Clinical trial results:
Secured access to crizotinib for patients with tumors harboring a genomic alteration on one of the biological targets of the drug.

Summary

EudraCT number	2013-000885-13
Trial protocol	FR
Global end of trial date	12 December 2023

Results information

Result version number	v1 (current)
This version publication date	21 June 2025
First version publication date	21 June 2025

Trial information

Trial identification

Sponsor protocol code	UC-0105/1303

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02034981
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	UNICANCER
Sponsor organisation address	101 rue de Tolbiac, Paris, France, 75015
Public contact	Nourredine AIT RAHMOUNE, UNICANCER, 33 0171936704, n.ait-rahmoune@unicancer.frr
Scientific contact	Nourredine AIT RAHMOUNE, UNICANCER, 33 0171936704, n.ait-rahmoune@unicancer.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	30 October 2020
Is this the analysis of the primary completion data?	Yes
Primary completion date	07 March 2018
Global end of trial reached?	Yes
Global end of trial date	12 December 2023
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The objective of this study is to explore the efficacy of crizotinib as a single agent across diverse type of tumors guided by the presence of identified activating molecular alterations in the crizotinib-target genes, per cohort, per pathology and per target.

Protection of trial subjects:

This study was conducted in compliance with the protocol, in accordance with the French national regulatory requirements and the Declaration of Helsinki (1964) and subsequent amendments, ICH Good Clinical Practice (GCP) Guidelines (CPMP/ICH/135/95), the European Directive (2001/20/CE) and the applicable local regulatory requirements and laws.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	05 August 2013
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy
Long term follow-up duration	2 Years
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	France: 238
Worldwide total number of subjects	238
EEA total number of subjects	238

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)	2
Children (2-11 years)	16
Adolescents (12-17 years)	9
Adults (18-64 years)	135

From 65 to 84 years	72
85 years and over	4

Subject disposition

Recruitment

Recruitment details:

From August 2013 to March 2018, 538 patients were screened of which 246 were included across 89 centers. Among patients included, 238 were treated and received at least one dose of crizotinib. Among the 238 patients included and treated 66 had an anomaly ALK, 122 an anomaly MET, 49 an anomaly ROS1 and one patient had abnormality FUSION ETV6-NTRK.

Pre-assignment

Screening details:

Twenty-two cohorts were identified, a cohort being defined as [one pathology, one target alteration]. The pediatric cohort which gathered several rare pediatric diseases harboring at least one crizotinib target alteration and a miscellaneous adults disease cohort were added. The expected treatment duration per patient was 6 months.

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	Crizotinib

Arm description:

All eligible patients entering the study received oral crizotinib, daily continuously:
- 250 mg twice daily (BID) for adults ≥ 18 years of age.
- 280 mg/m² twice daily (BID) for children and adolescents aged from one 1 to 17 (except ALCL).
- 165 mg/m² twice daily (BID) for ALCL patients aged from one 1 to 17 years.

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

Dosage and administration details:

- 250 mg twice daily (BID) for adults ≥ 18 years of age
- 280 mg/m2 twice daily (BID) for children and adolescents aged from one 1 to 17 (except ALCL).
- 165 mg/m² twice daily (BID) for ALCL patients aged from one 1 to 17.

The oral liquid formulation could be administered to adult patients with inability to swallow due to the compression of the tumor (e.g. dysphagia in anaplastic thyroid cancer).

Number of subjects in period 1	Crizotinib
Started	238
Completed	2
Not completed	236
Patient refusal	4
Physician decision	24
Disease progression	164
Other decision	2

Death	5
Adverse event	36
Promotor decision	1

Baseline characteristics

Reporting groups

Reporting group title	Overall trial (overall period)

Reporting group description:

246 patients were included and 238 patients received at least 1 dose of crizotinib. Among the 24 cohorts set up in this study, 13 cohorts did not enroll enough patients at stage 1 to perform the efficacy analysis.

9 cohorts that included and treated enough patients for efficacy and safety analysis:
1- Cohorts without efficacy signals in stage 1:
- Colorectal (MET-amp) cohort N°3
- Glioblastoma (MET-amp), cohort N°18
- Neuroblastoma (ALK-amp/ALK-mut) cohort N°15
2- Cohorts with efficacy signals in stage 1 but did not enroll patients in stage 2
- Oesogastric (MET-amp) cohort N°8
- IMT (ALK-trans or ROS1-trans) cohort N°16
3- Cohorts with efficacy signals in stage 1 that enrolled patients in stage 2
- NSCLC (ROS1-trans) cohort N°6
- NSCLC (MET-mut) cohort N°22
- NSCLC (MET-amp) cohort N°5
- ALCL (ALK-trans) cohort N°1

Reporting group values	Overall trial (overall period)	Total	
Number of subjects	238	238	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	2	2	
Children (2-11 years)	16	16	
Adolescents (12-17 years)	9	9	
Adults (18-64 years)	135	135	
From 65-84 years	72	72	
85 years and over	4	4	
Age continuous Units: years			
median	57		
full range (min-max)	1 to 92	-	
Gender categorical Units: Subjects			
Female	121	121	
Male	117	117	
ECOG performance status Units: Subjects			
ECOG 0	54	54	
ECOG 1	106	106	
ECOG 2	46	46	
Data missing	32	32	
Tumor site at screening			

Units: Subjects			
Colorectal cancer	18	18	
Stomach cancer	6	6	
cholangiocarcinoma	12	12	
Glioblastoma	13	13	
Neuroblastoma	9	9	
Ovary cancer	10	10	
Non small cell lung cancer	92	92	
Kidney cancer	6	6	
Rhabdomyosarcoma	1	1	
Breast cancer	3	3	
Thyroid cancer	4	4	
cancerALCLInflammatory myofibroblastic tumor	8	8	
ALCL	23	23	
Other cancer	29	29	
Esophageal cancer	3	3	
siteUnknown primary	1	1	
Type of anomaly Units: Subjects			
Patients with tumors having ALK molecular alterati	66	66	
Patients with tumors having with MET molecular alt	122	122	
Patients with tumors having ROS1 molecular alterat	49	49	
Rare fusion ETV6-NTRK3 molecular alteration.	1	1	
Molecular disease testing at baseline (Origin) Units: Subjects			
Metastases	72	72	
Primary tumor	166	166	

End points

End points reporting groups

Reporting group title	Crizotinib
Reporting group description:	
All eligible patients entering the study received oral crizotinib, daily continuously: - 250 mg twice daily (BID) for adults ≥ 18 years of age. - 280 mg/m² twice daily (BID) for children and adolescents aged from one 1 to 17 (except ALCL). - 165 mg/m² twice daily (BID) for ALCL patients aged from one 1 to 17 years.	
Subject analysis set title	Cohort N°3: Colorectal (MET-amp)
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Cohort N°3: Colorectal (MET-amp)	
Subject analysis set title	Cohort N°18: Glioblastoma (MET-amp)
Subject analysis set type	Full analysis
Subject analysis set description:	
Cohort N°18: Glioblastoma (MET-amp)	
Subject analysis set title	Cohort N°15: Neuroblastoma (ALK-amp/ALK-mut)
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Cohort N°15: Neuroblastoma (ALK-amp/ALK-mut)	
Subject analysis set title	Cohort N°8: Oesogastric (MET-amp)
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Cohort N°8: Oesogastric (MET-amp)	
Subject analysis set title	Cohort N°16: IMT (ALK-trans or ROS1-trans)
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Cohort N°16: IMT (ALK-trans or ROS1-trans)	
Subject analysis set title	Cohort N°6: NSCLC (ROS1-trans)
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Cohort N°6: NSCLC (ROS1-trans)	
Subject analysis set title	Cohort N°22: NSCLC (MET-mut)
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Cohort N°22: NSCLC (MET-mut)	
Subject analysis set title	Cohort N°5: NSCLC (MET-amp)
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Cohort N°5: NSCLC (MET-amp)	
Subject analysis set title	Cohort N°1: ALCL (ALK-trans)
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Cohort N°1: ALCL (ALK-trans)	

Primary: The objective response rate (ORR)

End point title	The objective response rate (ORR)[1]
End point description:	
Anti-tumor activity of crizotinib, as the primary objective of the trial, will be carried out by the determination of the objective response assessed in each cohort defined by a pathology associated with a crizotinib target alteration.	

The objective response is defined as either a complete response (CR) or partial response (PR) according to Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 criteria.
At the time of analyses, 13 of the 24 cohorts did not enroll enough patients to analyze efficacy at stage 1, with four cohorts that did not include patients.
NB:
- ALCL, anaplastic large cell lymphoma; ALK, anaplastic lymphoma kinase; ROS1, c-ros oncogene 1; NSCLC, non-small cell lung cancer;
- Patient in the NSCLC (ROS1-trans) cohort died early during treatment and was not evaluable after 2 cycles and during crizotinib treatment.
6 Patients in the ALCL (ALK-trans) cohort stopped crizotinib for another treatment and was not evaluable after 2 cycles and during crizotinib trt.

End point type	Primary

End point timeframe:

Determined after 8 weeks (2 cycles) of treatment.

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: This endpoint was descriptive; hence no statistical analysis to report

End point values	Cohort N°8: Oesogastric (MET-amp)	Cohort N°16: IMT (ALK-trans or ROS1-trans)	Cohort N°6: NSCLC (ROS1-trans)	Cohort N°22: NSCLC (MET-mut)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	9	8	37	28
Units: percent				
number (confidence interval 95%)	33.3 (7.5 to 70)	25 (3.2 to 65.1)	44.4 (27.9 to 61.9)	17.9 (6.1 to 36.9)

End point values	Cohort N°5: NSCLC (MET-amp)	Cohort N°1: ALCL (ALK-trans)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	25	25		
Units: percent				
number (confidence interval 95%)	16 (4.5 to 36.1)	67 (47 to 82)		

Statistical analyses

No statistical analyses for this end point

Secondary: Disease Control Rate (DCR)

End point title	Disease Control Rate (DCR)

End point description:

Disease Control Rate will be the percentage of patients with a CR, PR or Stable Disease (SD) according to RECIST at the end of cycle 2 (8 weeks) and at the end of cycle 4 (16 weeks) in the group of patients evaluable for response.

End point type	Secondary

End point timeframe:

After 8 weeks (2 cycles) and 16 weeks (4 cycles) of treatment

End point values	Cohort N°3: Colorectal (MET-amp)	Cohort N°18: Glioblastoma (MET-amp)	Cohort N°15: Neuroblastoma (ALK-amp/ALK-mut)	Cohort N°8: Oesogastric (MET-amp)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	13	8	8	9
Units: percent				
number (confidence interval 95%)				
DCR after 2 cycles	15.4 (1.9 to 45.4)	25 (3.2 to 65.1)	50 (15.7 to 84.3)	55.6 (21.2 to 86.3)
DCR after 4 cycles	0 (0 to 0)	0 (0 to 0)	37.5 (8.5 to 75.5)	44.4 (13.7 to 78.8)

End point values	Cohort N°16: IMT (ALK-trans or ROS1-trans)	Cohort N°6: NSCLC (ROS1-trans)	Cohort N°22: NSCLC (MET-mut)	Cohort N°5: NSCLC (MET-amp)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	8	37	28	25
Units: percent				
number (confidence interval 95%)				
DCR after 2 cycles	75 (34.9 to 96.8)	75 (67.2 to 93.6)	60.7 (40.6 to 78.5)	48 (27.8 to 68.7)
DCR after 4 cycles	62.5 (24.5 to 91.5)	69.4 (51.9 to 83.7)	42.9 (24.5 to 62.8)	36 (18.0 to 57.5)

End point values	Cohort N°1: ALCL (ALK-trans)			
Subject group type	Subject analysis set			
Number of subjects analysed	25			
Units: percent				
number (confidence interval 95%)				
DCR after 2 cycles	67 (47 to 82)			
DCR after 4 cycles	63 (43 to 79)			

Statistical analyses

No statistical analyses for this end point

Secondary: Response duration

End point title	Response duration

End point description:

Response duration will be the time interval between the date that the criteria of CR/PR (whichever is first recorded) are met for the first time and the first date of documented re-appearance of the disease

(recurrence, progression or death). If neither event has been observed, then the patient is censored at the date of the last follow up examination.

End point type	Secondary

End point timeframe:

Interval beetween the objective response (CR or PR) and time of progression, reccurrence or death

End point values	Cohort N°15: Neuroblastoma (ALK-amp/ALK-mut)	Cohort N°8: Oesogastric (MET-amp)	Cohort N°16: IMT (ALK-trans or ROS1-trans)	Cohort N°6: NSCLC (ROS1-trans)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	8	9	8	37
Units: Months				
number (not applicable)				
Duration of response, median	19.7	2.7	13.8	7.3

End point values	Cohort N°22: NSCLC (MET-mut)	Cohort N°5: NSCLC (MET-amp)	Cohort N°1: ALCL (ALK-trans)	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	28	25	25	
Units: Months				
number (not applicable)				
Duration of response, median	5.1	2.0	45.8	

Statistical analyses

No statistical analyses for this end point

Secondary: Progression-free survival (PFS)

End point title	Progression-free survival (PFS)

End point description:

Progression-free survival will be the time interval between the date of registration and the day of first documented sign of disease progression (first day when RECIST criteria of progression are met) or day of death whatever the cause (events). If neither event has been observed, then the patient is censored at the date of the last follow up examination.

End point type	Secondary

End point timeframe:

from registration until time of disease progression or death

End point values	Cohort N°3: Colorectal (MET-amp)	Cohort N°18: Glioblastoma (MET-amp)	Cohort N°15: Neuroblastoma (ALK-amp/ALK-mut)	Cohort N°8: Oesogastric (MET-amp)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	13	8	8	9
Units: Months				
number (not applicable)				
PFS median	1.8	1.8	2.7	3.2

End point values	Cohort N°16: IMT (ALK-trans or ROS1-trans)	Cohort N°6: NSCLC (ROS1-trans)	Cohort N°22: NSCLC (MET-mut)	Cohort N°5: NSCLC (MET-amp)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	8	37	28	25
Units: Months				
number (not applicable)				
PFS median	6.4	5.6	4.2	3.2

End point values	Cohort N°1: ALCL (ALK-trans)			
Subject group type	Subject analysis set			
Number of subjects analysed	25			
Units: Months				
number (not applicable)				
PFS median	10.1			

Statistical analyses

No statistical analyses for this end point

Secondary: Overall survival (OS)

End point title	Overall survival (OS)

End point description:

Overall survival will be the time interval between the date of registration and the date of death, whatever the cause of death. Patients still alive at follow-up are censored at the date of last follow up.

End point type	Secondary

End point timeframe:

from registration until date of death

End point values	Cohort N°3: Colorectal (MET-amp)	Cohort N°18: Glioblastoma (MET-amp)	Cohort N°8: Oesogastric (MET-amp)	Cohort N°6: NSCLC (ROS1-trans)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	13	8	9	37
Units: Months				
median (confidence interval 95%)	7 (3 to 14.2)	3.8 (0.9 to 8)	8.1 (1.7 to 24.6)	50 (36.7 to 54.5)

End point values	Cohort N°22: NSCLC (MET-mut)	Cohort N°5: NSCLC (MET-amp)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	28	25		
Units: Months				
median (confidence interval 95%)	8.8 (4.1 to 12.7)	7.7 (4.6 to 15.7)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Safety profile will be assessed during the whole treatment period (6 months expected in average) followed by a 2-year post-treatment follow-up period, and reported during the visits scheduled by the study flow chart

Adverse event reporting additional description:

For non serious adverse events only treatment-related adverse events (TRAEs) were available. The number of occurrence are not available and will be always noted "1".

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	16.1

Reporting groups

Reporting group title	Crizotinib

Reporting group description:

All eligible patients entering the study received oral crizotinib, daily continuously:
- 250 mg twice daily (BID) for adults ≥ 18 years of age.
- 280 mg/m² twice daily (BID) for children and adolescents aged from one 1 to 17 (except ALCL).
- 165 mg/m² twice daily (BID) for ALCL patients aged from one 1 to 17 years.

Serious adverse events	Crizotinib		
Total subjects affected by serious adverse events			
subjects affected / exposed	111 / 238 (46.64%)		
number of deaths (all causes)	189		
number of deaths resulting from adverse events	4		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Meningeal carcinomatosisc			
subjects affected / exposed	1 / 238 (0.42%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Rectal adenocarcinoma			
subjects affected / exposed	1 / 238 (0.42%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Tumor pain			
subjects affected / exposed	1 / 238 (0.42%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Urothelial carcinoma recurrent			
subjects affected / exposed	1 / 238 (0.42%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Vascular disorders			
Capillary leak syndrome			
subjects affected / exposed	1 / 238 (0.42%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cerebral hemorrhage			
subjects affected / exposed	1 / 238 (0.42%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Deep vein thrombosis leg			
subjects affected / exposed	1 / 238 (0.42%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Intracranial tumour haemorrhage			
subjects affected / exposed	1 / 238 (0.42%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Ischemic stroke			
subjects affected / exposed	1 / 238 (0.42%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Orthostatic hypotension			
subjects affected / exposed	1 / 238 (0.42%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 1		
Pulmonary embolism			
subjects affected / exposed	4 / 238 (1.68%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 1		
Thrombophlebitis			

subjects affected / exposed	1 / 238 (0.42%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Vena cava thrombosis				
subjects affected / exposed	1 / 238 (0.42%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
General disorders and administration site conditions				
Edema lower limb				
subjects affected / exposed	1 / 238 (0.42%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Fatigue				
subjects affected / exposed	1 / 238 (0.42%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Fever				
subjects affected / exposed	1 / 238 (0.42%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
General physical health deterioration				
subjects affected / exposed	3 / 238 (1.26%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Malaise				
subjects affected / exposed	1 / 238 (0.42%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Oedema lower limb				
subjects affected / exposed	2 / 238 (0.84%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 0			
Reduced general condition				

subjects affected / exposed	1 / 238 (0.42%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Immune system disorders			
GVH disease			
subjects affected / exposed	1 / 238 (0.42%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Reproductive system and breast disorders			
Prostatitis			
subjects affected / exposed	1 / 238 (0.42%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Acute dyspnea			
subjects affected / exposed	1 / 238 (0.42%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Acute respiratory distress syndrome			
subjects affected / exposed	1 / 238 (0.42%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Acute respiratory failure			
subjects affected / exposed	2 / 238 (0.84%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
ARDS			
subjects affected / exposed	1 / 238 (0.42%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Aspiration pneumonia			

subjects affected / exposed	1 / 238 (0.42%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Distress respiratory				
subjects affected / exposed	1 / 238 (0.42%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Dyspnea				
subjects affected / exposed	4 / 238 (1.68%)			
occurrences causally related to treatment / all	0 / 4			
deaths causally related to treatment / all	0 / 0			
Dyspnea exacerbated				
subjects affected / exposed	1 / 238 (0.42%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Haemoptysis				
subjects affected / exposed	1 / 238 (0.42%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hemoptysis				
subjects affected / exposed	1 / 238 (0.42%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Interstitial lung disease				
subjects affected / exposed	3 / 238 (1.26%)			
occurrences causally related to treatment / all	3 / 3			
deaths causally related to treatment / all	3 / 3			
Interstitial pneumonia				
subjects affected / exposed	1 / 238 (0.42%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 1			
Interstitial pneumonitis				

subjects affected / exposed	2 / 238 (0.84%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 1			
Nasal obstruction				
subjects affected / exposed	1 / 238 (0.42%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pleural effusion				
subjects affected / exposed	1 / 238 (0.42%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pneumonia				
subjects affected / exposed	2 / 238 (0.84%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Pneumonitis				
subjects affected / exposed	2 / 238 (0.84%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	1 / 1			
Pneumopathy				
subjects affected / exposed	2 / 238 (0.84%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 1			
Pneumothorax				
subjects affected / exposed	1 / 238 (0.42%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pulmonary embolism				
subjects affected / exposed	2 / 238 (0.84%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 1			
Psychiatric disorders				
Confusion				

subjects affected / exposed	1 / 238 (0.42%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Investigations				
ALT increased				
subjects affected / exposed	1 / 238 (0.42%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Aspartate aminotransferase increased				
subjects affected / exposed	1 / 238 (0.42%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
AST increased				
subjects affected / exposed	1 / 238 (0.42%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 1			
Blood pressure orthostatic decreased				
subjects affected / exposed	1 / 238 (0.42%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Creatinine increased				
subjects affected / exposed	1 / 238 (0.42%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Electrocardiogram QT corrected interval prolonged				
subjects affected / exposed	1 / 238 (0.42%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Electrocardiogram QTc interval prolonged				
subjects affected / exposed	2 / 238 (0.84%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			

Liver function tests raised				
subjects affected / exposed	2 / 238 (0.84%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 1			
QT interval prolonged				
subjects affected / exposed	3 / 238 (1.26%)			
occurrences causally related to treatment / all	3 / 3			
deaths causally related to treatment / all	0 / 0			
Raised liver function tests				
subjects affected / exposed	1 / 238 (0.42%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Transaminase value increased				
subjects affected / exposed	1 / 238 (0.42%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Transaminases increased				
subjects affected / exposed	1 / 238 (0.42%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Injury, poisoning and procedural complications				
Fall				
subjects affected / exposed	2 / 238 (0.84%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 2			
Femoral neck fracture				
subjects affected / exposed	1 / 238 (0.42%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Trochanteric femoral fracture				
subjects affected / exposed	1 / 238 (0.42%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			

Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	1 / 238 (0.42%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Atrial flutter			
subjects affected / exposed	1 / 238 (0.42%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Decompensation cardiac			
subjects affected / exposed	1 / 238 (0.42%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Pericardial effusion			
subjects affected / exposed	1 / 238 (0.42%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Accident cerebrovascular			
subjects affected / exposed	1 / 238 (0.42%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Aphasia			
subjects affected / exposed	1 / 238 (0.42%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cognitive disturbance			
subjects affected / exposed	1 / 238 (0.42%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Convulsion			
subjects affected / exposed	1 / 238 (0.42%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Dysgeusia				
subjects affected / exposed	1 / 238 (0.42%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 1			
Dysphasia				
subjects affected / exposed	1 / 238 (0.42%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Epileptic seizure				
subjects affected / exposed	1 / 238 (0.42%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Ischemic cerebral infarction				
subjects affected / exposed	1 / 238 (0.42%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Ischemic stroke				
subjects affected / exposed	1 / 238 (0.42%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Blood and lymphatic system disorders				
Anemia				
subjects affected / exposed	2 / 238 (0.84%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 0			
Febrile bone marrow aplasia				
subjects affected / exposed	1 / 238 (0.42%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Neutropenia				
subjects affected / exposed	4 / 238 (1.68%)			
occurrences causally related to treatment / all	4 / 4			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal disorders				

Abdominal pain			
subjects affected / exposed	1 / 238 (0.42%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Appendicitis			
subjects affected / exposed	1 / 238 (0.42%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Ascites			
subjects affected / exposed	1 / 238 (0.42%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Diarrhea			
subjects affected / exposed	2 / 238 (0.84%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Epigastric pain			
subjects affected / exposed	1 / 238 (0.42%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorder			
subjects affected / exposed	1 / 238 (0.42%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal perforation			
subjects affected / exposed	1 / 238 (0.42%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Indigestion			
subjects affected / exposed	1 / 238 (0.42%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Subocclusive syndrome			

subjects affected / exposed	1 / 238 (0.42%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vomiting			
subjects affected / exposed	4 / 238 (1.68%)		
occurrences causally related to treatment / all	5 / 6		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Hepatitis			
subjects affected / exposed	1 / 238 (0.42%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Skin and subcutaneous tissue disorders			
Photosensitivity			
subjects affected / exposed	1 / 238 (0.42%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Erythema multiforme			
subjects affected / exposed	1 / 238 (0.42%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Acute renal failure			
subjects affected / exposed	5 / 238 (2.10%)		
occurrences causally related to treatment / all	2 / 5		
deaths causally related to treatment / all	0 / 0		
Acute renal insufficiency			
subjects affected / exposed	1 / 238 (0.42%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hematuria			
subjects affected / exposed	1 / 238 (0.42%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Renal cyst				
subjects affected / exposed	3 / 238 (1.26%)			
occurrences causally related to treatment / all	3 / 3			
deaths causally related to treatment / all	0 / 1			
Renal failure				
subjects affected / exposed	1 / 238 (0.42%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Renal insufficiency				
subjects affected / exposed	3 / 238 (1.26%)			
occurrences causally related to treatment / all	1 / 3			
deaths causally related to treatment / all	0 / 0			
Urethral stenosis				
subjects affected / exposed	1 / 238 (0.42%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Musculoskeletal and connective tissue disorders				
Fractured vertebra (compression)				
subjects affected / exposed	1 / 238 (0.42%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Lumbar pain				
subjects affected / exposed	1 / 238 (0.42%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Multiple fractures				
subjects affected / exposed	1 / 238 (0.42%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pains in legs				
subjects affected / exposed	1 / 238 (0.42%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			

Infections and infestations			
Acute appendicitis			
subjects affected / exposed	1 / 238 (0.42%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Ascites infection			
subjects affected / exposed	1 / 238 (0.42%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Catheter infection			
subjects affected / exposed	2 / 238 (0.84%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Catheter related septicemia			
subjects affected / exposed	1 / 238 (0.42%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Diarrhea, Clostridium difficile			
subjects affected / exposed	1 / 238 (0.42%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Encephalitis herpes			
subjects affected / exposed	1 / 238 (0.42%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Erysipelas			
subjects affected / exposed	1 / 238 (0.42%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Klebsiella sepsis			
subjects affected / exposed	1 / 238 (0.42%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Legionella infection			

subjects affected / exposed	1 / 238 (0.42%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Lung infection				
subjects affected / exposed	1 / 238 (0.42%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pleural infection				
subjects affected / exposed	1 / 238 (0.42%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Pneumonia				
subjects affected / exposed	1 / 238 (0.42%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Pyelonephritis				
subjects affected / exposed	3 / 238 (1.26%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Sepsis				
subjects affected / exposed	2 / 238 (0.84%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Staphylococcal sepsis				
subjects affected / exposed	1 / 238 (0.42%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Urinary infection				
subjects affected / exposed	5 / 238 (2.10%)			
occurrences causally related to treatment / all	0 / 5			
deaths causally related to treatment / all	0 / 0			
Metabolism and nutrition disorders				
Anasarca				

subjects affected / exposed	1 / 238 (0.42%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Dehydration			
subjects affected / exposed	1 / 238 (0.42%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Diabetes			
subjects affected / exposed	1 / 238 (0.42%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hypokalemia			
subjects affected / exposed	1 / 238 (0.42%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hyponatremia			
subjects affected / exposed	1 / 238 (0.42%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Crizotinib		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	238 / 238 (100.00%)		
Investigations			
Alanine aminotranferase increased			
subjects affected / exposed	238 / 238 (100.00%)		
occurrences (all)	1		
Aspartate aminotransferase increased			
subjects affected / exposed	238 / 238 (100.00%)		
occurrences (all)	1		
Alkalines phosphatases increased			

subjects affected / exposed	238 / 238 (100.00%)		
occurrences (all)	1		
Bilirubine increased			
subjects affected / exposed	237 / 238 (99.58%)		
occurrences (all)	1		
QT prolongation			
subjects affected / exposed	235 / 238 (98.74%)		
occurrences (all)	1		
Cardiac disorders			
Bradycardia			
subjects affected / exposed	238 / 238 (100.00%)		
occurrences (all)	1		
Nervous system disorders			
Neuropathy peripheral motor			
subjects affected / exposed	237 / 238 (99.58%)		
occurrences (all)	1		
Peripheral neuropathy sensitive			
subjects affected / exposed	237 / 238 (99.58%)		
occurrences (all)	1		
Dizziness			
subjects affected / exposed	237 / 238 (99.58%)		
occurrences (all)	1		
Dysgeusia			
subjects affected / exposed	237 / 238 (99.58%)		
occurrences (all)	1		
Blood and lymphatic system disorders			
Neutropenia			
subjects affected / exposed	238 / 238 (100.00%)		
occurrences (all)	1		
Anemia			
subjects affected / exposed	238 / 238 (100.00%)		
occurrences (all)	1		
Leucopenia			
subjects affected / exposed	23 / 238 (9.66%)		
occurrences (all)	1		
Lymphopenia			

subjects affected / exposed	238 / 238 (100.00%)		
occurrences (all)	1		
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	236 / 238 (99.16%)		
occurrences (all)	1		
Oedema			
subjects affected / exposed	237 / 238 (99.58%)		
occurrences (all)	1		
Eye disorders			
Visuel disorders			
subjects affected / exposed	238 / 238 (100.00%)		
occurrences (all)	1		
Gastrointestinal disorders			
Vomiting			
subjects affected / exposed	238 / 238 (100.00%)		
occurrences (all)	1		
Nausea			
subjects affected / exposed	237 / 238 (99.58%)		
occurrences (all)	1		
Diarrhea			
subjects affected / exposed	238 / 238 (100.00%)		
occurrences (all)	1		
Constipation			
subjects affected / exposed	238 / 238 (100.00%)		
occurrences (all)	1		
Gastroesophageal disorders			
subjects affected / exposed	238 / 238 (100.00%)		
occurrences (all)	1		
Respiratory, thoracic and mediastinal disorders			
Pneumonia interstitial			
subjects affected / exposed	238 / 238 (100.00%)		
occurrences (all)	1		
Skin and subcutaneous tissue disorders			

Skin toxicities, Rash			
subjects affected / exposed	238 / 238 (100.00%)		
occurrences (all)	1		
Renal and urinary disorders			
Kidney cysts			
subjects affected / exposed	237 / 238 (99.58%)		
occurrences (all)	1		
Metabolism and nutrition disorders			
Loss of appetite			
subjects affected / exposed	237 / 238 (99.58%)		
occurrences (all)	1		
Hypophosphatemia			
subjects affected / exposed	237 / 238 (99.58%)		
occurrences (all)	1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
25 July 2014	- Modification of the inclusion criteria. - Modification of the non-inclusion criteria. - Modification of primary endpoint assessment: assessment of tumor response for glioblastomas was carried out according to the RANO criteria and according to the two-dimensional WHO criteria for pediatric patients with a high-grade glioma or brainstem tumor. - Concomitant treatments: Corticosteroids to control intracranial pressure in patients with primary or secondary brain tumors were authorized; Antiplatelet drugs and anticoagulant drugs in curative dosage were prohibited within 7 days before the first dose of crizotinib and throughout the treatment period. - Modification and opening of cohorts (Crizotinib treatment possible in all cohorts of all pathologies presenting brain metastases;Opening of the current cohort N° 18 "Glioblastoma, adults, MET amplified";Opening of the current cohort N° 18 "Glioblastoma, adults, MET amplified";Modification of cohort N° 19 "Anaplastic thyroid cancer, adults, ALK mutated";Precision of cohort N°21 "Miscellaneous rare pediatric diseases associated to at least one specific alteration in one crizotinib target, same or different from those listed above (i.e. AXL)" to clarify which pathologies could be addressed in the screening circuit and subsequently included in this cohort;Addition of current cohort N°24 "miscellaneous adult tumors" in which all new cases resulting from genome-wide profiling was included for crizotinib treatment. - Update of the rationale: clarification concerning cohort N°7 including patients suffering from breast cancer with ALK translocation and precisions regarding cohorts including patients with thyroid tumors. - Addition of a secondary objective taste assessment of the liquid form. - Precisions on crizotinib treatment. - Change of pharmaceutical service provider. - Addition of steering committee members. - Flow chart updated.
26 September 2016	- Modification and opening of cohorts (pening of the current cohort N°22 "NSCLC and pulmonary sarcomatoid carcinoma, adults, MET mutated;Opening of the current cohort N°23 "Glioblastoma, adults, MET polysomy of chromosome 7; Extension of the previous cohort N°16 "Inflammatory Myofibroblastic Tumor (IMT) children and adults ALK translocation" to "IMT, children and adults, ALK-translocated + ROS1-translocated; Extension of the previous cohort N°8 "Gastric cancer, adults, MET amplified" to "Gastric cancer and adenocarcinoma of the esophagus, adults, MET amplified; Extension of the previous cohort N°9 "Cholangiocarcinoma, adults, ROS1-translocated " to "Biliary carcinoma, adults, ROS1-translocated. - Prolongation of the inclusion period by one year (from 3 years to 4 years). - Crizotinib IB updated (Version October 2015). - Modification of exclusion criteria N°6 subsection j) and m) to include patient with hepatitis B or C who had already been treated and were non-replicating, and patients with stable cirrhosis with a Child-Pugh score equal to A. - Precisions of Serious Adverse Events definition and reporting. - Logos of the Inca and the Foundation ARC were updated.
13 September 2017	- Modification of the investigators list. - Prolongation of the inclusion period by 6 months (from 4 years to 4.5 years).

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported