



Clinical trial results:

A phase II non-randomized, single group assignment, open-label, multicenter study of efficacy and safety of IORlatinib (PF-06463922) monotherapy after failure of first-line second-generation ALK kinase inhibitor in patients with advanced ALK-positive non-small cell Lung cancer (ORAKLE)

Summary

EudraCT number	2019-002230-37
Trial protocol	FR
Global end of trial date	16 December 2024

Results information

Result version number	v1 (current)
This version publication date	28 March 2026
First version publication date	28 March 2026

Trial information

Trial identification

Sponsor protocol code	IFCT-1902
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04111705
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	IFCT
Sponsor organisation address	10 rue de la Grange-Batelière, Paris, France, 75009
Public contact	Contact, IFCT, contact@ifct.fr
Scientific contact	Contact, IFCT, contact@ifct.fr

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
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?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	13 February 2025
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	16 December 2024
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the efficacy of lorlatinib in patients with advanced ALK-positive NSCLC after disease progression on first-line treatment with brigatinib or alectinib.

Protection of trial subjects:

Algorithms for management of adverse events were provided in the protocol

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	21 July 2020
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	France: 23
Worldwide total number of subjects	23
EEA total number of subjects	23

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)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	15
From 65 to 84 years	8
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

23 patients were recruited in 15 sites in France from the 5th of august 2020 to the 30th of june 2022.
Each patient included received at least one dose of treatment.

Pre-assignment

Screening details:

Principal inclusion criteria are :

Age \geq 18 years

Histologically confirmed NSCLC

Unresectable locally advanced or metastatic with ALK rearrangement

Disease progression after one line of alectinib or brigatinib

Measurable disease

No progression in less than 6 month during the 1st line of treatment

No symptomatic CNS metastases

Period 1

Period 1 title	Overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Lorlatinib
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Arm description:

Only arm in the study.

Patients receive lorlatinib at 100mg once daily

Arm type	Experimental
Investigational medicinal product name	Lorlatinib
Investigational medicinal product code	
Other name	Lorviqua
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Lorlatinib

100 mg once per day.

1 cycle = 21 days

Treatment length is until progression / intolerable toxicity / death or withdrawal of consent whichever comes first.

Number of subjects in period 1	Lorlatinib
Started	23
Completed	0
Not completed	23
Patient refusal	1
Adverse event, non-fatal	2
Lack of efficacy	20

Baseline characteristics

Reporting groups

Reporting group title	Lorlatinib
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Reporting group description:

Only arm in the study.

Patients receive lorlatinib at 100mg once daily

Reporting group values	Lorlatinib	Total	
Number of subjects	23	23	
Age categorical			
Age characteristics on intent-to-treat population			
Units: Subjects			
Adults (18-64 years)	15	15	
From 65-84 years	8	8	
Age continuous			
Age characteristics on intent-to-treat population			
Units: years			
median	59.8		
full range (min-max)	33.5 to 78.7	-	
Gender categorical			
Gender on intent-to-treat population			
Units: Subjects			
Female	14	14	
Male	9	9	
Smoking population			
Number of smoking and non smoking patients on intent-to-treat population			
Units: Subjects			
Never smoker	16	16	
Former smoker	7	7	
Smoker	0	0	
Histological evidence			
Histological evidence of the cancer on intent-to-treat population			
Units: Subjects			
Yes	21	21	
No	2	2	
Cytological evidence			
Cytological evidence of cancer on intent-to-treat patients			
Units: Subjects			
Yes	13	13	
No	9	9	
Unknown	1	1	
Histological type			
Histological type for cancers			
Units: Subjects			
Adenocarcinoma	21	21	
Mixed carcinoma	1	1	
Squamous cell carcinoma	1	1	
TNM			

TNM at inclusion on intent-to-treat population			
Units: Subjects			
IIIC	1	1	
IVA	2	2	
IVB	20	20	
Performans status			
Performans status at inclusion on intent-to-treat population			
Units: Subjects			
PS 0	6	6	
PS 1	15	15	
PS 2	2	2	
Brain metastasis			
Brain metastasis at inclusion on intent-to-treat population			
Units: Subjects			
Yes	6	6	
No	17	17	
PD-L1 expression			
PD-L1 pexpression on intent-to-treat population			
Units: Subjects			
Highly positive ($\geq 50\%$)	5	5	
Positive (1-49%)	11	11	
Negative ($<1\%$)	6	6	
Unknown	1	1	
EGFR status			
EGFR status on intent-to-treat population			
Units: Subjects			
Wild-type	22	22	
Mutated	0	0	
Not done	1	1	
HER2 status			
HER2 status on intent-to-treat population			
Units: Subjects			
Wild-type	19	19	
Mutated	0	0	
Not done	4	4	
ALK status			
ALK status on intent-to-treat population			
Units: Subjects			
Wild-type	23	23	
Rearrangement	0	0	
Not done	0	0	
ROS1 status			
ROS1 status on intent-to-treat population			
Units: Subjects			
Wild-type	22	22	
Rearrangement	1	1	
Not done	0	0	
KRAS status			
KRAS status on intent-to-treat population			
Units: Subjects			
Wild-type	20	20	

Mutated	1	1	
Not done	2	2	
Other biomarkers			
Other biomarkers on intent-to-treat population			
Units: Subjects			
Yes	0	0	
No	23	23	
Cause of discontinuation			
Cause of treatment discontinuation			
Units: Subjects			
Disease progression	20	20	
Toxicity	2	2	
Patient's decision	1	1	
Pack-years for smokers			
Number of pack-years for smokers			
Units: Pack-years			
median	22		
full range (min-max)	10 to 30	-	
Duration of therapy without interruption			
Duration of therapy (month) without interruption days on intent-to-treat population			
Units: month			
median	4.1		
full range (min-max)	0.2 to 33.7	-	
Duration therapy with interruption			
Duration of therapy (months) with interruption days			
Units: Month			
median	4.1		
full range (min-max)	0.2 to 32.4	-	
Number of interruption days			
Number of interruption days on intent-to-treat population			
Units: Day			
median	0		
full range (min-max)	0 to 39	-	
Total dose of treatment			
Total dose of lorlatinib administered at the end of treatment on intent-to-treat population			
Units: Mg			
median	12600		
full range (min-max)	2100 to 94275	-	
Mean dose by day			
Mean dose of lorlatinib administered each day on intent-to-treat population			
Units: Mg			
median	100		
full range (min-max)	99.7 to 100	-	
Numbers of days with maximum dose			
Numbers of days of treatment with maximum dose on intent-to-treat population			
Units: Days			
median	126		
full range (min-max)	21 to 942	-	

Subject analysis sets

Subject analysis set title	Intent to treat
Subject analysis set type	Intention-to-treat
Subject analysis set description: All patients who were included are counted into this subject analysis set.	
Subject analysis set title	Eligible population
Subject analysis set type	Per protocol
Subject analysis set description: All patients in intention to treat without any critical deviation on inclusion or exclusion criteria.	
Subject analysis set title	Safety population
Subject analysis set type	Safety analysis
Subject analysis set description: All patients that received at least one dose of study treatment.	

Reporting group values	Intent to treat	Eligible population	Safety population
Number of subjects	23	22	23
Age categorical			
Age characteristics on intent-to-treat population			
Units: Subjects			
Adults (18-64 years)	15		15
From 65-84 years	8		8
Age continuous			
Age characteristics on intent-to-treat population			
Units: years			
median	59.8		59.8
full range (min-max)	33.5 to 78.7		33.5 to 78.7
Gender categorical			
Gender on intent-to-treat population			
Units: Subjects			
Female	14		14
Male	9		9
Smoking population			
Number of smoking and non smoking patients on intent-to-treat population			
Units: Subjects			
Never smoker	16		16
Former smoker	7		7
Smoker	0		0
Histological evidence			
Histological evidence of the cancer on intent-to-treat population			
Units: Subjects			
Yes	21		21
No	2		2
Cytological evidence			
Cytological evidence of cancer on intent-to-treat patients			
Units: Subjects			
Yes	13		13
No	9		9
Unknown	1		1
Histological type			
Histological type for cancers			
Units: Subjects			

Adenocarcinoma	21		21
Mixed carcinoma	1		1
Squamous cell carcinoma	1		1
TNM			
TNM at inclusion on intent-to-treat population			
Units: Subjects			
IIIC	1		1
IVA	2		2
IVB	20		20
Performans status			
Performans status at inclusion on intent-to-treat population			
Units: Subjects			
PS 0	6		6
PS 1	15		15
PS 2	2		2
Brain metastasis			
Brain metastasis at inclusion on intent-to-treat population			
Units: Subjects			
Yes	6		6
No	17		17
PD-L1 expression			
PD-L1 pexpression on intent-to-treat population			
Units: Subjects			
Highly positive ($\geq 50\%$)	5		5
Positive (1-49%)	11		11
Negative ($<1\%$)	6		6
Unknown	1		1
EGFR status			
EGFR status on intent-to-treat population			
Units: Subjects			
Wild-type	22		22
Mutated	0		0
Not done	1		1
HER2 status			
HER2 status on intent-to-treat population			
Units: Subjects			
Wild-type	19		19
Mutated	0		0
Not done	4		4
ALK status			
ALK status on intent-to-treat population			
Units: Subjects			
Wild-type	23		23
Rearrangement	0		0
Not done	0		0
ROS1 status			
ROS1 status on intent-to-treat population			
Units: Subjects			
Wild-type	22		22
Rearrangement	1		1
Not done	0		0

KRAS status			
KRAS status on intent-to-treat population			
Units: Subjects			
Wild-type	20		20
Mutated	1		1
Not done	2		2
Other biomarkers			
Other biomarkers on intent-to-treat population			
Units: Subjects			
Yes	0		0
No	23		23
Cause of discontinuation			
Cause of treatment discontinuation			
Units: Subjects			
Disease progression	20		20
Toxicity	2		2
Patient's decision	1		1
Pack-years for smokers			
Number of pack-years for smokers			
Units: Pack-years			
median	22		22
full range (min-max)	10 to 30		10 to 30
Duration of therapy without interruption			
Duration of therapy (month) without interruption days on intent-to-treat population			
Units: month			
median	4.1		4.1
full range (min-max)	0.2 to 33.7		0.2 to 33.7
Duration therapy with interruption			
Duration of therapy (months) with interruption days			
Units: Month			
median	4.1		4.1
full range (min-max)	0.2 to 32.4		0.2 to 32.4
Number of interruption days			
Number of interruption days on intent-to-treat population			
Units: Day			
median	0		0
full range (min-max)	0 to 39		0 to 39
Total dose of treatment			
Total dose of lorlatinib administered at the end of treatment on intent-to-treat population			
Units: Mg			
median	12600		12600
full range (min-max)	2100 to 94275		2100 to 94275
Mean dose by day			
Mean dose of lorvatinib administered each day on intent-to-treat population			
Units: Mg			
median	100		100
full range (min-max)	99.7 to 100		99.7 to 100
Numbers of days with maximum dose			
Numbers of days of treatment with maximum dose on intent-to-treat population			
Units: Days			
median	126		126

full range (min-max)	21 to 942		21 to 942
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End points

End points reporting groups

Reporting group title	Lorlatinib
Reporting group description: Only arm in the study. Patients receive lorlatinib at 100mg once daily	
Subject analysis set title	Intent to treat
Subject analysis set type	Intention-to-treat
Subject analysis set description: All patients who were included are counted into this subject analysis set.	
Subject analysis set title	Eligible population
Subject analysis set type	Per protocol
Subject analysis set description: All patients in intention to treat without any critical deviation on inclusion or exclusion criteria.	
Subject analysis set title	Safety population
Subject analysis set type	Safety analysis
Subject analysis set description: All patients that received at least one dose of study treatment.	

Primary: Objective response rate at 6 weeks (in eligible population)

End point title	Objective response rate at 6 weeks (in eligible population) ^[1]
End point description: Objective response (= complete response and partial response) on eligible population according to RECIST 1.1 assessed by the investigators.	
End point type	Primary
End point timeframe: From inclusion to 6 weeks post inclusion	
Notes: [1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point. Justification: Monoarm study.	

End point values	Eligible population			
Subject group type	Subject analysis set			
Number of subjects analysed	22			
Units: Patients				
Complete response	0			
Partial response	6			

Statistical analyses

No statistical analyses for this end point

Secondary: Progression free survival (in eligible population)

End point title	Progression free survival (in eligible population)
End point description: Progression free survival. PFS : The length of time between the date of treatment start and tumour	

progression or death (any cause).

End point type	Secondary
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End point timeframe:

From the date of treatment start to the date of event defined as the first documented disease progression or death from any cause.

End point values	Eligible population			
Subject group type	Subject analysis set			
Number of subjects analysed	22			
Units: Month				
median (confidence interval 95%)	5.7 (1.4 to 11.2)			

Statistical analyses

No statistical analyses for this end point

Secondary: Overall survival (in eligible population)

End point title	Overall survival (in eligible population)
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End point description:

Overall survival (OS) has been measured from the date of treatment start to the date of death from any cause.

End point type	Secondary
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End point timeframe:

From the date of treatment start to the date of death from any cause.

End point values	Eligible population			
Subject group type	Subject analysis set			
Number of subjects analysed	22			
Units: Month				
median (confidence interval 95%)	20.9 (10.2 to 44.5)			

Statistical analyses

No statistical analyses for this end point

Secondary: Overall survival at 6 months (in eligible population)

End point title	Overall survival at 6 months (in eligible population)
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End point description:

Overall survival from the date of treatment start to 6 months of treatment.

End point type	Secondary
End point timeframe:	
From the date of treatment start to 6 months of treatment.	

End point values	Eligible population			
Subject group type	Subject analysis set			
Number of subjects analysed	22			
Units: Month				
median (confidence interval 95%)	77.3 (53.7 to 89.8)			

Statistical analyses

No statistical analyses for this end point

Secondary: Overall survival at 12 months (in eligible population)

End point title	Overall survival at 12 months (in eligible population)
End point description:	
Overall survival from the date of treatment start to 12 months of treatment.	
End point type	Secondary
End point timeframe:	
From the date of treatment start to 12 months of treatment.	

End point values	Eligible population			
Subject group type	Subject analysis set			
Number of subjects analysed	22			
Units: month				
median (confidence interval 95%)	59.1 (36.1 to 76.2)			

Statistical analyses

No statistical analyses for this end point

Secondary: Overall survival at 18 months (in eligible population)

End point title	Overall survival at 18 months (in eligible population)
End point description:	
Overall survival from the date of treatment start to 18 months of treatment.	
End point type	Secondary

End point timeframe:

From the date of treatment start to 18 months of treatment.

End point values	Eligible population			
Subject group type	Subject analysis set			
Number of subjects analysed	22			
Units: Month				
median (confidence interval 95%)	54.5 (32.1 to 72.4)			

Statistical analyses

No statistical analyses for this end point

Secondary: Overall response rate at 6 weeks (in eligible population)

End point title	Overall response rate at 6 weeks (in eligible population)
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End point description:

Overall response rate (Best response) from inclusion to 6 weeks post inclusion according to RECIST 1.1 assessed by investigators.

End point type	Secondary
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End point timeframe:

From inclusion to 6 weeks post inclusion

End point values	Eligible population			
Subject group type	Subject analysis set			
Number of subjects analysed	22			
Units: Patients				
Partial response	9			
Stable disease	7			
Progressive disease	5			
Not evaluable	1			

Statistical analyses

No statistical analyses for this end point

Secondary: Progression free survival at 6 months (in eligible population)

End point title	Progression free survival at 6 months (in eligible population)
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End point description:

Progression free survival from the date of treatment start to 6 months. PFS : The length of time between the date of treatment start and tumour progression or death (any cause).

End point type	Secondary
End point timeframe:	
From the date of treatment start to 6 months	

End point values	Eligible population			
Subject group type	Subject analysis set			
Number of subjects analysed	22			
Units: month				
median (confidence interval 95%)	48 (26 to 67)			

Statistical analyses

No statistical analyses for this end point

Secondary: Progression free survival at 12 months (in eligible population)

End point title	Progression free survival at 12 months (in eligible population)
End point description:	
Progression free survival from the date of treatment start to 12 months. PFS : The length of time between the date of treatment start and tumour progression or death (any cause).	
End point type	Secondary
End point timeframe:	
From the date of treatment start to 12 months	

End point values	Eligible population			
Subject group type	Subject analysis set			
Number of subjects analysed	22			
Units: month				
median (confidence interval 95%)	27 (10.2 to 47.2)			

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of response (in eligible population)

End point title	Duration of response (in eligible population)
End point description:	
Duration of response (only for patients with an objective response (partial or complete)) from the first occurrence of an objective response (CR or PR), based on RECIST 1.1 to first documented disease progression or death	
End point type	Secondary

End point timeframe:

From the first occurrence of an objective response (CR or PR), based on RECIST 1.1 to first documented disease progression or death assessed by investigators

End point values	Eligible population			
Subject group type	Subject analysis set			
Number of subjects analysed	9 ^[2]			
Units: Month				
median (confidence interval 95%)	11.2 (1.3 to 16.4)			

Notes:

[2] - Only patients with a complete response or partial response

Statistical analyses

No statistical analyses for this end point

Secondary: Time to tumor response (in eligible population)

End point title	Time to tumor response (in eligible population)
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End point description:

Time to tumor response (for eligible patients with complete or partial response) from the first lorlatinib dose and the first occurrence of an objective response (CR or PR) based on RECIST 1.1 and assessed by investigators

End point type	Secondary
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End point timeframe:

From the first lorlatinib dose and the first occurrence of an objective response (CR or PR)

End point values	Eligible population			
Subject group type	Subject analysis set			
Number of subjects analysed	9 ^[3]			
Units: month				
median (full range (min-max))	1.3 (1.2 to 16.5)			

Notes:

[3] - 9 patients with complete or partial response

Statistical analyses

No statistical analyses for this end point

Secondary: Central Nervous System objective response rate

End point title	Central Nervous System objective response rate
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End point description:

CNS ORR is defined as the proportion of patients achieving an objective response (complete response (CR) or partial response (PR)) of the baseline measurable and non-measurable CNS disease according to RECIST 1.1 and Revised Assessment in Neuro Oncology (RANO) criteria, as assessed by investigators.

End point type	Secondary
End point timeframe:	
From inclusion to the end of study or death, which ever occurs first	

End point values	Eligible population			
Subject group type	Subject analysis set			
Number of subjects analysed	6 ^[4]			
Units: Patients				
Complete response	1			
Partial response	2			

Notes:

[4] - 6 patients with brain metastasis at inclusion

Statistical analyses

No statistical analyses for this end point

Secondary: Central Nervous System overall response rate

End point title	Central Nervous System overall response rate
End point description:	
CNS overall response rate (CNS best response) from inclusion to the end of the study or death, which ever occurs first, according to RECIST 1.1 and RANO criteria, assessed by investigators	
End point type	Secondary
End point timeframe:	
From inclusion to the end of study or death, which ever occurs first	

End point values	Eligible population			
Subject group type	Subject analysis set			
Number of subjects analysed	6 ^[5]			
Units: Patients				
Complete response	1			
Partial response	2			
Stable disease	1			
Progressive disease	1			
Not evaluable	1			

Notes:

[5] - 6 patients with brain metastasis at inclusion

Statistical analyses

No statistical analyses for this end point

Secondary: Central Nervous System Progression Free Survival (in eligible patients)

End point title	Central Nervous System Progression Free Survival (in eligible patients)
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patients)

End point description:

Central Nervous System Progression Free Survival (in eligible patients) from the date of treatment start to the first documented progression of the central nervous system according to RECISTS 1.1 and Revised Assessment in Neuro Oncology (RANO) criteria, as assessed by investigators.

End point type Secondary

End point timeframe:

From the date of treatment start to the first documented progression of the central nervous system.

End point values	Eligible population			
Subject group type	Subject analysis set			
Number of subjects analysed	22			
Units: Month				
median (confidence interval 95%)	18.4 (10.4 to 40.1)			

Statistical analyses

No statistical analyses for this end point

Secondary: Time to response of the Central Nervous System (in eligible patients)

End point title Time to response of the Central Nervous System (in eligible patients)

End point description:

Time to tumor response (for eligible patients with complete or partial response of the Central Nervous System) from the first lorlatinib dose and the first occurrence of an objective response (CR or PR) of the CNS based on RECIST 1.1 and Revised Assessment in Neuro Oncology (RANO) criteria, assessed by investigators

End point type Secondary

End point timeframe:

From the first lorlatinib dose and the first occurrence of an objective response (CR or PR) of the Central Nervous System

End point values	Eligible population			
Subject group type	Subject analysis set			
Number of subjects analysed	3 ^[6]			
Units: Month				
median (confidence interval 95%)	6.6 (1.3 to 13.3)			

Notes:

[6] - Eligible patients with an objective response of the Central Nervous System

Statistical analyses

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Timeframe for AE

Adverse event reporting additional description:

AE additional description

Assessment type	Non-systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	19.0
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Reporting groups

Reporting group title	Treated
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Reporting group description: -

Serious adverse events	Treated		
Total subjects affected by serious adverse events			
subjects affected / exposed	12 / 23 (52.17%)		
number of deaths (all causes)	15		
number of deaths resulting from adverse events	2		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Malignant neoplasm progression	Additional description: Malignant neoplasm progression		
subjects affected / exposed	6 / 23 (26.09%)		
occurrences causally related to treatment / all	0 / 7		
deaths causally related to treatment / all	0 / 1		
Cardiac disorders			
Cardiac failure congestive	Additional description: Cardiac failure congestive		
subjects affected / exposed	1 / 23 (4.35%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Headache	Additional description: Headache		
subjects affected / exposed	1 / 23 (4.35%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Seizure	Additional description: Seizure		

subjects affected / exposed	1 / 23 (4.35%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Oesophageal compression	Additional description: Oesophageal compression		
subjects affected / exposed	1 / 23 (4.35%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vomiting			
subjects affected / exposed	1 / 23 (4.35%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Dyspnoea	Additional description: Dyspnoea		
subjects affected / exposed	2 / 23 (8.70%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Pulmonary hypertension			
subjects affected / exposed	1 / 23 (4.35%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
COVID-19	Additional description: COVID-19		
subjects affected / exposed	1 / 23 (4.35%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Endophthalmitis			
subjects affected / exposed	1 / 23 (4.35%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pneumonia			
subjects affected / exposed	3 / 23 (13.04%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events		Treated		
Total subjects affected by non-serious adverse events				
subjects affected / exposed		23 / 23 (100.00%)		
Vascular disorders				
Hypertension		Additional description: Hypertension		
subjects affected / exposed		3 / 23 (13.04%)		
occurrences (all)		29		
Hot flush		Additional description: Hot flush		
subjects affected / exposed		1 / 23 (4.35%)		
occurrences (all)		1		
Hypotension		Additional description: Hypotension		
subjects affected / exposed		1 / 23 (4.35%)		
occurrences (all)		1		
Pulmonary embolism		Additional description: Pulmonary embolism		
subjects affected / exposed		1 / 23 (4.35%)		
occurrences (all)		1		
Varicose vein		Additional description: Varicose vein		
subjects affected / exposed		1 / 23 (4.35%)		
occurrences (all)		1		
General disorders and administration site conditions				
Fatigue		Additional description: Fatigue		
subjects affected / exposed		7 / 23 (30.43%)		
occurrences (all)		12		
Face oedema		Additional description: Face oedema		
subjects affected / exposed		1 / 23 (4.35%)		
occurrences (all)		1		
Influenza like illness		Additional description: Influenza like illness		
subjects affected / exposed		1 / 23 (4.35%)		
occurrences (all)		1		
Pain		Additional description: Pain		

subjects affected / exposed	5 / 23 (21.74%)		
occurrences (all)	8		
Oedema peripheral	Additional description: Oedema peripheral		
subjects affected / exposed	7 / 23 (30.43%)		
occurrences (all)	42		
Reproductive system and breast disorders			
Erectile dysfunction	Additional description: Erectile dysfunction		
subjects affected / exposed	1 / 23 (4.35%)		
occurrences (all)	17		
Peyronie's disease	Additional description: Peyronie's disease		
subjects affected / exposed	1 / 23 (4.35%)		
occurrences (all)	5		
Pelvic pain	Additional description: Pelvic pain		
subjects affected / exposed	1 / 23 (4.35%)		
occurrences (all)	1		
Vaginal discharge	Additional description: Vaginal discharge		
subjects affected / exposed	1 / 23 (4.35%)		
occurrences (all)	2		
Respiratory, thoracic and mediastinal disorders			
Acute respiratory failure	Additional description: Acute respiratory failure		
subjects affected / exposed	1 / 23 (4.35%)		
occurrences (all)	1		
Cough	Additional description: Cough		
subjects affected / exposed	4 / 23 (17.39%)		
occurrences (all)	23		
Dyspnoea	Additional description: Dyspnoea		
subjects affected / exposed	9 / 23 (39.13%)		
occurrences (all)	59		
Dysphonia	Additional description: Dysphonia		
subjects affected / exposed	1 / 23 (4.35%)		
occurrences (all)	1		
Hypoxia	Additional description: Hypoxia		
subjects affected / exposed	1 / 23 (4.35%)		
occurrences (all)	1		
Non-cardiac chest pain	Additional description: Non-cardiac chest pain		

subjects affected / exposed occurrences (all)	1 / 23 (4.35%) 1		
Pleural effusion	Additional description: Pleural effusion		
subjects affected / exposed occurrences (all)	2 / 23 (8.70%) 3		
Productive cough	Additional description: Productive cough		
subjects affected / exposed occurrences (all)	1 / 23 (4.35%) 1		
Pulmonary hypertension	Additional description: Pulmonary hypertension		
subjects affected / exposed occurrences (all)	1 / 23 (4.35%) 4		
Rhinorrhoea	Additional description: Rhinorrhoea		
subjects affected / exposed occurrences (all)	1 / 23 (4.35%) 2		
Sleep apnoea syndrome	Additional description: Sleep apnoea syndrome		
subjects affected / exposed occurrences (all)	2 / 23 (8.70%) 3		
Psychiatric disorders			
Anxiety	Additional description: Anxiety		
subjects affected / exposed occurrences (all)	2 / 23 (8.70%) 13		
Confusional state	Additional description: Confusional state		
subjects affected / exposed occurrences (all)	1 / 23 (4.35%) 1		
Insomnia	Additional description: Insomnia		
subjects affected / exposed occurrences (all)	1 / 23 (4.35%) 7		
Irritability	Additional description: Irritability		
subjects affected / exposed occurrences (all)	2 / 23 (8.70%) 29		
Investigations			
Alanine aminotransferase increased	Additional description: Alanine aminotransferase increased		
subjects affected / exposed occurrences (all)	2 / 23 (8.70%) 4		
Aspartate aminotransferase increased	Additional description: Aspartate aminotransferase increased		

subjects affected / exposed	1 / 23 (4.35%)		
occurrences (all)	9		
Blood alkaline phosphatase increased	Additional description: Blood alkaline phosphatase increased		
subjects affected / exposed	3 / 23 (13.04%)		
occurrences (all)	9		
Blood cholesterol increased	Additional description: Blood cholesterol increased		
subjects affected / exposed	19 / 23 (82.61%)		
occurrences (all)	153		
Blood creatine phosphokinase increased	Additional description: Blood creatine phosphokinase increased		
subjects affected / exposed	2 / 23 (8.70%)		
occurrences (all)	10		
Blood creatinine increased	Additional description: Blood creatinine increased		
subjects affected / exposed	1 / 23 (4.35%)		
occurrences (all)	10		
Blood lactate dehydrogenase increased	Additional description: Blood lactate dehydrogenase increased		
subjects affected / exposed	2 / 23 (8.70%)		
occurrences (all)	2		
Blood urea increased	Additional description: Blood urea increased		
subjects affected / exposed	1 / 23 (4.35%)		
occurrences (all)	2		
Gamma-glutamyltransferase increased	Additional description: Gamma-glutamyltransferase increased		
subjects affected / exposed	3 / 23 (13.04%)		
occurrences (all)	23		
Neutrophil count decreased	Additional description: Neutrophil count decreased		
subjects affected / exposed	1 / 23 (4.35%)		
occurrences (all)	15		
Platelet count decreased	Additional description: Platelet count decreased		
subjects affected / exposed	1 / 23 (4.35%)		
occurrences (all)	8		
Weight increased	Additional description: Weight increased		
subjects affected / exposed	1 / 23 (4.35%)		
occurrences (all)	19		
Injury, poisoning and procedural complications			

Limb injury subjects affected / exposed occurrences (all)	Additional description: Limb injury		
	1 / 23 (4.35%)		
	1		
Cardiac disorders Cardiac failure subjects affected / exposed occurrences (all) Ventricular tachycardia subjects affected / exposed occurrences (all)	Additional description: Cardiac failure		
	2 / 23 (8.70%)		
	2		
	Additional description: Ventricular tachycardia		
	1 / 23 (4.35%)		
	1		
Nervous system disorders Cerebral ischaemia subjects affected / exposed occurrences (all) Cognitive disorder subjects affected / exposed occurrences (all) Disturbance in attention subjects affected / exposed occurrences (all) Dysgeusia subjects affected / exposed occurrences (all) Dysaesthesia subjects affected / exposed occurrences (all) Dizziness subjects affected / exposed occurrences (all) Headache subjects affected / exposed occurrences (all) Memory impairment subjects affected / exposed occurrences (all) Peripheral motor neuropathy	Additional description: Cerebral ischaemia		
	1 / 23 (4.35%)		
	1		
	Additional description: Cognitive disorder		
	1 / 23 (4.35%)		
	7		
	Additional description: Disturbance in attention		
	1 / 23 (4.35%)		
	1		
	Additional description: Dysgeusia		
	1 / 23 (4.35%)		
	1		
	Additional description: Dysaesthesia		
	1 / 23 (4.35%)		
	1		
	Additional description: Dizziness		
	1 / 23 (4.35%)		
	1		
	Additional description: Headache		
	4 / 23 (17.39%)		
	11		
	Additional description: Memory impairment		
	2 / 23 (8.70%)		
	9		
	Additional description: Peripheral motor neuropathy		

subjects affected / exposed	1 / 23 (4.35%)		
occurrences (all)	1		
Seizure	Additional description: Seizure		
subjects affected / exposed	1 / 23 (4.35%)		
occurrences (all)	2		
Blood and lymphatic system disorders			
Anaemia	Additional description: Anaemia		
subjects affected / exposed	7 / 23 (30.43%)		
occurrences (all)	36		
Ear and labyrinth disorders			
Middle ear inflammation	Additional description: Middle ear inflammation		
subjects affected / exposed	1 / 23 (4.35%)		
occurrences (all)	1		
Tinnitus	Additional description: Tinnitus		
subjects affected / exposed	2 / 23 (8.70%)		
occurrences (all)	5		
Vertigo	Additional description: Vertigo		
subjects affected / exposed	2 / 23 (8.70%)		
occurrences (all)	3		
Eye disorders			
Conjunctivitis	Additional description: Conjunctivitis		
subjects affected / exposed	1 / 23 (4.35%)		
occurrences (all)	1		
Eye pain	Additional description: Eye pain		
subjects affected / exposed	1 / 23 (4.35%)		
occurrences (all)	1		
Ocular hyperaemia	Additional description: Ocular hyperaemia		
subjects affected / exposed	1 / 23 (4.35%)		
occurrences (all)	2		
Ocular hypertension	Additional description: Ocular hypertension		
subjects affected / exposed	1 / 23 (4.35%)		
occurrences (all)	1		
Periorbital oedema	Additional description: Periorbital oedema		
subjects affected / exposed	1 / 23 (4.35%)		
occurrences (all)	1		
Visual impairment	Additional description: Visual impairment		

subjects affected / exposed	1 / 23 (4.35%)		
occurrences (all)	6		
Vision blurred	Additional description: Vision blurred		
subjects affected / exposed	2 / 23 (8.70%)		
occurrences (all)	3		
Gastrointestinal disorders			
Abdominal distension	Additional description: Abdominal distension		
subjects affected / exposed	1 / 23 (4.35%)		
occurrences (all)	3		
Abdominal pain	Additional description: Abdominal pain		
subjects affected / exposed	4 / 23 (17.39%)		
occurrences (all)	7		
Constipation	Additional description: Constipation		
subjects affected / exposed	3 / 23 (13.04%)		
occurrences (all)	6		
Diarrhoea	Additional description: Diarrhoea		
subjects affected / exposed	4 / 23 (17.39%)		
occurrences (all)	21		
Dysphagia	Additional description: Dysphagia		
subjects affected / exposed	2 / 23 (8.70%)		
occurrences (all)	2		
Nausea	Additional description: Nausea		
subjects affected / exposed	3 / 23 (13.04%)		
occurrences (all)	5		
Oral dysaesthesia	Additional description: Oral dysaesthesia		
subjects affected / exposed	1 / 23 (4.35%)		
occurrences (all)	1		
Stomatitis	Additional description: Stomatitis		
subjects affected / exposed	2 / 23 (8.70%)		
occurrences (all)	4		
Vomiting	Additional description: Vomiting		
subjects affected / exposed	2 / 23 (8.70%)		
occurrences (all)	2		
Hepatobiliary disorders			
Portal vein thrombosis	Additional description: Portal vein thrombosis		

subjects affected / exposed	1 / 23 (4.35%)		
occurrences (all)	1		
Skin and subcutaneous tissue disorders			
Chronic cutaneous lupus erythematosus	Additional description: Chronic cutaneous lupus erythematosus		
subjects affected / exposed	1 / 23 (4.35%)		
occurrences (all)	1		
Dermatitis	Additional description: Dermatitis		
subjects affected / exposed	1 / 23 (4.35%)		
occurrences (all)	1		
Dry skin	Additional description: Dry skin		
subjects affected / exposed	1 / 23 (4.35%)		
occurrences (all)	3		
Erythema	Additional description: Erythema		
subjects affected / exposed	1 / 23 (4.35%)		
occurrences (all)	1		
Erythema multiforme	Additional description: Erythema multiforme		
subjects affected / exposed	2 / 23 (8.70%)		
occurrences (all)	6		
Hyperhidrosis	Additional description: Hyperhidrosis		
subjects affected / exposed	1 / 23 (4.35%)		
occurrences (all)	15		
Nail discolouration	Additional description: Nail discolouration		
subjects affected / exposed	1 / 23 (4.35%)		
occurrences (all)	1		
Nail disorder	Additional description: Nail disorder		
subjects affected / exposed	2 / 23 (8.70%)		
occurrences (all)	20		
Pruritus	Additional description: Pruritus		
subjects affected / exposed	2 / 23 (8.70%)		
occurrences (all)	2		
Skin hypopigmentation	Additional description: Skin hypopigmentation		
subjects affected / exposed	1 / 23 (4.35%)		
occurrences (all)	1		
Renal and urinary disorders			

Haematuria subjects affected / exposed occurrences (all)	Additional description: Haematuria	
	1 / 23 (4.35%)	
	1	
Pollakiuria subjects affected / exposed occurrences (all)	Additional description: Pollakiuria	
	1 / 23 (4.35%)	
	1	
Urinary incontinence subjects affected / exposed occurrences (all)	Additional description: Urinary incontinence	
	1 / 23 (4.35%)	
	1	
Musculoskeletal and connective tissue disorders		
	Additional description: Arthralgia	
	1 / 23 (4.35%)	
	1	
	Additional description: Back pain	
	3 / 23 (13.04%)	
	5	
	Additional description: Bone pain	
	3 / 23 (13.04%)	
	11	
	Additional description: Exostosis	
	1 / 23 (4.35%)	
	1	
	Additional description: Haemarthrosis	
	1 / 23 (4.35%)	
	1	
	Additional description: Flank pain	
	1 / 23 (4.35%)	
	1	
	Additional description: Musculoskeletal chest pain	
	3 / 23 (13.04%)	
	4	
	Additional description: Myalgia	
	1 / 23 (4.35%)	
	2	
	Additional description: Osteoarthritis	

subjects affected / exposed	1 / 23 (4.35%)		
occurrences (all)	1		
Rotator cuff syndrome	Additional description: Rotator cuff syndrome		
subjects affected / exposed	1 / 23 (4.35%)		
occurrences (all)	4		
Soft tissue disorder	Additional description: Soft tissue disorder		
subjects affected / exposed	1 / 23 (4.35%)		
occurrences (all)	5		
Infections and infestations			
COVID-19	Additional description: COVID-19		
subjects affected / exposed	1 / 23 (4.35%)		
occurrences (all)	2		
Endophthalmitis	Additional description: Endophthalmitis		
subjects affected / exposed	1 / 23 (4.35%)		
occurrences (all)	1		
Pneumonia	Additional description: Pneumonia		
subjects affected / exposed	3 / 23 (13.04%)		
occurrences (all)	4		
Rash pustular	Additional description: Rash pustular		
subjects affected / exposed	1 / 23 (4.35%)		
occurrences (all)	6		
Rhinitis	Additional description: Rhinitis		
subjects affected / exposed	1 / 23 (4.35%)		
occurrences (all)	1		
Urinary tract infection	Additional description: Urinary tract infection		
subjects affected / exposed	1 / 23 (4.35%)		
occurrences (all)	1		
Upper respiratory tract infection	Additional description: Upper respiratory tract infection		
subjects affected / exposed	1 / 23 (4.35%)		
occurrences (all)	1		
Metabolism and nutrition disorders			
Decreased appetite	Additional description: Decreased appetite		
subjects affected / exposed	1 / 23 (4.35%)		
occurrences (all)	2		
Hyperkalaemia	Additional description: Hyperkalaemia		

subjects affected / exposed	1 / 23 (4.35%)		
occurrences (all)	1		
Hypercalcaemia	Additional description: Hypercalcaemia		
subjects affected / exposed	1 / 23 (4.35%)		
occurrences (all)	2		
Hypertriglyceridaemia	Additional description: Hypertriglyceridaemia		
subjects affected / exposed	19 / 23 (82.61%)		
occurrences (all)	110		
Hypophosphataemia	Additional description: Hypophosphataemia		
subjects affected / exposed	1 / 23 (4.35%)		
occurrences (all)	1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
10 March 2020	<p>This first modification aims to:</p> <ul style="list-style-type: none">- Clarification of inclusion criterion #2 and exclusion criterion #1- Removal of blood urea and albumin testing- Clarification regarding the cardiac ultrasound to be performed at screening and every 6 months- Clarification regarding the frequency of blood samples for the ancillary biological study to be taken at inclusion and not on day 1 (C1J1)- Minor clarification of the definition of overall survival.- Change of the principal investigator for a center.
21 April 2021	<p>This second amendment adds:</p> <ul style="list-style-type: none">- Clarifications regarding screening tests- Clarification of the treatment plan- Clarification of the follow-up for adverse events after treatment- Modification of the treatment center supply- Clarification of non-serious adverse events of particular interest- Clarification of the reporting procedure in case of exposure to the product- Clarification of the steering committee meeting frequency- Modification of the frequency of a respiratory adverse event- Modification of the list of centers (removal of two centers and addition of two new centers)

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

The trial was terminated early leading to a small number of subjects analysed.
The early termination was due to the reimbursement obtention in France for the study product lorlatinib and the resulting decrease in inclusion rate.

Notes: