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

Summary

EudraCT number	2019-003696-19
Trial protocol	FI SE ES GB AT DE FR BE IE NL IT CZ
Global end of trial date	17 August 2023

Results information

Result version number	v1 (current)
This version publication date	06 March 2024
First version publication date	06 March 2024

Trial information

Trial identification

Sponsor protocol code	E7080-G000-230

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04154189
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Eisai Ltd.
Sponsor organisation address	European Knowledge Centre, Mosquito Way Hatfield, Hertfordshire, United Kingdom, AL10 9SN
Public contact	EMEA Medical Information, Eisai Ltd., +44 (0)208 600 1400, EUMedInfo@eisai.net
Scientific contact	EMEA Medical Information, Eisai Ltd., +44 (0)208 600 1400, EUMedInfo@eisai.net

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMEA-001119-PIP02-12
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	17 August 2023
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	17 August 2023
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate whether lenvatinib in combination with ifosfamide and etoposide (Arm A) was superior to ifosfamide and etoposide alone (Arm B) in improving PFS based on IIR assessments (hereafter referred to as "per IIR") using Response Evaluation Criteria in Solid Tumors (RECIST) 1.1, in children, adolescents, and young adults with relapsed or refractory osteosarcoma.

Protection of trial subjects:

This study was conducted in accordance with standard operating procedures (SOPs) of the sponsor (or designee), which are designed to ensure adherence to Good Clinical Practice (GCP) guidelines as required by the following: - Principles of the World Medical Association Declaration of Helsinki (World Medical Association, 2008) - International Council on Harmonisation (ICH) E6 Guideline for GCP (CPMP/ICH/135/95) of the European Agency for the Evaluation of Medicinal Products, Committee for Proprietary Medicinal Products, International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use - Title 21 of the United States (US) Code of Federal Regulations (US 21 CFR) regarding clinical studies, including Part 50 and Part 56 concerning informed subject consent and Institutional Review Board (IRB) regulations and applicable sections of US 21 CFR Part 312 - European Good Clinical Practice Directive 2005/28/EC and Clinical Trial Directive 2001/20/EC for studies conducted within any European Union (EU) country. All suspected unexpected serious adverse reactions were reported, as required, to the Competent Authorities of all involved EU member states. - Article 14, Paragraph 3, and Article 80-2 of the Pharmaceutical Affairs Law (Law No. 145, 1960) for studies conducted in Japan, in addition to Japan's GCP Subject Information and Informed Consent.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	23 March 2020
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Australia: 3
Country: Number of subjects enrolled	Hong Kong: 2
Country: Number of subjects enrolled	Korea, Republic of: 8
Country: Number of subjects enrolled	New Zealand: 1
Country: Number of subjects enrolled	Singapore: 1
Country: Number of subjects enrolled	Taiwan: 7
Country: Number of subjects enrolled	Czechia: 2
Country: Number of subjects enrolled	Finland: 2
Country: Number of subjects enrolled	France: 3
Country: Number of subjects enrolled	Israel: 3

Country: Number of subjects enrolled	Italy: 6
Country: Number of subjects enrolled	Netherlands: 2
Country: Number of subjects enrolled	Spain: 14
Country: Number of subjects enrolled	Sweden: 4
Country: Number of subjects enrolled	Switzerland: 2
Country: Number of subjects enrolled	United Kingdom: 13
Country: Number of subjects enrolled	Canada: 1
Country: Number of subjects enrolled	United States: 7
Worldwide total number of subjects	81
EEA total number of subjects	33

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	13
Adolescents (12-17 years)	47
Adults (18-64 years)	21
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Subjects took part in the study at 84 investigative sites in Austria, Australia, Belgium, Hong Kong, Korea, New Zealand, Singapore, Taiwan, Czech Republic, Finland, France, Israel, Ireland, Italy, Netherlands, Spain, Sweden, Switzerland, United Kingdom, Canada, and the United States.

Pre-assignment

Screening details:

A total of 99 subjects were screened, 18 failed screening. 81 subjects were enrolled and randomized, out of which 78 received the study treatment.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Treatment Arm A: Lenvatinib + Ifosfamide + Etoposide

Arm description:

Subjects received lenvatinib 14 milligrams per square meter (mg/m^2), capsules, orally, once daily, plus ifosfamide 3000 milligrams per square meter per day (mg/m^2/day), intravenously and etoposide 100 mg/m^2/day, intravenously. Ifosfamide and etoposide were administered on Days 1 to 3 of each 21-day cycle for up to 5 cycles. Lenvatinib was administered in continuous 21-day cycles. Treatment continued until disease progression (PD), development of unacceptable toxicity, subject choice, withdrawal of consent or discontinuation of study by the sponsor, whichever occurred first.

Arm type	Experimental
Investigational medicinal product name	Lenvatinib
Investigational medicinal product code	
Other name	E7080
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

Subjects received lenvatinib 14 mg/m^2, capsules, orally, once daily in continuous 21-day cycles until PD, development of unacceptable toxicity, subject choice, withdrawal of consent or discontinuation of study by the sponsor, whichever occurred first.

Investigational medicinal product name	Etoposide
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Subjects received etoposide 100 mg/m^2/day, intravenously on Days 1 to 3 of each 21-day cycle for up to 5 cycles.

Investigational medicinal product name	Ifosfamide
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Subjects received ifosfamide 3000 mg/m^2/day, intravenously on Days 1 to 3 of each 21-day cycle for up to 5 cycles.

Arm title	Treatment Arm B: Ifosfamide + Etoposide

Arm description:

Subjects received ifosfamide 3000 mg/m^2/day, intravenously and etoposide 100 mg/m^2/day, intravenously on Days 1 to 3 of each 21-day cycle for up to 5 cycles. Subjects who had PD per RECIST version (v) 1.1 were eligible for an optional lenvatinib treatment (14 mg/m^2, capsules, orally, once daily in continuous 21-day cycles until next PD, development of unacceptable toxicity, subject choice, withdrawal of consent or discontinuation of study by the sponsor, whichever occurred first) plus any remaining cycles of chemotherapy if 5 cycles were not completed prior to PD.

Arm type	Active comparator
Investigational medicinal product name	Lenvatinib
Investigational medicinal product code	
Other name	E7080
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

Subjects who had PD per RECIST v1.1 were eligible for an optional lenvatinib treatment 14 mg/m^2, capsules, orally, once daily in continuous 21-day cycles until next PD, development of unacceptable toxicity, subject choice, withdrawal of consent or discontinuation of study by the sponsor, whichever occurred first plus any remaining cycles of chemotherapy if 5 cycles were not completed prior to PD.

Investigational medicinal product name	Ifosfamide
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Subjects received ifosfamide 3000 mg/m^2/day, intravenously on Days 1 to 3 of each 21-day cycle for up to 5 cycles.

Investigational medicinal product name	Etoposide
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Subjects received etoposide 100 mg/m^2/day, intravenously on Days 1 to 3 of each 21-day cycle for up to 5 cycles.

Number of subjects in period 1	Treatment Arm A: Lenvatinib + Ifosfamide + Etoposide	Treatment Arm B: Ifosfamide + Etoposide
Started	40	41
Treated (Safety Analysis Set)	39	39
Optional Lenvatinib (Arm B only)	0	16
Completed	0	0
Not completed	40	41
Consent withdrawn by subject	4	6
Death	25	25
Other	11	10

Baseline characteristics

Reporting groups	
Reporting group title	Treatment Arm A: Lenvatinib + Ifosfamide + Etoposide
Reporting group description:	
Subjects received lenvatinib 14 milligrams per square meter (mg/m^2), capsules, orally, once daily, plus ifosfamide 3000 milligrams per square meter per day (mg/m^2/day), intravenously and etoposide 100 mg/m^2/day, intravenously. Ifosfamide and etoposide were administered on Days 1 to 3 of each 21-day cycle for up to 5 cycles. Lenvatinib was administered in continuous 21-day cycles. Treatment continued until disease progression (PD), development of unacceptable toxicity, subject choice, withdrawal of consent or discontinuation of study by the sponsor, whichever occurred first.	
Reporting group title	Treatment Arm B: Ifosfamide + Etoposide
Reporting group description:	
Subjects received ifosfamide 3000 mg/m^2/day, intravenously and etoposide 100 mg/m^2/day, intravenously on Days 1 to 3 of each 21-day cycle for up to 5 cycles. Subjects who had PD per RECIST version (v) 1.1 were eligible for an optional lenvatinib treatment (14 mg/m^2, capsules, orally, once daily in continuous 21-day cycles until next PD, development of unacceptable toxicity, subject choice, withdrawal of consent or discontinuation of study by the sponsor, whichever occurred first) plus any remaining cycles of chemotherapy if 5 cycles were not completed prior to PD.	

Reporting group values	Treatment Arm A: Lenvatinib + Ifosfamide + Etoposide	Treatment Arm B: Ifosfamide + Etoposide	Total
Number of subjects	40	41	81
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	4	9	13
Adolescents (12-17 years)	26	21	47
Adults (18-64 years)	10	11	21
From 65-84 years	0	0	0
85 years and over	0	0	0
Age Continuous Units: years			
arithmetic mean	15.6	14.3	
standard deviation	± 3.76	± 4.16	-
Sex: Female, Male Units: subjects			
Female	15	20	35
Male	25	21	46
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	2	3	5
Not Hispanic or Latino	38	33	71
Unknown or Not Reported	0	5	5
Race Units: Subjects			

White	24	26	50
Black or African American	1	1	2
Asian	13	7	20
American Indian or Alaskan Native	0	1	1
Other	2	4	6
Missing	0	2	2

End points

End points reporting groups

Reporting group title	Treatment Arm A: Lenvatinib + Ifosfamide + Etoposide

Reporting group description:

Subjects received lenvatinib 14 milligrams per square meter (mg/m^2), capsules, orally, once daily, plus ifosfamide 3000 milligrams per square meter per day (mg/m^2/day), intravenously and etoposide 100 mg/m^2/day, intravenously. Ifosfamide and etoposide were administered on Days 1 to 3 of each 21-day cycle for up to 5 cycles. Lenvatinib was administered in continuous 21-day cycles. Treatment continued until disease progression (PD), development of unacceptable toxicity, subject choice, withdrawal of consent or discontinuation of study by the sponsor, whichever occurred first.

Reporting group title	Treatment Arm B: Ifosfamide + Etoposide

Reporting group description:

Subjects received ifosfamide 3000 mg/m^2/day, intravenously and etoposide 100 mg/m^2/day, intravenously on Days 1 to 3 of each 21-day cycle for up to 5 cycles. Subjects who had PD per RECIST version (v) 1.1 were eligible for an optional lenvatinib treatment (14 mg/m^2, capsules, orally, once daily in continuous 21-day cycles until next PD, development of unacceptable toxicity, subject choice, withdrawal of consent or discontinuation of study by the sponsor, whichever occurred first) plus any remaining cycles of chemotherapy if 5 cycles were not completed prior to PD.

Subject analysis set title	Subjects from Treatment Arm A and B: Lenvatinib Suspension
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Subjects who were unable to swallow capsules received lenvatinib as an extemporaneous suspension prepared from the capsule. Subjects received lenvatinib 14 mg/m^2 once daily in continuous 21-day cycles until PD, development of unacceptable toxicity, subject request, withdrawal of consent, or discontinuation of study by the sponsor.

Primary: Progression-free Survival (PFS) by Independent Imaging Review (IIR) Assessment

End point title	Progression-free Survival (PFS) by Independent Imaging Review (IIR) Assessment

End point description:

PFS as assessed by IIR was defined as the time from the date of randomization to the date of the first documentation of PD or date of death (whichever occurred first), as determined using RECIST v1.1. PD was defined as at least a 20 percent (%) increase or 5 millimeter (mm) increase in the sum of diameters of target lesions (taking as reference the smallest sum on study) recorded since the treatment started or the appearance of 1 or more new lesions. PFS was analyzed using Kaplan-Meier method. FAS included all randomized subjects regardless of the treatment actually received.

End point type	Primary

End point timeframe:

From the date of randomization to the date of the first documentation of PD or date of death, whichever occurred first (up to 20.5 months)

End point values	Treatment Arm A: Lenvatinib + Ifosfamide + Etoposide	Treatment Arm B: Ifosfamide + Etoposide		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	40	41		
Units: months				
median (confidence interval 95%)	6.5 (5.7 to 8.2)	5.5 (2.9 to 6.5)		

Statistical analyses

Statistical analysis title	Treatment Arm A versus Treatment Arm B

Statistical analysis description:

Hazard ratio was based on Cox Proportional Hazard Model including treatment group as a factor and stratified by Age (less than [<]18 years, greater than or equal to [>=]18 years) in interactive response technology (IRT).

Comparison groups	Treatment Arm A: Lenvatinib + Ifosfamide + Etoposide v Treatment Arm B: Ifosfamide + Etoposide
Number of subjects included in analysis	81
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0396 [1]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.54
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.27
upper limit	1.08

Notes:

[1] - One-sided P value

Secondary: Percentage of Subjects with PFS at Month 4 (PFS-4m Rate) by IIR Assessment

End point title	Percentage of Subjects with PFS at Month 4 (PFS-4m Rate) by IIR Assessment

End point description:

PFS rate at 4 months as assessed by IIR was defined as the percentage of subjects who were alive and without PD at 4 months from the randomization date using RECIST v1.1. PD was defined as at least a 20% increase or 5 mm increase in the sum of diameters of target lesions (taking as reference the smallest sum on study) recorded since the treatment started or the appearance of 1 or more new lesions. PFS-4m rate, and 2-sided 95% confidence intervals (CIs) were calculated using Kaplan-Meier product-limit method and Greenwood Formula. FAS included all randomized subjects regardless of the treatment actually received.

End point type	Secondary

End point timeframe:

Month 4

End point values	Treatment Arm A: Lenvatinib + Ifosfamide + Etoposide	Treatment Arm B: Ifosfamide + Etoposide		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	40	41		
Units: percentage of subjects				
number (confidence interval 95%)	76.3 (59.3 to 86.9)	66.0 (47.7 to 79.2)		

Statistical analyses

Statistical analysis title	Treatment Arm A versus Treatment Arm B
Comparison groups	Treatment Arm A: Lenvatinib + Ifosfamide + Etoposide v Treatment Arm B: Ifosfamide + Etoposide
Number of subjects included in analysis	81
Analysis specification	Pre-specified
Analysis type	other[2]
P-value	= 0.1683 [3]
Method	Kaplan-Meier Method
Parameter estimate	Difference in Percentage
Point estimate	10.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-10.6
upper limit	31.1

Notes:

[2] - Difference in PFS rates, and 2-sided 95% CIs: CI and p-value constructed using the difference of the 2 Kaplan-Meier PFS rates (4 months) and the 2 corresponding Greenwood standard errors.
[3] - One-sided P value

Secondary: Percentage of Subjects with PFS at 1 Year or Month 12 (PFS-1y Rate) by IIR Assessment

End point title	Percentage of Subjects with PFS at 1 Year or Month 12 (PFS-1y Rate) by IIR Assessment

End point description:

PFS-1y rate as assessed by IIR was defined as the percentage of subjects who were alive and without PD at 1 year from randomization date using RECIST v1.1. PD was defined as at least a 20% increase or 5 mm increase in the sum of diameters of target lesions (taking as reference the smallest sum on study) recorded since the treatment started or the appearance of 1 or more new lesions. PFS-1y rate was estimated using Kaplan-Meier method. FAS included all randomized subjects regardless of the treatment actually received. "99999" signifies number and 95% confidence interval data could not be estimated because all subjects had an event or were censored before Month 12.

End point type	Secondary

End point timeframe:

Month 12 or 1 Year

End point values	Treatment Arm A: Lenvatinib + Ifosfamide + Etoposide	Treatment Arm B: Ifosfamide + Etoposide		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	40	41		
Units: percentage of subjects				
number (confidence interval 95%)	99999 (99999 to 99999)	14.9 (1.1 to 44.5)		

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival (OS)

End point title	Overall Survival (OS)

End point description:

OS was defined as the time from the date of randomization to the date of death from any cause. FAS included all randomized subjects regardless of the treatment actually received.

End point type	Secondary

End point timeframe:

From the date of randomization to the date of death from any cause (up to approximately 37.1 months)

End point values	Treatment Arm A: Lenvatinib + Ifosfamide + Etoposide	Treatment Arm B: Ifosfamide + Etoposide		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	40	41		
Units: months				
median (confidence interval 95%)	12.4 (10.4 to 19.8)	17.2 (11.1 to 22.3)		

Statistical analyses

Statistical analysis title	Treatment Arm A versus Treatment Arm B

Statistical analysis description:

Hazard ratio was based on a Cox Proportional Hazard Model including treatment group as a factor and stratified by Age (<18 years, >=18 years) in IRT. Efron method was used for ties.

Comparison groups	Treatment Arm A: Lenvatinib + Ifosfamide + Etoposide v Treatment Arm B: Ifosfamide + Etoposide
Number of subjects included in analysis	81
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3924
Method	Stratified Log-rank One-sided Test
Parameter estimate	Hazard ratio (HR)
Point estimate	0.93
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.53
upper limit	1.62

Secondary: Percentage of Subjects with Overall Survival at 1 Year or Month 12 (OS-1y)

End point title	Percentage of Subjects with Overall Survival at 1 Year or Month 12 (OS-1y)

End point description:

OS-1y was defined as the time from the date of randomization to the date of death from any cause assessed up to 1 year. OS rate and 2-sided 95% CI were calculated using Kaplan Meier product-limit method and Greenwood Formula. FAS included all randomized subjects regardless of the treatment actually received.

End point type	Secondary

End point timeframe:

Month 12 or 1 Year

End point values	Treatment Arm A: Lenvatinib + Ifosfamide + Etoposide	Treatment Arm B: Ifosfamide + Etoposide		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	40	41		
Units: percentage of subjects				
number (confidence interval 95%)	49.2 (28.5 to 67.0)	72.1 (54.2 to 83.9)		

Statistical analyses

Statistical analysis title	Treatment Arm A versus Treatment Arm B
Comparison groups	Treatment Arm A: Lenvatinib + Ifosfamide + Etoposide v Treatment Arm B: Ifosfamide + Etoposide
Number of subjects included in analysis	81
Analysis specification	Pre-specified
Analysis type	other[4]
P-value	= 0.0352 [5]
Method	Kaplan Meier Method
Parameter estimate	Difference in Percentage
Point estimate	-22.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-47.6
upper limit	1.9

Notes:

[4] - Difference and 95% CI: difference of 2 Kaplan-Meier OS-1y rates and corresponding Greenwood standard errors.
[5] - One-sided P value

Secondary: Objective Response Rate at Month 4 (ORR-4m) by IIR Assessment

End point title	Objective Response Rate at Month 4 (ORR-4m) by IIR Assessment

End point description:

ORR-4m was defined as the percentage of subjects with best overall response of complete response (CR) or partial response (PR) as determined by IIR using RECIST v1.1 within the first 4 months. CR: defined as the disappearance of all target and non-target lesions (non-lymph nodes). All pathological lymph nodes (whether target or non-target) must have a reduction in their short axis to less than (<) 10 mm. PR: defined as at least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters. 95% confidence interval (CI) of ORR was calculated using the

method of Clopper and Pearson. FAS included all randomized subjects regardless of the treatment actually received.

End point type	Secondary

End point timeframe:

Month 4

End point values	Treatment Arm A: Lenvatinib + Ifosfamide + Etoposide	Treatment Arm B: Ifosfamide + Etoposide		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	40	41		
Units: percentage of subjects				
number (confidence interval 95%)	15.0 (5.7 to 29.8)	7.3 (1.5 to 19.9)		

Statistical analyses

Statistical analysis title	Treatment Arm A versus Treatment Arm B
Comparison groups	Treatment Arm A: Lenvatinib + Ifosfamide + Etoposide v Treatment Arm B: Ifosfamide + Etoposide
Number of subjects included in analysis	81
Analysis specification	Pre-specified
Analysis type	other[6]
Parameter estimate	Difference in Percentage
Point estimate	7.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.4
upper limit	22.3

Notes:

[6] - Difference calculated as Treatment Arm A: Lenvatinib + Ifosfamide + Etoposide minus Treatment Arm B: Ifosfamide + Etoposide. 2-sided 95% CI: Miettinen-Nurminen (Score) confidence limits, stratified by randomization stratification factor age (<18 and >=18 years).

Secondary: ORR by IIR Assessment

End point title	ORR by IIR Assessment

End point description:

ORR by IIR was defined as the percentage of subjects with best overall response of CR or PR determined using RECIST v1.1. CR: defined as the disappearance of all target and non-target lesions (non-lymph nodes). All pathological lymph nodes (whether target or non-target) must have a reduction in their short axis to <10 mm. PR: defined as at least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters. 95% CI of ORR was calculated using the method of Clopper and Pearson. FAS included all randomized subjects regardless of the treatment actually received.

End point type	Secondary

End point timeframe:

From the date of randomization to the date of the first documentation of CR or PR, whichever occurred first (up to approximately 20.5 months)

End point values	Treatment Arm A: Lenvatinib + Ifosfamide + Etoposide	Treatment Arm B: Ifosfamide + Etoposide		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	40	41		
Units: percentage of subjects				
number (confidence interval 95%)	15.0 (5.7 to 29.8)	9.8 (2.7 to 23.1)		

Statistical analyses

Statistical analysis title	Treatment Arm A versus Treatment Arm B
Comparison groups	Treatment Arm A: Lenvatinib + Ifosfamide + Etoposide v Treatment Arm B: Ifosfamide + Etoposide
Number of subjects included in analysis	81
Analysis specification	Pre-specified
Analysis type	other[7]
Parameter estimate	Difference in Percentage
Point estimate	5.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-10.3
upper limit	20

Notes:

[7] - Difference calculated as Treatment Arm A: Lenvatinib + Ifosfamide + Etoposide minus Treatment Arm B: Ifosfamide + Etoposide. 2-sided 95% CI: Miettinen-Nurminen (Score) confidence limits, stratified by randomization stratification factor age (<18 and >=18 years).

Secondary: Number of Subjects With Treatment-emergent Adverse Events (TEAEs) and Treatment-emergent Serious Adverse Events (TESAEs)

End point title	Number of Subjects With Treatment-emergent Adverse Events (TEAEs) and Treatment-emergent Serious Adverse Events (TESAEs)

End point description:

TEAE was defined as an adverse event (AE) that emerged during time from first dose to 30 days following last dose of drug, having been absent at pretreatment or reemerged during treatment, having been present at pretreatment but stopped before treatment, or worsened in severity during treatment relative to pretreatment state, when AE was continuous. SAE was defined as untoward medical occurrence that at any dose resulted in death; was life threatening; resulted in persistent or significant disability; was congenital anomaly or medically important due to other reasons than above mentioned criteria. Safety Analysis Set included subjects who received at least 1 dose of any study drug.

End point type	Secondary

End point timeframe:

From first dose up to 30 days after the last dose of study drug (up to 40.8 months)

End point values	Treatment Arm A: Lenvatinib + Ifosfamide + Etoposide	Treatment Arm B: Ifosfamide + Etoposide		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	39	39		
Units: subjects				
Subjects with TEAEs	38	39		
Subjects with TESAEs	30	20		

Statistical analyses

No statistical analyses for this end point

Secondary: Treatment Arm A: Plasma Concentration of Lenvatinib

End point title	Treatment Arm A: Plasma Concentration of Lenvatinib[8]

End point description:

Plasma concentration of lenvatinib in subjects from Treatment Arm A (Lenvatinib + Ifosfamide + Etoposide) at different time points were reported. As planned, data for this endpoint was analyzed for treatment arm A only. Lenvatinib concentration in plasma was quantified using a validated liquid chromatography tandem mass spectrometry (LC-MS/MS) method. Population Pharmacokinetic (PK) Analysis Set included those subjects who received at least 1 dose of lenvatinib and had documented dose administration history and measurable plasma concentrations of lenvatinib. Here "number of subjects analyzed" signifies subjects who were evaluable for this endpoint. Here "n" signifies subjects who were evaluable for this endpoint at given time points.

End point type	Secondary

End point timeframe:

Cycle 1 Day 1: 0.5-4 hours and 6-10 hours post-dose; Cycle 1 Day 15: Pre-dose, 0.5-4 hours and 6-10 hours post-dose; Cycle 2 Day 1: Pre-dose (each Cycle length = 21 days)

Notes:

[8] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint was planned for treatment Arm A only.

End point values	Treatment Arm A: Lenvatinib + Ifosfamide + Etoposide			
Subject group type	Reporting group			
Number of subjects analysed	37			
Units: nanograms per milliliter (ng/mL)				
arithmetic mean (standard deviation)				
Cycle 1, Day 1: 0.5-4 hours post-dose (n=37)	147.9 (± 194.61)			
Cycle 1, Day 1: 6-10 hours post-dose (n=35)	217.8 (± 99.54)			
Cycle 1, Day 15: Pre-dose (n=36)	70.7 (± 43.48)			
Cycle 1, Day 15: 0.5-4 hours post-dose (n=37)	222.3 (± 203.07)			
Cycle 1, Day 15: 6-10 hours post-dose (n=35)	310.9 (± 106.79)			
Cycle 2, Day 1: Pre-dose (n=37)	70.2 (± 67.95)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in PedsQL Scale: Cancer Module Scale Score at Month 4

End point title	Change From Baseline in PedsQL Scale: Cancer Module Scale Score at Month 4

End point description:

HRQoL: PedsQL 3.0 Cancer Module Scale measured pediatric cancer-specific HRQoL. It included assessment of 8 dimensions: pain and hurt (2 items), nausea (5 items), procedural anxiety (3 items), treatment anxiety (3 items), worry (3 items), cognitive problems (3 items - toddlers [aged 2-4], 4 items - young children [aged 5-7]; 5 items for children aged >=8 years, adults), perceived physical appearance (3 items), communication (3 items). Each item was reported using a 5-point Likert scale, items were then reverse-scored and linearly transformed to a 0 to 100 scale. Cancer Module total score: sum of all items divided by the number of items answered on all the scales. Total score ranges from 0 to 100, where higher scores=better HRQoL, lower scores=worse HRQoL. HRQoL Analysis Set included all subjects who had received at least 1 dose of study drug and had completed at least 1 postbaseline PRO assessment. "Number of subjects analyzed" signifies subjects who were evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Baseline and Month 4

End point values	Treatment Arm A: Lenvatinib + Ifosfamide + Etoposide	Treatment Arm B: Ifosfamide + Etoposide		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16	4		
Units: score on a scale				
arithmetic mean (standard deviation)	2.66 (± 9.989)	2.08 (± 6.736)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Pediatric Quality of Life Inventory (PedsQL) Scale: Generic Core Scale Score at Month 4

End point title	Change From Baseline in Pediatric Quality of Life Inventory (PedsQL) Scale: Generic Core Scale Score at Month 4

End point description:

Health-Related Quality of Life (HRQoL): PedsQL 4.0 Generic Core Scale is a multidimensional scale. It included assessment of 4 dimensions: physical functioning (8 items), emotional functioning (8 items), social functioning (8 items), and school functioning (5 items - children greater than or equal to [>=] 5 years, adults; 3 items - toddlers [aged 2-4 years]). Each item was reported using a 5-point Likert scale,

items were then reverse-scored and linearly transformed to a 0 to 100 scale. Generic Core Scale total score: sum of all the items divided by the number of items answered across all the scales. Total score ranges from 0 to 100, where higher scores=better HRQoL, lower scores=worse HRQoL. HRQoL Analysis Set included all subjects who had received at least 1 dose of study drug and had completed at least 1 postbaseline patient-reported outcome (PRO) assessment. Here "number of subjects analyzed" signifies subjects who were evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Baseline and Month 4

End point values	Treatment Arm A: Lenvatinib + Ifosfamide + Etoposide	Treatment Arm B: Ifosfamide + Etoposide		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	4		
Units: score on a scale				
arithmetic mean (standard deviation)	2.61 (± 17.568)	2.65 (± 4.128)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects Categorized Based on Overall Palatability and Acceptability Questionnaire Responses for Suspension of Lenvatinib

End point title	Number of Subjects Categorized Based on Overall Palatability and Acceptability Questionnaire Responses for Suspension of Lenvatinib

End point description:

Palatability and acceptability of lenvatinib oral suspension formulation was assessed using the Palatability Questionnaire. In questionnaire, subjects were asked to answer palatability and acceptability of lenvatinib suspension considering elements: taste, appearance, smell, how does it feel in the mouth and overall acceptability in terms of 7 responses: Super good, really good, good, may be good or may be bad, bad, really bad, super bad. In this endpoint, number of subjects were reported per their overall palatability and acceptability responses. Palatability and acceptability analysis set included all subjects who received oral suspension of lenvatinib in Treatment Arm A and who received an optional lenvatinib suspension in Treatment Arm B and who answered at least 1 question in palatability questionnaire. As planned, combined data for Lenvatinib from Treatment Arm A and B was reported for this endpoint. "Number of subjects analyzed" signifies subjects evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Cycle 1 Day 1 (Cycle length = 21 days)

End point values	Subjects from Treatment Arm A and B: Lenvatinib Suspension			
Subject group type	Subject analysis set			
Number of subjects analysed	5			
Units: subjects				
Super Bad	0			
Really Bad	0			
Bad	0			
May be Good or May be Bad	2			
Good	2			
Really Good	0			
Super Good	1			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From first dose up to 30 days after the last dose of study drug (up to 40.8 months)

Adverse event reporting additional description:

Treatment Arm B safety data for Ifosfamide + Etoposide to Lenvatinib (optional) were reported separately. Deaths in Subject Disposition module versus Adverse Events module are different because deaths in Subject Disposition module are based on Full Analysis Set while deaths in Adverse Events module based on Safety Analysis Set.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	25.0

Reporting groups

Reporting group title	Treatment Arm A: Lenvatinib + Ifosfamide + Etoposide

Reporting group description:

Subjects received lenvatinib 14 mg/m^2, capsules, orally, once daily, plus ifosfamide 3000 mg/m^2/day, intravenously and etoposide 100 mg/m^2/day, intravenously. Ifosfamide and etoposide were administered on Days 1 to 3 of each 21-day cycle for up to 5 cycles. Lenvatinib was administered in continuous 21-day cycles. Treatment continued until PD, development of unacceptable toxicity, subject choice, withdrawal of consent or discontinuation of study by the sponsor, whichever occurred first.

Reporting group title	Treatment Arm B: Ifosfamide + Etoposide

Reporting group description:

Subjects received ifosfamide 3000 mg/m^2/day, intravenously and etoposide 100 mg/m^2/day, intravenously on Days 1 to 3 of each 21-day cycle for up to 5 cycles. Subjects who had PD per RECIST v1.1 were eligible for an optional lenvatinib treatment (14 mg/m^2, capsules, orally, once daily in continuous 21-day cycles until next PD, development of unacceptable toxicity, subject choice, withdrawal of consent or discontinuation of study by the sponsor, whichever occurred first) plus any remaining cycles of chemotherapy if 5 cycles were not completed prior to PD.

Reporting group title	Treatment Arm B: Ifosfamide+Etoposide to Lenvatinib (Optional)

Reporting group description:

Eligible subjects from Treatment Arm B: Ifosfamide+Etoposide who had PD per RECIST v1.1 received an optional lenvatinib treatment (14 mg/m^2, capsules, orally, once daily in continuous 21-day cycles until next PD, development of unacceptable toxicity, subject choice, withdrawal of consent or discontinuation of study by the sponsor, whichever occurred first) plus any remaining cycles of chemotherapy if 5 cycles were not completed prior to PD.

Serious adverse events	Treatment Arm A: Lenvatinib + Ifosfamide + Etoposide	Treatment Arm B: Ifosfamide + Etoposide	Treatment Arm B: Ifosfamide+Etoposide to Lenvatinib (Optional)
Total subjects affected by serious adverse events			
subjects affected / exposed	30 / 39 (76.92%)	20 / 39 (51.28%)	10 / 16 (62.50%)
number of deaths (all causes)	24	25	12
number of deaths resulting from adverse events	5	1	1
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Malignant pleural effusion			

subjects affected / exposed	4 / 39 (10.26%)	1 / 39 (2.56%)	0 / 16 (0.00%)
occurrences causally related to treatment / all	0 / 6	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 2	0 / 0	0 / 0
Cancer pain			
subjects affected / exposed	0 / 39 (0.00%)	1 / 39 (2.56%)	0 / 16 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metastases to central nervous system			
subjects affected / exposed	1 / 39 (2.56%)	0 / 39 (0.00%)	0 / 16 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metastases to heart			
subjects affected / exposed	1 / 39 (2.56%)	0 / 39 (0.00%)	0 / 16 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tumour pain			
subjects affected / exposed	0 / 39 (0.00%)	1 / 39 (2.56%)	0 / 16 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	1 / 39 (2.56%)	1 / 39 (2.56%)	0 / 16 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypertensive urgency			
subjects affected / exposed	1 / 39 (2.56%)	0 / 39 (0.00%)	0 / 16 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypertension			
subjects affected / exposed	1 / 39 (2.56%)	0 / 39 (0.00%)	1 / 16 (6.25%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			

Catheter site ulcer			
subjects affected / exposed	1 / 39 (2.56%)	0 / 39 (0.00%)	0 / 16 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyrexia			
subjects affected / exposed	6 / 39 (15.38%)	2 / 39 (5.13%)	1 / 16 (6.25%)
occurrences causally related to treatment / all	5 / 7	1 / 3	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pain			
subjects affected / exposed	0 / 39 (0.00%)	0 / 39 (0.00%)	1 / 16 (6.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oedema peripheral			
subjects affected / exposed	0 / 39 (0.00%)	0 / 39 (0.00%)	1 / 16 (6.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune system disorders			
Anaphylactic reaction			
subjects affected / exposed	0 / 39 (0.00%)	1 / 39 (2.56%)	0 / 16 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Drug hypersensitivity			
subjects affected / exposed	0 / 39 (0.00%)	1 / 39 (2.56%)	0 / 16 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	1 / 39 (2.56%)	1 / 39 (2.56%)	0 / 16 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Pneumothorax			
subjects affected / exposed	7 / 39 (17.95%)	1 / 39 (2.56%)	4 / 16 (25.00%)
occurrences causally related to treatment / all	8 / 12	0 / 1	7 / 8
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Pleural effusion			
subjects affected / exposed	1 / 39 (2.56%)	1 / 39 (2.56%)	0 / 16 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Hypoxia			
subjects affected / exposed	0 / 39 (0.00%)	1 / 39 (2.56%)	0 / 16 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory failure			
subjects affected / exposed	1 / 39 (2.56%)	1 / 39 (2.56%)	0 / 16 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Pulmonary embolism			
subjects affected / exposed	0 / 39 (0.00%)	0 / 39 (0.00%)	1 / 16 (6.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Product issues			
Device breakage			
subjects affected / exposed	0 / 39 (0.00%)	2 / 39 (5.13%)	0 / 16 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Device extrusion			
subjects affected / exposed	1 / 39 (2.56%)	0 / 39 (0.00%)	0 / 16 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Haemoglobin decreased			
subjects affected / exposed	0 / 39 (0.00%)	1 / 39 (2.56%)	0 / 16 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neutrophil count decreased			
subjects affected / exposed	1 / 39 (2.56%)	1 / 39 (2.56%)	0 / 16 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Platelet count decreased			
subjects affected / exposed	3 / 39 (7.69%)	0 / 39 (0.00%)	0 / 16 (0.00%)
occurrences causally related to treatment / all	3 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Transaminases increased			
subjects affected / exposed	1 / 39 (2.56%)	0 / 39 (0.00%)	0 / 16 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Post procedural haemorrhage			
subjects affected / exposed	1 / 39 (2.56%)	0 / 39 (0.00%)	0 / 16 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Postoperative wound complication			
subjects affected / exposed	1 / 39 (2.56%)	0 / 39 (0.00%)	0 / 16 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Wound dehiscence			
subjects affected / exposed	2 / 39 (5.13%)	1 / 39 (2.56%)	0 / 16 (0.00%)
occurrences causally related to treatment / all	2 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Cardiac failure			
subjects affected / exposed	1 / 39 (2.56%)	0 / 39 (0.00%)	0 / 16 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Nervous system disorders			
Seizure			
subjects affected / exposed	2 / 39 (5.13%)	1 / 39 (2.56%)	0 / 16 (0.00%)
occurrences causally related to treatment / all	0 / 2	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Posterior reversible encephalopathy syndrome			

subjects affected / exposed	1 / 39 (2.56%)	0 / 39 (0.00%)	0 / 16 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolic encephalopathy			
subjects affected / exposed	1 / 39 (2.56%)	0 / 39 (0.00%)	0 / 16 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Malignant spinal cord compression			
subjects affected / exposed	1 / 39 (2.56%)	0 / 39 (0.00%)	0 / 16 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Toxic encephalopathy			
subjects affected / exposed	3 / 39 (7.69%)	0 / 39 (0.00%)	0 / 16 (0.00%)
occurrences causally related to treatment / all	4 / 4	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Syncope			
subjects affected / exposed	1 / 39 (2.56%)	0 / 39 (0.00%)	0 / 16 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal cord compression			
subjects affected / exposed	0 / 39 (0.00%)	0 / 39 (0.00%)	1 / 16 (6.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 39 (2.56%)	0 / 39 (0.00%)	0 / 16 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Febrile neutropenia			
subjects affected / exposed	15 / 39 (38.46%)	7 / 39 (17.95%)	0 / 16 (0.00%)
occurrences causally related to treatment / all	26 / 27	10 / 10	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neutropenia			

subjects affected / exposed	1 / 39 (2.56%)	0 / 39 (0.00%)	0 / 16 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thrombocytopenia			
subjects affected / exposed	1 / 39 (2.56%)	0 / 39 (0.00%)	0 / 16 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	2 / 39 (5.13%)	0 / 39 (0.00%)	0 / 16 (0.00%)
occurrences causally related to treatment / all	2 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anal fistula			
subjects affected / exposed	1 / 39 (2.56%)	0 / 39 (0.00%)	0 / 16 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea			
subjects affected / exposed	1 / 39 (2.56%)	0 / 39 (0.00%)	1 / 16 (6.25%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nausea			
subjects affected / exposed	0 / 39 (0.00%)	1 / 39 (2.56%)	0 / 16 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			
subjects affected / exposed	0 / 39 (0.00%)	1 / 39 (2.56%)	1 / 16 (6.25%)
occurrences causally related to treatment / all	0 / 0	2 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Stomatitis			
subjects affected / exposed	1 / 39 (2.56%)	0 / 39 (0.00%)	0 / 16 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Constipation			

subjects affected / exposed	0 / 39 (0.00%)	0 / 39 (0.00%)	1 / 16 (6.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	1 / 39 (2.56%)	0 / 39 (0.00%)	0 / 16 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gallbladder obstruction			
subjects affected / exposed	1 / 39 (2.56%)	0 / 39 (0.00%)	0 / 16 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatitis acute			
subjects affected / exposed	1 / 39 (2.56%)	0 / 39 (0.00%)	0 / 16 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholecystitis acute			
subjects affected / exposed	0 / 39 (0.00%)	0 / 39 (0.00%)	1 / 16 (6.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Cystitis haemorrhagic			
subjects affected / exposed	1 / 39 (2.56%)	0 / 39 (0.00%)	0 / 16 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haematuria			
subjects affected / exposed	1 / 39 (2.56%)	0 / 39 (0.00%)	0 / 16 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal tubular injury			
subjects affected / exposed	0 / 39 (0.00%)	1 / 39 (2.56%)	0 / 16 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Proteinuria			

subjects affected / exposed	2 / 39 (5.13%)	0 / 39 (0.00%)	0 / 16 (0.00%)
occurrences causally related to treatment / all	3 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute kidney injury			
subjects affected / exposed	0 / 39 (0.00%)	0 / 39 (0.00%)	1 / 16 (6.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Pulmonary haemorrhage			
subjects affected / exposed	0 / 39 (0.00%)	0 / 39 (0.00%)	1 / 16 (6.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Bone pain			
subjects affected / exposed	1 / 39 (2.56%)	0 / 39 (0.00%)	0 / 16 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pain in extremity			
subjects affected / exposed	0 / 39 (0.00%)	0 / 39 (0.00%)	1 / 16 (6.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Bacteraemia			
subjects affected / exposed	0 / 39 (0.00%)	1 / 39 (2.56%)	0 / 16 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Escherichia sepsis			
subjects affected / exposed	1 / 39 (2.56%)	0 / 39 (0.00%)	0 / 16 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Device related infection			
subjects affected / exposed	0 / 39 (0.00%)	1 / 39 (2.56%)	0 / 16 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

COVID-19			
subjects affected / exposed	2 / 39 (5.13%)	0 / 39 (0.00%)	0 / 16 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infectious pleural effusion			
subjects affected / exposed	1 / 39 (2.56%)	0 / 39 (0.00%)	0 / 16 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infection			
subjects affected / exposed	0 / 39 (0.00%)	1 / 39 (2.56%)	0 / 16 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis			
subjects affected / exposed	1 / 39 (2.56%)	0 / 39 (0.00%)	0 / 16 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteomyelitis			
subjects affected / exposed	1 / 39 (2.56%)	0 / 39 (0.00%)	0 / 16 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia fungal			
subjects affected / exposed	1 / 39 (2.56%)	0 / 39 (0.00%)	0 / 16 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	2 / 39 (5.13%)	0 / 39 (0.00%)	1 / 16 (6.25%)
occurrences causally related to treatment / all	3 / 3	0 / 0	0 / 2
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
Pleural infection			
subjects affected / exposed	1 / 39 (2.56%)	0 / 39 (0.00%)	0 / 16 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Post procedural cellulitis			

subjects affected / exposed	1 / 39 (2.56%)	0 / 39 (0.00%)	0 / 16 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory syncytial virus infection			
subjects affected / exposed	1 / 39 (2.56%)	0 / 39 (0.00%)	0 / 16 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			
subjects affected / exposed	0 / 39 (0.00%)	2 / 39 (5.13%)	0 / 16 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin infection			
subjects affected / exposed	0 / 39 (0.00%)	1 / 39 (2.56%)	0 / 16 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Staphylococcal sepsis			
subjects affected / exposed	0 / 39 (0.00%)	1 / 39 (2.56%)	0 / 16 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Wound infection staphylococcal			
subjects affected / exposed	0 / 39 (0.00%)	1 / 39 (2.56%)	0 / 16 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular device infection			
subjects affected / exposed	0 / 39 (0.00%)	2 / 39 (5.13%)	0 / 16 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lower respiratory tract infection			
subjects affected / exposed	0 / 39 (0.00%)	0 / 39 (0.00%)	1 / 16 (6.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Hypokalaemia			

subjects affected / exposed	1 / 39 (2.56%)	0 / 39 (0.00%)	0 / 16 (0.00%)
occurrences causally related to treatment / all	5 / 5	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dehydration			
subjects affected / exposed	1 / 39 (2.56%)	0 / 39 (0.00%)	0 / 16 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Decreased appetite			
subjects affected / exposed	1 / 39 (2.56%)	0 / 39 (0.00%)	0 / 16 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypophosphataemia			
subjects affected / exposed	1 / 39 (2.56%)	0 / 39 (0.00%)	0 / 16 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Treatment Arm A: Lenvatinib + Ifosfamide + Etoposide	Treatment Arm B: Ifosfamide + Etoposide	Treatment Arm B: Ifosfamide+Etoposide to Lenvatinib (Optional)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	38 / 39 (97.44%)	39 / 39 (100.00%)	16 / 16 (100.00%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Malignant pleural effusion			
subjects affected / exposed	3 / 39 (7.69%)	1 / 39 (2.56%)	0 / 16 (0.00%)
occurrences (all)	4	1	0
Tumour pain			
subjects affected / exposed	1 / 39 (2.56%)	2 / 39 (5.13%)	0 / 16 (0.00%)
occurrences (all)	2	3	0
Cancer pain			
subjects affected / exposed	0 / 39 (0.00%)	0 / 39 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	2
Tumour haemorrhage			

subjects affected / exposed	0 / 39 (0.00%)	0 / 39 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	2
Vascular disorders			
Hypertension			
subjects affected / exposed	16 / 39 (41.03%)	0 / 39 (0.00%)	6 / 16 (37.50%)
occurrences (all)	39	0	8
Hypotension			
subjects affected / exposed	2 / 39 (5.13%)	2 / 39 (5.13%)	0 / 16 (0.00%)
occurrences (all)	2	2	0
General disorders and administration site conditions			
Face oedema			
subjects affected / exposed	2 / 39 (5.13%)	0 / 39 (0.00%)	0 / 16 (0.00%)
occurrences (all)	4	0	0
Asthenia			
subjects affected / exposed	2 / 39 (5.13%)	0 / 39 (0.00%)	1 / 16 (6.25%)
occurrences (all)	2	0	1
Fatigue			
subjects affected / exposed	13 / 39 (33.33%)	9 / 39 (23.08%)	4 / 16 (25.00%)
occurrences (all)	28	11	8
Generalised oedema			
subjects affected / exposed	1 / 39 (2.56%)	2 / 39 (5.13%)	0 / 16 (0.00%)
occurrences (all)	2	3	0
Impaired healing			
subjects affected / exposed	2 / 39 (5.13%)	0 / 39 (0.00%)	0 / 16 (0.00%)
occurrences (all)	3	0	0
Oedema			
subjects affected / exposed	2 / 39 (5.13%)	0 / 39 (0.00%)	0 / 16 (0.00%)
occurrences (all)	2	0	0
Pyrexia			
subjects affected / exposed	12 / 39 (30.77%)	5 / 39 (12.82%)	2 / 16 (12.50%)
occurrences (all)	16	6	2
Non-cardiac chest pain			
subjects affected / exposed	2 / 39 (5.13%)	0 / 39 (0.00%)	1 / 16 (6.25%)
occurrences (all)	3	0	1
Early satiety			

subjects affected / exposed	0 / 39 (0.00%)	0 / 39 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Infusion site bruising			
subjects affected / exposed	0 / 39 (0.00%)	0 / 39 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Oedema peripheral			
subjects affected / exposed	0 / 39 (0.00%)	0 / 39 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Infusion site swelling			
subjects affected / exposed	0 / 39 (0.00%)	0 / 39 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Reproductive system and breast disorders			
Pelvic pain			
subjects affected / exposed	0 / 39 (0.00%)	0 / 39 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Respiratory, thoracic and mediastinal disorders			
Epistaxis			
subjects affected / exposed	12 / 39 (30.77%)	2 / 39 (5.13%)	0 / 16 (0.00%)
occurrences (all)	23	2	0
Dyspnoea			
subjects affected / exposed	4 / 39 (10.26%)	3 / 39 (7.69%)	1 / 16 (6.25%)
occurrences (all)	6	3	1
Dysphonia			
subjects affected / exposed	2 / 39 (5.13%)	0 / 39 (0.00%)	1 / 16 (6.25%)
occurrences (all)	2	0	1
Cough			
subjects affected / exposed	7 / 39 (17.95%)	5 / 39 (12.82%)	1 / 16 (6.25%)
occurrences (all)	7	7	2
Hypoxia			
subjects affected / exposed	2 / 39 (5.13%)	0 / 39 (0.00%)	0 / 16 (0.00%)
occurrences (all)	3	0	0
Oropharyngeal pain			
subjects affected / exposed	4 / 39 (10.26%)	1 / 39 (2.56%)	1 / 16 (6.25%)
occurrences (all)	4	1	2
Pleural effusion			

subjects affected / exposed	2 / 39 (5.13%)	0 / 39 (0.00%)	0 / 16 (0.00%)
occurrences (all)	2	0	0
Pneumothorax			
subjects affected / exposed	8 / 39 (20.51%)	1 / 39 (2.56%)	3 / 16 (18.75%)
occurrences (all)	19	1	7
Pharyngeal inflammation			
subjects affected / exposed	0 / 39 (0.00%)	0 / 39 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Psychiatric disorders			
Depression			
subjects affected / exposed	3 / 39 (7.69%)	0 / 39 (0.00%)	1 / 16 (6.25%)
occurrences (all)	3	0	1
Insomnia			
subjects affected / exposed	3 / 39 (7.69%)	1 / 39 (2.56%)	2 / 16 (12.50%)
occurrences (all)	4	1	4
Anxiety			
subjects affected / exposed	3 / 39 (7.69%)	1 / 39 (2.56%)	1 / 16 (6.25%)
occurrences (all)	3	1	1
Confusional state			
subjects affected / exposed	0 / 39 (0.00%)	0 / 39 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Investigations			
Blood alkaline phosphatase increased			
subjects affected / exposed	3 / 39 (7.69%)	4 / 39 (10.26%)	1 / 16 (6.25%)
occurrences (all)	6	5	1
Amylase increased			
subjects affected / exposed	2 / 39 (5.13%)	0 / 39 (0.00%)	0 / 16 (0.00%)
occurrences (all)	2	0	0
Aspartate aminotransferase increased			
subjects affected / exposed	7 / 39 (17.95%)	5 / 39 (12.82%)	3 / 16 (18.75%)
occurrences (all)	25	11	4
Alanine aminotransferase increased			
subjects affected / exposed	7 / 39 (17.95%)	4 / 39 (10.26%)	1 / 16 (6.25%)
occurrences (all)	27	11	1
Blood bicarbonate decreased			

subjects affected / exposed	0 / 39 (0.00%)	3 / 39 (7.69%)	0 / 16 (0.00%)
occurrences (all)	0	7	0
Blood bilirubin increased			
subjects affected / exposed	3 / 39 (7.69%)	0 / 39 (0.00%)	0 / 16 (0.00%)
occurrences (all)	20	0	0
C-reactive protein increased			
subjects affected / exposed	4 / 39 (10.26%)	0 / 39 (0.00%)	0 / 16 (0.00%)
occurrences (all)	4	0	0
Blood lactate dehydrogenase increased			
subjects affected / exposed	1 / 39 (2.56%)	4 / 39 (10.26%)	1 / 16 (6.25%)
occurrences (all)	1	4	2
Blood thyroid stimulating hormone increased			
subjects affected / exposed	5 / 39 (12.82%)	0 / 39 (0.00%)	3 / 16 (18.75%)
occurrences (all)	6	0	3
Blood creatinine increased			
subjects affected / exposed	6 / 39 (15.38%)	0 / 39 (0.00%)	0 / 16 (0.00%)
occurrences (all)	9	0	0
Ejection fraction decreased			
subjects affected / exposed	4 / 39 (10.26%)	0 / 39 (0.00%)	1 / 16 (6.25%)
occurrences (all)	5	0	1
Electrocardiogram T wave abnormal			
subjects affected / exposed	2 / 39 (5.13%)	0 / 39 (0.00%)	0 / 16 (0.00%)
occurrences (all)	2	0	0
Gamma-glutamyltransferase increased			
subjects affected / exposed	4 / 39 (10.26%)	2 / 39 (5.13%)	2 / 16 (12.50%)
occurrences (all)	18	11	2
SARS-CoV-2 test positive			
subjects affected / exposed	0 / 39 (0.00%)	2 / 39 (5.13%)	0 / 16 (0.00%)
occurrences (all)	0	2	0
Neutrophil count decreased			
subjects affected / exposed	15 / 39 (38.46%)	13 / 39 (33.33%)	1 / 16 (6.25%)
occurrences (all)	79	38	1
Platelet count decreased			

subjects affected / exposed	23 / 39 (58.97%)	17 / 39 (43.59%)	3 / 16 (18.75%)
occurrences (all)	209	57	12
Lymphocyte count decreased			
subjects affected / exposed	5 / 39 (12.82%)	7 / 39 (17.95%)	1 / 16 (6.25%)
occurrences (all)	28	32	4
Weight decreased			
subjects affected / exposed	8 / 39 (20.51%)	4 / 39 (10.26%)	5 / 16 (31.25%)
occurrences (all)	13	4	10
Weight increased			
subjects affected / exposed	2 / 39 (5.13%)	0 / 39 (0.00%)	0 / 16 (0.00%)
occurrences (all)	5	0	0
White blood cell count decreased			
subjects affected / exposed	5 / 39 (12.82%)	13 / 39 (33.33%)	2 / 16 (12.50%)
occurrences (all)	38	47	8
Blood magnesium decreased			
subjects affected / exposed	0 / 39 (0.00%)	0 / 39 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Lipase increased			
subjects affected / exposed	0 / 39 (0.00%)	0 / 39 (0.00%)	2 / 16 (12.50%)
occurrences (all)	0	0	3
Blood pressure increased			
subjects affected / exposed	0 / 39 (0.00%)	0 / 39 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	2
Haemoglobin increased			
subjects affected / exposed	0 / 39 (0.00%)	0 / 39 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Injury, poisoning and procedural complications			
Allergic transfusion reaction			
subjects affected / exposed	2 / 39 (5.13%)	0 / 39 (0.00%)	0 / 16 (0.00%)
occurrences (all)	2	0	0
Procedural pain			
subjects affected / exposed	3 / 39 (7.69%)	0 / 39 (0.00%)	1 / 16 (6.25%)
occurrences (all)	6	0	1
Muscle rupture			

subjects affected / exposed	0 / 39 (0.00%)	0 / 39 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Cardiac disorders			
Tachycardia			
subjects affected / exposed	2 / 39 (5.13%)	3 / 39 (7.69%)	0 / 16 (0.00%)
occurrences (all)	3	3	0
Angina pectoris			
subjects affected / exposed	0 / 39 (0.00%)	0 / 39 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Palpitations			
subjects affected / exposed	0 / 39 (0.00%)	0 / 39 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Nervous system disorders			
Tremor			
subjects affected / exposed	3 / 39 (7.69%)	1 / 39 (2.56%)	0 / 16 (0.00%)
occurrences (all)	4	1	0
Headache			
subjects affected / exposed	14 / 39 (35.90%)	6 / 39 (15.38%)	5 / 16 (31.25%)
occurrences (all)	20	6	28
Toxic encephalopathy			
subjects affected / exposed	2 / 39 (5.13%)	0 / 39 (0.00%)	0 / 16 (0.00%)
occurrences (all)	2	0	0
Dizziness			
subjects affected / exposed	7 / 39 (17.95%)	2 / 39 (5.13%)	0 / 16 (0.00%)
occurrences (all)	8	4	0
Hypoaesthesia			
subjects affected / exposed	0 / 39 (0.00%)	0 / 39 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Aphasia			
subjects affected / exposed	0 / 39 (0.00%)	0 / 39 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Lethargy			
subjects affected / exposed	0 / 39 (0.00%)	0 / 39 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Migraine			

subjects affected / exposed	0 / 39 (0.00%)	0 / 39 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	28 / 39 (71.79%)	27 / 39 (69.23%)	2 / 16 (12.50%)
occurrences (all)	180	102	10
Leukopenia			
subjects affected / exposed	5 / 39 (12.82%)	4 / 39 (10.26%)	2 / 16 (12.50%)
occurrences (all)	53	27	2
Lymphopenia			
subjects affected / exposed	1 / 39 (2.56%)	4 / 39 (10.26%)	0 / 16 (0.00%)
occurrences (all)	17	26	0
Febrile neutropenia			
subjects affected / exposed	1 / 39 (2.56%)	4 / 39 (10.26%)	0 / 16 (0.00%)
occurrences (all)	1	4	0
Neutropenia			
subjects affected / exposed	9 / 39 (23.08%)	9 / 39 (23.08%)	3 / 16 (18.75%)
occurrences (all)	39	20	3
Thrombocytopenia			
subjects affected / exposed	6 / 39 (15.38%)	5 / 39 (12.82%)	0 / 16 (0.00%)
occurrences (all)	50	12	0
Pancytopenia			
subjects affected / exposed	0 / 39 (0.00%)	0 / 39 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Eosinophilia			
subjects affected / exposed	0 / 39 (0.00%)	0 / 39 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Eye disorders			
Eye pain			
subjects affected / exposed	2 / 39 (5.13%)	0 / 39 (0.00%)	0 / 16 (0.00%)
occurrences (all)	4	0	0
Dry eye			
subjects affected / exposed	2 / 39 (5.13%)	1 / 39 (2.56%)	0 / 16 (0.00%)
occurrences (all)	2	1	0
Gastrointestinal disorders			

Abdominal pain			
subjects affected / exposed	7 / 39 (17.95%)	3 / 39 (7.69%)	3 / 16 (18.75%)
occurrences (all)	18	4	12
Abdominal pain upper			
subjects affected / exposed	4 / 39 (10.26%)	1 / 39 (2.56%)	2 / 16 (12.50%)
occurrences (all)	6	1	3
Gastrooesophageal reflux disease			
subjects affected / exposed	2 / 39 (5.13%)	0 / 39 (0.00%)	1 / 16 (6.25%)
occurrences (all)	2	0	1
Diarrhoea			
subjects affected / exposed	14 / 39 (35.90%)	2 / 39 (5.13%)	4 / 16 (25.00%)
occurrences (all)	20	2	8
Gastritis			
subjects affected / exposed	0 / 39 (0.00%)	2 / 39 (5.13%)	0 / 16 (0.00%)
occurrences (all)	0	2	0
Constipation			
subjects affected / exposed	14 / 39 (35.90%)	5 / 39 (12.82%)	4 / 16 (25.00%)
occurrences (all)	20	6	6
Nausea			
subjects affected / exposed	23 / 39 (58.97%)	16 / 39 (41.03%)	5 / 16 (31.25%)
occurrences (all)	56	30	6
Mouth ulceration			
subjects affected / exposed	1 / 39 (2.56%)	2 / 39 (5.13%)	1 / 16 (6.25%)
occurrences (all)	1	2	1
Proctalgia			
subjects affected / exposed	3 / 39 (7.69%)	1 / 39 (2.56%)	0 / 16 (0.00%)
occurrences (all)	6	1	0
Stomatitis			
subjects affected / exposed	10 / 39 (25.64%)	6 / 39 (15.38%)	1 / 16 (6.25%)
occurrences (all)	14	7	3
Vomiting			
subjects affected / exposed	19 / 39 (48.72%)	11 / 39 (28.21%)	5 / 16 (31.25%)
occurrences (all)	44	17	12
Toothache			
subjects affected / exposed	2 / 39 (5.13%)	2 / 39 (5.13%)	0 / 16 (0.00%)
occurrences (all)	2	2	0

Gastrointestinal pain			
subjects affected / exposed	0 / 39 (0.00%)	0 / 39 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Dyspepsia			
subjects affected / exposed	0 / 39 (0.00%)	0 / 39 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Cheilitis			
subjects affected / exposed	0 / 39 (0.00%)	0 / 39 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Aphthous ulcer			
subjects affected / exposed	0 / 39 (0.00%)	0 / 39 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Dry mouth			
subjects affected / exposed	2 / 39 (5.13%)	0 / 39 (0.00%)	0 / 16 (0.00%)
occurrences (all)	2	0	0
Duodenitis			
subjects affected / exposed	0 / 39 (0.00%)	0 / 39 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Hepatobiliary disorders			
Hyperbilirubinaemia			
subjects affected / exposed	3 / 39 (7.69%)	0 / 39 (0.00%)	1 / 16 (6.25%)
occurrences (all)	5	0	1
Cholecystitis acute			
subjects affected / exposed	0 / 39 (0.00%)	0 / 39 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	3 / 39 (7.69%)	0 / 39 (0.00%)	0 / 16 (0.00%)
occurrences (all)	4	0	0
Dry skin			
subjects affected / exposed	5 / 39 (12.82%)	1 / 39 (2.56%)	0 / 16 (0.00%)
occurrences (all)	6	1	0
Palmar-plantar erythrodysaesthesia syndrome			
subjects affected / exposed	5 / 39 (12.82%)	0 / 39 (0.00%)	2 / 16 (12.50%)
occurrences (all)	11	0	2
Rash			

subjects affected / exposed	8 / 39 (20.51%)	1 / 39 (2.56%)	1 / 16 (6.25%)
occurrences (all)	13	1	1
Rash maculo-papular			
subjects affected / exposed	3 / 39 (7.69%)	1 / 39 (2.56%)	0 / 16 (0.00%)
occurrences (all)	3	1	0
Urticaria			
subjects affected / exposed	5 / 39 (12.82%)	1 / 39 (2.56%)	0 / 16 (0.00%)
occurrences (all)	7	1	0
Pain of skin			
subjects affected / exposed	0 / 39 (0.00%)	0 / 39 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Hair colour changes			
subjects affected / exposed	0 / 39 (0.00%)	0 / 39 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Pruritus			
subjects affected / exposed	0 / 39 (0.00%)	0 / 39 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Skin plaque			
subjects affected / exposed	0 / 39 (0.00%)	0 / 39 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Rash macular			
subjects affected / exposed	0 / 39 (0.00%)	0 / 39 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Renal and urinary disorders			
Dysuria			
subjects affected / exposed	2 / 39 (5.13%)	1 / 39 (2.56%)	1 / 16 (6.25%)
occurrences (all)	2	1	1
Glycosuria			
subjects affected / exposed	2 / 39 (5.13%)	4 / 39 (10.26%)	0 / 16 (0.00%)
occurrences (all)	2	7	0
Haematuria			
subjects affected / exposed	4 / 39 (10.26%)	2 / 39 (5.13%)	0 / 16 (0.00%)
occurrences (all)	11	2	0
Pollakiuria			
subjects affected / exposed	3 / 39 (7.69%)	0 / 39 (0.00%)	1 / 16 (6.25%)
occurrences (all)	3	0	1

Proteinuria			
subjects affected / exposed	21 / 39 (53.85%)	5 / 39 (12.82%)	6 / 16 (37.50%)
occurrences (all)	79	7	21
Endocrine disorders			
Hyperthyroidism			
subjects affected / exposed	3 / 39 (7.69%)	0 / 39 (0.00%)	0 / 16 (0.00%)
occurrences (all)	3	0	0
Hypothyroidism			
subjects affected / exposed	35 / 39 (89.74%)	0 / 39 (0.00%)	8 / 16 (50.00%)
occurrences (all)	52	0	9
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	15 / 39 (38.46%)	6 / 39 (15.38%)	4 / 16 (25.00%)
occurrences (all)	22	7	6
Arthralgia			
subjects affected / exposed	11 / 39 (28.21%)	6 / 39 (15.38%)	3 / 16 (18.75%)
occurrences (all)	24	6	4
Bone pain			
subjects affected / exposed	4 / 39 (10.26%)	1 / 39 (2.56%)	1 / 16 (6.25%)
occurrences (all)	5	1	1
Muscular weakness			
subjects affected / exposed	2 / 39 (5.13%)	1 / 39 (2.56%)	1 / 16 (6.25%)
occurrences (all)	4	1	1
Musculoskeletal chest pain			
subjects affected / exposed	5 / 39 (12.82%)	0 / 39 (0.00%)	0 / 16 (0.00%)
occurrences (all)	6	0	0
Musculoskeletal pain			
subjects affected / exposed	5 / 39 (12.82%)	1 / 39 (2.56%)	1 / 16 (6.25%)
occurrences (all)	6	3	1
Myalgia			
subjects affected / exposed	7 / 39 (17.95%)	0 / 39 (0.00%)	0 / 16 (0.00%)
occurrences (all)	15	0	0
Neck pain			
subjects affected / exposed	2 / 39 (5.13%)	0 / 39 (0.00%)	0 / 16 (0.00%)
occurrences (all)	2	0	0
Pain in extremity			

subjects affected / exposed	9 / 39 (23.08%)	5 / 39 (12.82%)	6 / 16 (37.50%)
occurrences (all)	14	5	21
Trismus			
subjects affected / exposed	2 / 39 (5.13%)	0 / 39 (0.00%)	0 / 16 (0.00%)
occurrences (all)	2	0	0
Muscle spasms			
subjects affected / exposed	0 / 39 (0.00%)	0 / 39 (0.00%)	2 / 16 (12.50%)
occurrences (all)	0	0	3
Infections and infestations			
COVID-19			
subjects affected / exposed	8 / 39 (20.51%)	1 / 39 (2.56%)	0 / 16 (0.00%)
occurrences (all)	9	1	0
Catheter site infection			
subjects affected / exposed	2 / 39 (5.13%)	0 / 39 (0.00%)	0 / 16 (0.00%)
occurrences (all)	2	0	0
Hand-foot-and-mouth disease			
subjects affected / exposed	2 / 39 (5.13%)	0 / 39 (0.00%)	0 / 16 (0.00%)
occurrences (all)	2	0	0
Wound infection			
subjects affected / exposed	2 / 39 (5.13%)	0 / 39 (0.00%)	0 / 16 (0.00%)
occurrences (all)	2	0	0
Rash pustular			
subjects affected / exposed	2 / 39 (5.13%)	0 / 39 (0.00%)	0 / 16 (0.00%)
occurrences (all)	2	0	0
Rhinitis			
subjects affected / exposed	4 / 39 (10.26%)	0 / 39 (0.00%)	0 / 16 (0.00%)
occurrences (all)	4	0	0
Herpes zoster			
subjects affected / exposed	2 / 39 (5.13%)	0 / 39 (0.00%)	0 / 16 (0.00%)
occurrences (all)	2	0	0
Gingivitis			
subjects affected / exposed	0 / 39 (0.00%)	0 / 39 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Influenza			
subjects affected / exposed	0 / 39 (0.00%)	0 / 39 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	2

Paronychia			
subjects affected / exposed	2 / 39 (5.13%)	1 / 39 (2.56%)	0 / 16 (0.00%)
occurrences (all)	3	2	0
Overgrowth bacterial			
subjects affected / exposed	0 / 39 (0.00%)	0 / 39 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Metabolism and nutrition disorders			
Hypoalbuminaemia			
subjects affected / exposed	4 / 39 (10.26%)	2 / 39 (5.13%)	1 / 16 (6.25%)
occurrences (all)	6	2	1
Dehydration			
subjects affected / exposed	2 / 39 (5.13%)	1 / 39 (2.56%)	0 / 16 (0.00%)
occurrences (all)	3	1	0
Hypervolaemia			
subjects affected / exposed	2 / 39 (5.13%)	0 / 39 (0.00%)	0 / 16 (0.00%)
occurrences (all)	4	0	0
Decreased appetite			
subjects affected / exposed	8 / 39 (20.51%)	5 / 39 (12.82%)	5 / 16 (31.25%)
occurrences (all)	10	6	10
Hypocalcaemia			
subjects affected / exposed	2 / 39 (5.13%)	4 / 39 (10.26%)	1 / 16 (6.25%)
occurrences (all)	8	9	1
Hypokalaemia			
subjects affected / exposed	5 / 39 (12.82%)	6 / 39 (15.38%)	1 / 16 (6.25%)
occurrences (all)	19	13	1
Hypomagnesaemia			
subjects affected / exposed	6 / 39 (15.38%)	3 / 39 (7.69%)	2 / 16 (12.50%)
occurrences (all)	17	5	2
Hypophosphataemia			
subjects affected / exposed	6 / 39 (15.38%)	7 / 39 (17.95%)	0 / 16 (0.00%)
occurrences (all)	26	9	0
Hyponatraemia			
subjects affected / exposed	3 / 39 (7.69%)	3 / 39 (7.69%)	3 / 16 (18.75%)
occurrences (all)	4	3	3
Hypercalcaemia			

subjects affected / exposed	0 / 39 (0.00%)	0 / 39 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Hyperkalaemia			
subjects affected / exposed	2 / 39 (5.13%)	1 / 39 (2.56%)	0 / 16 (0.00%)
occurrences (all)	2	1	0
Hypercholesterolaemia			
subjects affected / exposed	0 / 39 (0.00%)	0 / 39 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Vitamin D deficiency			
subjects affected / exposed	0 / 39 (0.00%)	0 / 39 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
09 March 2020	Amendment 01: • Revised definition of adequacy of bone marrow function in inclusion criterion no. 7 Per health authority request, added exclusion criterion no. 20 on contraindication to study drugs • Per health authority request, subjects who received other anticancer therapy, except as specified in the protocol, were required to discontinue study treatment • Optional pharmacodynamic blood sample collection moved from C1D8 to C1D15 to lessen subject burden.
10 September 2020	Amendment 02: • Revised primary objective and endpoint to PFS, and revised PFS rate at 4 months (PFS-4m) to be a secondary objective and endpoint; analyses updated accordingly • Added ORR as a secondary objective and endpoint • Added Exploratory objective and analysis of the difference in lesion removal between the 2 study arms • Updated and clarified definition for the Randomization Phase • Clarified tumor assessment requirements at the Off- Treatment visit and during Follow-up • Added option for subjects in Arm B to cross over to treatment with lenvatinib in Arm A, provided certain eligibility criteria were met • Updated inclusion criteria nos. 2, 3, 8, 11 and 13 and exclusion criteria nos. 17 and 19 • Added inclusion criterion no. 14: Prior treatment with lenvatinib was not permitted • PK and pharmacodynamic assessments updated per health authorities • Objectives and Endpoints were updated to specify review based on independent and investigator assessment • Added dental examinations to the study assessments • Added sections for the management of fistula formation, GI perforation, and QT prolongation.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported