.767	–
Proportional (%CV) (Patients studies)	35.5	1.88	–
Proportional (%CV) (TAD ≤ 2 h)	45.4	3.67	–
Additional (ng/mL) (TAD ≤ 2 h)	12.1	2.88	–

Abbreviations: %RSE: percent relative standard error of the estimate = SE/parameter estimate * 100; FIX: Estimates fixed with the estimates from final pk model for thyroid submission (adults). The %CV for both inter-subject and proportional residual variability is an approximation taken as the square root of the variance * 100; CL/F = apparent clearance, V1/F = apparent volume of central compartment; V2/F and V3/F = apparent volume of peripheral compartment; Q1 = inter-compartment clearance between V1 and V2; Q2 = inter-compartment clearance between V1 and V3; Ka = absorption rate constant; D1 = duration of zero order absorption; F1 = relative bioavailability of capsule to tablet formulation; TAD = Time after dose; CI = confidence interval; WGT = weight (kg); ALB =albumin, 0 (≥ ALB 30 g/L) or 1 (< ALB 30 g/L); ALP = Alkaline phosphatase measurement (IU/L) 0 (ALP ≤upper limit of normal) or 1 (ALP > upper limit of normal value); HV = 0 (cancer patients) or 1 (healthy subjects)

Pooled lenvatinib PK data from Studies 207 and 216, and adult healthy subjects and patients with cancer from Phase 1, 2 and 3 studies was described by this model (run no.011).

When age was evaluated as a continuous covariate for its effect on clearance of lenvatinib, in the presence of body weight effect, it was not statistically significant.

Goodness-of-fit-plots for the PK model for all studies and Studies 207 and 216 are presented below.

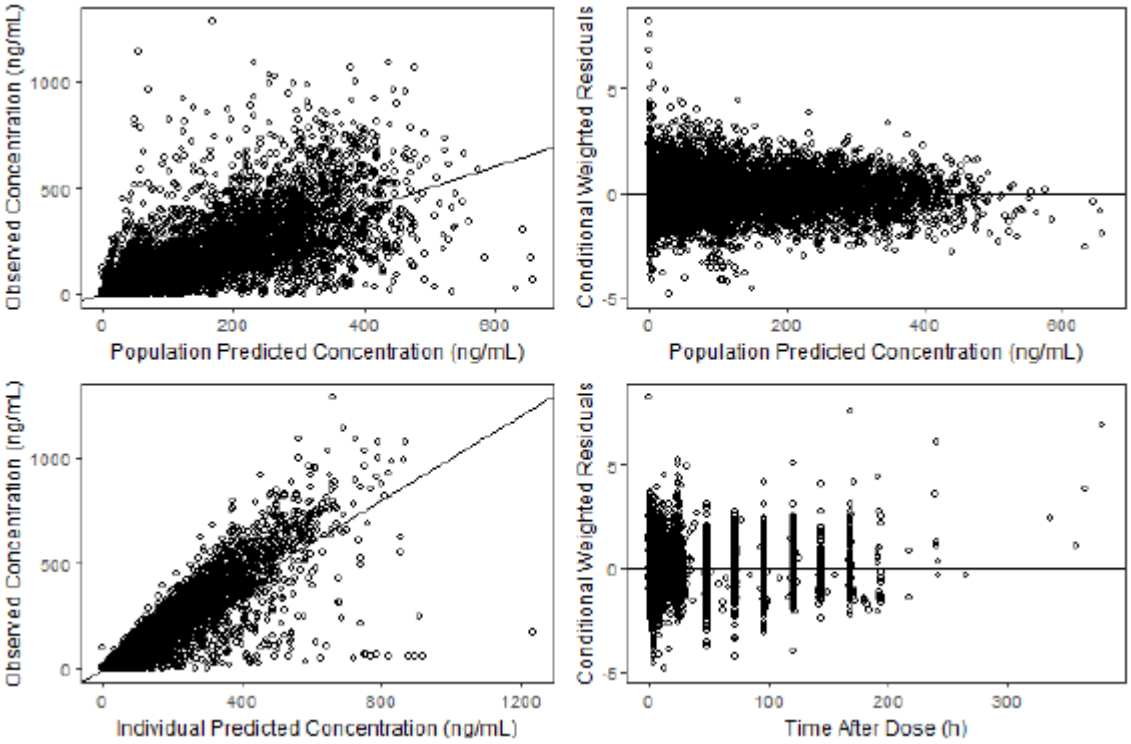


Figure 5 Goodness of Fit Plots for the PK Model for Lenvatinib (All Studies)

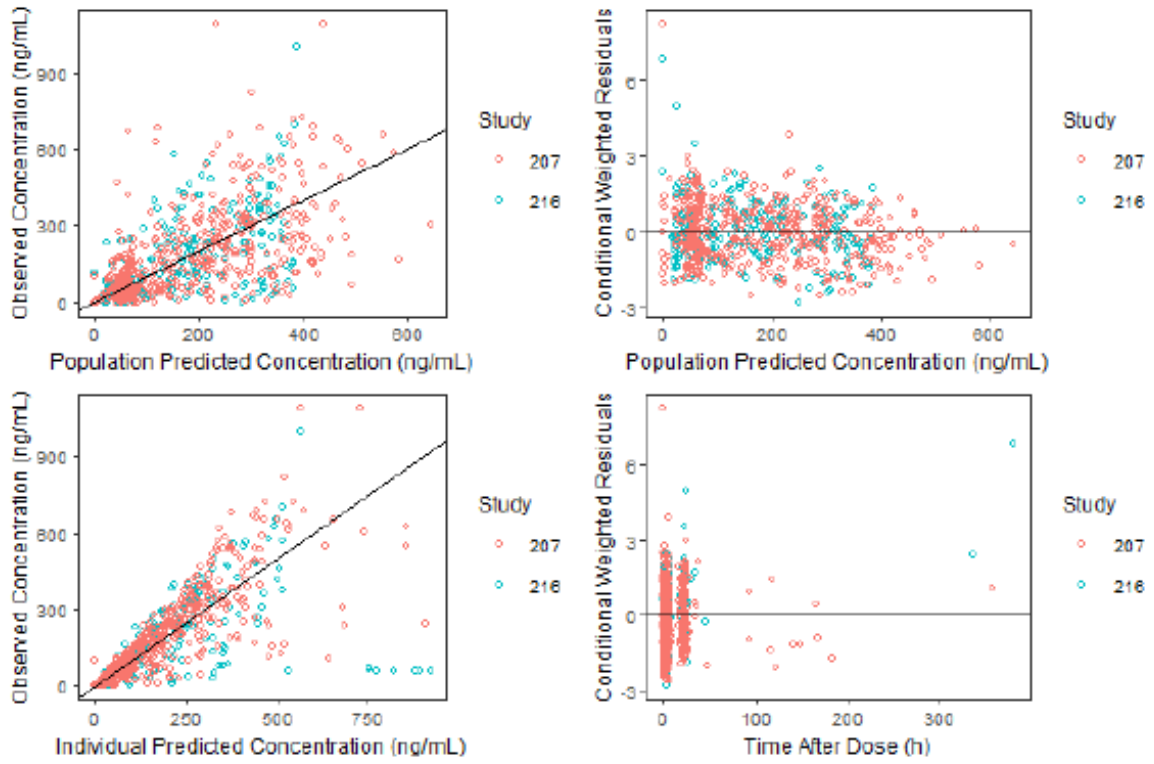


Figure 6 Goodness of Fit Plots for the PK Model for Lenvatinib (Studies 207 and 216)

Predictive performance of the final PK model was evaluated using prediction corrected visual predictive check (500 replicates). Prediction corrected visual predictive check (pcVPC) plots displayed a good agreement of simulated and observed data for Studies 207 and 216 across time, across the low, mid and high quantiles of data, showing good predictive performance of the model

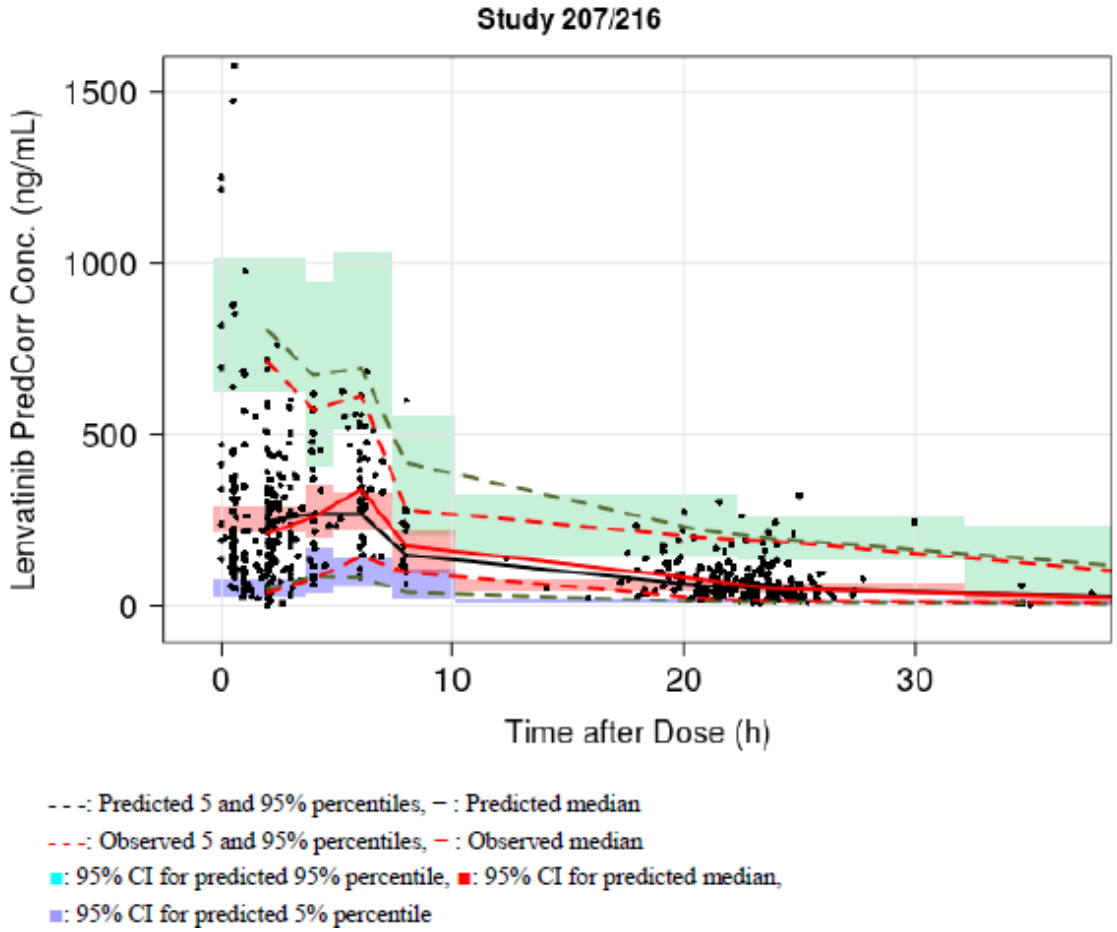


Figure 7 Prediction-Corrected Visual Predictive Check of Observed and Predicted Lenvatinib Plasma Concentration (Studies 207 and 216)

Summary of Individual Derived Pharmacokinetic Parameters of Lenvatinib for Children and Adolescents in Study 207

Individual lenvatinib AUC at steady state based on starting dose for subjects in study 207 are summarized by cohort and dose level in Figures below for Lenvatinib monotherapy (Cohort 1/2A/2B) and (Lenvatinib + Ifosfamide + Etoposide: Cohort 3A/3B), and compared with that for adult subjects who received the 24 mg lenvatinib dose (equivalent to 14 mg/m2) in Study 303. Model predicted systemic exposure levels at steady state (AUCss) are almost comparable between pediatic subjects who received the 14 mg/m2 lenvatinib dose in Study 207 and adult subjects who received the 24 mg lenvatinib dose (equivalent to 14 mg/m2) in Study 303.

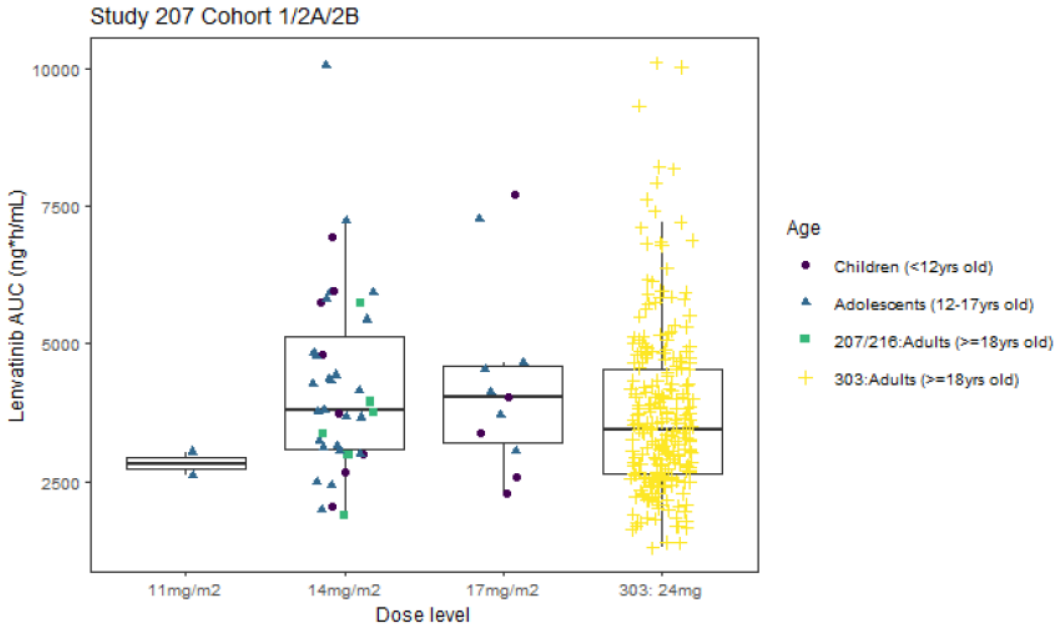


Figure 8

Boxplot of Model Predicted Lenvatinib AUC at Steady State (AUCss) Based on Starting Dose [Study 207 Cohort 1/2A/2B vs. Study 303]

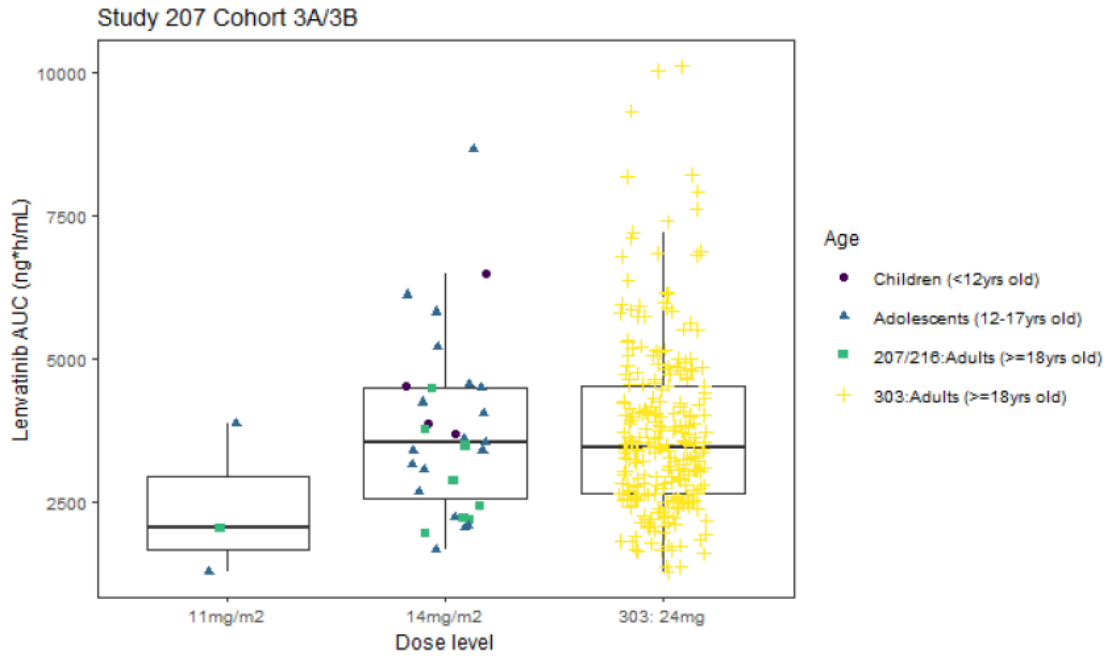


Figure 9 Boxplot of Model Predicted Lenvatinib AUC at Steady State (AUCss) Based on Starting Dose [Study 207 Cohort 3A/3B vs. Study 303]

The PK model for lenvatinib included body-weight effect on both clearance and volume parameters, whereby CL/F increased with increasing body weight. The decrease in CL/F in subjects with low body weight results in an increase in lenvatinib AUC. Lenvatinib CL/F was affected similarly by body weight and body surface area in paediatric subjects. BSA and body weight are highly correlated in paediatric subjects.

E-R efficacy analysis for Tumour Response (Study 207 Osteosarcoma)

Exposure-response (ER)analysis for tumour response was based on data from subjects with osteosarcoma of Cohort 2B/3A/3B in Study 207. No clear ER relationship could be seen.

E-R safety analysis for Individual AE (Study 207)

There appear to be some trends that subjects experienced hypertension or hypothyroidism have slightly higher AUC than subjects without them.

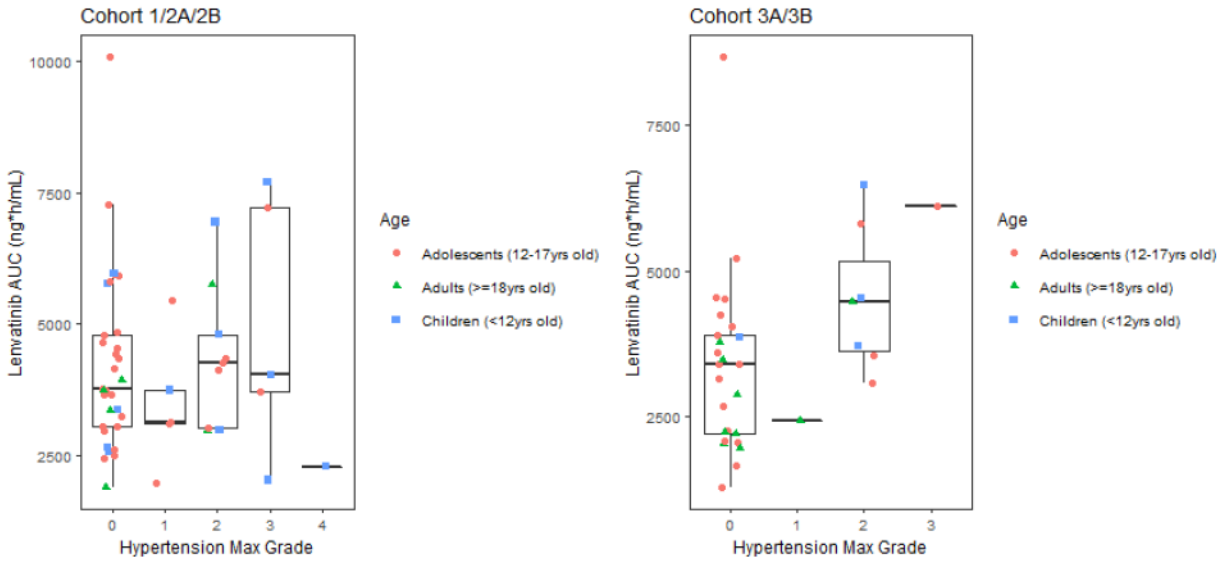


Figure 10 Boxplot of Lenvatinib AUC Based on Starting Dose by Max Grade of Hypertension (Study 207, Left: Cohort 1/2A/2B, Right: Cohort 3A/3B)

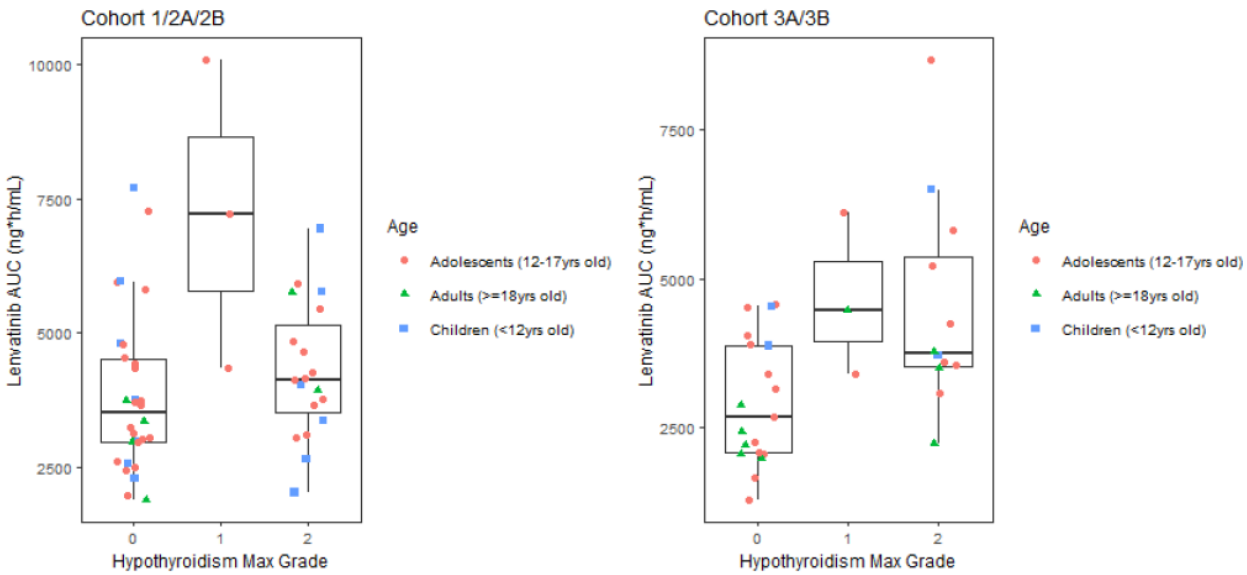


Figure 11 Boxplot of Lenvatinib AUC Based on Starting Dose by Max Grade of Hypothyroidism (Study 207, Left: Cohort 1/2A/2B, Right: Cohort 3A/3B)

Discussion on modelling and simulation analyses

The MAH characterised the pharmacokinetics of lenvatinib in paediatric population using a POPPK model, which was based on data collected in studies 207 and 216 in 86 paediatric patients (59 adolescents and 27 children). The POPPK model in adult patients was developed based on data in healthy volunteers and DTC patients. The choice of this dataset is not clearly justified. A discussion on the impact of disease/indication on the PK is lacking as well as discussion on the representativity of the data in paediatric and adult patients used for the POPPK model for the intended target population in DTC as per PIP Study 7. This is of particular relevance given that the tumour types in the paediatric dataset (mainly osteosarcoma) are different from those in the adult dataset where the initial model was developed. Bodyweight or BSA based dosing appear acceptable as these are highly correlated.

For DTC indication in paediatric patients the MAH should discuss the initial extrapolation strategy, based on PK matching, taking into account that PK data are available only in one paediatric patient with DTC. The objectives of the POPPK analyses do not clearly refer to the agreed objective for the PIP Study 7 to support the extrapolation of lenvatinib efficacy from adult to paediatric patients with DTC. The objectives specified in PIP Study 207 should be considered for the POPPK and PK/PD analyses. discussion on the representativity of the data in paediatric and adult patients used for the POPPK model for the intended target population in DTC as per PIP Study 7. **(OC)**

The MAH should discuss more in detail the rationale and the choice of the dataset for the adult POPPK model (DTC, monotherapy) and whether indication effects on PK are expected or known. The covariates chosen for the POPPK model are the same as for the model developed for adult patients, therefore assuming that that same covariate effect would be expected in the paediatric population with DTC as in adult population in DTC or in other indications. The choice of covariates should be justified specifically for paediatric patients with DTC. The choice of individual AEs for PK/PD analyses of exposure-safety in paediatric vs adult patients should be discussed based on the observed safety profiles. **(OC)**

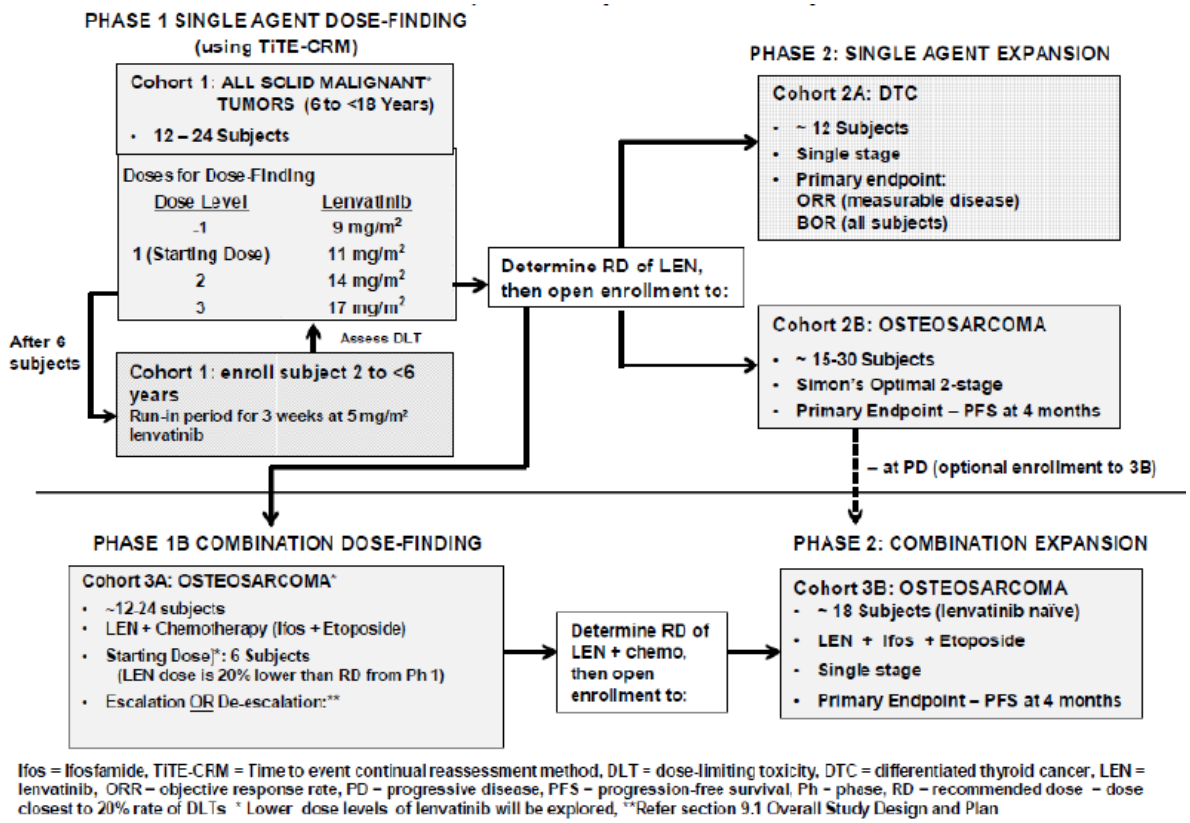
The conclusions of the MAH from the currently available POPPK analysis are generally agreed on:

- Lenvatinib oral clearance (CL/F) was affected by body weight. The decrease in CL/F in subjects with low body weight results in an increase in lenvatinib AUC. Lenvatinib CL/F was affected by body surface area with the same trend as with body weight in pediatric subjects. Thus, dosing lenvatinib by body surface area are supported by these results.
- In the presence of body weight effect, lenvatinib CL/F was not affected by age. Thus, no age-based dose adjustment is required.
- Predicted exposure levels (AUCss) in the 14 mg/m2 group in Study 207 are comparable to those in adult subjects from Study 303 receiving a fixed dose of 24 mg. 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 and hence the results support the current dosing scheme in study 207 based on BSA.
- No graphical relationship was observed in the inter-individual variability of CL/F between Cohort 3A/3B versus Cohort 1/2B/2B, therefore concomitant ifosfamide plus etoposide did not affect lenvatinib CL/F.
- No clear relationship could be seen in exposure-response analyses for tumour response.
- For exposure-response analyses for safety, there appear to be some trends that subjects experienced hypertension or hypothyroidism have slightly higher AUC than subjects without them.

2.3.4. Clinical studies

E7080-G000-207: Phase 1/2 Study of Lenvatinib in Children and Adolescents With Refractory or Relapsed Solid Malignancies and Young Adults with Osteosarcoma

Description



Ifos = Ifosfamide, TITE-CRM = Time to event continual reassessment method, DLT = dose-limiting toxicity, DTC = differentiated thyroid cancer, LEN = lenvatinib, ORR – objective response rate, PD – progressive disease, PFS – progression-free survival, Ph – phase, RD – recommended dose – dose closest to 20% rate of DLTs * Lower dose levels of lenvatinib will be explored, **Refer section 9.1 Overall Study Design and Plan

Figure 12 Study 207 design

Methods

Study participants

Inclusion Criteria

1. Histologically or cytologically confirmed diagnosis of solid malignant tumor

a. Cohort 1: **Any solid malignant tumor**

b. Cohort 2A: **DTC with one of the following histologic subtypes**:

a. Papillary thyroid cancer (PTC)

1. Follicular variant

2. Other variants (including, but not limited to, tall cell, columnar cell, cribriform-morular, solid, oxyphil, Warthin's-like, trabecular, tumor with nodular fasciitis-like stroma, Hürthle cell variant of papillary carcinoma, or poorly differentiated carcinomas)

b. Follicular thyroid cancer (FTC): 1. Hürthle cell 2. Clear cell 3. Insular

c. Cohort 2B, 3A, and 3B: **Relapsed or refractory osteosarcoma**

2. Relapsed or refractory solid tumor malignancy that has progressed on standard anticancer therapy with no available curative options. (Note: Osteosarcoma subjects must be in first or subsequent

relapse [≥ first relapse]). Only the osteosarcoma subjects enrolled to Cohorts 3A and 3B must be deemed candidates for ifosfamide and etoposide chemotherapy).

3. Evaluable or measurable disease that meets the following criteria

a. Subjects must have evaluable or measurable disease based on RECIST 1.1 using computed tomography/magnetic resonance imaging (CT/MRI)

b. Lesions that have had external beam radiotherapy (EBRT) or locoregional therapies such as radiofrequency (RF) ablation must have subsequently grown unequivocally to be deemed a target lesion

4. DTC subjects must be 131I-refractory/relapsed as defined by at least one of the following:

a. One or more evaluable or measurable lesions that do not demonstrate iodine uptake on any radioiodine scan OR

b. One or more evaluable or measurable lesions that have progressed based on RECIST 1.1, within 12 months of 131I therapy, despite demonstration of radioiodine avidity at the time of that treatment by pre- or post-treatment scanning. These subjects must not be eligible for possible curative surgery OR

c. Cumulative activity of 131I >400 millicuries (mCi) or 14.8 gigabecquerels (GBq), with the last dose administered at least 6 months prior to study entry

5. Subjects with DTC must be receiving thyroxine suppression therapy and levels of thyroid stimulating hormone (TSH) should not be elevated (TSH should be ≤5.50 mU/L). When tolerated by the subject, thyroxine dose should be changed to achieve TSH suppression (TSH <0.50 mU/L)

6. Subjects with known central nervous system (CNS) primary tumors or metastases who have completed brain therapy (such as radiotherapy, stereotactic radiosurgery, or surgical resection) and have remained clinically stable, asymptomatic, and off of steroids for 2 weeks prior to Cycle 1 Day 1 will be eligible

7. Male or female subjects age 2 years to <18 years (≤25 years for osteosarcoma subjects) at the time of informed consent

8. Lansky play score ≥50% or Karnofsky Performance Status score ≥50%. Use Karnofsky for subjects ≥ 16 years of age and Lansky for subjects <16 years of age

9. Life expectancy ≥ 3 months

10. Adequate bone marrow function as evidenced by:

a. absolute neutrophil count (ANC) ≥1.0 × 10^9/L (for Cohorts 3A and 3B leucocyte count ≥2 × 10^9/L; subjects with bone marrow involvement should have ANC ≥0.8 × 109/L and leucocyte count ≥1 × 10^9/L); b. hemoglobin ≥8.0 g/dL (a hemoglobin <8.0 g/dL is acceptable if it is corrected by growth factor or transfusion before starting lenvatinib); c. platelet count ≥ 75 × 109/L

11. Adequate liver function as evidenced by:

a. bilirubin ≤ 1.5 times the upper limit of normal (ULN)

b. alkaline phosphatase, alanine aminotransferase (ALT), and aspartate aminotransferase (AST) ≤3 × ULN (in the case of liver metastases ≤5 × ULN), unless there are bone metastases or bone primary tumor, in which case liver specific alkaline phosphatase must be separated from the total and used to assess the liver function instead of the total alkaline phosphatase

12. Adequate renal function as evidenced by:

a. Serum creatinine based on age/gender as below. If serum creatinine is greater than maximum serum creatinine for age/gender as shown in the table below, then creatinine clearance (or radioisotope glomerular filtration rate [GFR]) must be >70 mL/min/1.73 m2

Age	Maximum Serum Creatinine (mg/dL)	
	Male	Female
2 to < 6 years	0.8	0.8
6 to < 10 years	1	1
10 to < 13 years	1.2	1.2
13 to < 16 years	1.5	1.4
≥ 16 years	1.7	1.4

The threshold creatinine values in this table were derived from the Schwartz formula for estimating GFR (Schwartz, et al., 1985) using child length and stature data published by the CDC.

b. Urine dipstick <2+ for proteinuria. Subjects who have ≥2+ proteinuria on dipstick urinalysis should undergo a spot protein-creatinine (P/C) ratio that should be Grade <2 per CTCAE v4.03, and if possible, perform a 24-hour urine collection (children and adolescents ≤12 years of age must have ≤ 500 mg of protein/24 hours, and subjects >12 years of age must have ≤1 g of protein/24 hours)

c. No clinical evidence of nephrotic syndrome

13. Adequate cardiac function as evidenced by left ventricular ejection fraction (LVEF) ≥50%) at baseline as determined by echocardiography

14. Adequately controlled blood pressure (BP) with or without antihypertensive medications, defined as: a. BP <95th percentile for sex, age, and height/length at screening (as per National Heart Lung and Blood Institute [NHLBI] guidelines) and no change in antihypertensive medications within 1 week prior to Cycle 1 Day 1. Osteosarcoma subjects 18 to 25 years should have BP ≤150/90 mm Hg at screening and no change in antihypertensive therapy within 1 week prior to Cycle 1/Day 1.

15. Washout of 3 weeks in case of prior chemotherapy, 6 weeks if treatment included nitrosoureas; 4 weeks for definitive radiotherapy, and 2 weeks for palliative radiotherapy; 3 months from high-dose chemotherapy and stem cell rescue; 3 weeks from major surgery. Subjects must have recovered from the acute toxic effects of all prior anticancer therapy before enrollment into the study

16. Written and signed informed consent from the parent(s) or legal representative (guardian) and assent from the minor subject. Written informed consent from subjects ≥18 years.

17. Willing and able to comply with the protocol, scheduled follow-up, and management of toxicity as judged by the Investigator Cohort 3B (Combination Expansion): Osteosarcoma subjects who progressed in Cohorts 1 or 2B and opt to receive combination therapy:

18. Osteosarcoma subjects receiving combination therapy of lenvatinib with ifosfamide and etoposide only need to meet Inclusion Criteria Numbers 7 6 through 17 (after progression in Cohort 2B)

Exclusion Criteria

1. Any active infection or infectious illness unless fully recovered prior to dosing

2. Any medical or other condition that in the opinion of the investigator(s) would preclude the subject's participation in a clinical study

3. Other organ toxicity due to prior anticancer therapy (investigational agent, chemotherapy, or radiation therapy) except alopecia, and ototoxicity due to cisplatin not already covered in the inclusion/exclusion criteria, which has not recovered to Grade <2 per CTCAE v4.03

4. Known hypersensitivity to any component of the product (lenvatinib or ingredients)

5. Concurrent administration of any other antitumor therapy

6. Previous treatment with lenvatinib (except for subjects previously enrolled into Cohorts 1 or 2B of this study)

7. Two or more prior VEGF/VEGFR-targeted therapies

8. Currently receiving any investigational drug or device in another clinical trial or within 30 days preceding informed consent

9. A clinically significant ECG abnormality, including a marked baseline prolonged QT or QTc interval (eg, a repeated demonstration of a QTc interval >480 msec)

10. Gastrointestinal malabsorption or any other condition that in the opinion of the investigator might affect the absorption of lenvatinib

11. Gastrointestinal bleeding or active hemoptysis (bright red blood of at least ½ teaspoon) within 3 weeks prior to the first dose of study drug

12. Active second malignancy within 2 years prior to enrollment (in addition to the primary tumor types specified by cohort in Inclusion Criterion Number 1), but not including definitively treated superficial melanoma, carcinoma in-situ, basal or squamous cell carcinoma of the skin)

13. Previous treatment with ifosfamide and grade ≥3 nephrotoxicity or encephalopathy (Cohorts 3A and 3B)

14. Females who are breastfeeding or pregnant at Screening or Baseline (as documented by a positive beta-human chorionic gonadotropin [ß-hCG] (human chorionic gonadotropin [hCG]) test with a minimum sensitivity of 25 IU/L or equivalent units of ß-hCG [hCG]). A separate baseline assessment is required if a negative screening pregnancy test was obtained more than 72 hours before the first dose of study drug.

Cohort 3B (Combination Expansion): Osteosarcoma subjects who progressed in Cohorts 1 or 2B and opt to receive combination therapy:

15. Osteosarcoma subjects receiving combination therapy of lenvatinib with ifosfamide and etoposide should meet all the exclusion criteria, with the exception of Criterion Number 6

Treatments

Lenvatinib

Lenvatinib hard capsules containing 1, 4, or 10 mg lenvatinib, administered orally QD. The maximum dose administered during the study should not exceed 24 mg QD in any of the cohorts. An extemporaneous suspension of lenvatinib capsules should be used for children unable to swallow capsules.

Cohort 1 (Single-Agent Dose-Finding)

Lenvatinib administered orally QD on Days 1 to 28 of each 28-day cycle. Subjects 6 to <18 years: Lenvatinib will be administered orally QD. Study drug doses for Cohort 1 are displayed in the table below. The starting dose is 11 mg/m2 QD, which is 80% of the adult RD of 24 mg QD. The 80% starting dose is based on consensus reached for paediatric Phase 1 trials (Smith, et al., 1998; Lee, et al., 2005). If the dose of 11 mg/m2 (Dose Level 1) is not safe and tolerable, subjects will receive lenvatinib at the lower de-escalation dose of 9 mg/m2 (Dose Level -1).

Table 8. Lenvatinib Doses for Single-Agent Dose-Finding (Cohort 1)

Dose Level	Lenvatinib Once-Daily
-1	9 mg/m^2
1 (starting dose)	11 mg/m^2
2	14 mg/m^2
3	17 mg/m^2

Before dose administration on Day 1 of each cycle and prior to a change in dose due to dose reduction, the subject's dose of lenvatinib was calculated based on BSA, based on the subject's current height and body weight, as follows:

Scheduled dose (mg/m2) × BSA (m2) = lenvatinib dose (mg)

Body surface area was calculated using the method that was accepted and customarily used by the clinical site. Body surface area had to be calculated on Day 1 of each cycle based on the subject's current height and body weight and was not corrected for limb amputation. The dose was rounded to the nearest integer. After adjustment for BSA, the subject's daily dose of lenvatinib could not exceed 24 mg daily.

Subjects 2 to <6 years: Subjects will receive 5 mg/m2 during the 21-day Run-In Period. If these subjects do not experience any DLT, they will enter Cohort 1 Cycle 1 Day 1 and intrasubject dose escalation will take place as detailed in the Study Design section (Treatment Phase: Cohort 1).

Cohorts 2A and 2B (Single-Agent Expansion)

Lenvatinib administered orally QD at the single-agent RD (identified in Cohort 1) on Days 1 to 28 of each 28-day cycle to subjects with RR-DTC (Cohort 2A) or osteosarcoma (Cohort 2B).

The RD of Single-Agent lenvatinib determined in Cohort 1 was **14 mg/m2** as recommended by TiTE-CRM and confirmed by PSC.

Subjects in Cohorts 2A and 2B received 14 mg/m2 lenvatinib (equivalent to 24 mg QD, adult daily dose). After adjustment for BSA, the daily dose should not exceed 24 mg QD.

Cohort 3A (Combination Dose Finding)

Lenvatinib will be administered orally QD in combination with ifosfamide and etoposide from Day 1 to Day 3 of each cycle for a total of 5 cycles to subjects with relapsed or refractory osteosarcoma as described below. Lower doses may be administered depending on the safety information.

Table 9. Lenvatinib and Chemotherapy Doses for Combination Dose-Finding (Cohort 3A)

Dose Modification of Lenvatinib				
	Dose - Escalation	**Starting Dose**	**De-escalation 1**	**De-escalation 2**
Lenvatinib	RD (from Cohort 1)	20% lower than RD from Cohort 1	40% lower than RD from Cohort 1	60% lower than RD from Cohort 1

Dose Modification of Ifosfamide and Etoposide				
	No Dose Escalation	**Starting Dose**	**De-escalation 1***	**De-escalation 2***
Ifosfamide		3000 mg/m^2/day IV for 3 days	2400 mg/m^2/day IV for 3 days	1800 mg/m^2/day IV for 3 days
Etoposide		100 mg/m^2/day IV for 3 days	80 mg/m^2/day IV for 3 days	60 mg/m^2/day IV for 3 days

RD = recommended dose, *each De-escalation dose level is 20% lower than the Starting Dose.

The chemotherapy cycles will be repeated every 21 days.

Cohort 3B (Combination Expansion)

Subjects will receive lenvatinib at the RD determined to be safe and tolerable in Cohort 3A (Combination Dose-Finding) in combination with ifosfamide and etoposide. The chemotherapy cycles in Cohorts 3A and 3B will be repeated every 21 days.

Subjects in Cohorts 3A and 3B will receive ifosfamide and etoposide for a maximum of 5 cycles. Subjects who discontinue ifosfamide and etoposide in Cohorts 3A and 3B (e.g., due to toxicity) prior to completing 5 cycles may continue on single-agent lenvatinib if they are benefiting from the treatment at the discretion of the investigator. Subjects who discontinue lenvatinib prior to completing 5 cycles may continue on ifosfamide and etoposide at the investigator's discretion for 5 cycles.

The RD of the combination with ifosfamide and etoposide determined in Cohort 3A is lenvatinib 14 mg/m2/day + ifosfamide 3000 mg/m2/day and etoposide 100 mg/m2/day as recommended by the above rules and confirmed by the PSC.

Cohort 3B will receive lenvatinib 14 mg/m2/day + ifosfamide 3000 mg/m2/day and etoposide 100 mg/m2/day

Lenvatinib Dose Reduction and Interruption Instructions

Dose interruptions, dose reductions, or treatment discontinuation were allowed for subjects who experienced lenvatinib-related toxicity. Once the dose was reduced, it could not be increased at a later date. Doses in the Dose Adjustment column in the Table below are based on a presumed starting dose of 11 mg/m2. Dose reductions occur in succession based on the previous dose level. Each dose level reduction is a 20% reduction from the previous dose. Once the dose has been reduced, it cannot be increased at a later date.

Table 10. Criteria for Temporary Discontinuation of Study Drug, Dose Reduction, and Resumption of Treatment

Treatment-Related Toxicity[a,b] including hepatic injury and thromboembolic events	Management	Dose Adjustment
Grade 1		
	Continue treatment	No change
Intolerable Grade 2[c] or Grade 3[e]		
First occurrence	Interrupt until resolved to Grade 0-1 or baseline	8.8 mg/m^2 (or 20% reduction of the starting dose) orally once daily (QD) (one-level reduction)
Second occurrence (same toxicity or new toxicity)	Interrupt until resolved to Grade 0-1 or baseline	7.0 mg/m^2 (or 20% reduction of the previous dose) orally QD (one-level reduction)
Third occurrence (same toxicity or new toxicity)	Interrupt until resolved to Grade 0-1 or baseline	5.6 mg/m^2 (or 20% reduction of the previous dose) orally QD (one-level reduction)
Fourth occurrence (same toxicity or new toxicity)	Interrupt until resolved to Grade 0-1 or baseline	Discuss with sponsor
Grade 4[d]: Discontinue Study Treatment		

Note: For grading see Common Terminology Criteria for Adverse Events version 4.0 (Appendix 2). Collect all CTC grades of adverse events, decreasing and increasing grade.

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

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

c: Applicable only to Grade 2 toxicities judged by the subject and/or physician to be intolerable. Not applicable to abnormal clinical laboratory values that are not clinically relevant based on the judgment of the investigator.

d: Excluding laboratory abnormalities judged to be non-life-threatening, in which case manage as Grade 3.

e. Obese subjects with weight loss do not need to return to baseline or Grade 1 weight loss to restart lenvatinib. There should be no weight loss for at least 1 week, and subjects should be started at the lower dose and normal Body Mass Index (BMI) should be used for future dose reductions. Obesity is defined as body mass index (BMI) percentiles corresponding to 30 kg/m^2, related to the age of the children. (Cole TJ., et al 2000) or BMI $\geq$ the 95th percentile for children and teens of the same age and sex. (Ogden CL et al, 2002) (Appendix 9 and 10).

Management of Ifosfamide- and Etoposide-Associated Toxicity

All sites participating in this study had considerable experience with administering chemotherapy. Blood counts were closely monitored during and prior to the next cycle of chemotherapy. Chemotherapy-associated myelosuppression was managed by administration of granulocyte-colony stimulating factor (G-CSF). Pegylated G-CSF or G-CSF was to be administered at least 24 to 72 hours after completion of ifosfamide-etoposide chemotherapy; G-CSF was used until the subject's white blood cell (WBC) count was $\geq 1 \times 109$/L. Guidelines for dose modification for ifosfamide- and etoposide-associated toxicities are provided in Table 4 in the protocol.

Details of ifosfamide and etoposide dose interruptions and reductions as well as management of toxicity can be found in the Summary of Product Characteristics (SmPC) for each agent, and were

followed per local and institutional guidelines.

Objectives

Primary objectives

Cohort 1 (Single-Agent Dose-Finding)

- Identify the recommended dose (RD) of lenvatinib as a single agent in children and adolescents with relapsed or refractory solid malignant tumours

Cohort 2 (Single-Agent Expansion)

- Evaluate the activity of lenvatinib in 2 separate malignancy groups:

o Cohort 2A: 131I-refractory differentiated thyroid cancer: by objective response rate (ORR) for subjects with measurable disease and by best overall response (BOR) for all subjects.

o Cohort 2B: Relapsed or refractory osteosarcoma: by progression-free survival at 4 months (PFS-4)

Note: The tumour types under study in the Single-Agent Expansion portion of the study may be modified based on preliminary efficacy and safety signals observed in Cohort 1 of the study.

Cohort 3 (Combination Dose-Finding and Expansion)

- Cohort 3A (Combination Dose-Finding)

To identify the RD of lenvatinib in combination with ifosfamide and etoposide in osteosarcoma subjects

- Cohort 3B (Combination Expansion)

Evaluate the activity of lenvatinib in combination with ifosfamide and etoposide in osteosarcoma subjects by PFS-4

Secondary Objectives

Cohort 1 (Single-Agent Dose-Finding)

- Assess the safety and toxicity profile of lenvatinib in children and adolescents

- Evaluate the activity of lenvatinib as assessed by best overall response (BOR), objective response rate (ORR), duration of response (DOR), progression free survival (PFS), time to progression (TTP), based on RECIST 1.1, disease control rate (DCR), and clinical benefit rate (CBR)

- Examine blood and tumour biomarkers and correlate with clinical response to lenvatinib

- Determine population-based pharmacokinetic (PK) parameters of lenvatinib

- Assess the palatability and acceptability of the suspension formulation of lenvatinib

Cohort 2 (Single-Agent Expansion)

- Assess the safety and toxicity profile of lenvatinib in children and adolescents, and young adults with relapsed or refractory osteosarcoma

- Evaluate the efficacy of lenvatinib as assessed by BOR(osteosarcoma only), ORR (osteosarcoma only), DOR (measurable DTC and osteosarcoma only), PFS, TTP, DCR and CBR

- Examine blood and tumour biomarkers and correlate with clinical response to lenvatinib

- Determine population-based PK parameters of lenvatinib

- Assess the palatability and acceptability of the suspension formulation of lenvatinib Cohort 3 (Combination Dose-Finding and Expansion)

- Assess the safety and toxicity of lenvatinib in combination with ifosfamide and etoposide in children and adolescents, and young adults with relapsed or refractory osteosarcoma

- Evaluate the efficacy of lenvatinib as assessed by BOR, ORR, DOR, PFS, TTP, DCR and CBR

- Examine blood and tumor biomarkers and correlate with clinical response to lenvatinib

- Determine population-based PK parameters of lenvatinib

- Assess the palatability and acceptability of the suspension formulation of lenvatinib

Exploratory Objective

- Explore the relationship of lenvatinib exposure to clinical response in children and adolescents (assessed during Cohort 1 [Single-Agent Dose-Finding] and Cohort 2 [Single-Agent Expansion])

- Evaluate the efficacy of lenvatinib as assessed by overall survival (OS)

Cohort 3A (Combination-Therapy Dose-Finding) and 3B (Combination-Therapy Expansion)

• Assess the safety and toxicity of lenvatinib in combination with ifosfamide and etoposide in children, adolescents, and young adults with relapsed or refractory osteosarcoma

• Evaluate the efficacy of lenvatinib as assessed by best overall response (BOR), objective response rate (ORR), duration of response (DOR), progression-free survival (PFS), time to progression (TTP), disease control rate (DCR), and clinical benefit rate (CBR)

• Examine blood and tumour biomarkers and correlate with clinical response to lenvatinib

• Determine population-based pharmacokinetic (PK) parameters of lenvatinib

• Assess the palatability and acceptability of the oral suspension formulation of lenvatinib

Exploratory Objectives

• Evaluate overall survival (OS)

Outcomes/endpoints

Cohort 1 (Single-Agent Dose-Finding)

Primary Endpoint

RD based on the TiTE-CRM design.

Secondary Endpoints

- Efficacy: BOR over the treatment period, ORR, DOR, Disease Control Rate (DCR, defined as the percentage of subjects with measurable disease who have a BOR of CR or PR or stable disease (SD) or subjects with evaluable disease who have a BOR of CR or Non-CR/Non-PD. To be assigned a best overall response of SD or Non-CR/Non-PD, the time from the first administration of study drug until the date of documented SD or Non-CR/Non-PD should be ≥7 weeks), Clinical Benefit Rate (CBR, defined as the percentage of subjects with measurable disease who have a BOR of CR or PR or durable SD lasting ≥23 weeks or subjects with evaluable disease who have a BOR of CR or durable Non-CR/Non-PD lasting ≥23 weeks), PFS (defined as the time from the date of the first administration of study drug until the date of first documentation of PD or death (whichever occurs first)), TTP defined as the time from the date of the first administration of study drug until the date of first documentation of disease progression

- Safety: AEs, SAEs, clinical laboratory values, vital signs, 12-lead ECG, urine dipstick, occult blood in stool, Lansky Play Scores or Karnofsky performance status scores, physical examination findings, and height and closure of proximal tibial plates during treatment and follow-up

- Plasma lenvatinib exposure

- Assessment of blood or tumor biomarkers that correlate with clinical response to lenvatinib treatment or AEs associated with lenvatinib treatment

-Palatibility and acceptability of the suspension formulation of lenvatinib

Exploratory Endpoints

- Time to OS defined as the time from the date of the first administration of study drug until the date of death from any cause. Subjects who are lost to follow-up and those who are alive at the date of data cutoff will be censored at the date the subject was last known to be alive (or the data cutoff date).

Cohort 2

Primary Endpoints

- Cohort 2A: DTC: ORR (CR + PR) for subjects with measurable disease and BOR for all subjects based on RECIST 1.1

- Cohort 2B: Osteosarcoma: PFS-4, ie, the proportion of subjects who are alive and free of disease progression at 4 months after the first dose based on RECIST 1.1

The PFS-4 rate will be calculated using PFS-4 evaluable subjects. These are defined as follows.

PFS-4 evaluable subjects:

• includes subjects who were treated with study medication at least 16 weeks;

• includes subjects who died or radiologically progressed within 16 weeks after the first administration of study medication. These subjects are not considered free of progression at 4 months;

• includes subjects who received anticancer treatment within 16 weeks after the first administration of study medication. These subjects are not considered free of progression at 4 months;

• excludes those who discontinue the study due to AE or reasons other than disease progression, death, or receiving anticancer treatment within 16 weeks after the first administration of study medication;

• excludes subjects administered any study medication with no baseline or no postbaseline tumor assessments.

Secondary Endpoints

- Efficacy

o BOR over the treatment period (osteosarcoma group)

o ORR (measurable osteosarcoma group)

o DOR (measurable DTC and osteosarcoma group)

o Disease Control Rate (DCR) defined as the percentage of subjects with measurable disease who have a BOR of CR or PR or stable disease (SD) or subjects with evaluable disease who have a BOR of CR or Non-CR/Non-PD. To be assigned a best overall response of SD or Non-CR/Non-PD, the time from the

first administration of study drug until the date of documented SD or Non-CR/Non-PD should be ≥7 weeks.

o Clinical Benefit Rate (CBR) defined as the percentage of subjects with measurable disease who have a BOR of CR or PR or durable SD lasting ≥23 weeks or subjects with evaluable disease who have a BOR of CR or durable Non-CR/Non-PD lasting ≥23 weeks

o PFS defined as the time from the date of first administration of study drug to the date of first documentation of disease progression or date of death, whichever occurs first

o TTP defined as the time from the date of the first administration of study drug until the date of first documentation of disease progression

- Safety AEs, SAEs, clinical laboratory values, vital signs, 12-lead ECGs, urine dipstick, occult blood in stool, Lansky play scores or Karnofsky performance status scores, physical examination findings, and height and closure of proximal tibial plates during treatment and follow-up

- Plasma lenvatinib exposure parameters

- Assessment of blood or tumor biomarkers that correlate with clinical response to lenvatinib treatment or AEs associated with lenvatinib treatment

- Palatibility and acceptability of the suspension formulation of lenvatinib

Exploratory Endpoints

o Time to OS

Cohort 3

Primary Endpoint

- Cohort 3A: RD of the combination treatment (lenvatinib + etoposide + ifosfamide)

- Cohort 3B: PFS-4, ie, the proportion of subjects who are alive and free of disease progression 4 months after the first dose based on RECIST 1.1

The PFS-4 rate will be calculated using PFS-4 evaluable subjects. These are defined as follows.

PFS-4 evaluable subjects:

• includes subjects who were treated with study medication at least 18 weeks

• includes subjects who died or radiologically progressed within 18 weeks after the first administration of study medication. These subjects are not considered free of progression at 4 months.

• includes subjects who received anticancer treatment within 18 weeks after the first administration of study medication. These subjects are not considered free of progression at 4 months.

• excludes those who discontinue the study due to AE or other reasons than disease progression, death, or receiving anticancer treatment within 18 weeks after the first administration of study medication

• excludes subjects administered any study medication but had no baseline or no postbaseline tumour assessments.

Secondary Endpoints

- Efficacy

o BOR over the treatment period

o ORR (measurable osteosarcoma group)

o DOR

o Disease Control Rate (DCR) defined as the percentage of subjects with measurable disease who have a BOR of CR or PR or stable disease (SD) or subjects with evaluable disease who have a BOR of CR or Non-CR/Non-PD. To be assigned a best overall response of SD or Non-CR/Non-PD, the time from the first administration of study drug until the date of documented SD or Non-CR/Non-PD should be ≥7 weeks.

o Clinical Benefit Rate (CBR) defined as the percentage of subjects with measurable disease who have a BOR of CR or PR or durable SD lasting ≥23 weeks or subjects with evaluable disease who have a BOR of CR or durable Non-CR/Non-PD lasting ≥23 weeks

o PFS defined as the time from the date of first administration of study drug to the date of first documentation of disease progression or date of death, whichever occurs first

o TTP defined as the time from the date of the first administration of study drug until the date of first documentation of disease progression

-Safety

o AEs, SAEs, clinical laboratory values, vital signs, 12-lead ECGs, urine dipstick, occult blood in stool, Lansky play scores or Karnofsky performance status scores, physical examination findings, and height and closure of proximal tibial plates during treatment and follow-up

- Plasma lenvatinib exposure parameters

- Assessment of blood or tumor biomarkers that correlate with clinical response to lenvatinib treatment or AEs associated with lenvatinib treatment

- Palatability and acceptability of the suspension formulation of lenvatinib

Exploratory Endpoints

o Time to OS

Sample size

Approximately 69 to 108 subjects were planned for this study.

Cohort 1 (Single-Agent Dose-Finding)

Approximately 12 to 24 subjects based on TiTE-CRM algorithm (Cheung and Chappell, 2000).

Cohort 2 (Single-Agent Expansion)

Approximately 27 to 42 subjects: DTC group (12 subjects) and osteosarcoma group (15 to 30 subjects).

Cohort 2A: DTC Group

Approximately 12 subjects with evaluable or measurable disease were planned to be enrolled in Cohort 2A due to limited number of pediatric patients with DTC.

Cohort 2B: Osteosarcoma Group

A minimum of 15 PFS-4 evaluable subjects will be assessed in cohort 2B. The sample size estimates were based on Simon's Optimal Two-Stage Design (Simon, 1989). If fewer than 5 subjects who are

alive and free of disease progression at 4 months after first dose date are observed among the 15 evaluable subjects in Stage I, accrual in the cohort will be suspended.

Otherwise, if at any time during Stage I of the cohort, at least 5 subjects who are alive and free of disease progression at 4 months after first dose date are recorded among the 15 evaluable subjects, enrollment in the cohort will continue seamlessly for a total of approximately 27 evaluable subjects. If, at the end of the second stage for the cohort, at least 10 subjects who are alive and free of disease progression at 4 months are recorded among the 27 subjects in the cohort, study drug will be considered active in the population.

The above sample size estimates are based on the following assumptions: the null hypothesis PFS-4 (H0) is $\leq$ 25%, and the alternative hypothesis PFS-4 (H1) is $\geq$ 45%. One-sided Type I error (α) = 0.1, and power = 80%. To account for nonevaluable subjects, a total of 15-30 osteosarcoma subjects will be enrolled for Cohort 2B.

Cohort 3 (Combination Dose-Finding and Expansion)

Cohort 3A (Combination Dose-Finding)

Approximately 12 to 24 osteosarcoma subjects for whom ifosfamide and etoposide are considered a treatment option

Cohort 3B (Combination Expansion)

With the following assumptions: p0=25%, p1=50%, 1-sided α=10%, β=20%, where p0 is an unacceptable rate of PFS, p1 is the target rate of PFS, α is the probability of declaring lenvatinib effective when the true rate is p0, and β is the probability of declaring lenvatinib not effective if the true rate is p1, a sample size of 15 subjects will provide a statistical power of 80%. To account for nonevaluable subjects, a total of 18 lenvatinib-naïve subjects will be enrolled for Cohort 3B, along with some subjects enrolled from Cohorts 1 and 2B.

Randomisation and blinding (masking)

The study is open-label.

Statistical Methods

Efficacy will be evaluated based on the as-treated population (Safety Analysis Set).

The Safety Analysis Set is defined as subjects who receive any study drug.

The Pharmacokinetic Analysis Set is defined as subjects in Safety Analysis Set who have at least 1 measurable postdose plasma concentration with an adequately documented dosing history. Pharmacokinetic data will be summarized using n, mean, standard deviation, coefficient of variation (% CV), geometric mean, median, minimum and maximum. Survival data (PFS and OS) will be estimated using Kaplan-Meier methods.

Each cohort will have its own cutoff date for the final analysis for CSR reporting purposes.

For Cohorts 1 and 3A, the data cutoff will occur when the RD is determined and the last enrolled subject completes 6 cycles of treatment or discontinues before the end of Cycle 6, whichever occurs first or pending discussion with the PSC.

For DTC and osteosarcoma subjects in Cohorts 2A, 2B, and 3B, the cutoff will be after all subjects enrolled have either completed 6 cycles or have discontinued treatment before the end of Cycle 6, whichever occurs first.

Table 11. Summary of Efficacy Analyses

Efficacy Variable	Analysis Set	Statistical Method	Tumor Assessments
PFS-4	Full Analysis Set, Per Protocol Analysis Set	Number (percent) of subjects who are alive, free of disease progression, and did not receive anticancer medication 4 months after the first dose, and its exact 80 and 95% CIs using method of Clopper and Pearson. Cohort 2B: PFS-4 rate will be tested using a Null hypothesis that PFS-4 is ≤25% tested against the alternative hypothesis of a PFS-4 ≥45%, using the 1-sample exact test of a single proportion, at the 1-sided 0.1 level. Cohort 3B: PFS-4 rate will be tested using a Null hypothesis that PFS-4 is ≤25% tested against the alternative hypothesis of a PFS-4 ≥50%, using the 1-sample exact test of a single proportion, at the 1-sided 0.1 level.	Investigator
ORR	Full Analysis Set, Per Protocol Analysis Set	Number (percent) of subjects (with PR + CR) and its exact 95% CI using method of Clopper and Pearson.	Investigator
PFS	Full Analysis Set, Per Protocol Analysis Set	KM method: Median, Q1, and Q2 PFS will be presented, with 2-sided 95% CIs (Brookmeyer and Crowley). Cumulative probability of PFS at 4 and 12 months will be presented with 2-sided 80 and 95% CIs (Greenwood using the log-log). KM plot will also be provided.	Investigator
OS	Full Analysis Set	KM method: Median, Q1, and Q2 OS, and cumulative probability of OS at 4 and 12 months will be presented. 2-sided 95% CIs (Brookmeyer and Crowley for quartiles and Greenwood using log-log for probability of 4 and 12 Months). KM plot will also be provided.	Not Applicable
BOR	Full Analysis Set, Per Protocol Analysis Set	Number (percent) and 95% exact CIs will be provided for each BOR category	Investigator
DOR	Full Analysis Set, Per Protocol Analysis Set	KM method: Median, Q1, and Q2 PFS will be presented, with 2-sided 95% CIs (Brookmeyer and Crowley).	Investigator
TTP	Full Analysis Set, Per Protocol Analysis Set	Kaplan-Meier method: Median, Q1, and Q2 TTP will be presented with 2-sided 95% CIs (Brookmeyer and Crowley). Cumulative probability of TTP at 4 and 12 months will be presented with 2-sided 80 and 95% CIs (Greenwood using log-log). Kaplan-Meier plot will also be provided.	Investigator
DCR	Full Analysis Set	Number (percent) of subjects (measurable disease with CR + PR + stable disease [SD] ≥ 7 weeks, evaluable disease with CR + Non-CR/Non-PD ≥ 7 weeks) and its exact 95% CI using method of Clopper and Pearson.	Investigator
CBR	Full Analysis Set	Number (percent) of subjects (measurable disease with CR+ PR + SD≥ 23weeks, evaluable disease with CR + Non-CR/Non-PD ≥ 23 weeks) and its exact 95% CI using method of Clopper and Pearson.	Investigator

Results

Participant flow

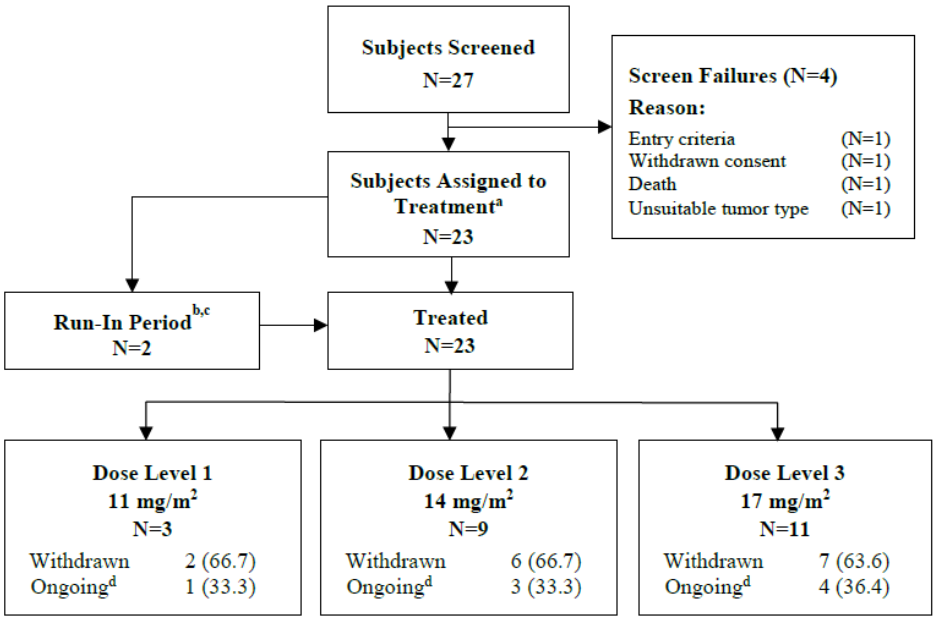


Figure 13 Subject Disposition and Primary Reason for Withdrawal from the Study by Dose Group – Cohort 1 (Single-Agent Dose-Finding), Full Analysis Set.

Clinical cutoff date: 31 Mar 2017. a: Subjects who were confirmed to meet eligibility criteria specified by the protocol. b: Subjects 2 to <6 years of age were required to enter a 3-week Run-In Period and receive 5 mg/m2 to confirm tolerability prior to being assigned to 1 of 3 dose levels in Cohort 1. c: Two subjects entered the Run-In Period; 1 was enrolled at the 11 mg/m2 and 1 at the 14 mg/m2 dose level in Cohort 1 in the Treatment Phase. d: Refers to subjects still receiving study drug or in survival follow-up as of the cutoff date. Source: Table 14.1.1.3 and Listing 16.2.1.1.1.

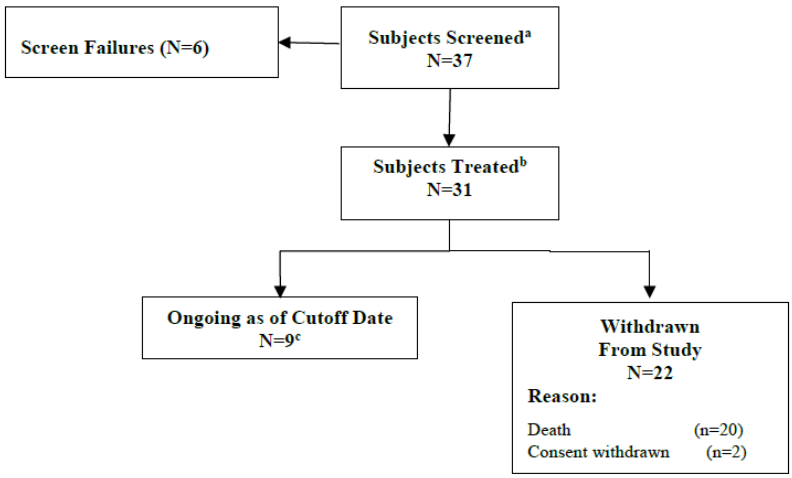


Figure 14 Subject Disposition and Primary Reason for Withdrawal from the Study – Cohort 2B (Single-Agent Expansion in Osteosarcoma), Full Analysis Set.

Clinical cutoff date: 02 Aug 2018 (Cohort 2B). **No subjects with differentiated thyroid cancer enrolled in Cohort 2A prior to the cutoff date**. Therefore, only subjects from Cohort 2B (osteosarcoma) are included. a: Subjects who were confirmed to meet eligibility criteria specified by the protocol. b: All subjects in Cohort 2B were

assigned to the 14 mg/m2 dose level. c: Refers to subjects who were still receiving study drug or who were in survival follow-up a of the cutoff date. Source: Table 14.1.1.3B and Listing 16.2.1.1.1B.

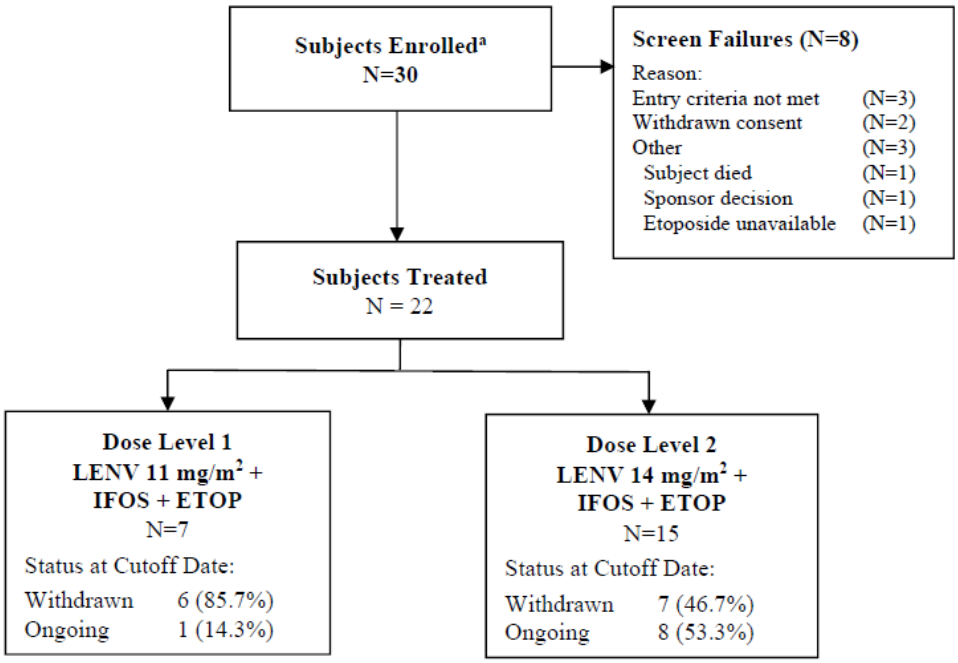


Figure 15 Subject Disposition and Primary Reason for Withdrawal from the Study by Dose Level – Combination-Therapy Cohort 3A (Dose-Finding), Full Analysis Set.

Data cutoff date: 03 Jun 2019 (Cohort 3A). Ifosfamide (IFOS) 3000 mg/m² and etoposide (ETOP) 100 mg/m2 were administered IV on Days 1 to 3 of each 21-day cycle for 5 cycles in addition to lenvatinib once daily on all days of each cycle. IV = intravenous(ly), LENV = lenvatinib. a: Subjects who signed informed consent and were confirmed to have met eligibility criteria specified by the protocol. Source: Table 14.1.3.2.1.3A and Listing 16.2.1.1.1.3A.

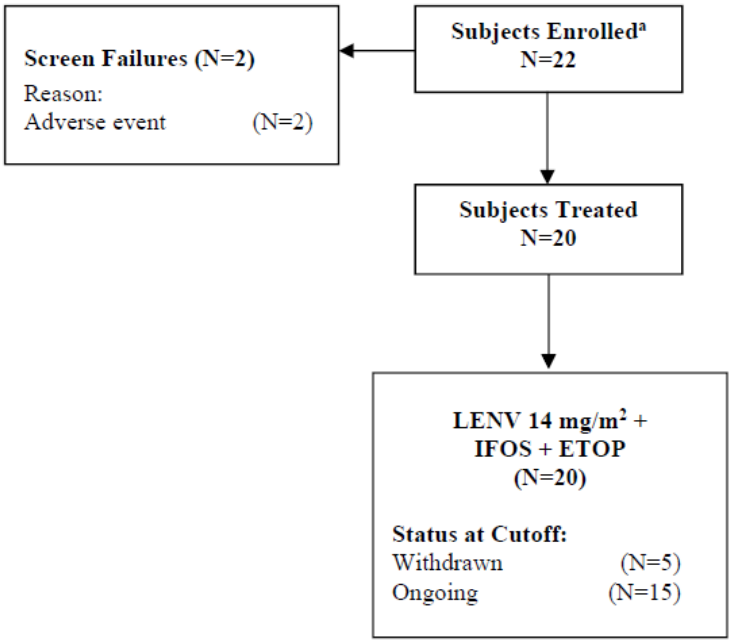


Figure 16 Subject Disposition and Primary Reason for Withdrawal from the Study – Combination-Therapy Cohort 3B (Combination Expansion), Full Analysis Set.

Data cutoff date: 18 Jul 2019. All subjects received ifosfamide (IFOS) 3000 mg/m2 and etoposide (ETOP) 100 mg/m2 IV on Days 1 to 3 of each 21-day cycle for 5 cycles in addition to lenvatinib once daily on all days of each cycle. IV = intravenous(ly), LENV = lenvatinib. a: Subjects who were confirmed to meet eligibility criteria specified by the protocol. Source: Table 14.1.3.2.2.3B and Listing 16.2.1.1.2.3B.

Recruitment

Study Period for Single-Agent Cohorts

Multicenter: Subjects enrolled at 13 sites, 1 site in the US and 12 sites among 5 European countries (France, Germany, Italy, Spain, the UK). First subject signed informed consent: 29 Dec 2014 (Cohort 1); Clinical cutoff dates for primary analysis: 31 Mar 2017 (Cohort 1), 31 May 2019 (Cohort 2A), and 02 Aug 2018 (Cohort 2B)

Study Period for Combination-Therapy Cohorts

Multicenter: Subjects enrolled at 17 sites, 1 site in the US and 16 sites among 5 European countries. First subject signed informed consent: 09 May 2016 (Cohort 3A) Data cutoff dates for primary analysis: 03 Jun 2019 (Cohort 3A) and 18 Jul 2019 (Cohort 3B)

Baseline data

Table 12. Selected Demographic and Baseline Characteristics – Single-Agent Lenvatinib Cohort 1 (Dose-Finding) and Cohort 2B (Expansion), Full Analysis Set

Parameter	Dose-Finding Phase (Cohort 1)				Expansion (Cohort 2B)
	11 mg/m² (N=3)	14 mg/m² (N=9)	17 mg/m² (N=11)	Total (N=23)	14 mg/m² (N=31)
Age					
Mean (SD)	10.7 (7.09)	11.4 (4.80)	12.0 (3.35)	11.6 (4.27)	14.9 (3.27)
Median	12.0	15.0	12.0	12.0	15.0
Min, Max	3, 17	5, 17	6, 17	3, 17	9, 22
Age category					
2 – <6 years	1 (33.3)	1 (11.1)	0	2 (8.7)	0
6 – <18 years	2 (66.7)	8 (88.9)	11 (100.0)	21 (91.3)	24 (77.4)
6 – <12 years	0	3 (33.3)	5 (45.5)	8 (34.8)	4 (12.9)
12 – <16 years	1 (33.3)	4 (44.4)	4 (36.4)	9 (39.1)	14 (45.2)
16 – <18 years	1 (33.3)	1 (11.1)	2 (18.2)	4 (17.4)	6 (19.4)
18 – 25 years	0	0	0	0	7 (22.6)
Sex, n (%)					
Male	2 (66.7)	4 (44.4)	6 (54.5)	12 (52.2)	13 (41.9)
Female	1 (33.3)	5 (55.6)	5 (45.5)	11 (47.8)	18 (58.1)
Race, n (%)					
White	2 (66.7)	5 (55.6)	3 (27.3)	10 (43.5)	20 (64.5)
Other[a]	0	0	1 (9.1)	1 (4.3)	2 (6.5)
Missing	1 (33.3)	4 (44.4)	7 (63.6)	12 (52.2)	9 (29.0)
Ethnicity					
Hispanic or Latino	1 (33.3)	1 (11.1)	2 (18.2)	4 (17.4)	4 (12.9)
Not Hispanic or Latino	1 (33.3)	4 (44.4)	4 (36.4)	9 (39.1)	15 (48.4)
Missing	1 (33.3)	4 (44.4)	5 (45.5)	10 (43.5)	12 (38.7)
Lansky Play Score, n (%)					
60	0	0	0	0	1 (3.2)
70	0	1 (11.1)	1 (9.1)	2 (8.7)	2 (6.5)
80	0	3 (33.3)	3 (27.3)	6 (26.1)	4 (12.9)
90	0	1 (11.1)	3 (27.3)	4 (17.4)	10 (32.3)
100	2 (66.7)	3 (33.3)	2 (18.2)	7 (30.4)	1 (3.2)
Missing	1 (33.3)	1 (11.1)	2 (18.2)	4 (17.4)	13 (41.9)
KPS score, n (%)					
70	0	0	0	0	1 (3.2)
80	0	0	0	0	1 (3.2)
90	0	0	0	0	5 (16.1)
100	0	0	2 (18.2)	2 (8.7)	6 (19.4)
Missing	3 (100.0)	9 (100.0)	9 (81.8)	21 (91.3)	18 (58.1)
BSA (m²)					
Mean (SD)	1.2 (0.51)	1.2 (0.47)	1.2 (0.37)	1.2 (0.41)	1.5 (0.32)
Median	1.3	1.4	1.2	1.3	1.5
Min, Max	0.6, 1.6	0.7, 2.1	0.7, 1.9	0.6, 2.1	0.9, 2.1

Clinical cutoff dates: 31 Mar 2017 (Cohort 1) and 02 Aug 2018 (Cohort 2B).

Table 13. Baseline Disease Characteristics – Single-Agent Lenvatinib

Cohort 1 (Dose-Finding) and Cohort 2B (Expansion), Full Analysis Set

	Dose-Finding Phase (Cohort 1)				Expansion (Cohort 2B)
	11 mg/m² (N=3)	14 mg/m² (N=9)	17 mg/m² (N=11)	Total (N=23)	14 mg/m² (N=31)
Time From First Solid Tumor Diagnosis to First Dose, mo					
Mean (SD)	17.0 (7.33)	29.3 (17.43)	46.3 (38.24)	35.8 (30.01)	30.9 (22.77)
Median	17.5	28.0	36.5	28.0	23.5
Min, Max	9.4, 24.0	6.2, 55.6	8.1, 124.5	6.2, 124.5	8.0, 97.6
Time From Diagnosis of Metastatic Disease to First Dose, mo					
Mean (SD)	6.7 (4.71)	13.0 (11.53)	30.0 (21.53)	20.6 (19.05)	20.3 (22.31)
Median	9.2	9.2	31.9	10.7	10.3
Min, Max	1.3, 9.7	0.4, 34.3	8.1, 64.2	0.4, 64.2	0.9, 90.2
Age at Cancer Diagnosis, y					
Mean (SD)	9.3 (6.66)	9.0 (5.66)	8.2 (4.24)	8.7 (4.90)	12.4 (2.50)
Median	11.0	12.0	8.0	10.0	13.0
Min, Max	2.0, 15.0	1.0, 16.0	2.0, 15.0	1.0, 16.0	7.0, 19.0
Solid Tumor Type, n (%)					
Rhabdomyosarcoma	1 (33.3)	0	1 (9.1)	2 (8.7)	—
Neuroblastoma	0	0	3 (27.3)	3 (13.0)	—
Ewing sarcoma	0	3 (33.3)	1 (9.1)	4 (17.4)	—
Osteosarcoma	1 (33.3)	0	0	1 (4.3)	31 (100.0)
Other	1 (33.3)	6 (66.7)	6 (54.5)	13 (56.5)[a]	—
Target Lesion, n (%)					
Non-lymph node	3 (100.0)	9 (100.0)	10 (90.9)	22 (95.7)	29 (93.5)
Lymph node	0	1 (11.1)	1 (9.1)	2 (8.7)	5 (16.1)
Tumor Grade					
Gx	0	0	1 (9.1)	1 (4.3)	4 (12.9)
G1	0	0	0	0	0
G2	0	0	0	0	2 (6.5)
G3	0	0	2 (18.2)	2 (8.7)	4 (12.9)
G4	0	2 (22.2)	2 (18.2)	4 (17.4)	9 (29.0)
Unknown	3 (100.0)	7 (77.8)	6 (54.5)	16 (69.6)	12 (38.7)

Clinical cutoff dates: 31 Mar 2017 (Cohort 1) and 02 Aug 2018 (Cohort 2B).
Data for Cohorts 1 and 2B are presented in the same table for convenience and not for comparison purposes.
Percentages based on total number of subjects within relevant treatment group in the Full Analysis Set.
Max = maximum, Min = minimum.
a: "Other" includes 3 subjects with alveolar rhabdomyosarcoma.
Source: Table 14.1.4.1.2 (Cohort 1) and Table 14.1.4.1.2B (Cohort 2B).

Table 14. Previous Anticancer Medications – Single-Agent Lenvatinib Cohort 1 (Dose-Finding) and Cohort 2B (Expansion), Full Analysis Set

	Lenvatinib Dose-Finding Phase (Cohort 1)				Expansion (Cohort 2B)
	11 mg/m² (N=3)	14 mg/m² (N=9)	17 mg/m² (N=11)	Total (N=23)	14 mg/m² (N=31)
Neoadjuvant	2 (66.7)	3 (33.3)	4 (36.4)	9 (39.1)	23 (74.2)
Consolidation	0	2 (22.2)	1 (9.1)	3 (13.0)	1 (3.2)
Maintenance	0	4 (44.4)	3 (27.3)	7 (30.4)	2 (6.5)
Previous Anticancer Agents Used by >20% of Subjects in Either Cohort, n (%)[c,d]					
Doxorubicin	1 (33.3)	7 (77.8)	8 (72.7)	16 (69.6)	30 (96.8)
Ifosfamide	2 (66.7)	8 (88.9)	6 (54.5)	16 (69.6)	27 (87.1)
Vincristine	1 (33.3)	5 (55.6)	10 (90.9)	16 (69.6)	0
Temozolomide	0	4 (44.4)	8 (72.7)	12 (52.2)	1 (3.2)
Cyclophosphamide	0	4 (44.4)	7 (63.6)	11 (47.8)	3 (9.7)
Irinotecan	1 (33.3)	3 (33.3)	7 (63.6)	11 (47.8)	1 (3.2)
Etoposide	1 (33.3)	5 (55.6)	4 (36.4)	10 (43.5)	19 (61.3)
Carboplatin	0	3 (33.3)	4 (36.4)	7 (30.4)	2 (6.5)
Cisplatin	1 (33.3)	1 (11.1)	5 (45.5)	7 (30.4)	31 (100.0)
Dactinomycin	1 (33.3)	1 (11.1)	4 (36.4)	6 (26.1)	0
Topotecan	0	2 (22.2)	4 (36.4)	6 (26.1)	0
Docetaxel	2 (66.7)	3 (33.3)	0	5 (21.7)	10 (32.3)
Gemcitabine	2 (66.7)	3 (33.3)	0	5 (21.7)	11 (35.5)
Methotrexate	1 (33.3)	0	1 (9.1)	2 (8.7)	30 (96.8)
Mifamurtide	0	0	0	0	7 (22.6)

Clinical cutoff dates: 31 Mar 2017 (Cohort 1) and 02 Aug 2018 (Cohort 2B). Table does not include data for subjects who received prior anti-VEGF agents. Rows containing only zeroes are omitted from the intext table. Data for Cohorts 1 and 2B are presented in the same table for convenience and not for comparison purposes. Percentages based on total number of subjects within relevant treatment group in the Full Analysis Set. Previous therapy excluded radiotherapy and surgery. Max = maximum, Min = minimum, VEGF = vascular endothelial growth factor. a: Subjects with no record of prior therapy regimen were categorized into zero regimen. b: Based on subjects who received previous anticancer medications. c: Subjects could be counted in multiple categories. d: Incidence of ≥20% in either Cohort 1 or Cohort 2B overall. Sorted by descending frequency overall in Cohort 1. e: Three subjects from Cohort 1 are excluded from this table. Two subjects in Cohort 1 had undergone only prior anticancer procedures. The third subject received only prior sorafenib, an anti-VEGF agent. Source: Table 14.1.4.2.4 (Cohort 1) and Table 14.1.4.2.4B (Cohort 2B).

No subjects in Cohort 1 or Cohort 2B had received prior radioiodine treatment.

Prior Radiation Therapy

In Cohort 1, 19 (82.6%) of the 23 subjects received prior radiation therapy. The median time since last radiotherapy regimen to the first dose of study drug was 7.3, 11.7, and 16.6 months for the 11 mg/m2, 14 mg/m2, and 17 mg/m2 dose levels, respectively. The most frequent site of radiation was the bone (n=8), followed by the brain (n=5). A total of 13 subjects (56.5%) had disease progression at the tumor site following radiotherapy.

In Cohort 2B, 10 (32.3%) of the 31 subjects received prior radiation therapy. The median time since last radiotherapy regimen to the first dose of study drug was 3.9 months. Five subjects received radiation to the bone, and 5 to the viscera, including the lung. The same proportion of subjects had or did not have PD at the tumor site following prior radiotherapy (n=5, 16.1%).

Table 15. Selected Demographic and Baseline Characteristics –Combination-Therapy Cohort 3A (Dose-Finding) and Cohort 3B (Expansion), Full Analysis Set

	Dose-Finding (Cohort 3A)			Expansion (Cohort 3B)
	LENV 11 mg/m² + IFOS+ETOP (N=7)	LENV 14 mg/m² + IFOS+ETOP (N=15)	Total (N=22)	LENV 14 mg/m² + IFOS+ETOP (N=20)
Age				
Mean (SD)	15.1 (3.63)	14.2 (4.74)	14.5 (4.35)	15.8 (4.05)
Median	15.0	14.0	14.0	15.5
Min, Max	11, 20	5, 25	5, 25	7, 23
Age Group				
2 – <6 years	0	1 (6.7)	1 (4.5)	0
6 – <18 years	5 (71.4)	11 (73.3)	16 (72.7)	15 (75.0)
6 – <12 years	1 (14.3)	2 (13.3)	3 (13.6)	2 (10.0)
12 – <16 years	3 (42.9)	8 (53.3)	11 (50.0)	8 (40.0)
16 – <18 years	1 (14.3)	1 (6.7)	2 (9.1)	5 (25.0)
18 – 25 years	2 (28.6)	3 (20.0)	5 (22.7)	5 (25.0)
Sex, n (%)				
Male	5 (71.4)	10 (66.7)	16 (68.2)	13 (65.0)
Female	2 (28.6)	5 (33.3)	7 (31.8)	7 (35.0)
Race, n (%)				
White	6 (85.7)	14 (93.3)	20 (90.9)	13 (65.0)
Other	0	0	0	3 (15.0)
Missing	1 (14.3)	1 (6.7)	2 (9.1)	4 (20.0)
Ethnicity, n (%)				
Hispanic or Latino	1 (14.3)	4 (26.7)	5 (22.7)	3 (15.0)
Not Hispanic or Latino	5 (71.4)	8 (53.3)	13 (59.1)	10 (50.0)
Missing	1 (14.3)	3 (20.0)	4 (18.2)	7 (35.0)
Lansky Play Score, n (%)				
70	0	3 (20.0)	3 (13.6)	1 (5.0)
80	2 (28.6)	4 (26.7)	6 (27.3)	2 (10.0)
90	0	1 (6.7)	1 (4.5)	2 (10.0)
100	2 (28.6)	3 (20.0)	5 (22.7)	5 (25.0)
Missing	3 (42.9)	4 (26.7)	7 (31.8)	10 (50.0)
KPS Score				
70	0	1 (6.7)	1 (4.5)	0
90	1 (14.3)	0	1 (4.5)	3 (15.0)
100	2 (28.6)	0	2 (9.1)	7 (35.0)
Missing	4 (57.1)	14 (93.3)	18 (81.8)	10 (50.0)
BSA (m²)				
Mean (SD)	1.5 (0.29)	1.5 (0.33)	1.5 (0.31)	1.6 (0.28)
Median	1.6	1.5	1.6	1.6
Min, Max	1.1, 1.9	0.8, 2.0	0.8, 2.0	0.9, 1.9

Data cutoff dates: 03 Jun 2019 (Cohort 3A) and 18 Jul 2019 (Cohort 3B). Data for Cohorts 3A and 3B are presented in the same table for convenience and not for comparison purposes. All subjects received ifosfamide (IFOS) 3000 mg/m2 and etoposide (ETOP) 100 mg/m2 IV on Days 1 to 3 of each 21-day cycle for 5 cycles in addition to lenvatinib once daily on all days of each cycle. Percentages are based on the number of subjects assigned and treated in the relevant cohorts. Rows including only zeroes are not presented in the intext table. BSA = body surface area, IV = intravenous(ly), KPS = Karnofsky Performance Status, LENV = lenvatinib, max = maximum, min = minimum. Source: Table 14.1.6.1.3A (Cohort 3A) and Table 14.1.6.2.3B (Cohort 3B).

Table 16. Baseline Disease Characteristics – Combination-Therapy

Cohort 3A (Dose-Finding) and Cohort 3B (Expansion), Full Analysis Set

	Dose-Finding (Cohort 3A)		Expansion (Cohort 3B)
	LENV 11 mg/m^2 + IFOS+ETOP (N=7)	LENV 14 mg/m^2 + IFOS+ETOP (N=15)	LENV 14 mg/m^2 + IFOS+ETOP (N=20)
Time Since First Osteosarcoma Diagnosis to First Dose of Study, mo			
Mean (SD)	19.8 (17.62)	19.9 (17.15)	22.7 (17.12)
Median	16.8	12.4	18.7
Min, Max	3.2, 53.0	2.2, 56.1	5.3, 85.7
Age at First Osteosarcoma Diagnosis, y			
Mean (SD)	13.7 (2.87)	12.5 (4.52)	13.9 (3.86)
Median	14.0	12.0	14.0
Min, Max	10.0, 18.0	4.0, 23.0	5.0, 22.0
Time Since Last Progression to First Dose of Study Drug, mo			
Mean (SD)	0.9 (0.43)	1.0 (0.55)	0.8 (0.55)
Median	0.7	1.1	0.8
Min, Max	0.4, 1.5	0.3, 2.1	0.2, 2.2
Time Since Metastatic Diagnosis to First Dose of Study Drug, mo			
Mean (SD)	10.4 (11.13)	10.3 (8.76)	11.3 (7.80)
Median	4.6	8.4	10.4
Min, Max	1.5, 28.1	0.8, 27.7	0.8, 27.8
Age at First Metastatic Osteosarcoma Diagnosis, y			
Mean (SD)	14.4 (3.69)	13.4 (5.03)	14.9 (4.08)
Median	14.0	12.5	15.0
Min, Max	10.0, 20.0	4.0, 25.0	7.0, 23.0
Site of Metastasis			
Lung only	4 (57.1)	10 (66.7)	14 (70.0)
Bone only	1 (14.3)	0	2 (10.0)
Bone + Lung	2 (28.6)	4 (26.7)	3 (15.0)

Data cutoff dates: 03 Jun 2019 (Cohort 3A) and 18 Jul 2019 (Cohort 3B).
Data for Cohorts 3A and 3B are presented in the same table for convenience and not for comparison purposes.
All subjects received ifosfamide (IFOS) 3000 mg/m^2 and etoposide (ETOP) 100 mg/m^2 IV on Days 1 to 3 of each 21-day cycle for 5 cycles in addition to lenvatinib once daily on all days of each cycle.
Percentages are based on the number of subjects assigned and treated in the relevant cohorts.
IV = intravenous(ly), LENV = lenvatinib, max = maximum, min = minimum.
Source: Table 14.1.7.1.3A (Cohort 3A) and Table 14.1.7.2.3B (Cohort 3B); Table 14.1.7.1 (Combined Cohorts 3A and 3B).

Cohort 3A (Combination Dose-Finding)

There were no clinically relevant differences in baseline characteristics between the dose levels in Cohort 3A. The median age of patients at the time of first osteosarcoma diagnosis was 14.0 years and 12.0 years for the 11 and 14 mg/m2 dose levels, respectively. Seven subjects had bone lesions at Baseline.

Cohort 3B (Combination Expansion)

The median age of patients at the time of first osteosarcoma diagnosis was 14.0 years. Five subjects

had bone lesions at Baseline

Table 17. Previous Anticancer Medications – Combination-Therapy

Cohort 3A (Dose-Finding) and Cohort 3B (Expansion), Full Analysis Set

	Dose-Finding (Cohort 3A)		Expansion (Cohort 3B)
	LENV 11 mg/m^2 + IFOS+ETOP (N=7)	LENV 14 mg/m^2 + IFOS+ETOP (N=15)	LENV 14 mg/m^2 + IFOS+ETOP (N=20)
Subjects Who Received Any Previous Anticancer Medication, n (%)	7 (100.0)	15 (100.0)	20 (100.0)
No. (%) of Previous Therapy Regimens [a]			
0	0	0	0
1	3 (42.9)	10 (66.7)	4 (20.0)
2	2 (28.6)	4 (26.7)	8 (40.0)
≥3	2 (28.6)	1 (6.7)	8 (40.0)
Best Response to Last Prior Medication [b]			
Complete response	0	1 (6.7)	0
Partial response	2 (28.6)	2 (13.3)	2 (10.0)
Stable disease	0	7 (46.7)	3 (15.0)
Progressive disease	3 (42.9)	3 (20.0)	11 (55.0)
Not evaluable	0	1 (6.7)	1 (5.0)
Unknown	2 (28.6)	1 (6.7)	3 (15.0)
Duration of Treatment With Last Prior Medication, mo			
Mean (SD)	6.2 (7.76)	8.3 (5.85)	5.2 (5.01)
Median	2.1	8.2	3.6
Min, Max	1.3, 23.0	0.1, 24.7	0.8, 20.1
Time from End of Last Medication to First Dose of Study Drug,[c] mo			
Mean (SD)	4.7 (3.57)	6.6 (10.54)	4.9 (4.66)
Median	5.5	1.7	3.5
Min, Max	0.7, 9.7	0.7, 38.7	0.2, 17.4
Type of Prior Medication,[d] n (%)			
Adjuvant	1 (14.3)	7 (46.7)	15 (75.0)
Therapeutic	4 (57.1)	7 (46.7)	9 (45.0)
Neoadjuvant	5 (71.4)	8 (53.3)	17 (85.0)
Consolidation	0	0	2 (10.0)
Maintenance	0	0	0
Unknown	0	0	2 (10.0)
Prior Anticancer Medication in ≥2 Subjects,[d,e] n (%)			
Cisplatin	7 (100.0)	15 (100.0)	19 (95.0)
Docetaxel	2 (28.6)	2 (13.3)	7 (35.0)
Doxorubicin	7 (100.0)	15 (100.0)	19 (95.0)
Etoposide	2 (28.6)	4 (26.7)	8 (40.0)
Gemcitabine	2 (28.6)	2 (13.3)	7 (35.0)
Ifosfamide	3 (42.9)	7 (46.7)	14 (70.0)
Methotrexate	7 (100.0)	14 (93.3)	19 (95.0)
Mifamurtide	2 (28.6)	3 (20.0)	6 (30.0)

Data cutoff dates: 03 Jun 2019 (Cohort 3A) and 18 Jul 2019 (Cohort 3B).
Data for Cohorts 3A and 3B are presented in the same table for convenience and not for comparison purposes.
All subjects received ifosfamide (IFOS) 3000 mg/m^2 and etoposide (ETOP) 100 mg/m^2 IV on Days 1 to 3 of each 21-day cycle for 5 cycles in addition to lenvatinib once daily on all days of each cycle.
Percentages are based on the number of subjects assigned and treated in the relevant cohorts.
IV = intravenous(ly), LENV = lenvatinib, max = maximum, min = minimum, WHO = World Health Organization.
a: Subjects with no record of prior therapy regimen were categorized as having zero regimens.
b: Best Response was summarized only for subjects who received any previous anticancer therapy.
c: Based on subjects who received previous anticancer medications.
d: Subjects could be counted in multiple categories.
e: WHO Drug Dictionary Version 2018 B2 was used to code prior medications.
Source: Table 14.1.8.1.3A (Cohort 3A) and Table 14.1.8.2.3B (Cohort 3B).

Number analysed

Cohort 1: Planned: 12 to 24, based on TiTE-CRM algorithm; Treated: 23

Cohort 2A: Planned: 12; Treated: 1

Cohort 2B: Planned: 15-30; Treated: 31

Cohort 3A: Planned: Approximately 12 to 24 subjects; Treated: 22

Cohort 3B: Planned: Approximately 18; Treated: 20

Efficacy results

Analysis sets in Cohort 3

Table 18. Data Analysis Sets – Combination-Therapy Cohort 3A (Dose-Finding) and Cohort 3B (Expansion), Full Analysis Set

	Dose-Finding (Cohort 3A)		Expansion (Cohort 3B)
	LENV 11 mg/m^2 + IFOS+ETOP n	LENV 14 mg/m^2 + IFOS+ETOP n	LENV 14 mg/m^2 + IFOS+ETOP n
Full Analysis Set[a]	7	15	20
Safety Analysis Set[b]	11	11	20
Subjects Evaluable for PFS-4[c]	6	12	15
Per Protocol Analysis Set[d]	7	12	18
Pharmacokinetic Analysis Set[e]	11	11	20
DLT Analysis Set[f]	9	9	NA
Palatability Analysis Set[g]	0	1	4

Data cutoff dates: 03 Jun 2019 (Cohort 3A) and 18 Jul 2019 (Cohort 3B). Data for Cohorts 3A and 3B are presented in the same table for convenience and not for comparison purposes. All subjects received ifosfamide (IFOS) 3000 mg/m2 and etoposide (ETOP) 100 mg/m2 IV on Days 1 to 3 of each 21-day cycle for 5 cycles in addition to lenvatinib once daily on all days of each cycle. Percentages are based on the number of subjects assigned and treated in the relevant cohorts. DLT = dose-limiting toxicity, IV = intravenous, PFS-4 = progression-free survival at Month 4. a: Full Analysis Set included all subjects who enrolled in the study. b: Safety Analysis Set included all subjects who received at least 1 dose of study drug and was based on actual dose received. Because lenvatinib dose was capped at 24 mg/day, in Cohort 3A, 3 subjects in the Safety Analysis Set were assigned to a lower dose level than that in the Full Analysis Set for the purpose of analysis. c: Subjects who were evaluable for PFS-4 either were treated for at least 18 weeks, had radiological PD, died, or received new anticancer treatment within 18 weeks after first dose, and includes those who discontinued study treatment for an AE or reason other than PD, death, or starting a new anticancer medication. d: Per Protocol Analysis Set included those subjects (1) who received at least 1 dose of assigned study drug, (2) who had no major protocol deviations, or (3) who had both baseline and at least 1 postbaseline tumor assessment. e: Pharmacokinetic Analysis Set included all subjects who received at least 1 dose of any study drug and had evaluable lenvatinib concentration data. f: DLT Analysis Set included all subjects who either (a) experienced DLT during Cycle 1 or (b) received all scheduled doses of study drug during Cycle 1 and completed Cycle 1 without having DLT. g: Subjects who received oral suspension of lenvatinib and completed at least 1 question on the Palatability Questionnaire. Source: Tables 14.1.4.1.3A and 14.2.1.1.1.3A (Cohort 3A) and Tables 14.1.4.2.3B and 14.2.1.1.2.3B (Cohort 3B).

Changes in the Conduct of the Study or Planned Analyses

The original protocol was approved on 08 May 2014. There were 4 protocol amendments.

Changes After Database Lock

The SAP was not updated to reflect the following changes to the analysis Plan

OS was changed from an exploratory to a secondary objective in Protocol Amendment 04, after the data cutoff date for this CSR, in order to align the protocol with the EU pediatric investigational plan. However, the analysis approach for overall survival remained unchanged. The analysis approach for OS remains unchanged. Protocol Amendment 04 was finalized after the data cut off for CSR

For Cohorts 3A and 3B, graphical displays of maximum tumor shrinkage in target lesions, defined as the maximum percentage change in the sum of the diameters of the target lesions at data cutoff, were prepared. Tumor resection during and posttreatment is presented in data listings.

Data for the 14 mg/m2 dose level for Cohort 3A and Cohort 3B were combined to perform exploratory pooled analyses of selected exposure and efficacy parameters.

The following were included as exploratory endpoints after finalization of the SAP:

- PFS-4 rate, PFS and OS for the pooled 14 mg/m2 lenvatinib dose level groups in Cohorts 3A and 3B
- Tumor shrinkage of target lesions in Cohorts 3A and 3B
- Tumor resection in Cohorts 3A and 3B

Table 19. Summary of Protocol Amendments

Protocol Amendment Number	Date	No. Subjects Enrolled at Time of Amendment[a]	Highlights of Major Changes
1	12 Sep 2014	0	Details added to define Grade 4 hypertension. Change in ANC level in inclusion criteria. Contraceptive period was extended in the inclusion criteria. Management of PRES added to Treatment section.
2	14 Apr 2015	3	Secondary objective of observing bone growth changed to assessing palatability of oral suspension and acceptability of study drug. Details added to dose escalation procedures for single-agent lenvatinib and combination therapy. Use of ECOG PS changed to KPS. Previous treatment with ifosfamide and neurotoxicity added to exclusion criteria. 21-day treatment cycle added for combination therapy. Details added for management of toxicity for subjects receiving combination therapy. Updates to study drug administration and permitted concomitant medications. Measurement of tibial growth plates and fecal occult blood tests added to baseline assessments.
3	01 Sep 2016	24	Different standards set for hematologic toxicity for subjects receiving combination therapy. RD for single-agent lenvatinib in Cohort 1 determined to be 14 mg/m^2, with a maximum lenvatinib dosage of 24 mg daily. Procedures added for study drug administration when subject underwent surgery. Details added regarding frequency of tumor assessments. Exploratory endpoint of OS added. Estimated number of enrolled subjects with RR-DTC reduced and subjects with osteosarcoma increased. Sites of tumor assessments were updated for subjects with RR-DTC and osteosarcoma as advised by the PSC, to align with the standard of care.
4	12 Nov 2019[b]	54	OS changed from an exploratory to a secondary objective
			Clarified the procedure for procurement of study drug for subjects continuing study treatment at the time of the data cutoff date for the primary analysis
			Clarified the timing for collection of blood samples for pharmacodynamic and biomarker analysis for subjects ongoing after the data cutoff date for the primary analysis

ANC = absolute neutrophil count, ECOG PS = Eastern Cooperative Oncology Group Performance Status, KPS = Karnofsky Performance Status, OS = overall survival, PRES = posterior reversible encephalopathy syndrome, PSC = Protocol Steering Committee, RD = recommended dose, RR-DTC = radioiodine refractory-differentiated thyroid cancer.

a: Enrollment in the study, regardless of cohort assignment.

b: Protocol Amendment 04 was finalized after the data cut off dates for this clinical study report (ie, 03 Jun 2019 for Cohort 3A and 18 Jul 2019 for Cohort 3B). Thus, ensuing changes are not reflected in the text of this report.

Cohort 1 (solid malignancies; N=23):

Primary Endpoint:

• The **RD** of lenvatinib was determined to be **14 mg/m2 QD**, based on TiTE-CRM design.

Per the protocol definition, the recommended dose level was the one with the DLT rate closest to the targeted 20%. Based on the following assumptions:

(a) a power model for the probability of DLT:

F(d, a)=(pd)exp(a)

where F(d,a) is the estimated probability of DLT at dose-level d and pd is the probability of DLT at dose d

(b) prior DLT probabilities of 0.03, 0.10, 0.20, 0.33 at the 9 mg/m2, 11 mg/m2, 14 mg/m2, and 17 mg/m2 dose levels, respectively, the final posterior probabilities of DLT derived from the TiTE-CRM model based on 20 evaluable subjects were 0.015, 0.064, 0.147, and 0.267 for the 4 dose levels, respectively.

The posterior DLT probability of the 14 mg/m2 dose level of 0.147 was the closest to the target 20% rate and 14 mg/m2 was determined to be the RD.

Dose-limiting toxicities (DLTs) were assessed during Cycle 1 in subjects enrolled in Cohort 1 (Dose-Escalation) using the TiTE-CRM schema.

Enrollment started with 2 subjects at the 11 mg/m2 dose level (Dose 1). These 2 subjects did not experience DLT; therefore, the dose level was escalated to 14 mg/m2 and an additional 4 subjects were treated with lenvatinib at this dose level without DLT.

Subsequently, the dose level was escalated to 17 mg/m2. Eleven subjects were assigned to the 17 mg/m2 dose level. Two subjects at the assigned 17 mg/m2 dose level (the 8th and 11th subjects treated at that dose level) had DLTs in Cycle 1. However, these 2 subjects received an actual lenvatinib dose of 14 mg/m2, either because of dose capping at 24 mg for high BSA or dosing error.

Concurrently, a third subject, who was younger than 6 years of age, had DLT at the 14 mg/m2 dose level. The dose level was de-escalated to 14 mg/m2, and an additional 4 subjects were assigned to this dose level. Overall, 3 subjects, all at an actual dose of 14 mg/m2, experienced DLT.

Table 20. Dose-Limiting Toxicities in Cycle 1 – Cohort 1 (Dose-Finding), Safety Analysis Set

	Lenvatinib					
Subject ID	Assigned Dose Level[a]	Actual Dosage Received	Dose-Limiting Toxicity	Grade	Study Drug Action Taken	Outcome
PPD	17 mg/m^2	14 mg/m^2	ALT increased	3→2[a]	Interruption	Unresolved
PPD	14 mg/m^2	14 mg/m^2	Hypertension	3	Dose reduction	Resolved
PPD	17 mg/m^2	14 mg/m^2	Hypertension	4	Discontinued	Resolved

Adverse events coded using MedDRA version 21.1.
Adverse events graded using CTCAE v 4.03.
ALT = alanine aminotransferase, CTCAE = Common Terminology Criteria for Adverse Events, MedDRA = Medical Dictionary for Regulatory Activities.
a: Grade 3 at onset, which improved to Grade 2 (reported as resolving) after first dose interruption, and then continued unresolved.
Source: Listings 16.2.5.1 and 16.2.7.6.

Consequently, Biostatistics performed the planned TiTE-CRM calculations to determine the RD, which was defined as the dose level that resulted in a DLT rate closest to the targeted rate of 20%. The RD of single-agent lenvatinib was determined to be 14 mg/m2.

Secondary Efficacy Endpoints:

All tumor assessments were based on investigators' assessments using RECIST 1.1.

• **ORR**: Overall (across all dose levels): **0 in 22 subjects** with measurable disease

• **Disease Control Rate**: Overall: **52%** (95% CI: 30.6, 73.2)

• **Clinical Benefit Rate**: Overall: **30%** (95% CI: 13.2, 52.9)

• **PFS**: median, **5.0 months** (95% CI: 1.6, 10.6)

◦ **Median (95% CI) follow-up time for PFS**: **9.2 months** (95% CI: 3.5, 20.2)

• **TTP**: Overall: median, **5.5 months** (95% CI: 1.6, 10.6)

Exploratory Efficacy Endpoints:

• **OS**: Overall: median, **7.7 months** (95% CI: 5.5, NE)

◦ **Median follow-up time for OS: 16.5 months** (95% CI: 14.2, 21.3)

• **Tumour Resection**: 2 subjects had resection of nontarget lesions during treatment with lenvatinib.

Complete neck dissection and thyroidectomy in 1 subject with papillary thyroid carcinoma, and partial spinal laminectomy in 1 subject with Ewing sarcoma.

Cohort 2A (RR-DTC; N=1):

One patient with RR-DTC had a BOR of confirmed PR as of the cutoff date.

Cohort 2B (relapsed/refractory osteosarcoma; N=31):

Primary Efficacy Endpoint:

• **PFS-4 rate (binomial estimate):**

◦ **29%** (95% CI: 14.2, 48.0) based on all 31 subjects in the **FAS**

An analysis of the binomial estimate for PFS-4 including all 31 subjects in the FAS resulted in a rate of 29.0% (95% CI: 14.2, 48.0), with a P-value of 0.3662

◦ **32%** (95% CI: 15.9, 52.4) based on 28 **evaluable subjects**

Table 21. Progression-Free Survival at Four Months – Single-Agent Lenvatinib

Cohort 2B (Expansion), Evaluable Subjects Analysis Set

	14 mg/m^2 (N=31)
Subjects evaluable for PFS-4[a]	28
PFS rate at 4 months, n (%)	9 (32.1)
95% CI of PFS-4[b]	(15.9, 52.4)
80% CI of PFS-4[b]	(20.4, 45.9)
P-value[c]	0.2499

Clinical cutoff date: 02 Aug 2018 (Cohort 2B). Percentage based on total number of subjects evaluable for PFS-4. a: Analysis includes only subjects evaluable for PFS-4, based on binomial estimate. Subjects evaluable for PFS-4 either were treated for at least 16 weeks, had radiological PD, died, or started new anticancer treatment within 16 weeks after first dose, and excluded those who discontinued study drug due to an AE or reason other than PD, death, or receiving another anticancer medication. b: 95% CI based

on Clopper/Pearson method. c: P-value based on 1-sided exact test of a single proportion using the null hypothesis that PFS-4 was ≤ 25%. Source: Table 14.2.1.1B.

• **PFS-4 rate (KM estimate): 37.8%** (95% CI: 20.0, 55.4) based on all 31 subjects

Table 22. Progression-Free Survival Based on Investigator Assessment Using RECIST 1.1 – Single-Agent Lenvatinib Cohort 2B (Expansion), Full Analysis Set

	14 mg/m² (N=31)
Subjects with Events, n (%)	23 (74.2)
Progressive disease	23 (74.2)
Death	0
Censored subjects, n (%)	8 (25.8)
No postbaseline tumor assessment	2 (6.5)
New anticancer treatment started	4 (12.9)
No progression at the time of data cutoff	1 (3.2)
No progression at the time of treatment discontinuation	1 (3.2)
Median PFS (95% CI) [a], mo	3.0 (1.8, 5.4)
PFS Rate (%) (95% CI) at:[b]	
4 months	37.8 (20.0, 55.4)
12 months	5.9 (0.4, 22.9)
PFS Rate (%) (80% CI) at:[b]	
4 months	37.8 (25.9, 49.6)
12 months	5.9 (1.3, 15.7)
Median follow-up time for PFS (95% CI), mo	16.6 (5.5, 16.6)

Clinical cutoff date: 02 Aug 2018.
Percentages based on total number of subjects within relevant treatment group in the Full Analysis Set.
Censored subjects include those subjects who had no baseline tumor assessment, had no progression, started new anticancer treatment, or discontinued treatment for reasons other than PD.
Subjects who died or had PD after missing more than 1 visit/tumor assessment were also censored.
KM = Kaplan-Meier, PFS = progression-free survival, RECIST = Response Evaluation Criteria in Solid Tumors.
a: Point estimates based on KM methodology; 95% CI based on Brookmeyer and Crowley method.
b: Point estimates based on KM methodology; CIs estimated based on Greenwood formula using log-log transformation.
Source: Table 14.2.2.1B.

• The binomial (PFS-4 evaluable set) and KM (FAS) estimates of PFS-4 rate were close to the **prespecified PFS-4 rate of 37%.**

• The 95% CIs from the 3 estimates are similar (overlap).

• Based on PFS-4, results indicate that lenvatinib has antitumor activity in pediatric and young adult subjects with relapsed/refractory osteosarcoma

All tumour assessments were based on investigators' assessments using RECIST 1.1.

As of the clinical cutoff date of 02 Aug 2018, 23 of the 31 subjects (82.8%) in Cohort 2B had a progression event (PD or death) per the investigator assessments based on RECIST 1.1.

Secondary Efficacy Endpoints:

• **PFS**: median, **3.0 months** (95% CI: 1.8, 5.4), follow-up time: 16.6 months (95% CI: 5.5, 16.6)

• TTP: median, 3.0 months (95% CI: 1.8, 5.4)

• **ORR**: n=2 PRs, **6.7%** (95% CI: 0.8, 22.1) in 30 subjects with measurable disease

• Duration of Response: median, 4.6 months (95% CI: NE, NE)

• Disease Control Rate: 52% (95% CI: 33.1, 69.8)

• Clinical Benefit Rate: 23% (95% CI: 9.6, 41.1)

Exploratory Efficacy Endpoints:

• Overall Survival: median, 10.0 months (95% CI: 5.6, 12.3)

Table 23. Summary of OS Single-Agent Lenvatinib

Cohort 1 (Dose-Finding) and Cohort 2B (Expansion), Full Analysis Set

	Lenvatinib Dose-Finding Phase (Cohort 1)				Expansion (Cohort 2B)
	11 mg/m² (N=3)	14 mg/m² (N=9)	17 mg/m² (N=11)	Total (N=23)	14 mg/m² (N=31)
Deaths, n (%)	2 (66.7)	6 (66.7)	7 (63.6)	15 (65.2)	20 (64.5)
Overall Survival, months					
Median (95% CI)[a]	8.1 (3.8, NE)	7.4 (1.3, NE)	7.7 (2.7, NE)	7.7 (5.5, NE)	10.0 (5.6, 12.3)
Censored subjects, n (%)					
Consent withdrawn	0	0	0	0	2 (6.5)
Alive	1 (33.3)	3 (33.3)	4 (36.4)	8 (34.8)	9 (29.0)
Overall Survival Rate (%) (95% CI) at:[b]					
4 months	66.7 (5.4, 94.5)	66.7 (28.2, 87.8)	81.8 (44.7, 95.1)	73.9 (50.9, 87.3)	82.9 (63.6, 92.5)
12 months	33.3 (0.9, 77.4)	33.3 (7.8, 62.3)	36.4 (11.2, 62.7)	34.8 (16.6, 53.7)	34.9 (15.8, 54.8)
Median follow-up time for OS (95% CI)[c]	14.2 (NE, NE)	14.6 (14.4, 21.3)	17.9 (15.5, 20.6)	16.4 (14.2, 20.6)	13.5 (7.9, 17.5)

Clinical cutoff dates: 31 Mar 2017 (Cohort 1) and 02 Aug 2018 (Cohort 2B).
Data for Cohorts 1 and 2B are presented in the same table for convenience and not for comparison purposes.
Percentages based on total number of subjects within relevant treatment group in the Full Analysis Set.
KM = Kaplan-Meier.
a: Point estimates based on KM methods; 95% CIs based on a generalized Brookmeyer and Crowley method.
b: Point estimates based on KM methods; 95% CIs based on Greenwood formula using log-log transformation.
c: Estimates for OS follow-up time are calculated in the same way as the KM estimate of OS but with the meaning of 'censor' and 'event' status indicator reversed.
Source: Table 14.2.3.1 (Cohort 1) and Table 14.2.3.1B (Cohort 2B).

◦ Median follow-up time for OS: 13.5 months (95% CI: 7.9, 17.5)

• Tumor Resection: 5 subjects had resection of metastatic pulmonary lesion(s) during or after study treatment. Four of the 5 subjects had complete resection and 1 had partial resection.

Cohort 3A (n=22) (Full Analysis Set)

Primary Endpoint

The RD of lenvatinib in combination with chemotherapy, was determined to be 14 mg/m2 QD. The RDs of ifosfamide and etoposide were 3000 mg/m2 and 100 mg/m2, respectively.

The RD was defined as the dose of lenvatinib in combination with ifosfamide and etoposide that resulted in no more than 1 dose-limiting toxicity (DLT) per 6 subjects, or hematologic DLT in 1 subject and nonhematologic DLT in another subject, per 6 subjects, upon repeating the same dose level. DLTs were assessed only in Cycle 1. The determination of DLTs was made jointly by the sponsor and the protocol steering committee after safety data were evaluated; subsequent decisions were made based

on the number of DLTs that occurred in the 6 evaluable subjects enrolled at the prior dose level, in accordance with the rules for dose escalation and de-escalation.

The RD was investigated using a dose-finding strategy that initiated lenvatinib at a starting dose 20% lower than the single-agent RD (14 mg/m2) as determined in Cohort 1. Each subject's BSA-adjusted lenvatinib dosage could not exceed 24 mg once daily (QD). Subjects whose daily dose of lenvatinib was capped at 24 mg because of a high BSA, and who did not experience DLT, were to be replaced for the purpose of determining the RD. The starting dosages of ifosfamide and etoposide were in line with the standard of care in Europe and could not be escalated.

Dose-limiting toxicities (DLTs) were assessed during Cycle 1 in subjects enrolled in Cohort 3A (Combination Dose-Finding). One subject had a DLT at the 11 mg/m2 dose level and 2 subjects had DLTs at the 14 mg/m2 dose level. Two of the 3 subjects had DLTs of thrombocytopenia. Consequently, the RD of single-agent lenvatinib was determined to be 14 mg/m2 and was used as the RD in Cohort 3B.

Table 24. Dose-Limiting Toxicities in Cycle 1 – Combination-Therapy Cohort 3A (Dose-Finding), Safety Analysis Set

Subject ID	Assigned Lenvatinib Dose Level	DLT (AE Preferred Term) [a]	Study Day of DLT [b]	Grade	Study Drug Action Taken/	Outcome
PPD	11 mg/m^2	Thrombocytopenia [c]	8	3	Dose not changed	Not recovered
PPD	14 mg/m^2	**Thrombocytopenia** [a,d]	4	2	Dose not changed	Not recovered
		Epistaxis	9	3	Dose not changed	Recovered
PPD	14 mg/m^2	Oral dysaesthesia	5	2	Dose not changed	Recovered
		Back pain	6	2	Dose not changed	Recovered
		Muscle spasms	11	3	Dose not changed	Recovered

Data cutoff dates: 03 Jun 2019 (Cohort 3A) and 18 Jul 2019 (Cohort 3B).
Adverse events (AEs) coded using MedDRA version 21.1.
Adverse events graded using Common Terminology Criteria for Adverse Events (CTCAE) v 4.03.
All subjects received ifosfamide (IFOS) 3000 mg/m^2 and etoposide (ETOP) 100 mg/m^2 IV on Days 1 to 3 of Cycle 1 in addition to lenvatinib once daily for the entire 21-day cycle.
For subjects who had multiple occurrences of the same event, only the first occurrence is presented in the intext table.
IV = intravenous(ly), MedDRA = Medical Dictionary for Regulatory Activities.
a: Events reported to be serious by the investigator are **bolded**.
b: Study Day listed is first day (start) of the event.
c: Subject PPD had 1 continual event of thrombocytopenia during Cycle 1, which fluctuated in severity ranging from Grades 3 to 4.
d: Subject PPD had 1 continual event of thrombocytopenia during Cycle 1, which fluctuated in severity ranging from Grades 2 to 4. The event was reported as serious on Day 8.
Source: Listing 16.2.7.8.1.3A.

Secondary Efficacy Endpoints

All tumor assessments were based on investigators' assessments using RECIST 1.1.

- PFS and TTP: median (95% CI), 12.0 months (7.1, not estimable [NE])

-Median (95% CI) follow-up time for PFS: 6.9 months (2.8, 10.9)

- Objective Response Rate: n=2 PRs, 9.5% (95% CI: 1.2, 30.4) based on 21 subjects with measurable disease

- Duration of Response: 6.1 and 6.9 months, respectively, for the 2 responders (DOR was censored for both subjects after surgical resection of target lesions)

- Disease Control Rate: 72.7% (95% CI: 49.8, 89.3)

- Clinical Benefit Rate: 40.9% (95% CI: 20.7, 63.6)

Exploratory Efficacy Endpoints

- PFS-4 rate (binomial estimate): 54.5% (95% CI: 32.2, 75.6) based on all 22 subjects

- PFS-4 rate (binomial estimate): 66.7% (95% CI: 41.0, 86.7) based on 18 evaluable subjects.

- PFS-4 rate (Kaplan-Meier [KM] estimate): 80.2% (95% CI: 55.4, 92.1) based on all 22 subjects.

- Median OS: 16.3 months (95% CI: 12.6, 28.0). As of the data cutoff date of 03 Jun 2019 for Cohort 3A, 12 (54.5%) of the 22 subjects in Cohort 3A had died.

- Tumor Resection: 11 subjects had resection of ≥1 tumor lesion: 9 during the Treatment Phase and 2 during posttreatment follow-up (1 bone only; 1 bone and lung, 9 lung only). Ten of the 11 subjects had complete resection and 1 had partial resection.

Cohort 3B (n=20) (Full Analysis Set)

All tumor assessments were based on investigators' assessments using RECIST 1.1.

Primary Efficacy Endpoint

- **PFS-4 rate** (binomial estimate):

- **50%** (95% CI: 27.2, 72.8) based on the **FAS** (all 20 subjects); P=0.0139

- **66.7%** (95% CI: 38.4, 88.2) based on 15 **evaluable subjects**; P=0.0008

Table 25. PFS Rate at 4 Months Based on Investigator Assessment Using RECIST 1.1 – Cohort 3B (Combination Expansion), Subjects Evaluable for PFS-4

	LENV 14 mg/m^2 + IFOS+ETOP (N=20)
Subjects evaluable for PFS-4[a]	15
PFS rate at 4 months, n (%)	10 (66.7)
95% CI of PFS-4[b]	(38.4, 88.2)
80% CI of PFS-4[b]	(46.8, 82.8)
P value[c]	0.0008

Data cutoff date: 18 Jul 2019.
All subjects received ifosfamide (IFOS) 3000 mg/m^2 and etoposide (ETOP) 100 mg/m^2 IV on Days 1 to 3 of each 21-day cycle for 5 cycles in addition to lenvatinib once daily on all days of each cycle.
Percentage based on total number of subjects evaluable for PFS-4.
AE = adverse event, IV = intravenous(ly), LENV = lenvatinib, PD = disease progression, PFS = progression-free survival, RECIST = Response Evaluation Criteria in Solid Tumors.
a: Analysis includes only subjects evaluable for PFS-4, based on binomial estimate. Subjects evaluable for PFS-4 either were treated for at least 18 weeks, had radiological PD, died, or started new anticancer treatment within 18 weeks after first dose, and excluded those who discontinued study drug for an AE or reason other than PD, death, or starting new anticancer medication.
b: 95% CI based on Clopper/Pearson method.
c: *P* value based on 1-sided exact test of a single proportion using the null hypothesis that PFS-4 was ≤25%.
Source: Table 14.2.1.1.2.3B.

- The improvement in PFS-4 rate (binomial estimate) was statistically significant for both populations compared with the prespecified PFS-4 rate of 25% in the null hypothesis, and was clinically meaningful.

- **PFS-4 rate (KM estimate): 77.4%** (95% CI: 50.3, 90.9) based on all 20 subjects

- Based on PFS-4, results indicate that lenvatinib in combination with chemotherapy has antitumor activity in pediatric and young adult subjects with relapsed/refractory osteosarcoma

Secondary Efficacy Endpoints

- PFS and TTP: median (95% CI), 6.9 months (4.2, NE)

- Median (95% CI) follow-up time for PFS was 5.8 months (5.3, 8.8)

- **ORR**: n=3 PRs, **16.7%** (95% CI: 3.6, 41.4), based on 18 subjects with measurable disease

- Duration of Response: 1.5, 4.6, and 6.2 months, respectively, in the 3 responders (DOR censored for all 3 subjects at data cutoff date)

Exploratory Efficacy Endpoints

- **Overall Survival**:

Median OS was not estimable (95% CI: 7.3 mo, NE). As of the data cutoff date of 18 Jul 2019 for Cohort 3B, 3 (15%) of the 20 subjects had died

- Median follow-up time was 8.1 months (95% CI: 5.2, 9.5)

- Tumour Resection: 2 subjects had tumour resection during or after study treatment; both were partial resections of a lung lesion Ad Hoc Analyses of Subjects who Received Lenvatinib 14 mg/m2 in Cohorts 3A and 3B Combined (N=35)

Exploratory pooled analyses for 14 mg/m2 dose level (Cohorts 3A and 3B)

Exploratory pooled analyses were performed for the 14 mg/m2 dose level group across both cohorts combined (hereafter referred to as the pooled 14 mg/m2 dose level) for PFS-4 rate, PFS, ORR, and OS.

Progression-Free Survival Rate at 4 Months

- **PFS-4 rate (binomial** estimate): 66.7% (95% CI: 46.0, 83.5) based on 27 **evaluable subjects**.

Table 26. PFS at 4 Months Based on Investigator Assessment Using RECIST 1.1 –

Pooled 14 mg/m2 Dose Level, Combination-Therapy

Cohort 3A (Dose-Finding) and Cohort 3B (Expansion), Subjects Evaluable for PFS-4

	LENV 14 mg/m^2 + IFOS+ETOP, n (%)		
	Cohort 3A (N=15)	Cohort 3B (N=20)	Total (N=35)
Subjects Evaluable for PFS-4 [a]	12	15	27
PFS rate at 4 months, n(%)	8 (66.7)	10 (66.7)	18 (66.7)
95% CI of PFS-4[b]	(34.9, 90.1)	(38.4, 88.2)	(46.0, 83.5)
80% CI of PFS-4[b]	(44.1, 84.6)	(46.8, 82.8)	(52.5, 78.8)
P value[c]	0.0028	0.0008	<0.0001

Data cutoff dates: 03 Jun 2019 (Cohort 3A) and 18 Jul 2019 (Cohort 3B). All subjects received ifosfamide (IFOS) 3000 mg/m2 and etoposide (ETOP) 100 mg/m2 IV on Days 1 to 3 of each 21-day cycle for 5 cycles in addition to lenvatinib once daily on all days of each cycle. Percentages based on total number of subjects within relevant treatment group in the Full Analysis Set. Tumor

assessments based on RECIST 1.1. IV = intravenous(ly), LENV = lenvatinib, NE = not estimable, PD = disease progression, PFS = progression free survival, RECIST = Response Evaluation Criteria in Solid Tumors. a: Subjects evaluable for PFS-4 either were treated for at least 16 weeks or had radiological PD, died, or started new anticancer treatment within 16 weeks after first dose, and excluded those who discontinued study drug due to AE or reason other than PD, death, or started a new anticancer medication. b: 95% CI based on Clopper and Pearson methodology. c: P value based on 1-sided exact test of a single proportion using the null hypothesis that PFS-4 was ≤25%. Source: Table 14.2.1.1.

Progression-Free Survival

- PFS: median, 8.7 months (95% CI: 4.5,12.0), median follow-up time for PFS was 5.8 months (95% CI: 4.2, 8.8)

- **PFS-4 (KM estimate): 79.9%** (95% CI: 60.5, 90.5) based on **all 35 subjects**.

Table 27. PFS Based on Investigator Assessment Using RECIST 1.1 –

Pooled 14 mg/m2 Dose Level, Combination-Therapy

Cohort 3A (Dose-Finding) and Cohort 3B (Expansion), Full Analysis Set

	LENV 14 mg/m^2 + IFOS+ETOP, n (%)		
	Cohort 3A (N=15)	Cohort 3B (N=20)	Total (N=35)
Subjects with Events, n (%)	5 (33.3)	10 (50.0)	15 (42.9)
Progressive disease	5 (33.3)	10 (50.0)	15 (42.9)
Death	0	0	0
Censored subjects, n (%)	10 (66.7)	10 (50.0)	20 (57.1)
New anticancer therapy started	7 (46.7)	2 (10.0)	9 (25.7)
No PD at data cutoff	0	5 (25.0)	5 (14.3)
No PD at time of treatment discontinuation	2 (13.3)	1 (5.0)	3 (8.6)
No postbaseline tumor assessment	0	2 (10.0)	2 (5.7)
Death or PD after missing more than 1 assessment	1 (6.7)	0	1 (2.9)
Median PFS (95% CI)[a], months	12.0 (11.1, 16.1)	6.9 (4.2, NE)	8.7 (4.5, 12.0)
PFS Rate (%) (95% CI)[b] at:			
4 months	85.1 (52.3, 96.1)	77.4 (50.3, 90.9)	79.9 (60.5, 90.5)
12 months	28.4 (1.1, 70.5)	NE (NE, NE)	16.1 (1.1, 48.0)
PFS Rate (%) (80% CI)[b] at:			
4 months	85.1 (67.0, 93.7)	77.4 (61.4, 87.4)	79.9 (68.4, 87.6)
12 months	28.4 (5.4, 58.0)	NE (NE, NE)	16.1 (3.6, 36.6)
Follow-up time for PFS (months)[a,c]			
Median (95% CI)	4.2 (2.7,10.9)	5.8 (5.3, 8.8)	5.8 (4.2, 8.8)

Data cutoff dates: 03 Jun 2019 (Cohort 3A) and 18 Jul 2019 (Cohort 3B). All subjects received ifosfamide (IFOS) 3000 mg/m2 and etoposide (ETOP) 100 mg/m2 IV on Days 1 to 3 of each 21-day cycle for 5 cycles in addition to lenvatinib once daily on all days of each cycle. Percentages based on total number of subjects within relevant treatment group in the Full Analysis Set. Censored subjects include those subjects who had no baseline tumor assessment, had no progression, started new anticancer treatment, or discontinued treatment for reasons other than PD. IV = intravenous(ly), KM = Kaplan-Meier, LENV = lenvatinib, NE = not estimable, PD = disease progression, PFS = progression-free survival, RECIST = Response Evaluation Criteria in Solid Tumors. a: Point estimates based on Kaplan-Meier methodology; 95% CI estimated with a generalized Brookmeyer and Crowley method.. b: Point estimates based on KM method; 95% CIs based on Greenwood formula using log-log transformation. c: Estimates for PFS follow-up time were calculated in the same way as for the KM estimate of PFS, but with the meaning of 'censor' and 'event' status indicators reversed. Source: Table 14.2.2.1.

Objective Response Rate

ORR for the pooled 14 mg/m2 dose levels was **9.4%** (95% CI: 2.0, 25.0)

Table 28. Summary of ORR Based on Investigator Assessment Using RECIST 1.1 – Pooled 14 mg/m2 Dose Level, Combination-Therapy Cohort 3A (Dose-Finding) and Cohort 3B (Expansion), Full Analysis Set

	LENV 14 mg/m^2 + IFOS+ETOP, n (%)		
	Cohort 3A	**Cohort 3B**	**Total**
Subjects With Measurable Disease	n=14	n=18	n=32
Best Overall Response			
Partial Response (PR), n (%)	0	3 (16.7)	3 (9.4)
Stable Disease (SD), n (%)	10 (71.4)	9 (50.0)	19 (59.4)
Progressive Disease (PD), n (%)	2 (14.3)	4 (22.2)	6 (18.8)
Not Evaluable /Unknown, n (%) [a]	2 (14.3)	2 (11.1)	4 (12.5)
Objective Response Rate (CR + PR), n (%)	0.0	3 (16.7)	3 (9.4)
95% CI of ORR [b]	(0.0, 23.2)	(3.6, 41.4)	(2.0, 25.0)
Duration of Objective Response, months[c]			
Median (95% CI)		NE (NE, NE)	NE (NE, NE)
Subjects With Evaluable Disease[d]	n=1	n=2	n=3
Best Overall Response, n (%)			
Non-CR/Non-PD	1 (100.0)	2 (100.0)	3 (100.0)
Subjects With Measurable or Evaluable Disease[d]	n=15	n=20	n=35
Disease Control Rate [e], n (%)	11 (73.3)	14 (70.0)	25 (71.4)
95% CI of DCR [b]	(44.9, 92.2)	(45.7, 88.1)	(53.7, 85.4)
Clinical Benefit Rate [f], n (%)	5 (33.3)	8 (40.0)	13 (37.1)
95% CI of CBR [b]	(11.8, 61.6)	(19.1, 63.9)	(21.5, 55.1)

Data cutoff dates: 03 Jun 2019 (Cohort 3A) and 18 Jul 2019 (Cohort 3B). All subjects received ifosfamide (IFOS) 3000 mg/m2 and etoposide (ETOP) 100 mg/m2 IV on Days 1 to 3 of each 21-day cycle for 5 cycles in addition to lenvatinib once daily on all days of each cycle. Percentages based on total number of subjects within relevant treatment group in the Full Analysis Set. Rows containing only zeroes are not presented in the intext table. IV = intravenous(ly), LENV = lenvatinib, NE = not estimable or not evaluable, ORR = objective response rate, RECIST = Response Evaluation Criteria in Solid Tumors. a: Not Evaluable means best overall response of NE or SD of <7 weeks duration. Unknown means no data were available on the case report form. b: 95% CI constructed using the method of Clopper and Pearson. c: Point estimates based on Kaplan-Meier methodology; 95% CI are estimated with a generalized Brookmeyer and Crowley method. d: Includes subjects with only nontarget lesions. e: Disease Control Rate defined as CR + PR + SD ≥7 weeks for subjects with measurable disease or CR + non-CR/non-PD ≥7 weeks for subjects with evaluable disease. f: Clinical Benefit Rate defined as CR + PR + durable SD ≥23 weeks for subjects with measurable disease or CR + non-CR/non-PD ≥23 weeks for subjects with evaluable disease. Source: Table 14.2.1.1.

Overall survival

Overall Survival: 9 subjects died as of the cutoff date. Median OS was 16.3 months (95% CI: 12.6, NE), median follow-up time for OS was 9.6 months (95% CI: 7.9, 12.1)

Table 29. Summary of Overall Survival – Pooled 14 mg/m2 Dose Level, Cohorts 3A (Dose-Finding) and 3B (Expansion) Combined, Full Analysis Set

	LENV 14 mg/m² + IFOS+ETOP		
	Cohort 3A (N=15)	Cohort 3B (N=20)	Total (N=35)
Deaths, n (%)	6 (40.0)	3 (15.0)	9 (25.7)
Overall Survival, months			
Median (95% CI)[a]	NE (8.8,NE)	NE (7.3,NE)	16.3 (12.6, NE)
Censored subjects, n (%)	9 (60.0)	17 (85.0)	26 (74.3)
Consent withdrawn	1 (6.7)	2 (10.0)	3 (8.6)
Alive	8 (53.3)	15 (75.0)	23 (65.7)
Overall Survival Rate (%) (95% CI)[a] at:			
4 months	86.7 (56.4, 96.5)	94.4 (66.6, 99.2)	90.8 (74.1, 96.9)
12 months	79.4 (48.8, 92.9)	NE (NE, NE)	78.7 (57.9, 90.1)
Follow-up time for OS[a,c], months			
Median (95% CI)	20.3 (11.5, 23.0)	8.1 (5.2, 9.5)	9.6 (7.9, 12.1)

Data cutoff dates: 03 Jun 2019 (Cohort 3A) and 18 Jul 2019 (Cohort 3B). All subjects received ifosfamide (IFOS) 3000 mg/m2 and etoposide (ETOP) 100 mg/m2 IV on Days 1 to 3 of each 21-day cycle for 5 cycles in addition to lenvatinib once daily on all days of each cycle. Percentages based on total number of subjects within relevant treatment group in the Full Analysis Set. IV = intravenous(ly), LENV = lenvatinib, OS = overall survival. a: Point estimates based on Kaplan-Meier methodology; 95% CI based on a generalized Brookmeyer and Crowley method. b: Point estimates based on KM methods; 95% CIs based on Greenwood formula using log-log transformation. c: Estimates for OS follow-up time are calculated in the same way as the KM estimate of OS but with the meaning of 'censor' and 'event' status indicator reversed. Source: Table 14.2.4.1.

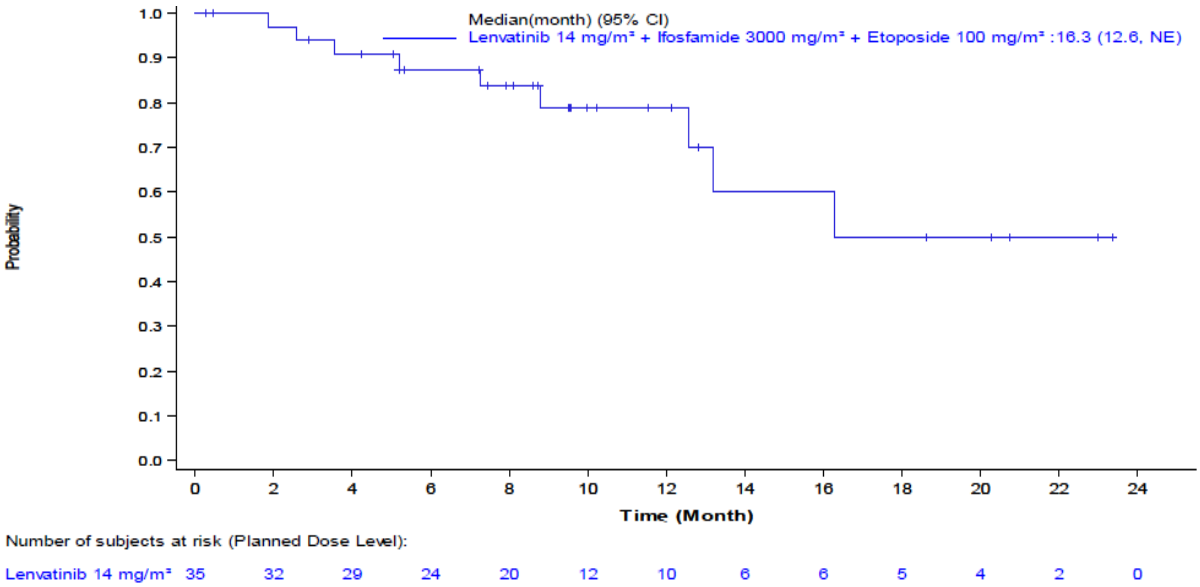


Figure 17 Kaplan-Meier Curve for Overall Survival – Pooled 14 mg/m2 Dose Level, Combination-Therapy Cohort 3A (Dose-Finding) and Cohort 3B (Expansion), Full Analysis Set

Data cutoff dates: 03 Jun 2019 (Cohort 3A) and 18 Jul 2019 (Cohort 3B). Median estimated with Kaplan-Meier methodology and 95% CI constructed using a generalized Brookmeyer and Crowley method.+ Censored observations. Source: Figure 14.2.6.

Safety results

Safety Results (Safety Analysis Set)

All events described herein were treatment-emergent.

Cohort 1 (solid malignancies; N=23)

- DLTs (Cycle 1) occurred in 3 of 11 subjects at the RD of 14 mg/m2 dose level: hypertension (n=2) and alanine aminotransferase (ALT) increased (n=1)

- Median duration of lenvatinib was 4.6, 1.8, and 1.8 months for the 11, 14, and 17 mg/m2 groups, respectively

- AEs occurred in all 23 subjects; the most frequently reported (≥50%) AEs were decreased appetite, diarrhoea, hypothyroidism, and vomiting. One subject had Grade 1 pneumothorax.

-Grade ≥3 AEs occurred in 20 subjects (87.0%); the most frequently reported (≥10%) were hypertension, alanine aminotransferase increased, and proteinuria

- Grade ≥3 treatment-related AEs were reported for 14 subjects (60.9%); events that occurred in >1 subject were hypertension (n=5), proteinuria (2), and weight decreased (2)

- Five subjects (21.7%) had Grade 5 AEs: cardiac arrest, cardio-respiratory arrest, depressed level of consciousness, pleural effusion, and respiratory distress. All were considered by the investigator to be secondary to PD and not related to study drug.

- Nonfatal SAEs were reported for 14 subjects (60.9%); the following occurred in >1 subject each were cancer pain (n=3) and hypertension, pain in extremity, pneumonia, and pyrexia (n=2 each)

- AEs led to discontinuation of lenvatinib in 4 subjects (17.4%); no individual AE led to discontinuation in >1 subject

- AEs led to lenvatinib dose reduction or interruption in 18 subjects (78.3%); the most frequently reported (≥10%) were decreased appetite and weight decreased

- Clinically significant events (CSEs) associated with lenvatinib occurred in 22 subjects (95.7%); the following occurred in ≥20% of subjects: hypothyroidism, haemorrhage, hypertension, weight loss, hepatotoxicity, and proteinuria

- Grade ≥3 CSEs occurred in 12 subjects (52.2%). The following occurred in ≥10% of subjects: hepatotoxicity (n=6), hypertension (6), and proteinuria (3)

- Haematology laboratory values were Grade 3 or Grade 4 during study treatment for platelet count decreased (n=3), lymphocyte count decreased (2), and haemoglobin decreased (2). Neutropenia and platelet count decreased were reported as SAEs in 1 subject each. One subject discontinued lenvatinib treatment because of platelet count decreased.

- Clinical chemistry laboratory values were Grade 3 or Grade 4 for ALT (n=3), aspartate aminotransferase (2), amylase (2) and sodium (1) increased and potassium (1) and sodium (3) decreased during study treatment. Amylase increased and lipase increased were reported as SAEs in 1 subject each. No subject discontinued lenvatinib treatment because of a clinical chemistry abnormality.

- Increased blood pressure (BP) and weight loss occurred early during treatment; both are known side effects of lenvatinib.

- There were no remarkable changes in mean or median values for any electrocardiogram (ECG) parameters over time, including calculated QTc values.

Cohort 2A (RR-DTC; N=1):

- As of the cutoff date (31 May 2019), the subject had received 185 days (7 cycles) of study drug

- The subject experienced the following TEAEs: abdominal, back and neck pain, acne, diarrhea, hypertension, hypertriglyceridemia, hyperuricemia, insomnia, pyrexia, and thyroglobulin increased.

Diarrhea was reported as Grade 3. None were serious.

Cohort 2B (relapsed/refractory osteosarcoma; N=31):

- AEs occurred in 29 subjects (93.5%); the most frequently reported (≥40%) were decreased appetite, headache, vomiting, hypothyroidism, and proteinuria

- Grade ≥3 AEs were reported in 20 subjects (64.5%); events in >2 subjects were back pain and tumor pain

- 28 subjects (90.3%) had TEAEs reported by the investigator to be treatment-related, which were Grade ≥3 in 7 subjects (22.6%). The most frequently reported treatment-related TEAEs, occurring in 30% or more of subjects were decreased appetite, hypertension, and hypothyroidism.

- Four subjects (12.9%) had Grade 5 AEs during treatment: cardio-respiratory arrest (n=2) and respiratory failure or respiratory distress (1 each). All were considered by the investigator to be secondary to PD and not related to study drug.

- Nonfatal SAEs occurred in 20 subjects (64.5%). Events that occurred in >1 subject each were back pain (n=4), pneumothorax (4), dyspnea (3), tumour pain (3), and platelet count decreased (2).

- AEs led to discontinuation of lenvatinib in 4 subjects (12.9%); no individual TEAE led to discontinuation in >1 subject

- AEs led to lenvatinib dose reduction or interruption in 20 subjects (64.5%); the most frequently reported (≥10%) were nausea and vomiting

- Clinically significant events associated with lenvatinib occurred in 29 subjects (93.5%). The following occurred in ≥20% of subjects: hypothyroidism, proteinuria, hypertension, weight loss, haemorrhage, and hepatotoxicity.

- Grade ≥3 CSEs occurred in 7 subjects (22.6%). Hepatotoxicity, pneumothorax, and weight loss occurred in 2 subjects each. All others occurred in 1 subject each.

- Pneumothorax occurred in 5 subjects (16.1%), reported as serious for 3 subjects and severe (Grade 3) for 2 subjects. All 5 had pulmonary lesions at Baseline.

- Haematology laboratory values were Grade 3 or Grade 4 (ie, decreases) during study treatment for haemoglobin (n=1), lymphocyte count (2), neutrophil count (2), platelet count (3), and white blood cell count (3). Platelet count decreased was an SAE in 2 subjects. No subject discontinued treatment for a hematologic laboratory abnormality.

- Clinical chemistry laboratory values were Grade 3 or Grade 4 during study treatment for ALT (n=1) and alkaline phosphatase (4) increased, and albumin (1), phosphorus (1), and sodium (2) decreased.

No abnormal clinical chemistry laboratory values were SAEs or led to discontinuation of treatment.

- Increased BP and weight loss occurred early during treatment; both are known side effects of lenvatinib

- There were no remarkable changes in mean or median values for any ECG parameters over time, including calculated QTc values

Treatment-Emergent Adverse Events

Cohorts 1 and 2B

Table 30. Overview of Treatment-Emergent Adverse Events – Single-Agent Lenvatinib Cohort 1 (Dose-Finding) and Cohort 2B (Expansion) Phase, Safety Analysis Set

	Lenvatinib Dose-Finding Phase (Cohort 1)			Expansion (Cohort 2B)
	11 mg/m² (N=5) n (%)	14 mg/m² (N=11) n (%)	17 mg/m² (N=7) n (%)	14 mg/m² (N=31) n (%)
TEAEs	5 (100.0)	11 (100.0)	7 (100.0)	29 (93.5)
Treatment-related[a]	5 (100.0)	8 (72.7)	7 (100.0)	28 (90.3)
Dose-limiting toxicity[b]	0	3 (27.3)	0	NA
CTCAE Grade ≥3	4 (80.0)	10 (90.9)	6 (85.7)	20 (64.5)
Treatment-related Grade ≥3	2 (40.0)	6 (54.5)	6 (85.7)	7 (22.6)
Treatment-emergent SAEs	2 (40.0)	7 (63.6)	5 (71.4)	21 (67.7)
Death[c]	1 (20.0)	3 (27.3)	1 (14.3)	4 (12.9)
Treatment-related SAEs	0	3 (27.3)	3 (42.9)	9 (29.0)
Treatment-related death[c]	0	0	0	0
TEAEs leading to discontinuation of study drug	0	3 (27.3)	1 (14.3)	4 (12.9)
Treatment-related TEAEs leading to study drug discontinuation[d]	0	1 (9.1)	0	1 (3.2)
TEAEs leading to study drug dose reduction	2 (40.0)	4 (36.4)	3 (42.9)	9 (29.0)
Treatment-related TEAEs leading to study drug dose reduction[d]	2 (40.0)	4 (36.4)	3 (42.9)	9 (29.0)
TEAEs leading to study drug interruption	3 (60.0)	9 (81.8)	5 (71.4)	18 (58.1)

Clinical cutoff dates: 31 Mar 2017 (Cohort 1) and 02 Aug 2018 (Cohort 2B). Data for Cohorts 1 and 2B are presented in the same table for convenience and not for comparison purposes. Percentages based on total number of subjects within the relevant treatment group for the Safety Analysis Set. For each row category, a subject with 2 or more adverse events in that category is counted only once. Adverse events coded using MedDRA version 21.1. Adverse events were graded using CTCAE version 4.03. The dose of lenvatinib was based on BSA and capped at 24 mg/day. Due to the dose capping, 5 subjects in Cohort 1 received a lower dose than planned dose level and were assigned to either the 11 mg/m2 or the 14 mg/m2 dose level for the purpose of analysis. Eight subjects in Cohort 2B received a lower dose than the planned dose level of 14 mg/m2 due to dose capping, but were included in the 14 mg/m2 dose level for analysis purposes. AE = adverse event, BSA = body surface area, CTCAE = Common Terminology Criteria for AEs, MedDRA = Medical Dictionary for Regulatory Activities, NA = not applicable, SAE = serious AE, TEAE = treatment-emergent AE. a: Treatment-related TEAEs include AEs that were considered by the investigator to be possibly or probably related to study drug or that had a missing causality on the case report form. b: AEs that met the criteria defined in the protocol as a dose-limiting toxicity. c: Fatal TEAEs for any cause. Fatal SAEs were also reported in total SAEs. d: Incidence determined using the data listings. Source: Tables 14.3.1.2.1, 14.3.1.5.6, and 14.3.2.2.2 and Listings 16.2.7.4 and 16.2.7.5 (Cohort 1); Tables 14.3.1.2.1B, 14.3.1.5.6B, and 14.3.2.2.2B and Listings 16.2.7.4B and 16.2.7.5B (Cohort 2B).

Cohorts 3A and 3B

Table 31. Overview of Treatment-Emergent Adverse Events – Combination- Therapy Cohort 3A (Dose-Finding) and Cohort 3B (Expansion), Safety Analysis Set

	Dose-Finding Phase (Cohort 3A)			Expansion (Cohort 3B)
	LENV 11 mg/m^2 + IFOS+ETOP (N=11) n (%)	LENV 14 mg/m^2 + IFOS+ETOP (N=11) n (%)	Total (N=22) n (%)	LENV 14 mg/m^2 + IFOS+ETOP (N=20) n (%)
TEAEs	11 (100.0)	11 (100.0)	22 (100.0)	20 (100.0)
Treatment-related[a]	11 (100.0)	11 (100.0)	22 (100.0)	19 (95.0)
Dose-limiting toxicity[b]	1 (9.1)	2 (18.2)	3 (13.6)	NA
CTCAE Grade of:				
≥3	10 (90.9)	11 (100.0)	21 (95.5)	20 (100.0)
3	10 (90.9)	11 (100.0)	21 (95.5)	20 (100.0)
4	9 (81.8)	8 (72.7)	17 (77.3)	16 (80.0)
5	2 (18.2)	0	2 (9.1)	2 (10.0)
Treatment-related Grade ≥3[a]	10 (90.9)	9 (81.8)	19 (86.4)	19 (95.0)
Treatment-emergent SAEs [c]	7 (63.6)	9 (81.8)	16 (72.7)	15 (75.0)
Fatal	2 (18.2)	0	2 (9.1)	2 (10.0)
Nonfatal SAEs	7 (63.6)	9 (81.8)	16 (72.7)	15 (75.0)
Treatment-related SAEs[c]	6 (54.5)	6 (54.5)	12 (54.5)	12 (60.0)
Treatment-related death	0	0	0	0
TEAEs leading to study drug discontinuation	3 (27.3)	3 (27.3)	6 (27.3)	1 (5.0)
Lenvatinib + both chemo agents	1 (9.1)	2 (18.2)	3 (13.6)	0
Lenvatinib[c]	3 (27.3)	2 (18.2)	5 (22.7)	0
Both chemo agents[d]	1 (9.1)	2 (18.2)	3 (13.6)	1 (5.0)
Ifosfamide only[d]	1 (9.1)	3 (27.3)	4 (18.2)	1 (5.0)
Etoposide only[d]	1 (9.1)	2 (18.2)	3 (13.6)	1 (5.0)
TEAEs leading to study drug dose reduction	9 (81.8)	7 (63.6)	16 (72.7)	13 (65.0)
Lenvatinib + both chemo agents	2 (18.2)	0	2 (9.1)	2 (10.0)
Lenvatinib [d]	9 (81.8)	7 (63.6)	16 (72.7)	11 (55.0)
Both chemo agents[e]	2 (18.2)	1 (9.1)	3 (13.6)	5 (25.0)
Ifosfamide only	2 (18.2)	1 (9.1)	3 (13.6)	5 (25.0)
Etoposide only	3 (27.3)	1 (9.1)	4 (18.2)	5 (25.0)
TEAEs leading to study drug interruption	7 (63.6)	5 (45.5)	12 (54.5)	12 (60.0)
Lenvatinib + both chemo agents	0	1 (9.1)	1 (4.5)	0
Lenvatinib [d]	7 (63.6)	5 (45.5)	12 (54.5)	12 (60.0)
Both chemo agents[e]	0	1 (9.1)	1 (4.5)	0
Ifosfamide only	1 (9.1)	1 (9.1)	2 (9.1)	0
Etoposide only	0	1 (9.1)	1 (4.5)	0

Data cutoff dates: 03 Jun 2019 (Cohort 3A) and 18 Jul 2019 (Cohort 3B). Data for Cohorts 3A and 3B are presented in the same table for convenience and not for comparison purposes. All subjects received ifosfamide (IFOS) 3000 mg/m2 and etoposide (ETOP) 100 mg/m2 IV on Days 1 to 3 of each Data cutoff dates: 03 Jun 2019 (Cohort 3A) and 18 Jul 2019 (Cohort 3B). Data for Cohorts 3A and 3B are presented in the same table for convenience and not for comparison purposes. All subjects received ifosfamide (IFOS) 3000 mg/m2 and etoposide (ETOP) 100 mg/m2 IV on Days 1 to 3 of each 21-day cycle for 5 cycles in addition to lenvatinib once daily on all days of each cycle. Percentages based on total number of subjects within the relevant treatment group for the Safety Analysis Set. For each row category, a subject with 2 or more adverse events in that category is counted only once. The dose of lenvatinib was based on BSA and capped at 24 mg/day. Due to the dose capping, 3 subjects in Cohort 3A received a lower dose than planned, and were assigned to the 11 mg/m2 dose level for the purpose of analysis. Five subjects in Cohort 3B received a lower dose than the planned dose level of 14 mg/m2 due to dose capping, but were included in the 14 mg/m2 dose level for analysis purposes. Adverse events were coded using MedDRA version 21.1. Adverse events were graded using Common Terminology Criteria for Adverse Events (CTCAE) version 4.03. BSA = body surface area, IV = intravenous(ly), LENV = lenvatinib, MedDRA = Medical Dictionary for Regulatory Activities, SAE = serious adverse event, TEAE = treatment-emergent adverse event. a: Treatment-related TEAEs include AEs that were considered by the investigator to be possibly or probably related to study drug or that had a missing causality on the case report form. b: Adverse events that met criteria defined per protocol as dose-limiting toxicity. c: Subjects with fatal SAEs may also be reported in the category of nonfatal SAEs. Subjects may be in multiple categories for nonfatal SAEs (data not shown). d: Drug discontinuation, reduction or interruption for lenvatinib, regardless of action taken for chemo agents. e: Drug discontinuation, reduction or interruption for chemotherapy agents, regardless of action taken for lenvatinib. Source: Tables 14.3.1.2.1.1.1.3A, 14.3.1.2.2.5.1.3A, and 14.3.2.3.1.3A (Cohort 3A) and Tables 14.3.1.2.1.1.2.3B, 14.3.1.2.2.5.2.3B, and 14.3.2.3.2.3B (Cohort 3B).

Results by age category

Adverse events were analysed by age category (2 to <6 years, 6 to <18 years, and ≥18 years) for both Cohorts 3A and 3B. Few subjects were enrolled in each age category.

Cohort 1 (Dose-Finding)

In Cohort 1, 2 subjects were 2 to <6 years of age and 21 subjects were 6 to <18 years of age. All 23 subjects experienced TEAEs.

Age Category: 2 to <6 Years

Both subjects 2 to <6 years of age experienced hypothyroidism and hypertension, among other TEAEs (eg, diarrhea, fatigue, pyrexia). One of the 2 subjects had 3 SAEs: hypertension, pneumonia, and cancer pain; all were Grade 3. The hypertension was considered by the investigator to be related to lenvatinib.

Age Category: 6 to <18 Years

The most frequently reported TEAEs in subjects 6 to <18 years of age, occurring in 40% or more of subjects, in descending order of frequency were decreased appetite, vomiting, abdominal pain, diarrhea, hypothyroidism, weight decreased, headache, and pyrexia. Eight of the 21 subjects (38.1%) had hypertension. Thirteen subjects (61.9%) aged 6 to <18 years had 1 or more SAEs. All were reported by 1 subject each, with the exception of cancer pain (n=2, 20.0%).

Cohort 2B (Expansion)

In Cohort 2B, 24 subjects were aged 6 to <18 years and 7 were 18 years or older. All 24 subjects aged 6 to <18 years and 5 subjects (71.4%) ≥18 years experienced TEAEs.

Age Category: 6 to <18 Years

The most frequently reported TEAEs in subjects 6 to <18 years of age, occurring in 40% or more of subjects, were proteinuria, decreased appetite, vomiting, headache, and hypothyroidism.

A total of 18 subjects (75.0%) in this age category had a treatment-emergent SAE. Pneumothorax was reported as serious in 4 subjects. Other SAEs reported by more than 2 subjects each were back pain (n=3) and tumor pain (n=3).

Age Category: ≥18 Years

The most frequently reported TEAEs in subjects ≥18 years of age, occurring in 50% or more of subjects, in descending order of frequency, were headache, pyrexia, asthenia, constipation, cough, decreased appetite, dysphonia, and diarrhea. Three of the 7 subjects (42.9%) aged ≥18 years had a treatment-emergent SAE. No SAEs were reported by more than 1 subject each in this age category. None of the subjects had serious pneumothorax.

Cohort 3A (Combination Dose-Finding)

In Cohort 3A, 1 subject was **2 to <6**, 16 subjects were **6 to <18**, and 5 subjects were ≥**18 years** of age. All 22 subjects experienced TEAEs. The most frequently reported TEAEs in subjects 6 to <18 years of age (>60% of subjects in that age group), in descending order of frequency, were: anemia, nausea, vomiting, diarrhea, and neutropenia.

The single subject in the 2 to <6 years age category, who received lenvatinib 14 mg/m2 in combination with chemotherapy, experienced multiple TEAEs, most notably Grade 4 neutrophil count decreased and platelet count decreased.

All 5 subjects aged ≥18 years had TEAEs, and all 5 had at least one Grade ≥3 TEAE. The most frequently reported TEAEs (any grade), occurring in 80% of subjects in that age group, were: constipation, hypothyroidism, lymphocyte count decreased, stomatitis, vomiting, and WBC count decreased.

Sixteen subjects (72.7%) in Cohort 3A had at least 1 SAE as follows: 1 (100%) aged 2 to <6 years, 10 (62.5%) aged 6 to <18 years, and 5 (100%) aged ≥18 years.

Cohort 3B (Combination Expansion)

In Cohort 3B, no subjects were **2 to <6**, 15 subjects were **6 to <18**, and 5 subjects were **≥18 years** of age. All 20 subjects experienced TEAEs. The most frequently reported TEAEs (any grade) in subjects 6 to <18 years of age, occurring in >50% of subjects (in descending order of frequency) were: anemia, WBC count decreased, nausea, vomiting, diarrhea, and proteinuria. All 15 subjects experienced a Grade ≥3 TEAE.

In the 5 subjects aged ≥18 years, 4 subjects each had asthenia, diarrhea, nausea, and platelet count decreased. All 5 subjects had 1 or more Grade 3/4 TEAEs. Fifteen subjects (75.0%) in Cohort 3B had at least 1 SAE as follows: 12 (80.0%) aged 6 to <18 years and 3 (60.0%) aged ≥18 years. The most frequently reported SAEs in both age groups were neutrophil count decreased, platelet count decreased, and WBC count decreased.

Deaths

Cohort 1 (Dose-Finding)

As of the clinical cutoff date of 31 Mar 2017, 15 deaths occurred in Cohort 1, 5 of which were treatment-emergent and 10 of which occurred >30 days posttreatment.

All 5 treatment-emergent deaths were assessed by the investigator as secondary to disease progression and not related to study drug. The TEAEs leading to death, reported for 1 subject each, were cardiac arrest, cardiorespiratory arrest, depressed level of consciousness, pleural effusion, and respiratory distress.

Cohort 2B (Expansion)

As of the clinical cutoff date of 02 Aug 2018, 20 deaths occurred in Cohort 2B, 4 of which were treatment-emergent and 16 of which occurred >30 days posttreatment. All 4 treatment-emergent deaths were assessed by the investigator as secondary to disease progression and not related to study drug. The TEAEs leading to death were cardiorespiratory arrest (n=2), respiratory failure (n=1), and respiratory distress (n=1).

Cohort 3A (Combination Dose-Finding)

As of the data cutoff date of 03 Jun 2019, 12 deaths occurred in Cohort 3A, 2 of which were treatment-emergent (Table 37). Both treatment-emergent deaths were considered by the investigator to be AEs associated with PD; neither were reported by the investigator as related to study treatment. The 2 TEAEs leading to death, reported for 1 subject each, were brain injury and dyspnea.

Cohort 3B (Combination Expansion)

As of the data cutoff date of 18 Jul 2019, 3 deaths occurred in Cohort 3B, 2 of which were treatment-emergent (Table 37). Both treatment-emergent deaths were considered by the investigator to be AEs associated with PD; neither were reported by the investigator as related to study treatment. The TEAEs leading to death were dyspnea and malignant neoplasm progression.

Severe, Serious and Clinically Significant Adverse Events

Table 32. Severe (Grade 3 or Higher) Treatment-Emergent Adverse Events That Occurred in Two or More Subjects Overall in Either Cohort* – Single-Agent Lenvatinib Cohort 1 (Dose-Finding) and Cohort 2B (Expansion), Safety Analysis Set

System Organ Class MedDRA Preferred Term	Lenvatinib Dose-Finding Phase (Cohort 1)			Expansion (Cohort 2B)
	11 mg/m^2 (N=5) n (%)	14 mg/m^2 (N=11) n (%)	17 mg/m^2 (N=7) n (%)	14 mg/m^2 (N=31) n (%)
Subjects with any Grade ≥3 TEAE	4 (80.0)	10 (90.9)	6 (85.7)	20 (64.5)
Blood and lymphatic system disorders	**1 (20.0)**	**2 (18.2)**	**1 (14.3)**	**1 (3.2)**
Anemia	0	1 (9.1)	1 (14.3)	1 (3.2)
Thrombocytopenia	1 (20.0)	1 (9.1)	0	0
Cardiac disorders	**0**	**2 (18.2)**	**0**	**2 (6.5)**
Cardio-respiratory arrest	0	1 (9.1)	0	2 (6.5)
Infections and infestations	**1 (20.0)**	**1 (9.1)**	**0**	**2 (6.5)**
Pneumonia	1 (20.0)	1 (9.1)	0	0
Investigations	**1 (20.0)**	**5 (45.5)**	**4 (57.1)**	**4 (12.9)**
ALT increased	0	2 (18.2)	1 (14.3)	0
AST increased	0	0	2 (28.6)	0
GGT increased	0	1 (9.1)	1 (14.3)	0
Platelet count decreased	0	1 (9.1)	1 (14.3)	2 (6.5)
Weight decreased	1 (20.0)	1 (9.1)	0	2 (6.5)
Metabolism and nutrition disorders	**0**	**1 (9.1)**	**1 (14.3)**	**4 (12.9)**
Decreased appetite	0	1 (9.1)	1 (14.3)	2 (6.5)
Hyponatremia	0	0	1 (14.3)	2 (6.5)
Musculoskeletal and connective tissue disorders	**1 (20.0)**	**1 (9.1)**	**3 (42.9)**	**8 (25.8)**
Back pain	0	1 (9.1)	1 (14.3)	5 (16.1)
Musculoskeletal pain	0	0	1 (14.3)	2 (6.5)
Neoplasms, benign, malignant, and unspecified (including cysts and polyps)	**0**	**2 (18.2)**	**1 (14.3)**	**4 (12.9)**
Cancer pain	0	2 (18.2)	0	0
Tumor pain	0	0	1 (14.3)	3 (9.7)
Renal and urinary disorders	**0**	**1 (9.1)**	**3 (42.9)**	**1 (3.2)**
Proteinuria	0	1 (9.1)	2 (28.6)	1 (3.2)
Respiratory, thoracic, and mediastinal disorders	**1 (20.0)**	**1 (9.1)**	**2 (28.6)**	**6 (19.4)**
Dyspnea	0	0	1 (14.3)	2 (6.5)
Pneumothorax	0	0	0	2 (6.5)
Respiratory distress	1 (20.0)	1 (9.1)	0	1 (3.2)
Vascular disorders	**0**	**2 (18.2)**	**3 (42.9)**	**2 (6.5)**
Hypertension	0	2 (18.2)	3 (42.9)	1 (3.2)

Clinical cutoff dates: 31 Mar 2017 (Cohort 1) and 02 Aug 2018 (Cohort 2B). Cutoff based on preferred term for subjects overall in either Cohort 1 or Cohort 2B. Incidence for SOCs is based on all subjects. Data for Cohorts 1 and 2B are presented in the same table for convenience and not for comparison purposes. Percentages based on total number of subjects within the relevant treatment group for the Safety Analysis Set. The dose of lenvatinib was based on BSA and capped at 24 mg/day. Due to the dose capping, 5 subjects in Cohort 1 received a lower dose than planned dose level, and were assigned to either the 11 mg/m2 or the 14 mg/m2 dose level for the purpose of analysis. Eight subjects in Cohort 2B received a lower dose than the planned dose level of 14 mg/m2 due to dose capping, but were included in the 14 mg/m2 dose level for analysis purposes. Subjects with 2 or more AEs of the same preferred term were counted only once at the highest grade. Adverse events coded using MedDRA version 21.1. Adverse events graded using (CTCAE) version 4.03. AE = adverse event, ALT = alanine aminotransferase, AST = aspartate aminotransferase, BSA = body surface area, CTCAE = Common Terminology Criteria for AEs, GGT = gamma-glutamyl transferase, MedDRA = Medical Dictionary for Regulatory Activities, SOC = system organ class, TEAE = treatment-emergent AE. Source: Table 14.3.1.3.1 (Cohort 1) and Table 14.3.1.3.1B (Cohort 2B).

Table 33. Severe (Grade 3 or Higher) Treatment-Emergent Adverse Events That Occurred in 10% or More of Subjects* – Combination-Therapy Cohort 3A (Dose-Finding) and Cohort 3B (Expansion), Safety Analysis Set

	Dose-Finding Phase (Cohort 3A)			Expansion (Cohort 3B)
MedDRA Preferred Term	LENV 11 mg/m² + IFOS+ETOP (N=11) n (%)	LENV 14 mg/m² + IFOS+ETOP (N=11) n (%)	Total (N=22) n (%)	LENV 14 mg/m² + IFOS+ETOP (N=20) n (%)
Subjects with Any Grade ≥3 TEAE	*10 (90.9)*	*11 (100.0)*	*21 (95.5)*	*20 (100.0)*
Anaemia	6 (54.5)	6 (54.5)	12 (54.5)	12 (60.0)
Neutropenia	5 (45.5)	6 (54.5)	11 (50.0)	8 (40.0)
Thrombocytopenia	5 (45.5)	4 (36.4)	9 (40.9)	5 (25.0)
White blood cell count decreased	5 (45.5)	4 (36.4)	9 (40.9)	13 (65.0)
Febrile neutropenia	5 (45.5)	3 (27.3)	8 (36.4)	3 (15.0)
Platelet count decreased	2 (18.2)	4 (36.4)	6 (27.3)	10 (50.0)
Epistaxis	2 (18.2)	3 (27.3)	5 (22.7)	1 (5.0)
Lymphocyte count decreased	3 (27.3)	2 (18.2)	5 (22.7)	6 (30.0)
Diarrhoea	3 (27.3)	1 (9.1)	4 (18.2)	3 (15.0)
Hypophosphataemia	3 (27.3)	1 (9.1)	4 (18.2)	3 (15.0)
Leukopenia	1 (9.1)	2 (18.2)	3 (13.6)	3 (15.0)
Neutrophil count decreased	1 (9.1)	2 (18.2)	3 (13.6)	9 (45.0)
Pain in extremity	2 (18.2)	1 (9.1)	3 (13.6)	0
Pneumothorax	2 (18.2)	1 (9.1)	3 (13.6)	0[a]
Stomatitis	2 (18.2)	1 (9.1)	3 (13.6)	1 (5.0)
Hypokalaemia	2 (18.2)	0	2 (9.1)	3 (15.0)
Dehydration	0	1 (9.1)	1 (4.5)	2 (10.0)
Lymphopenia	1 (9.1)	0	1 (4.5)	2 (10.0)
Vomiting	0	1 (9.1)	1 (4.5)	2 (10.0)
Nausea	0	0	0	2 (10.0)

Data cutoff dates: 03 Jun 2019 (Cohort 3A) and 18 Jul 2019 (Cohort 3B). * Cutoff based on incidence of individual PTs in ≥10% of total subjects in either Cohort 3A or 3B. Data for Cohorts 3A and 3B are presented in the same table for convenience and not for comparison purposes. Percentages based on total number of subjects within relevant treatment group for Safety Analysis Set. All subjects received ifosfamide (IFOS) 3000 mg/m2 and etoposide (ETOP) 100 mg/m2 IV on Days 1 to 3 of each 21-day cycle for 5 cycles in addition to lenvatinib once daily on all days of each cycle. The dose of lenvatinib was based on BSA and capped at 24 mg/day. Due to the dose capping, 3 subjects in Cohort 3A received a lower dose than planned, and were assigned to the 11 mg/m2 dose level for the purpose of analysis. Five subjects in Cohort 3B received a lower dose than the planned dose level of 14 mg/m2 due to dose capping, but were included in the 14 mg/m2 dose level for analysis purposes. Adverse events coded using MedDRA version 21.1. Adverse events graded using Common Terminology Criteria for Adverse Events (CTCAE) version 4.03. Subjects with 2 or more AEs of the same preferred term were counted only once at the highest grade. AE = adverse event, BSA = body surface area, IV = intravenous(ly), LENV = lenvatinib, MedDRA = Medical Dictionary for Regulatory Activities, PT = preferred term, TEAE = treatment-emergent adverse event. a: One subject (15031002) in Cohort 3B had a serious pneumothorax event; however, it was Grade 2. See Sections 12.3.1.2 and 12.4.1.3.7 for details. Source: Table 14.3.1.2.1.5.1.3A (Cohort 3A) and Table 14.3.1.2.1.5.2.3B (Cohort 3B)

Table 34. Nonfatal Treatment-Emergent Serious Adverse Events That Occurred in Two or More Subjects in Total – Single-Agent Lenvatinib Cohort 1 (Dose-Finding) and Cohort 2B (Expansion), Safety Analysis Set

System Organ Class MedDRA Preferred Term	Lenvatinib Dose-Finding Phase (Cohort 1)			Expansion (Cohort 2B)
	11 mg/m^2 (N=5) n (%)	14 mg/m^2 (N=11) n (%)	17 mg/m^2 (N=7) n (%)	14 mg/m^2 (N=31) n (%)
Subjects with any SAE	2 (40.0)	7 (63.6)	5 (71.4)	20 (64.5)
General disorders and Administration Site Conditions	**0**	**2 (18.2)**	**1 (14.3)**	**3 (9.7)**
Pyrexia	0	1 (9.1)	1 (14.3)	1 (3.2)
Infections	**1 (20.0)**	**1 (9.1)**	**0**	**1 (3.2)**
Pneumonia	1 (20.0)	1 (9.1)	0	0
Investigations	**0**	**3 (27.3)**	**2 (28.6)**	**2 (6.5)**
Platelet count decreased	0	1 (9.1)	0	2 (6.5)
Musculoskeletal and Connective Tissue disorders	**0**	**1 (9.1)**	**3 (42.9)**	**6 (19.4)**
Arthralgia	0	0	1 (14.3)	1 (3.2)
Back pain	0	1 (9.1)	0	4 (12.9)
Pain in extremity	0	0	2 (28.6)	0
Neoplasms, Benign, Malignant, and Unspecified (including cysts and polyps)	**0**	**3 (27.3)**	**0**	**4 (12.9)**
Cancer pain	0	3 (27.3)	0	0
Tumor pain	0	0	0	3 (9.7)
Respiratory, Thoracic, and Mediastinal disorders	**1 (20.0)**	**0**	**1 (14.3)**	**8 (25.8)**
Dyspnea	0	0	0	3 (9.7)
Pneumothorax	0	0	0	4 (12.9)
Respiratory distress	1 (20.0)	0	0	1 (3.2)
Vascular disorders	**0**	**2 (18.2)**	**0**	**3 (9.7)**
Hypertension	0	2 (18.2)	0	1 (3.2)

Clinical cutoff dates: 31 Mar 2017 (Cohort 1) and 02 Aug 2018 (Cohort 2B).

Data for Cohorts 1 and 2B are presented in the same table for convenience and not for comparison purposes. Percentages based on total number of subjects within the relevant treatment group for the Safety Analysis Set. The dose of lenvatinib was based on BSA and capped at 24 mg/day. Due to the dose capping, 5 subjects in Cohort 1 received a lower dose than planned dose level, and were assigned to either the 11 mg/m2 or the 14 mg/m2 dose level for the purpose of analysis. Eight subjects in Cohort 2B received a lower dose than the planned dose level of 14 mg/m2 due to dose capping, but were included in the 14 mg/m2 dose level for analysis purposes. Adverse events coded using MedDRA version 21.1. BSA = body surface area, MedDRA = Medical Dictionary for Regulatory Activities, SAE = serious adverse event. Source: Table 14.3.2.2.4 (Cohort 1) and Table 14.3.2.2.4B (Cohort 2B).

Table 35. Treatment-Emergent Clinically Significant Events Identified by SMQ or CMQ, Overall and Severe Incidence* – Single-Agent Lenvatinib Cohort 1 (Dose-Finding) and Cohort 2B (Expansion), Safety Analysis Set

	Lenvatinib Dose-Finding Phase (Cohort 1)						Expansion (Cohort 2B)	
	11 mg/m² (N=5) n (%)		14 mg/m² (N=11) n (%)		17 mg/m² (N=7) n (%)		14 mg/m² (N=31) n (%)	
Clinically Significant Event	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3
Subjects with any Clinically Significant TEAEs	5 (100.0)	1 (20.0)	10 (90.9)	6 (54.5)	7 (100.0)	5 (71.4)	29 (93.5)	7 (22.6)
Subjects with any TEAE in the CSE category of: [a]								
Arterial thromboembolic events	0	0	1 (9.1)	1 (9.1)	0	0	1 (3.2)	1 (3.2)
Cardiac dysfunction	0	0	1 (9.1)	0	1 (14.3)	0	5 (16.1)	0
Fistula formation	0	0	0	0	0	0	0	0
GI perforation	0	0	0	0	0	0	0	0
Hemorrhage	2 (40.0)	0	5 (45.5)	1 (9.1)	4 (57.1)	1 (14.3)	8 (25.8)	0
Hepatotoxicity	0	0	5 (45.5)	3 (27.3)	4 (57.1)	3 (42.9)	7 (22.6)	2 (6.5)
Hypertension	2 (40.0)	0	4 (36.4)	2 (18.2)	4 (57.1)	4 (57.1)	11 (35.5)	1 (3.2)
Hypocalcemia	0	0	0	0	0	0	1 (3.2)	0
Hypothyroidism	3 (60.0)	0	6 (54.5)	0	3 (42.9)	0	22 (71.0)	0
Impaired wound healing	0	0	0	0	0	0	0	0
Palmar-plantar erythrodysaesthesia	2 (40.0)	0	2 (18.2)	0	0	0	2 (6.5)	0
Pneumothorax	1 (20.0)	0	0	0	0	0	5 (16.1)	2 (6.5)
PRES	0	0	0	0	0	0	0	0
Proteinuria	0	0	3 (27.3)	1 (9.1)	3 (42.9)	2 (28.6)	14 (45.2)	1 (3.2)
QT prolongation	0	0	0	0	0	0	2 (6.5)	0
Renal events	0	0	1 (9.1)	0	2 (28.6)	0	2 (6.5)	0
Weight loss	3 (60.0)	1 (20.0)	4 (36.4)	1 (9.1)	3 (42.9)	0	11 (35.5)	2 (6.5)

Table 36. Treatment-Emergent Clinically Significant Events Identified by SMQ or CMQ, by Worst Grade –Combination-Therapy Cohort 3A (Dose-Finding) and Cohort 3B (Expansion), Safety Analysis Set

	Dose-Finding Phase (Cohort 3A)						Expansion (Cohort 3B)	
	LENV 11 mg/m² + IFOS+ETOP (N=11) n (%)		LENV 14 mg/m² + IFOS+ETOP (N=11) n (%)		Total (N=22) n (%)		LENV 14 mg/m² + IFOS+ETOP (N=20) n (%)	
Clinically Significant Event	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3
Subjects with any Clinically Significant TEAEs	11 (100.0)	5 (45.5)	10 (90.9)	5 (45.5)	21 (95.5)	10 (45.5)	19 (95.0)	3 (15.0)
Subjects with any TEAE in the CSE category of: [a]								
Arterial thromboembolic events	1 (9.1)	0	0	0	1 (4.5)	0	0	0
Cardiac dysfunction	1 (9.1)	0	1 (9.1)	0	2 (9.1)	0	2 (10.0)	1 (5.0)
Fistula formation	1 (9.1)	0	0	0	1 (4.5)	0	0	0
GI perforation	0	0	0	0	0	0	0	0
Hemorrhage	9 (81.8)	2 (18.2)	7 (63.6)	3 (27.3)	16 (72.7)	5 (22.7)	12 (60.0)	1 (5.0)
Hepatotoxicity	5 (45.5)	1 (9.1)	2 (18.2)	0	7 (31.8)	1 (4.5)	6 (30.0)	1 (5.0)
Hypertension	3 (27.3)	0	5 (45.5)	1 (9.1)	8 (36.4)	1 (4.5)	3 (15.0)	0
Hypocalcemia	3 (27.3)	0	0	0	3 (13.6)	0	0	0
Hypothyroidism	8 (72.7)	0	8 (72.7)	0	16 (72.7)	0	11 (55.0)	0
Impaired wound healing	0	0	0	0	0	0	0	0
Palmar-plantar erythrodysaesthesia	1 (9.1)	0	3 (27.3)	0	4 (18.2)	0	0	0
Pneumothorax	2 (18.2)	2 (18.2)	4 (36.4)	1 (9.1)	6 (27.3)	3 (13.6)	1 (5.0)	0
PRES	0	0	0	0	0	0	0	0
Proteinuria	3 (27.3)	2 (18.2)	5 (45.5)	0	8 (36.4)	2 (9.1)	9 (45.0)	1 (5.0)
QT prolongation	1 (9.1)	0	1 (9.1)	0	2 (9.1)	0	0	0
Renal events	3 (27.3)	0	2 (18.2)	0	5 (22.7)	0	2 (10.0)	1 (5.0)
Weight loss	6 (54.5)	0	3 (27.3)	0	9 (40.9)	0	4 (20.0)	1 (5.0)

Data cutoff dates: 03 Jun 2019 (Cohort 3A) and 18 Jul 2019 (Cohort 3B). Data for Cohorts 3A and 3B are presented in the same table for convenience and not for comparison purposes. All subjects received ifosfamide (IFOS) 3000 mg/m2 and etoposide (ETOP) 100 mg/m2 IV on Days 1 to 3 of each 21-day cycle for 5 cycles in addition to lenvatinib once daily on all days of each cycle. Percentages based on total number of subjects within the relevant treatment group for the Safety Analysis Set. Subjects with multiple AEs in the same CSE category were counted once for that CSE category. The dose of lenvatinib was based on BSA and capped at 24 mg/day. Due to the dose capping, 3 subjects in Cohort 3A received a lower dose than planned, and were assigned to the 11 mg/m2 dose level for the purpose of analysis. Five subjects in Cohort 3B received a lower dose than the planned dose level of 14 mg/m2 due to dose capping, but were included in the 14 mg/m2 dose level for analysis purposes. Adverse events coded using MedDRA version 21.1. Adverse events graded using Common Terminology Criteria for Adverse Events (CTCAE) version 4.03. a: CSE categories are based on either standard or customized MedDRA queries. Source: Table 14.3.3.1.1.1.3A (Cohort 3A) and Table 14.3.3.1.1.2.3B (Cohort 3B).

Dose adjustments

Table 37. Dose Reductions and Interruptions – Single-Agent Lenvatinib

Cohort 1 (Dose-Finding) and Cohort 2B (Expansion), Safety Analysis Set

	Lenvatinib Dose-Finding Phase (Cohort 1)			Expansion (Cohort 2B)
	11 mg/m^2 (N=5) n (%)	14 mg/m^2 (N=11) n (%)	17 mg/m^2 (N=7) n (%)	14 mg/m^2 (N=31) n (%)
Total Number of Subjects with				
Dose interruption	2 (40.0)	5 (45.5)	3 (42.9)	13 (41.9)
Dose reduction	2 (40.0)	5 (45.5)	3 (42.9)	9 (29.0)
Subjects with Any Dose Reduction				
Cycle of First Dose Reduction, n (%)				
Cycle 1	0	2 (18.2)	0	1 (3.2)
Cycle 2	0	1 (9.1)	1 (14.3)	6 (19.4)
Cycle 3	0	0	0	0
Cycle 5	1 (20.0)	0	1 (14.3)	1 (3.2)
Cycle ≥6	1 (20.0)	2 (18.2)	1 (14.3)	1 (3.2)
Frequency of Dose Reductions, n (%)				
1	0	3 (27.3)	3 (42.9)	4 (12.9)
2	1 (20.0)	2 (18.2)	0	2 (6.5)
3	1 (20.0)	0	0	3 (9.7)
≥4	0	0	0	0
Time to First Dose Reduction (days)				
N	2	5	3	9
Mean (SD)	141.5 (40.31)	87.2 (85.60)	104.0 (56.47)	64.0 (47.48)
Median	141.5	37.0	132.0	44.0
Min, Max	113.0, 170.0	11.0, 212.0	39.0, 141.0	25.0, 170.0
Subjects with Any Dose Interruption				
Cycle of First Interruption, n (%)				
Cycle 1	1 (20.0)	2 (18.2)	0	7 (22.6)
Cycle 2	0	1 (9.1)	1 (14.3)	2 (6.5)
Cycle 3	0	1 (9.1)	0	0
Cycle 4	0	0	0	1 (3.2)
Cycle 5	0	0	1 (14.3)	2 (6.5)
Cycle ≥6	1 (20.0)	1 (9.1)	0	1 (3.2)
Frequency of Interruptions, n (%)				
1	0	1 (9.1)	3 (42.9)	7 (22.6)
2	2 (40.0)	2 (18.2)	0	3 (9.7)
3	0	1 (9.1)	0	2 (6.5)
≥4	0	1 (9.1)	0	1 (3.2)

Clinical cutoff dates: 31 Mar 2017 (Cohort 1) and 02 Aug 2018 (Cohort 2B). Data for Cohorts 1 and 2B are presented in the same table for convenience and not for comparison purposes. Percentages based on total number of subjects within the relevant treatment group for the Safety Analysis Set. Dose reductions and interruptions are based on dose administration data on the case report form. The dose of lenvatinib was based on BSA and capped at 24 mg/day. Due to this dose capping, 5 subjects in Cohort 1 received a lower dose than their planned dose level, and were assigned to either the 11 mg/m2 or the 14 mg/m2 dose level for the purpose of analysis. Eight subjects in Cohort 2B also received a lower dose than the planned dose level of 14 mg/m2 due to dose capping, but were included in the 14 mg/m2 dose level for analysis purposes. BSA = body surface area, Max = maximum, Min = minimum. Source: Table 14.3.1.1.3 (Cohort 1) and Table 14.3.1.1.3B (Cohort 2B).

Table 38. Treatment-Emergent Adverse Events Leading to Dose Reduction/Interruption of Lenvatinib in Two or More Subjects in Either Cohort – Single-Agent Lenvatinib Cohort 1 (Dose-Finding) and Cohort 2B (Expansion), Safety Analysis Set

MedDRA Preferred Term	Lenvatinib Dose-Finding Phase (Cohort 1)						Expansion (Cohort 2B)	
	11 mg/m² (N=5)		14 mg/m² (N=11)		17 mg/m² (N=7)		14 mg/m² (N=31)	
Grade:	Any	3-4	Any	3-4	Any	3-4	Any	3-4
Subjects with any TEAE that resulted in dose reduction or interruption, n (%)	3 (60.0)	3 (60.0)	10 (90.9)	8 (72.7)	5 (71.4)	3 (42.9)	20 (64.5)	11 (35.5)
Nausea	1 (20.0)	0	0	0	0	0	4 (12.9)	0
Vomiting	1 (20.0)	0	1 (9.1)	0	0	0	4 (12.9)	0
Pneumothorax	1 (20.0)	0	0	0	0	0	3 (9.7)	2 (6.5)
Diarrhea	0	0	0	0	0	0	2 (6.5)	1 (3.2)
Dyspnea	1 (20.0)	0	0	0	0	0	2 (6.5)	1 (3.2)
Proteinuria	0	0	1 (9.1)	1 (9.1)	1 (14.3)	0	2 (6.5)	1 (3.2)
Pyrexia	1 (20.0)	0	0	0	0	0	2 (6.5)	0
Abdominal pain	1 (20.0)	0	1 (9.1)	0	0	0	1 (3.2)	1 (3.2)
Decreased appetite	2 (40.0)	0	2 (18.2)	1 (9.1)	0	0	1 (3.2)	0
Hypertension	0	0	1 (9.1)	1 (9.1)	1 (14.3)	0	1 (3.2)	0
Myalgia	1 (20.0)	1 (20.0)	1 (9.1)	0	0	0	1 (3.2)	0
Pain	1 (20.0)	0	1 (9.1)	1 (9.1)	0	0	0	0
Pneumonia	1 (20.0)	1 (20.0)	1 (9.1)	1 (9.1)	0	0	0	0
Weight decreased	1 (20.0)	1 (20.0)	2 (18.2)	1 (9.1)	1 (14.3)	0	0	0

Clinical cutoff dates: 31 Mar 2017 (Cohort 1) and 02 Aug 2018 (Cohort 2B). Data for Cohorts 1 and 2B are presented in the same table for convenience and not for comparison purposes. Table sorted in descending frequency for Cohort 2B. Percentages based on total number of subjects within the relevant treatment group for the Safety Analysis Set. Subjects having the same AE multiple times are counted only once. The dose of lenvatinib was based on BSA and capped at 24 mg/day. Due to the dose capping, 5 subjects in Cohort 1 received a lower dose than planned dose level, and were assigned to either the 11 mg/m2 or the 14 mg/m2 dose level for the purpose of analysis. Eight subjects in Cohort 2B received a lower dose than the planned dose level of 14 mg/m2 due to dose capping, but were included in the 14 mg/m2 dose level for analysis purposes. Adverse events coded using MedDRA version 21.1.Adverse events graded using CTCAE version 4.03. BSA = body surface area, CTCAE = Common Terminology Criteria for Adverse Events, MedDRA = Medical Dictionary for Regulatory Activities, TEAE = treatment-emergent adverse event. Source: Tables 14.3.2.4.1 and 14.3.2.4.1.1 (Cohort 1) and Tables 14.3.2.4.1B and 14.3.2.4.1.1B (Cohort 2B).

Table 39. Treatment-Emergent Adverse Events Leading to Dose Reduction/Interruption of Lenvatinib in Two or More Subjects in Either Cohort – Combination-Therapy Cohort 3A (Dose-Finding) and Cohort 3B (Expansion), Safety Analysis Set

MedDRA Preferred Term	Dose-Finding Phase (Cohort 3A)						Expansion (Cohort 3B)	
	LENV 11 mg/m² + IFOS+ETOP (N=11) n (%)		LENV 14 mg/m² + IFOS+ETOP (N=11) n (%)		Total (N=22) n (%)		LENV 14 mg/m² + IFOS+ETOP (N=20) n (%)	
Grade:	Any	3-4	Any	3-4	Any	3-4	Any	3-4
Subjects with any TEAE that resulted in dose reduction or interruption, n (%)	10 (90.9)	8 (72.7)	8 (72.7)	5 (45.5)	18 (81.8)	13 (59.1)	14 (70.0)	10 (50.0)
Abdominal pain	1 (9.1)	0	2 (18.2)	0	3 (13.6)	0	2 (10.0)	1 (5.0)
Arthralgia	2 (18.2)	0	1 (9.1)	0	3 (13.6)	0	0	0
Febrile neutropenia	3 (27.3)	3 (27.3)	0	0	3 (13.6)	3 (13.6)	3 (15.0)	3 (15.0)
Pain in extremity	3 (27.3)	2 (18.2)	0	0	3 (13.6)	2 (9.1)	0	0
Palmar-Plantar erythrodysaesthesia	1 (9.1)	0	2 (18.2)	0	3 (13.6)	0	0	0
Pneumothorax	2 (18.2)	2 (18.2)	1 (9.1)	1 (9.1)	3 (13.6)	3 (13.6)	1 (5.0)	0
Thrombocytopenia	2 (18.2)	2 (18.2)	1 (9.1)	1 (9.1)	3 (13.6)	3 (13.6)	2 (10.0)	1 (5.0)
Diarrhea	1 (9.1)	1 (9.1)	1 (9.1)	0	2 (9.1)	1 (4.5)	4 (20.0)	2 (10.0)
Ejection fraction decreased	1 (9.1)	0	1 (9.1)	0	2 (9.1)	0	0	0
Hypertension	0	0	2 (18.2)	1 (9.1)	2 (9.1)	1 (4.5)	0	0
Nausea	2 (18.2)	0	0	0	2 (9.1)	0	3 (15.0)	0
Periostitis	1 (9.1)	0	1 (9.1)	0	2 (9.1)	0	0	0
Asthenia	1 (9.1)	0	0	0	1 (4.5)	0	2 (10.0)	0
Epistaxis	1 (9.1)	1 (9.1)	0	0	1 (4.5)	1 (4.5)	2 (10.0)	1 (5.0)
Proteinuria	1 (9.1)	1 (9.1)	0	0	1 (4.5)	1 (4.5)	2 (10.0)	1 (5.0)
Vomiting	1 (9.1)	0	0	0	1 (4.5)	0	2 (10.0)	1 (5.0)
Platelet count decreased	0	0	0	0	0	0	5 (25.0)	4 (20.0)
White blood cell count decreased	0	0	0	0	0	0	3 (15.0)	3 (15.0)
Abdominal pain upper	0	0	0	0	0	0	2 (10.0)	0
Bradycardia	0	0	0	0	0	0	2 (10.0)	0
Neutrophil count decreased	0	0	0	0	0	0	2 (10.0)	2 (10.0)

Data cutoff dates: 03 Jun 2019 (Cohort 3A) and 18 Jul 2019 (Cohort 3B). Data for Cohorts 3A and 3B are presented in the same table for convenience and not for comparison purposes. Table sorted in descending frequency in total column for Cohort 3B. Subject with 2 or more AEs in the same system organ class (or having the same preferred term) is counted only once for that system organ class (or preferred term). Percentages based on total number of subjects within the relevant treatment group for the Safety Analysis Set. All subjects received ifosfamide (IFOS) 3000 mg/m2 and etoposide (ETOP) 100 mg/m2 IV on Days 1 to 3 of each 21-day cycle for 5 cycles in addition to lenvatinib once daily on all days of each cycle. The dose of lenvatinib was based on BSA and capped at 24 mg/day. Due to the dose capping, 3 subjects in Cohort 3A received a lower dose than planned, and were assigned to the 11 mg/m2 dose level for the purpose of analysis. Five subjects in Cohort 3B received a lower dose than the planned dose level of 14 mg/m2 due to dose capping, but were included in the 14 mg/m2 dose level for analysis purposes. Adverse events coded using MedDRA version 21.1. Adverse events graded using Common Terminology Criteria for Adverse Events (CTCAE) version 4.03. BSA = body surface area, IV = intravenous(ly), LENV = lenvatinib, MedDRA = Medical Dictionary for Regulatory Activities, TEAE = treatment-emergent adverse event. Source: Tables 14.3.1.2.3.1.1.3A and 14.3.1.2.3.2.1.3A (Cohort 3A) and Tables 14.3.1.2.3.1.2.3B and 14.3.1.2.3.2.2.3B (Cohort 3B).

Table 40. Treatment-Emergent Adverse Events Leading to Dose Reduction/Interruption of Ifosfamide – Combination-Therapy Cohort 3A (Dose-Finding) and Cohort 3B (Expansion), Safety Analysis Set

MedDRA Preferred Term	Dose-Finding Phase (Cohort 3A)						Expansion (Cohort 3B)	
	LENV 11 mg/m² + IFOS+ETOP (N=11) n (%)		LENV 14 mg/m² + IFOS+ETOP (N=11) n (%)		Total (N=22) n (%)		LENV 14 mg/m² + IFOS+ETOP (N=20) n (%)	
Grade:	Any	3-4	Any	3-4	Any	3-4	Any	3-4
Subjects with any TEAE that resulted in dose reduction or interruption, n (%)	3 (27.3)	2 (18.2)	2 (18.2)	0	5 (22.7)	2 (9.1)	5 (25.0)	3 (15.0)
Arthralgia	1 (9.1)	0	0	0	1 (4.5)	0	0	0
Febrile neutropenia	1 (9.1)	1 (9.1)	0	0	1 (4.5)	1 (4.5)	0	0
Thrombocytopenia	0	0	1 (9.1)	0	1 (4.5)	0	1 (5.0)	1 (5.0)
Toxic encephalopathy	1 (9.1)	1 (9.1)	0	0	1 (4.5)	1 (4.5)	0	0
Wound dehiscence	0	0	1 (9.1)	0	1 (4.5)	0	0	0
Pyrexia	0	0	0	0	0	0	2 (10.0)	0
Bradycardia	0	0	0	0	0	0	1 (5.0)	0
Vulvitis	0	0	0	0	0	0	1 (5.0)	1 (5.0)
White blood cell count decreased	0	0	0	0	0	0	1 (5.0)	1 (5.0)

Data cutoff dates: 03 Jun 2019 (Cohort 3A) and 18 Jul 2019 (Cohort 3B).

Table 41. Treatment-Emergent Adverse Events Leading to Dose Reduction/Interruption of Etoposide – Combination-Therapy Cohort 3A (Dose-Finding) and Cohort 3B (Expansion), Safety Analysis Set

MedDRA Preferred Term	Dose-Finding Phase (Cohort 3A)						Expansion (Cohort 3B)	
	LENV 11 mg/m² + IFOS+ETOP (N=11) n (%)		LENV 14 mg/m² + IFOS+ETOP (N=11) n (%)		Total (N=22) n (%)		LENV 14 mg/m² + IFOS+ETOP (N=20) n (%)	
Grade:	Any	3-4	Any	3-4	Any	3-4	Any	3-4
Subjects with any TEAE that resulted in dose reduction or interruption, n (%)	3 (27.3)	2 (18.2)	2 (18.2)	0	5 (22.7)	2 (9.1)	5 (25.0)	3 (15.0)
Thrombocytopenia	1 (9.1)	0	1 (9.1)	0	2 (9.1)	0	1 (5.0)	1 (5.0)
Arthralgia	1 (9.1)	0	0	0	1 (4.5)	0	0	0
Febrile neutropenia	1 (9.1)	1 (9.1)	0	0	1 (4.5)	1 (4.5)	0	0
Stomatitis	1 (9.1)	1 (9.1)	0	0	1 (4.5)	1 (4.5)	0	0
Wound dehiscence	0	0	1 (9.1)	0	1 (4.5)	0	0	0
Pyrexia	0	0	0	0	0	0	2 (10.0)	0
Bradycardia	0	0	0	0	0	0	1 (5.0)	0
Vulvitis	0	0	0	0	0	0	1 (5.0)	1 (5.0)
White blood cell count decreased	0	0	0	0	0	0	1 (5.0)	1 (5.0)

Data cutoff dates: 03 Jun 2019 (Cohort 3A) and 18 Jul 2019 (Cohort 3B).

Adverse Events that Resulted in Discontinuation of Study Drug

Cohort 3A (Combination Dose-Finding)

Discontinuation of All 3 Study Drugs

In Cohort 3A, 3 subjects (13.6%) discontinued all 3 study drugs (13.6%): 1 (9.1%) at the 11 mg/m2 dose level and 2 (18.2%) at the 14 mg/m2 dose level. The TEAEs that resulted in treatment discontinuation in the 3 subjects were 1) malignant pleural effusion ("worsening of pleural effusion due to progressive disease" per the investigator), 2) pneumothorax, and 3) blood lactate dehydrogenase (LDH) increased and hypothyroidism. One TEAE, malignant pleural effusion, was Grade 4 and 1 TEAE, pneumothorax, was Grade 3; the remaining 2 were Grade 1 or Grade 2.

Discontinuation of Lenvatinib

In Cohort 3A, TEAEs led to discontinuation of lenvatinib in 5 subjects (22.7%): 3 (27.3%) at the 11 mg/m2 dose level and 2 (18.2%) at the 14 mg/m2 dose level. For 3 subjects, the TEAE that led to discontinuation was Grade ≥3. No TEAE led to discontinuation in more than 1 subject each.

Discontinuation of Ifosfamide

In Cohort 3A, TEAEs led to discontinuation of ifosfamide in 4 subjects (18.2%): 1 (9.1%) at the 11 mg/m2 dose level and 3 (27.3%) at the 14 mg/m2 dose level. For 2 subjects, the TEAE that led to discontinuation was Grade ≥3. No TEAE led to discontinuation in more than 1 subject each.

Discontinuation of Etoposide

In Cohort 3A, TEAEs led to discontinuation of etoposide in 3 subjects (13.6%): 1 (9.1%) at the 11 mg/m2 dose level and 2 (18.2%) at the 14 mg/m2 dose level (Table 49). For 1 subject, the TEAE that led to discontinuation was Grade 4. No TEAE led to discontinuation in more than 1 subject each.

Cohort 3B (Combination Expansion)

Discontinuation of Any Study Drug

In Cohort 3B, 1 subject (5.0%) discontinued ifosfamide and etoposide for Grade 3 venoocclusive disease. This event resulted in a dose reduction of lenvatinib. No other subjects in Cohort 3B discontinued study treatment because of a TEAE.

Radiographic Findings of Proximal Tibial Growth Plates

In Cohort 1, 12 subjects had an open proximal tibial growth plate at Baseline. One subject, assigned to the 14 mg/m2 dose level, had an abnormality at Baseline. At the Off-treatment visit, 1 subject's tibial growth plate had closed and 1 remained open without abnormality. The remaining 10 subjects did not have a follow-up radiograph at the end of the study, including the subject who had an abnormality at Baseline.

In Cohort 2B, 11 subjects had an open proximal tibial growth plate at Baseline, all without abnormality. At the Off-treatment visit, 5 subjects' tibial growth plate remained open without abnormality and 6 subjects did not have a follow-up radiograph.

In Cohort 3A, 20 of the 22 subjects had a radiographic scan of the proximal tibial growth plates. Eight subjects had an open proximal tibial growth plate at Baseline. Two of the 8 subjects, one each assigned to the 11 and 14 mg/m2 dose levels, had an abnormality at Baseline. Neither subject had a follow-up assessment at the Off-treatment visit. The 6 remaining subjects with open growth plates at Baseline either had an open growth plate at the Off-treatment visit (n=2), or a follow-up scan was not performed (n=4).

In Cohort 3B, 11 of the 20 subjects had a radiographic scan of the proximal tibial growth plates at Baseline. Five subjects had an open proximal tibial growth plate at Baseline, all without abnormality. Of the 5 subjects with open growth plates at Baseline, 3 subjects were not assessed at the Off-treatment visit, 1 subject's tibial growth plate remained open without abnormality, and 1 subject's growth plate had closed.

Palatability questionnaire

One of the secondary objectives of the Study 207 was to assess the palatability and acceptability of the oral suspension formulation of lenvatinib.

The palatability and acceptability of the oral suspension formulation of lenvatinib was assessed using the Palatability Questionnaire. Measurement of palatability was assessed using the Hedonic scale,

which is a visual analog scale (Guinard, 2001). All subjects who received the suspension formulation completed the questionnaire according to the Schedule of Assessments in the protocol. If a subject was unable to complete the questionnaire, the questionnaire was completed by a parent or legal guardian.

Three subjects in Cohort 1 and 1 subject in Cohort 2B took the suspension. Ratings for overall acceptability were really bad, super bad, and good for the 3 subjects in Cohort 1, respectively. The subject in Cohort 2B rated the overall acceptability of the suspension as good. Two subjects in Cohort 3A and 5 subjects in Cohort 3B took lenvatinib as an oral suspension.

Five subjects (1 in Cohort 3A, 4 in Cohort 3B) completed the palatability questionnaire. Overall acceptability of the lenvatinib suspension was rated as good by the subject in Cohort 3A. In Cohort 3B, the 4 subjects rated the overall acceptability of the lenvatinib suspension as follows: good (n=1), may be good or may be bad (n=1), bad (n=1), and really bad (n=1), respectively.

2.3.5. Discussion on clinical aspects

Design and conduct of clinical studies

The Study 207 (Study E7080-G000-207) was the first study in paediatric patients with lenvatinib monotherapy and in combination with chemotherapy. This Phase 1/2 open-label study of lenvatinib in children and adolescents with refractory or relapsed solid malignancies and young adults with osteosarcoma was conducted in 5 cohorts:

• Cohort 1, a single-agent dose-finding study of lenvatinib in children with relapsed or refractory solid tumors to determine the RD

• Cohort 2, an assessment of the efficacy of single-agent lenvatinib at the RD in subjects with either

- 131I-refractory DTC (Cohort 2A) or

- relapsed or refractory osteosarcoma (Cohort 2B)

• Cohort 3A, combination dose-finding study of lenvatinib plus chemotherapy (ifosfamide and etoposide) in subjects with relapsed or refractory osteosarcoma to determine the RD of the combination as well as the safety and tolerability of the combination

• Cohort 3B, combination expansion study with lenvatinib, at the RD, plus chemotherapy (ifosfamide and etoposide) in subjects with relapsed or refractory osteosarcoma who either were lenvatinib-naïve or had disease progression after treatment with single-agent lenvatinib in Cohorts 1 or 2B

The primary objectives were to identify the RD and to evaluate the activity of lenvatinib as a single agent and in combination with chemotherapy (ifosfamide and etoposide). Dose-limiting toxicities were defined based on known lenvatinib and chemotherapy drug toxicities, but also included any unexpected toxicities. As regards combination with chemotherapy, the MAH hypothesized that vascular normalization would allow increased uptake of drugs into tumour tissue. Ifosfamide-based chemotherapy, with or without etoposide, has been used as part of standard therapy options for the treatment of relapsed osteosarcoma since the early 1980s (Fan, et al., 2015). Thus, ifosfamide and etoposide were selected as the chemotherapy agents for combination with lenvatinib based on their use in the relapsed setting.

Lenvatinib was provided as 1-, 4-, and 10-mg capsules. Each subject's dose was based on their body surface area (BSA), according to his/her assigned dose level (11 or 14 mg/m2 in Cohort 3A or 14 mg/m2 in Cohort 3B). After dose adjustment for BSA, the maximum lenvatinib dose could not exceed 24 mg/day. Lenvatinib was self-administered orally once daily, at the same time each day (either with or without

food) in continuous 21-day cycles. Subjects who could not swallow capsules whole could receive lenvatinib as an extemporaneous suspension.

The palatability and acceptability of the oral suspension formulation of lenvatinib was also assessed.

After determination of the recommended dose in Cohort 1, an expansion phase was conducted to assess the efficacy and safety of single-agent lenvatinib in subjects with RR-DTC (Cohort 2A) or relapsed/refractory osteosarcoma (Cohort 2B). Subjects received ifosfamide+etoposide according to approved dosing regimens for a maximum of 5 cycles. Subjects received lenvatinib once daily, which could be continued as a single agent after the completion / discontinuation of ifosfamide+etoposide until disease progression (PD), development of unacceptable toxicity, noncompliance, investigator or subject request, initiation of a new anticancer therapy, withdrawal of consent, or sponsor's termination of the study Assessments (Cohort 3).

Due to the bone-producing nature of osteosarcoma, radiographic objective responses are rare.

For the Cohorts 2B and 3B, the primary endpoint chosen was PFS-4 as assessed by Response Evaluation Criteria in Solid Tumors (RECIST) 1.1. PFS rate at a fixed time point was chosen as measure of activity of anticancer drugs for osteosarcoma because of the limitations of ORR in osteosarcoma (Omer, et al., 2017; Lagmay, et al., 2016; Grignani, et al., 2012). Although there is no consensus on time point, due to the role of surgery in the management of disease, the selected time point must not delay surgery. At the time Study 207 was planned, single-agent sorafenib demonstrated clinical activity in relapsed disease based on a PFS-4 rate of 46% (Grignani, et al., 2012), leading to its inclusion in the NCCN and ESMO treatment guidelines for osteosarcoma (NCCN, 2019; ESMO, 2018). Subsequent studies of novel therapies have also used PFS-4 as the primary endpoint. The use of a 4-month time point also coincides with the completion of chemotherapy. Accordingly, Study 207 used PFS-4 as the primary efficacy outcome measure and permitted surgery of pre-existing lesions after completion of 4 months of therapy, although the study was not designed to determine eligibility for subsequent surgery.

Therefore, Study 207 used PFS-4 as the primary outcome measure of activity in osteosarcoma and permitted surgery of pre-existing lesions after completion of 4 months of therapy. The investigator performed tumor assessments using RECIST 1.1 during the Pretreatment Phase, every 6 weeks during the Treatment Phase, and in the posttreatment period until the subject had PD or until another anticancer therapy was initiated, whichever occurred first. Investigator-determined response assessments were performed at each assessment time point.

Secondary objectives of the study were standard assessments in cancer trials and included safety, toxicity, tumour response (PFS, BOR, DOR, TTP, ORR, DCR and CBR), and determination of PK parameters. Overall survival was also updated from an exploratory objective to a secondary objective (Protocol Amendment 04).

The ultimate goal of treatment in osteosarcoma is surgical resection, which is prognostic for treatment outcomes (Leary, et al., 2013; Bacci, et al., 2005; Chou, et al., 2005; Kempf-Bielack, et al., 2005; Hawkins and Arndt, 2003). For patients who are unable to achieve complete resection, the disease is almost universally fatal (ESMO, 2018).

Subjects with histologically or cytologically confirmed relapsed (≥1 relapse) or refractory osteosarcoma were eligible for inclusion in Cohorts 3A and 3B. Subjects had to have evaluable or measurable disease per RECIST 1.1, adequate organ (eg, bone marrow, renal, hepatic, cardiac) function, life expectancy of at least 3 months, Lansky play score or Karnofsky Performance Status (KPS) score of ≥50%, appropriate washout periods following prior therapy, no more than 1 prior VEGF/VEGFR-targeted therapy for their cancer, and no clinically significant abnormalities that could have interfered with the subjects' participation in the study or analysis of their data as outlined in the protocol.

Dose interruptions, dose reductions, or treatment discontinuation were allowed for subjects who experienced lenvatinib-related toxicity. Once the dose was reduced, it could not be increased at a later date.

The original protocol was approved on 08 May 2014. There were 4 protocol amendments. Major changes, focusing on those that affected Cohort 3. Protocol Amendment 04 was finalized after the data cut off for this CSR; therefore, the resulting changes are not reflected in the body of this CSR. However, the changes are included in Table 4 for completeness. In Amendment 04, overall survival was changed from an exploratory to a secondary objective in order to align the protocol with the EU paediatric investigational plan. However, the analysis approach for overall survival remained unchanged.

Efficacy data and additional analyses

Results of treatment with single-agent lenvatinib in solid tumours (Cohort 1), relapsed/refractory differentiated thyroid carcinoma (Cohort 2A), and osteosarcoma (Cohort 2B), were reported separately in a dedicated CSR distinct from the CSR for Cohorts 3A and 3B with combination therapy.

Selection of the starting dose for monotherapy and combination with chemotherapy

The RD of lenvatinib was determined to be 14 mg/m2 QD in Cohort 1 and this was the dosage used in Cohort 2. For dose-finding, the starting dosage of lenvatinib, 11 mg/m2/day, was 80% of the adult dosage of 24 mg QD in RR-DTC. The maximum tolerated dose and recommended Phase 2 dose of single-agent lenvatinib of 14 mg/m2 QD provides comparable exposure to the recommended daily dose of single-agent lenvatinib (24 mg QD) in adults with RR-DTC. Dose-limiting toxicities occurred in 3 subjects, all at the 14 mg/m2 dose level, and included hypertension (n=2) and ALT increased (n=1).

In Cohort 3A, escalating doses of single-agent lenvatinib were administered orally once daily in combination with ifosfamide 3000 mg/m2 and etoposide 100 mg/m2, administered IV on Days 1 to 3 of each 21-day cycle. The starting dosage of lenvatinib, 11 mg/m2/day, was 20% lower than the RD determined in Cohort 1 (14 mg/m2 lenvatinib). Dose-limiting toxicities occurred in 3 subjects, and included thrombocytopenia in 2 subjects, 1 subject each at the 11 and 14 mg/m2 dose levels. A third subject, at the 14 mg/m2 dose level, had DLTs of oral dysesthesia, back pain, and muscle spasms. The 14 mg/m2 lenvatinib dose level (with daily dose capped at 24 mg QD) was identified as the recommended dose (RD) in combination with chemotherapy. This dose is the same as the RD determined in the monotherapy Phase 1 dose-finding Cohort 1, and is equivalent to the RD of lenvatinib in adults with DTC (24 mg QD).

DTC

Due to the rarity of RR-DTC in paediatric patients, only 1 subject with this disease was enrolled in Cohort 2A, despite implementing measures to improve enrolment. Data for this patient are not included in the main analysis, but are descriptively summarized in Section 14.3.3 of the CSR.

This patient had a BOR of confirmed PR. This patient was diagnosed with papillary thyroid cancer in 2017, was enrolled at lenvatinib 14 mg/m2. On 2018 (Day 1), lenvatinib was initiated at an actual dose of 24 mg QD. During the study, he experienced the following nonserious adverse events: abdominal, back and neck pain, acne, diarrhoea, hypertension, hypertriglyceridemia, hyperuricemia, insomnia, pyrexia, and thyroglobulin increased. All TEAEs were Grade 1 or 2, except for Grade 3 diarrhoea, which started on Day 35. On Day 45, the treatment with lenvatinib was interrupted for Grade 3 diarrhoea; treatment was restarted on Day 48 at a reduced dose of 11 mg/m2. As of the cutoff date of 2019, the subject has received lenvatinib for 185 days and treatment was ongoing. At that time, the subject had achieved a best overall response of confirmed partial response.

In order to support the extrapolation of the efficacy of lenvatinib from adult patients to pediatric patients with RR-DTC, a population PK analysis was performed (please refer to M&S section above). The data show that predicted exposure levels for 14 mg/m2 QD lenvatinib are comparable to adults with RR-DTC who received lenvatinib at a fixed dose of 24 mg QD. Moreover, data from the PK analysis support BSA-based dosing.

Although the presentation of DTC in adult and paediatric patients differs, there is no evidence to suggest that RR-DTC in the adult and paediatric population represent a different disease. Furthermore, the treatment strategy for both populations is the same. Thus, given the comparable exposure observed and the similarity in the biological course of disease, the expected response to lenvatinib can be considered similar in both the pediatric and adult populations, with RR-DTC. However, the extrapolation strategy should be justified by the MAH (please refer to the related OCs).

Osteosarcoma

Paediatric osteosarcoma represents an area of high unmet need. Patients with osteosarcoma were enrolled in Cohorts 2A (lenvatinib monotherapy), 3A and 3B (combination of lenvatinib with chemotherapy).

A total of 31 subjects with relapsed/refractory osteosarcoma enrolled in Cohort 2B. Inconsistent with the prevalence of osteosarcoma, the majority of subjects were female. Osteosarcoma also has a slightly higher incidence in black and Hispanic ethnic groups compared with whites (Mirabello, et al., 2009; Bleyer, et al., 2006). However, all but 1 investigational site in this study were in Europe, and 20 of the 31 subjects were white, 2 were of another racial background and, for 9 subjects, race was not collected on the CRF. Only 4 subjects were reported as Hispanic.

In Cohort B, a total of 42 subjects with relapsed/refractory osteosarcoma (22 and 20 in Cohort 3A and Cohort 3B, respectively) were treated. Consistent with the known prevalence of osteosarcoma, the majority of subjects were male. All but 1 investigational site in this study were located in Europe, and 33 of the 42 subjects were white, 3 were of another racial background, and, for 9 subjects, race was not collected on the CRF. Only 8 subjects were reported as Hispanic.

Thus, subject demographics in this study appear to reflect those of the European countries involved and not necessarily the epidemiology of the disease. Nonetheless, no racial differences are expected based on previous results observed throughout the lenvatinib development program and the biology of osteosarcoma.

As regards prior anticancer treatment, in Cohort 3A, 9 subjects (40.9%) received at least 2 prior anticancer regimens, and 3 subjects (13.6%) received 3 or more prior regimens. The most frequently used prior anticancer medications were cisplatin, doxorubicin, and methotrexate. All 22 subjects had received a prior anthracycline. Ten subjects (45.5%) had received prior ifosfamide, 6 of them in combination with etoposide. No subjects in Cohort 3A had received prior anti-VEGF therapy. Overall, response to the subjects' most recent prior therapy was low. Four (18.2%) of the 22 subjects had a PR; 1 additional subject (4.5%) had a CR. The median duration of the most recent prior anticancer therapy was 2.1 and 8.2 months for subjects in the 11 and 14 mg/m2 dose level groups, respectively.

In Cohort 3A, 21 of 22 subjects (95.5%) of subjects underwent a prior anticancer procedure. Seven of the subjects (31.8%) underwent a prior lung resection. Refer to Section 11.1.2.2 for subjects who received prior radiation therapy to the lung.

The majority (80%) of subjects in Cohort 3B had received 2 or more prior anticancer regimens; 40% had received 3 or more prior regimens. Prior anticancer medications used by >50% of subjects (in descending frequency) were cisplatin, doxorubicin, methotrexate, and ifosfamide. Nineteen subjects (95%) had received a prior anthracycline. Fourteen subjects (70%) had received prior ifosfamide, 8 of

them in combination with etoposide. One subject (5%) received prior anti-VEGF therapy, namely bevacizumab. All 20 subjects (100.0%) underwent a prior anticancer procedure. Eleven (55.0%) of the subjects underwent a prior lung resection. Response to the subjects' most Response to the subjects' most recent prior therapy was low. Two (10%) of the 20 subjects had a PR; no subject had a CR.

The median duration of the most recent prior anticancer therapy was 3.6 months. As regards prior radiation therapy, in Cohort 3A, 2 subjects (9.1%), both in the 14 mg/m2 dose level group, received prior radiation therapy to miscellaneous sites or to skull/spine/thorax/pelvic bones.

The median time since last radiotherapy regimen to the first dose of study drug was 12.8 months overall. Both subjects had disease progression at the tumor site following radiotherapy.

In Cohort 3B, 1 subject (5.0%) received prior radiation therapy to the brain, which ended 1.4 months before entering Study 207. The subject did not have disease progression at the tumour site following radiotherapy.

Efficacy

Results for study treatment in subjects with relapsed/refractory osteosarcoma are based on PFS-4 rate, a benchmark for activity in clinical trials in this disease.

Cohort 2B – monotherapy with lenvatinib is osteosarcoma patients

In Cohort 2B, the binomial estimate (Evaluable Set) and KM estimate of PFS-4 rate were 32.1% and 37.8%, respectively, and were close to the prespecified PFS-4 rate (37%) at the end of the second stage of Simon's optimal 2-stage design, suggesting a signal of activity for lenvatinib monotherapy in osteosarcoma. PFS-4 rate based on all 31 subjects in the FAS was 29% (95% CI: 14.2, 48.0). Median overall PFS was 3.0 months. Median TTP was 3.0 months. ORR was 6.7%, 2 subjects achieved a partial response; median duration of response was 4.6 months. Thirteen subjects (43.3%) with measurable disease attained a BOR of SD. Median OS was 10.0 months

Efficacy results, based on PFS-4 rate, supported by PFS, BOR and ORR, suggest that single-agent lenvatinib may have antitumor activity in osteosarcoma. However, the null hypothesis cannot be ruled out because the study did not meet the prespecified boundary, possibly because of sampling variability and the small number of subjects.

The ultimate goal of treatment in osteosarcoma is surgical resection; overall, 5 subjects in Cohort 2B had pre-existent metastatic pulmonary lesion(s) and 4 of these subjects achieved complete surgical resection following study treatment.

Cohort 3A and 3B– combination of lenvatinib with chemotherapy is osteosarcoma patients

Cohort 3A was the dose-finding phase for combination therapy. This study met its primary endpoints for dose-finding in Cohort 3A and assessment of activity in Cohort 3B. After determination of the recommended dose in Cohort 3A, an expansion phase was conducted to assess the efficacy and safety of lenvatinib in combination with chemotherapy in subjects with relapsed/refractory osteosarcoma (Cohort 3B).

In Cohort 3, results for study treatment in subjects with relapsed/refractory osteosarcoma are also based on PFS-4 rate, a benchmark for efficacy in clinical trials in this disease.

In this heavily pretreated population, the PFS-4 rate (binomial estimate) based on all subjects (n=20) in Cohort 3B was 50% (95% CI: 27.2, 72.8). The binomial estimate of the PFS-4 rate based on the Evaluable Set (n=15) was 66.7%. These estimates were statistically significant (P=0.0139 and P=0.0008, respectively) compared with the prespecified PFS-4 rate of 25% for the null hypothesis. The KM estimate for PFS-4 was 77.4% (all subjects). In addition, the PFS-4 rate (binomial estimate) was

66.7% (95% CI: 60.5, 90.5) for the pooled 14 mg/m2 dose level groups in Cohorts 3A and 3B (evaluable subjects n=27; P<0.0001).

Median PFS across all time points was 12.0 months in Cohort 3A and 6.9 months in Cohort 3B. Median PFS for the pooled 14 mg/m2 dose level groups for Cohorts 3A and 3B combined was 8.7 months (95% CI: 4.5,12.0). PFS further supports as a key secondary endpoint assessed by investigators using RECIST 1.1 supports findings for the PFS-4.

Two subjects in Cohort 3A had an objective response (both confirmed PRs). In Cohort 3B, 3 subjects had a confirmed PR (ORR = 16.7%) based on investigator assessments using RECIST 1.1.

The ORR for the pooled 14 mg/m2 dose levels was 9.4% (95% CI: 2.0, 25.0).

Clinical benefit rate was 40.9% (95% CI: 20.7, 63.6) in Cohort 3A: 57.1% (95% CI: 18.4, 90.1) and 33.3% (95% CI: 11.8, 61.6) for the 11 and 14 mg/m2 dose level groups, respectively.

In Cohort 3B, CBR was 40.0% (95% CI: 19.1, 63.9). Median OS was 16.3 months in Cohort 3A and not estimable in Cohort 3B (95% CI: 7.3, NE).

Median OS for the pooled 14 mg/m2 dose levels for Cohorts 3A and 3B combined was 16.3 months (95% CI: 12.6, NE).

In Cohorts 3A and 3B, 13 subjects overall underwent tumor resection, 10 of whom achieved complete resection. In Cohort 3A, 10 subjects (55%) had resection of lung lesions (n=9) and/or bone (n=2) during study treatment or within 30 days posttreatment. All 10 subjects had a complete resection. One additional subject had a partial resection of a lung lesion 122 days posttreatment. In Cohort 3B, 2 subjects (10%) had tumour resections during treatment or within 30 days posttreatment. Both were partial resections of a lung lesion.

Although the pattern of relapse (lung only, bone only, lung and bone) was similar across the 2 cohorts, a higher proportion of subjects in Cohort 3B had received 3 or more prior anticancer medications (40% vs 14%) and had PD as best response to their last chemotherapy regimen (55% vs 27%) compared with subjects in Cohort 3A.

Overall, these data suggest that lenvatinib in combination with ifosfamide and etoposide has activity in relapsed/refractory osteosarcoma.

Safety in monotherapy

Lenvatinib appears to have, based on limited data, an acceptable safety profile in cancer patients aged 2 to 25 years when treatment is initiated at 14 mg/m2 QD (based on BSA; maximum dose of 24 mg QD) and adjusted by a dose-titration algorithm to manage toxicity.

The adverse events reported in this study were manageable and, overall, are consistent with the known safety profile of single-agent lenvatinib in adult cancer populations.

However the incidence of pneumothorax of 11% (6/54) was higher than that observed previously with single-agent lenvatinib in adults (DTC lenvatinib monotherapy, 1.1%; non-DTC lenvatinib monotherapy, 0.5%).

Five of the 6 subjects with pneumothorax, all in Cohort 2B, had lung masses at Baseline, and 4 of the 5 subjects had radiotherapy prior to receiving the first dose of study drug. None of the 6 subjects who experienced pneumothorax had undergone resection of a lung lesion prior to study entry; however, 1 subject had lung resection during study treatment and had a subsequent event of pneumothorax. The incidence of pneumothorax observed in Study 207 is most likely associated with the subjects' underlying osteosarcoma and presence of lung metastases.

Pneumothorax is recognized as a complication in osteosarcoma (Grosu, et al., 2019; Tariq, et al., 2018; Gan, et al., 2015; Fayda, et al., 2012). It is more common in patients with pulmonary metastasis from sarcomas than those with primary pulmonary neoplasms; the incidence is also increased after prior chemotherapy (Fiorelli, et al., 2011). Pneumothorax has been reported as an adverse event in other clinical trials of TKIs, with rates of Grade 3/ 4 events ranging from 3% to 16% in adult and pediatric patients with advanced soft tissue sarcoma or osteosarcoma (Fayda, et al., 2012; Grignani, et al., 2012; Italiano, et al., 2018; Verschoor and Gelderblom, 2014; Xie, et al., 2019). In a Phase 1 trial of bevacizumab plus sorafenib combined with low-dose cyclophosphamide in 44 patients with refractory or recurrent solid tumors, the incidence of pneumothorax was 25%; all 11 subjects had pulmonary lesions at study entry (Interiano, et al., 2015). Therefore, the incidence of pneumothorax in this study is similar to that for other TKIs and is consistent with the incidence in patients with relapsed/refractory osteosarcoma.

Overall, 14 and 21 subjects in Cohort 1 and Cohort 2B, respectively, had a treatment-emergent SAE, including fatal and nonfatal events. For 6 subjects in Cohort 1 and 9 subjects in Cohort 2B, the SAE was considered by the investigator to be treatment-related. Serious AEs appeared to be mainly due to comorbidities or the subjects' underlying cancer. The most frequently reported nonfatal SAEs were cancer pain (13.0%) in Cohort 1 and (approximately 10% or more of subjects, in descending frequency) back pain, pneumothorax, dyspnea, and tumor pain in Cohort 2B.

As required per protocol, the management of lenvatinib toxicities (Grade 3 or 4 and intolerable Grade 2) required an interruption until resolution of event, followed by restarting treatment at a lower dose of lenvatinib (dose reduction) once the toxicity returned to baseline level or improved to Grade 0 or 1. For 9 subjects each in Cohort 1 (39.1%) and Cohort 2B (29.0%), a TEAE led to lenvatinib dose reduction.

Discontinuations of treatment for a TEAE were reported in 17.4% of subjects in Cohort 1 and 16.1% of patients in Cohort 2B. No TEAE led to discontinuation in more than 1 subject each.

Clinically significant events occurred frequently (95.7% of subjects in Cohort 1 and 93.5% of subjects in Cohort 2B); however, few led to treatment discontinuation.

At the time of data cutoff, deaths had been reported for 65.2% of subjects in Cohort 1 and 64.5% of subjects in Cohort 2B. Five deaths in Cohort 1 and 3 deaths in Cohort 2B were attributed primarily to a TEAE, most frequently cardiac arrest or cardiorespiratory arrest. All of these deaths due to AEs were determined by the investigator to be associated with PD and to be unrelated to lenvatinib.

Safety in combination

The RD for lenvatinib in combination with chemotherapy in this paediatric cancer population was determined to be 14 mg/m2 once daily in combination with ifosfamide 3000 mg/m2 and etoposide 100 mg/m2 administered IV on Days 1 to 3 of each 21-day cycle.

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

Treatment-emergent AEs occurred in all 22 subjects (100%) in Cohort 3A; the nature of these TEAEs was similar across the 2 dose levels. The most frequently reported TEAEs in Cohort 3A overall, occurring in 50% or more of subjects (in descending order of frequency), were vomiting, anemia, nausea, diarrhea, hypothyroidism, abdominal pain, arthralgia, epistaxis, neutropenia, constipation, headache, and pain in extremity

Anemia, neutropenia, and/or thrombocytopenia were the most frequently reported AEs overall for lenvatinib in combination with chemotherapy (>50% of subjects in Cohort 3A, and >75% of subjects in Cohort 3B). Other common AEs (≥50% of subjects in either Cohort 3A or Cohort 3B) with the combination included gastrointestinal AEs (abdominal pain, constipation, diarrhea, nausea, vomiting), arthralgia, epistaxis, headache, hypothyroidism, and pain in extremity. These events were consistent with the safety profile of the chemotherapy agents and lenvatinib as a single agent.

Treatment-emergent nonfatal SAEs occurred in 72.7% and 75.0% of subjects in Cohort 3A and Cohort 3B, respectively. The most frequently reported nonfatal SAEs (>20% of subjects) with combination therapy in either Cohort 3A or Cohort 3B were hematologic in nature (ie, neutrophil count decreased/neutropenia, febrile neutropenia, platelet count decreased/ thrombocytopenia, WBC count decreased).

Grade ≥3 TEAEs occurred in 95.5% and 100% of subjects in Cohort 3A and Cohort 3B, respectively The most frequently reported Grade 3/4 TEAEs (occurring in>75% of subjects overall in Cohort 3A or Cohort 3B) were hematologic in nature, based on grouped terms (ie, anemia/decreased hemoglobin, neutropenia/decreased neutrophil count, and/or thrombocytopenia/decreased platelet count); however, no hematologic AEs were Grade 5 or led to treatment discontinuation.

Clinically significant events (CSEs) occurred in 95.5% and 95.0% of subjects in Cohort 3A and Cohort 3B, respectively; these were Grade ≥3 in 45.5% and 15.0% of subjects, respectively. The most frequently reported CSEs (>40% of subjects, in descending frequency) were hemorrhage, hypothyroidism, proteinuria, and weight loss. The majority of these frequently occurring CSEs were Grade 1 or Grade 2 and seldom led to treatment discontinuation.

A total of 7 (16.7%) of the 42 subjects in Cohort 3A (n=6) and Cohort 3B (n=1) developed pneumothorax during treatment. Five subjects had relevant medical history for developing pneumothorax (surgical resection of pulmonary lesions (n=3), thoracotomy (n=1), or thoracic radiotherapy (but not resection; n=1) prior to study entry). Six of the 7 subjects had preexisting lung metastases at Baseline. Pneumothorax was reported as serious Grade 2 or Grade 3 events in 5 of the 7 subjects, which resulted in dose modification (n=4) or treatment discontinuation (n=1). Three of these subjects experienced pneumothorax during study treatment. The incidence of pneumothorax observed in Study 207 is most likely associated with the subjects' underlying osteosarcoma and presence of lung metastases.

Clinical laboratory data, vital sign and ECG data, physical examination findings, and other observations related to safety did not reveal any new safety signals. One subject, in Cohort 3A, had Grade 3 hypertension. Hypertension was not reported as an SAE in any subject.

Myelosuppressive TEAEs occurred frequently with combination treatment than with single-agent lenvatinib. Anaemia, neutropenia, leukopenia, and/or thrombocytopenia were reported in 95.5% (n=21/22) of subjects in Cohort 3A and 95% (n=19/20) of subjects in Cohort 3B. This is in contrast to 39.1% (9/23) of subjects in Cohort 1 and 58.1% (18/31) of subjects in Cohort 2B, who received single-agent lenvatinib. Moreover in Cohorts 1 and 2B, only 2 subjects (8.7%) and 7 subjects (22.6%), respectively, were considered by the investigator to have a treatment-related hematologic TEAE.

Neutropenia, thrombocytopenia, and anemia are well-known effects of cytotoxic chemotherapy agents, including ifosfamide and etoposide (see ifosfamide and etoposide package inserts). Eighteen subjects (81.8%) in Cohort 3A and 16 subjects (80.0%) in Cohort 3B received immunostimulants for neutropenia, including filgrastim, pegfilgrastim, and G-CSF, among others. Four subjects in Cohort 3A had a dose modification of both ifosfamide and etoposide for febrile neutropenia and/or thrombocytopenia. In Cohort 3B, 1 subject each had dose reductions of ifosfamide and etoposide for thrombocytopenia and WBC count decreased. Furthermore, no subject discontinued any of the 3 study drugs because of myelosuppressive effects. Thus, these AEs were well managed during the study.

These results are consistent with results observed with single-agent lenvatinib in Cohorts 1 and 2B, in which 6 (11.1%) of the 54 subjects developed pneumothorax during treatment.

Dose adjustments

Adverse events led to dose reduction of lenvatinib in 72.7% and 55.0% of subjects in Cohort 3A and Cohort 3B, respectively. Events that most frequently (total n=5 or 6 subjects in Cohorts 3A and 3B combined) led to lenvatinib dose modification (reduction/interruption) overall were abdominal pain, diarrhea, febrile neutropenia, nausea, platelet count decreased, and thrombocytopenia. Most of the remaining TEAEs that led to dose reduction occurred in 3 or fewer subjects each.

Adverse events led to dose reduction of ifosfamide and/or etoposide in 18.2% and 25.0% of subjects in Cohort 3A and Cohort 3B, respectively. Events that each led to dose reduction of chemotherapy in 2 subjects overall were pyrexia and thrombocytopenia. The remaining AEs that led to dose reduction of one or both chemotherapy agents occurred in 1 subject each.

Based on the AE CRF, 27.3% and 5.0% of subjects in Cohort 3A and Cohort 3B, respectively, discontinued treatment for an AE. No individual TEAE led to discontinuation of any study drug in more than 1 subject each.

Treatment-emergent AEs led to dose reduction of lenvatinib in 11 subjects (55.0%). The TEAEs that led most frequently to dose reduction of lenvatinib (>2 subjects in order of decreasing frequency) were platelet count decreased, diarrhea, and WBC count decreased. All other TEAEs leading to dose reduction of lenvatinib were each reported by 1 or 2 subjects.

As required per protocol, the management of lenvatinib toxicities (Grades 3 or 4 and intolerable Grade 2) required an interruption until resolution of event, followed by a dose reduction once the toxicity returned to baseline level or improved to Grade 0 or 1. A TEAE led to lenvatinib dose modifications in 18 subjects (81.8%) in Cohort 3A and 14 subjects (70.0%) in Cohort 3B. Within the 2 cohorts, nearly all TEAEs that led to dose modification occurred in 3 or fewer subjects each. In Cohort 3B, however, platelet count decreased and diarrhea led to dose modification in 5 and 4 subjects, respectively.

Dose reductions of ifosfamide or etoposide each occurred in 22.7% of subjects in Cohort 3A and in 25% of subjects in Cohort 3B. The only TEAEs that led to dose modification of chemotherapy in more than 1 subject was pyrexia (n=2 in Cohort 3A) and thrombocytopenia (n=3, 2 in Cohort 3A, 1 in Cohort 3B). For 1 event of thrombocytopenia, only the dose of etoposide was reduced. For all other events leading to dose reduction, the investigator reduced the dose of both chemotherapy agents.

Discontinuation of at least 1 study drug was reported for 6 subjects (27.3%) in Cohort 3A and 1 subject (5.0%) in Cohort 3B. Based on disposition data, AEs were cited by the investigators as the primary reason for ending treatment in 2 subjects (9.1%) in Cohort 3A and no subjects in Cohort 3B. In Cohort 3A, pleural effusion led to the discontinuation of all 3 study drugs in 1 subject and only lenvatinib in 1 subject. All other TEAEs led to discontinuation in 1 subject each. In Cohort 3B, 1 subject (5.0%) discontinued both ifosfamide and etoposide for Grade 3 veno-occlusive disease. This event resulted in a dose reduction of lenvatinib.

Deaths, Other Serious Adverse Events, and Significant Adverse Events

Overall in Cohort 3A, all 22 subjects (100%) had TEAEs reported by the investigator to be treatment-related. The most frequently reported treatment-related TEAEs, occurring in 40% or more of subjects (in decreasing frequency) were: anemia, nausea, neutropenia, abdominal pain, hypothyroidism, vomiting, diarrhea, epistaxis, and thrombocytopenia. The majority of remaining treatment-related TEAEs were reported for 1 or 2 subjects each.

Nineteen subjects (86.4%) had a treatment-related TEAE that was Grade 3 or higher. However, no treatment-related Grade 5 TEAEs were reported. The most frequently reported treatment-related Grade 3 or Grade 4 TEAEs, occurring in 30% or more of subjects (in descending frequency) were anemia, neutropenia, thrombocytopenia, febrile neutropenia, and WBC count decreased. The majority of remaining treatment-related Grade 3 and 4 TEAEs occurred in 1 or 2 subjects each.

Overall in Cohort 3B, 19 subjects (75.0%) had TEAEs reported by the investigator to be treatment-related. The most frequently reported treatment-related TEAEs, occurring in 40% or more of subjects (in decreasing frequency) were: anaemia, nausea, diarrhoea, vomiting, WBC count decreased, platelet count decreased, neutrophil count decreased, neutropenia, and proteinuria. The majority of remaining treatment-related TEAEs were reported for 1 or 2 subjects each. See Section 12.4.1.3 for further details about CSEs.

Nineteen subjects (75.0%) had a severe (Grade ≥3) treatment-related TEAE. However, no treatment-related Grade 5 TEAEs were reported. The most frequently reported treatment-related Grade 3/4 TEAEs, occurring in ≥25% of subjects (in descending order of frequency), were anemia, WBC count decreased, platelet count decreased, neutrophil count decreased, neutropenia, and thrombocytopenia. The majority of remaining treatment-related Grade 3/4 TEAEs occurred in 1 or 2 subjects each. Of note, most of the haematological TEAEs reported were reported by the investigator to be both treatment-related and Grade 3/4.

Overall, the AE profile of study treatment in this pediatric study is consistent with the known profiles of the individual agents in adults. The nature of the fatal and nonfatal SAEs and TEAEs leading to dose modification or discontinuation of study drug in this study are not unexpected for a population with relapsed/refractory osteosarcoma and the known toxicity profiles of the individual agents. The AEs were expected, well tolerated, and manageable. Overall, more than 90% of subjects in Cohort 3A (n=20/22) and Cohort 3B (n=18/20) had 1 or more hematologic TEAEs (eg, febrile neutropenia, thrombocytopenia, anemia. A total of 16 subjects (5 in Cohort 3A and 11 in Cohort 3B) had a dose modification of lenvatinib (interruption and/or reduction), but none discontinued treatment for or died of a hematologic event. In Cohort 3A, 3 subjects also had a dose reduction of ifosfamide and/or etoposide for febrile neutropenia or thrombocytopenia.

In Cohort 3A, subjects who received 11 mg/m2 had a longer median duration of treatment than those in the 14 mg/m2 dose level group: 54.0 and 20.0 weeks, respectively. Median number of cycles of treatment received was 17 and 6 for the 11 and 14 mg/m2 dose levels, respectively. However, the rate of TEAEs (including Grade ≥3 TEAEs and SAEs) was similar across the 2 dose levels. All results must be interpreted with caution due to the small numbers of subjects within each dose level (n=11 subjects each) in Cohort 3A, as well as the nonrandomized study design.

At the time of data cutoff, 15 subjects (12 in Cohort 3A and 3 in Cohort 3B) had died. Four of the deaths (2 in Cohort 3A and 2 in Cohort 3B) occurred during the treatment period. These 4 deaths were each attributed to a TEAE associated with progressive disease; none were considered by the investigator to be related to study treatment.

Overall, 16 (72.7%) and 15 (75.0%) subjects in Cohort 3A and Cohort 3B, respectively, had a treatment-emergent SAE, including fatal and nonfatal events. In Cohort 3A, the most frequently occurring SAEs were febrile neutropenia (n=8) and pneumothorax (n=4). In Cohort 3B, the most frequently reported SAEs were all hematologic in nature (ie, decreases in neutrophil count, platelet count, red blood cell count). For 12 subjects each in Cohort 3A and Cohort 3B, the SAE was considered by the investigator to be treatment-related. Overall, the predominant SAEs appeared to be mainly due to the known toxicities of the chemotherapeutic agents, followed by comorbidities or complications of the subjects' underlying cancer.

Clinically significant events occurred frequently (95.5% of subjects in Cohort 3A and 95.0% of subjects in Cohort 3B); however, only 2 led to treatment discontinuation. One subject discontinued treatment for hypothyroidism, and 1 subject discontinued treatment for pneumothorax. These results suggest that the dose modification algorithm was successful in allowing subjects to remain on treatment rather than discontinue treatment for toxicity.

Overall, the nature of the fatal and nonfatal SAEs and TEAEs leading to dose modification or discontinuation of study drug in this study are not unexpected for a population with relapsed/refractory osteosarcoma and the toxicity profile of lenvatinib and the chemotherapy agents. The results indicate that lenvatinib plus chemotherapy was tolerable and generally safe when TEAEs were managed appropriately.

Conclusions

Results for study treatment in subjects with relapsed/refractory osteosarcoma are based on PFS-4 rate, a benchmark for efficacy in clinical trials in this disease. In Cohort 3B, the binomial estimates of 50% (n=10/20) and 66.7% (n=10/15) for the FAS and Evaluable Sets, respectively, were statistically significant (P=0.0139 and P=0.0008, respectively) compared with the prespecified PFS-4 rate of 25% in the null hypothesis, indicating activity of the triple combination in osteosarcoma. Median PFS was 6.9 months, which further supports this finding, also supported by other secondary endpoints.

Overall, 13 subjects (31.0%) in Cohorts 3A and 3B underwent surgical resection of pre-existing tumor lesion(s) and 10 subjects achieved complete resection, an goal in osteosarcoma treatment.

Lenvatinib appears to have an acceptable safety profile at 14 mg/m2 QD (based on BSA; maximum dose of 24 mg QD) in combination with ifosfamide and etoposide. When adjusted by a dose-titration algorithm to manage toxicity, the rate of dose modifications is relatively high (dose reduction of lenvatinib occurred in 72.7% and 55.0% of patients in Cohort 3A and Cohort 3B). The adverse events were consistent with the known safety profile of single-agent lenvatinib in adult cancer populations as well as the known AEs for ifosfamide and etoposide, such as myelosuppression.

Overall, further development of lenvatinib in combination with chemotherapy in osteosarcoma patients is supported by currently available data and the ongoing Study 8 will provide further results in this indication. 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.

Other concerns to be addressed by the MAH:

Exploratory pooled analyses were performed for the 14 mg/m2 dose level group across both cohorts combined (the pooled 14 mg/m2 dose level) for PFS-4 rate, PFS, ORR, and OS. Analysis for Progression-Free Survival Rate at 4 Months (binomial estimate) based on data in 35 patients (according to the ITT principle) should be provided. Integrated summary of safety with the pooled 14 mg/m2 dose level of lenvatinib in monotherapy and combination with chemotherapy in paediatric patients (including by age groups, e.g. adolescents vs younger paediatric patients) should be provided, as well as discussion on tolerability (e.g. dose reductions, interruptions, discontinuation due to AE, in comparison with data in adult patients). **(OC)**

Palatability and acceptability of the suspension formulation of lenvatinib is one of the secondary endpoints of the Study 207. The aggregated results from different cohorts and their applicability should be discussed. **(OC)**

The MAH did not suggest an extension of indication to paediatric patients with DTC and/or any changes to the SmPC. The MAH should discuss the current claim and a text proposal to include relevant

information obtained from Study 207 in sections 4.2, 4.8 and 5.1 of the SmPC, and PK data in section 5.2 should be submitted. **(OC)**

3. Rapporteur's overall conclusion and recommendation

☐ **Fulfilled:**

☒ **Not fulfilled:**

Based on the data submitted, the MAH should provide additional analyses of data as part of this procedure. (see section "Request for supplementary information")

4. Request for supplementary information

Other concerns

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

1) For DTC indication in paediatric patients the MAH should discuss the initial extrapolation strategy, based on PK matching, taking into account that PK data are available only in one paediatric patient with DTC. The objectives of the POPPK analyses do not clearly refer to the agreed objective for the PIP Study 7 to support the extrapolation of lenvatinib efficacy from adult to paediatric patients with DTC. The objectives specified in PIP Study 207 should be considered for the POPPK and PK/PD analyses. discussion on the representativity of the data in paediatric and adult patients used for the POPPK model for the intended target population in DTC as per PIP Study 7.

2) The MAH should discuss more in detail the rationale and the choice of the dataset for the adult POPPK model (DTC, monotherapy) and whether indication effects on PK are expected or known. The covariates chosen for the POPPK model are the same as for the model developed for adult patients, therefore assuming that that same covariate effect would be expected in the paediatric population with DTC as in adult population in DTC or in other indications. The choice of covariates should be justified specifically for paediatric patients with DTC. The choice of individual AEs for PK/PD analyses of exposure-safety in paediatric vs adult patients should be discussed based on the observed safety profiles.

3) Exploratory pooled analyses were performed for the 14 mg/m2 dose level group across both cohorts combined (the pooled 14 mg/m2 dose level) for PFS-4 rate, PFS, ORR, and OS. Analysis for Progression-Free Survival Rate at 4 Months (binomial estimate) based on data in 35 patients (according to the ITT principle) should be provided. Integrated summary of safety with the pooled 14 mg/m2 dose level of lenvatinib in monotherapy and combination with chemotherapy in paediatric patients (including by age groups, e.g. adolescents vs younger paediatric patients) should be provided, as well as discussion on tolerability (e.g. dose reductions, interruptions, discontinuation due to AE, in comparison with data in adult patients).

4) Palatability and acceptability of the suspension formulation of lenvatinib is one of the secondary endpoint of the Study 207. The aggregated results from different cohorts and their applicability should be discussed.

5) The MAH did not suggest an extension of indication to paediatric patients with DTC and/or any changes to the SmPC. The MAH should discuss the current claim and a text proposal to include relevant information obtained from Study 207 in sections 4.2, 4.8 and 5.1 of the SmPC, and PK data in section 5.2 should be submitted.

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

5. Responses to the request for supplementary information

Question 1

For DTC indication in paediatric patients the MAH should discuss the initial extrapolation strategy, based on PK matching, taking into account that PK data are available only in one paediatric patient with DTC. The objectives of the POPPK analyses do not clearly refer to the agreed objective for the PIP Study 7 to support the extrapolation of lenvatinib efficacy from adult to paediatric patients with DTC. The objectives specified in PIP Study 207 should be considered for the POPPK and PK/PD analyses. discussion on the representativity of the data in paediatric and adult patients used for the POPPK model for the intended target population in DTC as per PIP Study 7.

Summary of the MAH's response

Marketing Authorisation Holder (MAH) would like to clarify that there is no plan to seek a paediatric indication for differentiated thyroid cancer (DTC) or any other type of cancer, based on the results of Study E7080-G000-207 (hereafter, Study 207) or Study E7080-G000-230 (hereafter Study 230), which is the other paediatric clinical study in the Paediatric Investigation Plan (PIP) (EMEA-001119-PIP02-12-M08), and as such there is no further need to perform any extrapolation of adult data to the paediatric population. Therefore, based on this strategy the MAH believes that the Agency's question is no longer applicable.

Assessment of the MAH's response

There is no plan to submit a paediatric indication for DTC or any other type of cancer by the MAH, and thus extrapolation of adult data to the paediatric population is not proposed.

Conclusion

Issue not pursued.

Question 2

The MAH should discuss more in detail the rationale and the choice of the dataset for the adult POPPK model (DTC, monotherapy) and whether indication effects on PK are expected or known. The covariates chosen for the POPPK model are the same as for the model developed for adult patients, therefore assuming that that same covariate effect would be expected in the paediatric population with DTC as in adult population in DTC or in other indications. The choice of covariates should be justified specifically for paediatric patients with DTC. The choice of individual AEs for PK/PD analyses of exposure-safety in paediatric vs adult patients should be discussed based on the observed safety profiles.

Summary of the MAH's response

During the clinical development of lenvatinib for use in adults, the MAH has performed several population pharmacokinetic (POPPK) analyses on pooled data to support the currently approved indications and all relevant PK/pharmacodynamic (PD) reports have been submitted to the Agency. In the most recent report submitted in support of the advanced endometrial carcinoma indication (CPMS-E7080-015R-v1 submitted under Lenvima electronic Common Technical Document seq. no. 0112) the effect of indication (ie, tumor type) on PK was assessed and was shown to be minimal and of no clinical relevance, as agreed by the Committee for Medicinal Products for Human Use. The effect of other covariates was consistent in all POPPK analysis, regardless of indication.

With regards to adverse events (AEs), based on several exposure-response analyses for most frequent treatment-emergent AEs, including hypothyroidism, hypertension, weight decrease, vomiting, and proteinuria, data has shown that the observed safety profile of lenvatinib is similar across studies with different indications, regardless of body weight or age. Again this data has previously been submitted in support of the approved indications (DTC, hepatocellular carcinoma [HCC], renal cell carcinoma [RCC], and advanced endometrial cancer).

As mentioned above, the MAH does not plan to seek a paediatric indication for DTC or any other type of cancer, based on the results of Study 207 or Study 230, and as such, there is no further need to perform any additional exposure-response analysis for most frequent AEs. In both paediatric studies, the safety profile in paediatric patients is consistent with the known safety profile of lenvatinib in adults.

Assessment of the MAH's response
The MAH considered that the currently available PK-PD data and results from POPPK analyses can be applicable regardless of age and indication. No further exposure-response analyses on safety in the paediatric patients are proposed.

Conclusion

Issue not pursued.

Question 3

Exploratory pooled analyses were performed for the 14 mg/m2 dose level group across both cohorts combined (the pooled 14 mg/m2 dose level) for PFS-4 rate, PFS, ORR, and OS. Analysis for Progression-Free Survival Rate at 4 Months (binomial estimate) based on data in 35 patients (according to the ITT principle) should be provided. Integrated summary of safety with the pooled 14 mg/m2 dose level of lenvatinib in monotherapy and combination with chemotherapy in paediatric patients (including by age groups, e.g. adolescents vs younger paediatric patients) should be provided, as well as discussion on tolerability (e.g. dose reductions, interruptions, discontinuation due to AE, in comparison with data in adult patients).

Summary of the MAH's response
Analysis for progression-free survival rate at 4 months (binomial estimate) based on data in 35 patients (according to the intention to treat [ITT] principle) has been presented in the published article, "Lenvatinib with etoposide plus ifosfamide in patients with refractory or relapsed osteosarcoma (ITCC-050): A multicentre, open-label, multicohort, phase 1/2 study", Gaspar, et al., 2021 (https://doi.org/10.1016/S1470-2045(21)00387-9). The source table is Supplemental Table 3 on page 6 of the supplement to the published article. The published article and its supplement are enclosed in the Appendix of this response document.

The MAH does not plan to seek a paediatric indication based on Study 207 as such, the MAH believes that neither an integrated summary of safety with the pooled 14 mg/m2 dose level of lenvatinib in monotherapy and combination with chemotherapy in paediatric patients, nor an additional discussion on tolerability from this study are warranted

Assessment of the MAH's response
The applicant submitted the published article to present the efficacy analysis (including progression-free survival rate) at 4 months (binomial estimate) based on data in 35 patients across both cohorts combined (the pooled 14 mg/m2 dose level).

Neither further integrated summary of safety with the pooled 14 mg/m2 dose level of lenvatinib in monotherapy and combination with chemotherapy, nor an additional discussion on tolerability from this study are submitted.

Conclusion

Issue not pursued.

Question 4

Palatability and acceptability of the suspension formulation of lenvatinib is one of the secondary endpoint of the Study 207. The aggregated results from different cohorts and their applicability should be discussed.

Summary of the MAH's response
As highlighted by the agency, a secondary endpoint of Study 207 was to assess the palatability and acceptability of the oral suspension formulation of lenvatinib using the Palatability Questionnaire. All subjects who received the suspension formulation and completed at least 1 question on the Palatability Questionnaire were included in the Palatability Analysis Set. Three subjects in Cohort 1 and 1 subject in Cohort 2B received the suspension. Ratings for overall acceptability were really bad, super bad, and good for the 3 subjects in Cohort 1, respectively. The subject in Cohort 2B rated the overall acceptability of the suspension as good. Two subjects in Cohort 3A and 5 subjects in Cohort 3B took lenvatinib as an oral suspension. Five subjects (1 in Cohort 3A, 4 in Cohort 3B) completed the palatability questionnaire. Overall acceptability of the lenvatinib suspension was rated as good by the subject in Cohort 3A, and good, may be good or may be bad; bad and really bad (n=1 subject for each rating) for the subjects in Cohort 3B.

The MAH does not plan to seek a paediatric indication, based on Study 207 or Study 230, for either DTC or any other type of cancer; therefore, the MAH believes further discussion regarding the palatability and acceptability of the suspension formulation of lenvatinib is not warranted.

Assessment of the MAH's response
The applicant provided the results on palatability and acceptability of the suspension formulation of lenvatinib in the Study 207 as per request.

No further discussion regarding the palatability and acceptability of the suspension formulation of lenvatinib is considered warranted by the MAH.

Conclusion

Issue not pursued.

Question 5

The MAH did not suggest an extension of indication to paediatric patients with DTC and/or any changes to the SmPC. The MAH should discuss the current claim and a text proposal to include relevant information obtained from Study 207 in sections 4.2, 4.8 and 5.1 of the SmPC, and PK data in section 5.2 should be submitted.

Summary of the MAH's response
The MAH does not plan to seek a paediatric indication based on Studies 207 or 230 from the PIP.

A Type 2 variation to update the Summary of Product Characteristics (SmPC) with the outcome of both of these studies is planned in 2023, and upon completion of the ongoing Full Compliance Check.

Updates to SmPC sections: 4.2, 4.8, 5.1, and 5.2 will be proposed. As the proposed text will be based on both studies, the MAH plans to provide the text at the time of the variation submission.

Assessment of the MAH's response

No SmPC changes are proposed in this variation. The update of SmPC (sections: 4.2, 4.8, 5.1, 5.2) with the complete outcome of two studies will be submitted as a Type 2 variation in 2023.

Conclusion

Issue resolved with recommendation.

The MAH is recommended to submit as committed the update of the relevant SmPC sections to propose inclusion additional information in paediatric patients.

6. Rapporteur's overall conclusion and recommendation

The MAH is recommended to submit as committed the update of the relevant SmPC sections to propose inclusion additional information in paediatric patients.