Clinical trial results:
A Phase II, open label, multi-center, multi-arm study of ceritinib in patients with advanced solid tumors and hematological malignancies characterized by genetic abnormalities of anaplastic lymphoma kinase (ALK)

Summary

EudraCT number	2015-000814-23
Trial protocol	ES DE CZ FR DK IT
Global end of trial date	20 August 2018

Results information

Result version number	v1 (current)
This version publication date	02 September 2019
First version publication date	02 September 2019

Trial information

Trial identification

Sponsor protocol code	CLDK378A2407

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02465528
WHO universal trial number (UTN)	-
Other trial identifiers	Eudract: 2015-000814-23

Notes:

Sponsors

Sponsor organisation name	Novartis Pharma AG
Sponsor organisation address	CH-4002, Basel, Switzerland,
Public contact	Study Director, Novartis Pharma AG, 41 613241111, Novartis.email@novartis.com
Scientific contact	Study Director, Novartis Pharma AG, 41 613241111, Novartis.email@novartis.com

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	20 August 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	20 August 2018
Global end of trial reached?	Yes
Global end of trial date	20 August 2018
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

Assess the antitumor activity of ceritinib as measured by disease control rate (DCR) determined by Investigators.

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and the International Conference on Harmonization (ICH) Good Clinical Practice (GCP) guidelines. All the local regulatory requirements pertinent to safety of trial subjects were also followed during the conduct of the trial.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	06 May 2016
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	Spain: 8
Country: Number of subjects enrolled	Czech Republic: 2
Country: Number of subjects enrolled	France: 3
Country: Number of subjects enrolled	Korea, Republic of: 4
Country: Number of subjects enrolled	Denmark: 1
Country: Number of subjects enrolled	Italy: 1
Country: Number of subjects enrolled	Thailand: 2
Country: Number of subjects enrolled	Israel: 1
Worldwide total number of subjects	22
EEA total number of subjects	15

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	0

months)	
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	18
From 65 to 84 years	4
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

A minimum of 10 and a maximum of 20 subjects were to be enrolled in each arm (tumor type)

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Anaplastic large cell lymphoma (ALCL)

Arm description:

Patients with a diagnosis of ALCL histologically or cytologically confirmed to be ALK-positive

Arm type	Experimental
Investigational medicinal product name	Ceritinib
Investigational medicinal product code	LDK378
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Ceritinib was administered orally once daily at a dose of 750 mg (5 capsules of 150 mg ceritinib) on a continuous dosing schedule. A complete treatment cycle was defined as 28 days of once daily continuous treatment with ceritinib.

Arm title	Inflammatory myofibroblastic tumor (IMT)

Arm description:

Patients diagnosed with IMT with a confirmed translocation involving the ALK gene

Arm type	Experimental
Investigational medicinal product name	Ceritinib
Investigational medicinal product code	LDK378
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Ceritinib was administered orally once daily at a dose of 750 mg (5 capsules of 150 mg ceritinib) on a continuous dosing schedule. A complete treatment cycle was defined as 28 days of once daily continuous treatment with ceritinib.

Arm title	Glioblastoma (GBM)

Arm description:

Patients with GBM with a translocation involving the ALK gene

Arm type	Experimental
Investigational medicinal product name	Ceritinib
Investigational medicinal product code	LDK378
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Ceritinib was administered orally once daily at a dose of 750 mg (5 capsules of 150 mg ceritinib) on a continuous dosing schedule. A complete treatment cycle was defined as 28 days of once daily continuous treatment with ceritinib.

Arm title	Any other ALK-positive tumor

Arm description:

Patients with any other ALK-positive tumor. Patients in this arm included adenocarcinoma (n= 2), sarcoma (1) and other (2).

Arm type	Experimental
Investigational medicinal product name	Ceritinib
Investigational medicinal product code	LDK378
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Ceritinib was administered orally once daily at a dose of 750 mg (5 capsules of 150 mg ceritinib) on a continuous dosing schedule. A complete treatment cycle was defined as 28 days of once daily continuous treatment with ceritinib.

Number of subjects in period 1	Anaplastic large cell lymphoma (ALCL)	Inflammatory myofibroblastic tumor (IMT)	Glioblastoma (GBM)
Started	1	4	12
Completed	0	0	0
Not completed	1	4	12
Consent withdrawn by subject	-	-	2
Physician decision	-	-	1
Adverse event, non-fatal	-	-	-
Study terminated by sponsor	1	2	-
Progressive disease	-	2	9

Number of subjects in period 1	Any other ALK-positive tumor
Started	5
Completed	0
Not completed	5
Consent withdrawn by subject	-
Physician decision	-
Adverse event, non-fatal	1
Study terminated by sponsor	-
Progressive disease	4

Baseline characteristics

Reporting groups	
Reporting group title	Anaplastic large cell lymphoma (ALCL)
Reporting group description:	
Patients with a diagnosis of ALCL histologically or cytologically confirmed to be ALK-positive	
Reporting group title	Inflammatory myofibroblastic tumor (IMT)
Reporting group description:	
Patients diagnosed with IMT with a confirmed translocation involving the ALK gene	
Reporting group title	Glioblastoma (GBM)
Reporting group description:	
Patients with GBM with a translocation involving the ALK gene	
Reporting group title	Any other ALK-positive tumor
Reporting group description:	
Patients with any other ALK-positive tumor. Patients in this arm included adenocarcinoma (n= 2), sarcoma (1) and other (2).	

Reporting group values	Anaplastic large cell lymphoma (ALCL)	Inflammatory myofibroblastic tumor (IMT)	Glioblastoma (GBM)
Number of subjects	1	4	12
Age, Customized Units: Subjects			
18 to <65	1	4	10
65 to <=75	0	0	2
Age Continuous Units: years			
arithmetic mean	36.0	42.8	49.3
standard deviation	± 999.9	± 19.41	± 15.40
Sex: Female, Male Units: Subjects			
Female	1	3	6
Male	0	1	6
Race/Ethnicity, Customized Units: Subjects			
Caucasian	0	1	10
Asian	1	1	1
Other	0	2	1

Reporting group values	Any other ALK-positive tumor	Total	
Number of subjects	5	22	
Age, Customized Units: Subjects			
18 to <65	3	18	
65 to <=75	2	4	
Age Continuous Units: years			
arithmetic mean	57.4		
standard deviation	± 14.64	-	

Sex: Female, Male Units: Subjects			
Female	1	11	
Male	4	11	
Race/Ethnicity, Customized Units: Subjects			
Caucasian	2	13	
Asian	3	6	
Other	0	3	

End points

End points reporting groups

Reporting group title	Anaplastic large cell lymphoma (ALCL)
Reporting group description:	
Patients with a diagnosis of ALCL histologically or cytologically confirmed to be ALK-positive	
Reporting group title	Inflammatory myofibroblastic tumor (IMT)
Reporting group description:	
Patients diagnosed with IMT with a confirmed translocation involving the ALK gene	
Reporting group title	Glioblastoma (GBM)
Reporting group description:	
Patients with GBM with a translocation involving the ALK gene	
Reporting group title	Any other ALK-positive tumor
Reporting group description:	
Patients with any other ALK-positive tumor. Patients in this arm included adenocarcinoma (n= 2), sarcoma (1) and other (2).	

Primary: Disease Control Rate (DCR) based on investigator assessments for participants with at least 16 weeks of treatment

End point title	Disease Control Rate (DCR) based on investigator assessments for participants with at least 16 weeks of treatment[1]
End point description:	
The DCR is defined as the percentage of patients with complete response (CR), partial response (PR) or stable disease (SD) at 16 weeks from the start of ceritinib treatment. The assessment criteria are: Solid Tumors (RECIST 1.1., Response Evaluation Criteria in Solid Tumors); GBM (RECIST 1.1 and RANO, Response Evaluation in Neuro-Oncology); Hematologic tumors (Cheson).	
End point type	Primary
End point timeframe:	
Baseline up to approximately 16 weeks	

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: No analysis was done for this endpoint

End point values	Anaplastic large cell lymphoma (ALCL)	Inflammatory myofibroblastic tumor (IMT)	Glioblastoma (GBM)	Any other ALK-positive tumor
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	1[2]	4[3]	12[4]	5[5]
Units: percentage of participants				
number (confidence interval 95%)	100.00 (2.5 to 100.0)	75.00 (19.4 to 99.4)	0.0 (0.0 to 26.5)	40.0 (5.3 to 85.3)

Notes:

[2] - n=1

[3] - n=3

[4] - n=0

[5] - n=2

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Response Rate (ORR) per investigator assessment

End point title	Overall Response Rate (ORR) per investigator assessment

End point description:

ORR is defined as the percentage of patients with best overall response of complete response (CR) or partial response (PR) based on local assessment according to RECIST 1.1, RANO or Cheson hematological criteria.

End point type	Secondary

End point timeframe:

Baseline, every 8 weeks until disease progression or end of treatment, whichever came first assessed up to approximately 84 weeks

End point values	Anaplastic large cell lymphoma (ALCL)	Inflammatory myofibroblastic tumor (IMT)	Glioblastoma (GBM)	Any other ALK-positive tumor
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	1[6]	4[7]	12[8]	5[9]
Units: percentage of participants				
number (confidence interval 95%)	100.0 (2.5 to 100.0)	75.0 (19.4 to 99.4)	0.0 (0 to 26.5)	0.0 (0.0 to 52.2)

Notes:

[6] - n=1

[7] - n=3

[8] - n=0

[9] - n=0

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Response (DOR) per investigator assessment

End point title	Duration of Response (DOR) per investigator assessment[10]

End point description:

DOR is defined as the time from date of first documented CR or PR to date of first documented disease progression or death due to any cause

End point type	Secondary

End point timeframe:

Baseline, every 8 weeks until disease progression or end of treatment, whichever came first, assessed up to approximately 84 weeks

Notes:

[10] - 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: No analysis was done for this endpoint

End point values	Anaplastic large cell lymphoma (ALCL)	Inflammatory myofibroblastic tumor (IMT)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1[11]	3[12]		
Units: weeks				
median (confidence interval 95%)	999.9 (999.9 to 999.9)	999.9 (3.0 to 999.9)		

Notes:

[11] - n=0

[12] - n=1

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Response (TTR) per investigator assessment

End point title	Time to Response (TTR) per investigator assessment

End point description:

TTR is defined as the time from date of the first dose to date of first documented response (CR or PR)

End point type	Secondary

End point timeframe:

Baseline, every 8 weeks until disease progression or end of treatment, whichever came first, assessed up to approximately 84 weeks

End point values	Anaplastic large cell lymphoma (ALCL)	Inflammatory myofibroblastic tumor (IMT)	Glioblastoma (GBM)	Any other ALK-positive tumor
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	1[13]	4[14]	12[15]	5[16]
Units: weeks				
median (confidence interval 95%)	7.1 (0.999 to 999.9)	16.4 (6.3 to 999.9)	999.9 (999.9 to 999.9)	999.9 (999.9 to 999.9)

Notes:

[13] - n=1

[14] - n=3

[15] - n=0

[16] - n=4

Statistical analyses

No statistical analyses for this end point

Secondary: Progression Free Survival (PFS) per investigator assessments

End point title	Progression Free Survival (PFS) per investigator assessments

End point description:

PFS is defined as the time from the date of first dose of ceritinib to the date of first documented disease progression or death from any cause

End point type	Secondary

End point timeframe:

Baseline, every 8 weeks until disease progression or death from any cause, assessed for up to approximately 84 weeks

End point values	Anaplastic large cell lymphoma (ALCL)	Inflammatory myofibroblastic tumor (IMT)	Glioblastoma (GBM)	Any other ALK-positive tumor
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	0[17]	2[18]	9[19]	5[20]
Units: weeks				
median (confidence interval 95%)	(to)	999.9 (3.7 to 999.9)	1.7 (1.1 to 2.7)	1.7 (1.6 to 5.1)

Notes:

[17] - No participants met the criteria for PFS, n=0

[18] - n=2

[19] - n=9

[20] - n=5

Statistical analyses

No statistical analyses for this end point

Secondary: Percent of on treatment participant deaths during treatment and 30 day follow-up

End point title	Percent of on treatment participant deaths during treatment and 30 day follow-up

End point description:

Deaths due to any cause during treatment and 30 day follow-up

End point type	Secondary

End point timeframe:

Baseline up to approximately 84 weeks

End point values	Anaplastic large cell lymphoma (ALCL)	Inflammatory myofibroblastic tumor (IMT)	Glioblastoma (GBM)	Any other ALK-positive tumor
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	0[21]	0[22]	3	1
Units: percent of participants				
number (not applicable)			25.0	20.0

Notes:

[21] - no deaths in this arm

[22] - no deaths in this arm

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events were collected from first dose of study treatment until end of study treatment plus 28 days post treatment, up to maximum duration of approximately 84 weeks

Adverse event reporting additional description:

Any sign or symptom that occurs during the study treatment plus 30 days post treatment.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	21.0

Reporting groups

Reporting group title	Inflammatory Myofibroblastic Tumor
Reporting group description:	
Inflammatory Myofibroblastic Tumor	
Reporting group title	Anaplastic Large Cell Lymphoma
Reporting group description:	
Anaplastic Large Cell Lymphoma	
Reporting group title	Any other ALK+ tumor
Reporting group description:	
Any other ALK+ tumor	
Reporting group title	All Subjects
Reporting group description:	
All Subjects	
Reporting group title	Glioblastoma
Reporting group description:	
Glioblastoma	

Serious adverse events	Inflammatory Myofibroblastic Tumor	Anaplastic Large Cell Lymphoma	Any other ALK+ tumor
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 4 (50.00%)	0 / 1 (0.00%)	4 / 5 (80.00%)
number of deaths (all causes)	0	0	1
number of deaths resulting from adverse events	0	0	0
Investigations			
Haemoglobin decreased			
subjects affected / exposed	0 / 4 (0.00%)	0 / 1 (0.00%)	1 / 5 (20.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Transaminases increased			

subjects affected / exposed	0 / 4 (0.00%)	0 / 1 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Head injury			
subjects affected / exposed	0 / 4 (0.00%)	0 / 1 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Embolism			
subjects affected / exposed	0 / 4 (0.00%)	0 / 1 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Cerebrovascular accident			
subjects affected / exposed	0 / 4 (0.00%)	0 / 1 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Depressed level of consciousness			
subjects affected / exposed	0 / 4 (0.00%)	0 / 1 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemorrhage intracranial			
subjects affected / exposed	0 / 4 (0.00%)	0 / 1 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hydrocephalus			
subjects affected / exposed	0 / 4 (0.00%)	0 / 1 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypersomnia			
subjects affected / exposed	0 / 4 (0.00%)	0 / 1 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Intracranial pressure increased			
subjects affected / exposed	0 / 4 (0.00%)	0 / 1 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Paraesthesia			
subjects affected / exposed	0 / 4 (0.00%)	0 / 1 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Seizure			
subjects affected / exposed	0 / 4 (0.00%)	0 / 1 (0.00%)	1 / 5 (20.00%)
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	0 / 4 (0.00%)	0 / 1 (0.00%)	1 / 5 (20.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thrombocytopenia			
subjects affected / exposed	0 / 4 (0.00%)	0 / 1 (0.00%)	2 / 5 (40.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	0 / 4 (0.00%)	0 / 1 (0.00%)	1 / 5 (20.00%)
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 / 4 (0.00%)	0 / 1 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyrexia			
subjects affected / exposed	1 / 4 (25.00%)	0 / 1 (0.00%)	2 / 5 (40.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Gastrointestinal disorders			
Stomatitis			
subjects affected / exposed	0 / 4 (0.00%)	0 / 1 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Dermatitis allergic			
subjects affected / exposed	0 / 4 (0.00%)	0 / 1 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dermatitis bullous			
subjects affected / exposed	1 / 4 (25.00%)	0 / 1 (0.00%)	0 / 5 (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
Paraneoplastic pemphigus			
subjects affected / exposed	1 / 4 (25.00%)	0 / 1 (0.00%)	0 / 5 (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
Renal and urinary disorders			
Haematuria			
subjects affected / exposed	0 / 4 (0.00%)	0 / 1 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nephrotic syndrome			
subjects affected / exposed	0 / 4 (0.00%)	0 / 1 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal failure			
subjects affected / exposed	0 / 4 (0.00%)	0 / 1 (0.00%)	1 / 5 (20.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Cellulitis			

subjects affected / exposed	0 / 4 (0.00%)	0 / 1 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung infection			
subjects affected / exposed	0 / 4 (0.00%)	0 / 1 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	0 / 4 (0.00%)	0 / 1 (0.00%)	1 / 5 (20.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyelonephritis			
subjects affected / exposed	1 / 4 (25.00%)	0 / 1 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tooth infection			
subjects affected / exposed	0 / 4 (0.00%)	0 / 1 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	0 / 4 (0.00%)	0 / 1 (0.00%)	1 / 5 (20.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypercalcaemia			
subjects affected / exposed	0 / 4 (0.00%)	0 / 1 (0.00%)	1 / 5 (20.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperglycaemia			
subjects affected / exposed	0 / 4 (0.00%)	0 / 1 (0.00%)	1 / 5 (20.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypoalbuminaemia			

subjects affected / exposed	0 / 4 (0.00%)	0 / 1 (0.00%)	1 / 5 (20.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyponatraemia			
subjects affected / exposed	0 / 4 (0.00%)	0 / 1 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	All Subjects	Glioblastoma	
Total subjects affected by serious adverse events			
subjects affected / exposed	16 / 22 (72.73%)	10 / 12 (83.33%)	
number of deaths (all causes)	4	3	
number of deaths resulting from adverse events	0	0	
Investigations			
Haemoglobin decreased			
subjects affected / exposed	1 / 22 (4.55%)	0 / 12 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transaminases increased			
subjects affected / exposed	1 / 22 (4.55%)	1 / 12 (8.33%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Head injury			
subjects affected / exposed	1 / 22 (4.55%)	1 / 12 (8.33%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Embolism			
subjects affected / exposed	1 / 22 (4.55%)	1 / 12 (8.33%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Cerebrovascular accident			

subjects affected / exposed	1 / 22 (4.55%)	1 / 12 (8.33%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Depressed level of consciousness			
subjects affected / exposed	1 / 22 (4.55%)	1 / 12 (8.33%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhage intracranial			
subjects affected / exposed	2 / 22 (9.09%)	2 / 12 (16.67%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hydrocephalus			
subjects affected / exposed	1 / 22 (4.55%)	1 / 12 (8.33%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
Hypersomnia			
subjects affected / exposed	1 / 22 (4.55%)	1 / 12 (8.33%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intracranial pressure increased			
subjects affected / exposed	1 / 22 (4.55%)	1 / 12 (8.33%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Paraesthesia			
subjects affected / exposed	1 / 22 (4.55%)	1 / 12 (8.33%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Seizure			
subjects affected / exposed	1 / 22 (4.55%)	0 / 12 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			

subjects affected / exposed	1 / 22 (4.55%)	0 / 12 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia			
subjects affected / exposed	2 / 22 (9.09%)	0 / 12 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	1 / 22 (4.55%)	0 / 12 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oedema peripheral			
subjects affected / exposed	1 / 22 (4.55%)	1 / 12 (8.33%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	4 / 22 (18.18%)	1 / 12 (8.33%)	
occurrences causally related to treatment / all	0 / 4	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Stomatitis			
subjects affected / exposed	1 / 22 (4.55%)	1 / 12 (8.33%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Dermatitis allergic			
subjects affected / exposed	1 / 22 (4.55%)	1 / 12 (8.33%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dermatitis bullous			
subjects affected / exposed	1 / 22 (4.55%)	0 / 12 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Paraneoplastic pemphigus			
subjects affected / exposed	1 / 22 (4.55%)	0 / 12 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Haematuria			
subjects affected / exposed	1 / 22 (4.55%)	1 / 12 (8.33%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nephrotic syndrome			
subjects affected / exposed	1 / 22 (4.55%)	1 / 12 (8.33%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure			
subjects affected / exposed	1 / 22 (4.55%)	0 / 12 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Cellulitis			
subjects affected / exposed	1 / 22 (4.55%)	1 / 12 (8.33%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung infection			
subjects affected / exposed	1 / 22 (4.55%)	1 / 12 (8.33%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	1 / 22 (4.55%)	0 / 12 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis			
subjects affected / exposed	1 / 22 (4.55%)	0 / 12 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Tooth infection			
subjects affected / exposed	1 / 22 (4.55%)	1 / 12 (8.33%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	1 / 22 (4.55%)	0 / 12 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypercalcaemia			
subjects affected / exposed	1 / 22 (4.55%)	0 / 12 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperglycaemia			
subjects affected / exposed	2 / 22 (9.09%)	1 / 12 (8.33%)	
occurrences causally related to treatment / all	2 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoalbuminaemia			
subjects affected / exposed	1 / 22 (4.55%)	0 / 12 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia			
subjects affected / exposed	1 / 22 (4.55%)	1 / 12 (8.33%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Inflammatory Myofibroblastic Tumor	Anaplastic Large Cell Lymphoma	Any other ALK+ tumor
Total subjects affected by non-serious adverse events			
subjects affected / exposed	4 / 4 (100.00%)	1 / 1 (100.00%)	5 / 5 (100.00%)
General disorders and administration site conditions			

Asthenia			
subjects affected / exposed	0 / 4 (0.00%)	0 / 1 (0.00%)	4 / 5 (80.00%)
occurrences (all)	0	0	4
Fatigue			
subjects affected / exposed	1 / 4 (25.00%)	0 / 1 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Gait disturbance			
subjects affected / exposed	0 / 4 (0.00%)	0 / 1 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Oedema			
subjects affected / exposed	0 / 4 (0.00%)	0 / 1 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	1
Oedema peripheral			
subjects affected / exposed	0 / 4 (0.00%)	0 / 1 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Pain			
subjects affected / exposed	1 / 4 (25.00%)	0 / 1 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	1 / 4 (25.00%)	0 / 1 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Dyspnoea			
subjects affected / exposed	0 / 4 (0.00%)	0 / 1 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Epistaxis			
subjects affected / exposed	0 / 4 (0.00%)	0 / 1 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Lung disorder			
subjects affected / exposed	1 / 4 (25.00%)	0 / 1 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Respiratory disorder			
subjects affected / exposed	0 / 4 (0.00%)	0 / 1 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Psychiatric disorders			

Anxiety			
subjects affected / exposed	0 / 4 (0.00%)	0 / 1 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	1
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	3 / 4 (75.00%)	1 / 1 (100.00%)	1 / 5 (20.00%)
occurrences (all)	4	1	1
Amylase increased			
subjects affected / exposed	2 / 4 (50.00%)	0 / 1 (0.00%)	0 / 5 (0.00%)
occurrences (all)	4	0	0
Aspartate aminotransferase increased			
subjects affected / exposed	3 / 4 (75.00%)	1 / 1 (100.00%)	1 / 5 (20.00%)
occurrences (all)	5	2	4
Blood alkaline phosphatase increased			
subjects affected / exposed	2 / 4 (50.00%)	1 / 1 (100.00%)	1 / 5 (20.00%)
occurrences (all)	3	1	1
Blood bilirubin abnormal			
subjects affected / exposed	1 / 4 (25.00%)	0 / 1 (0.00%)	0 / 5 (0.00%)
occurrences (all)	2	0	0
Blood bilirubin increased			
subjects affected / exposed	1 / 4 (25.00%)	0 / 1 (0.00%)	0 / 5 (0.00%)
occurrences (all)	2	0	0
Blood creatinine increased			
subjects affected / exposed	2 / 4 (50.00%)	0 / 1 (0.00%)	0 / 5 (0.00%)
occurrences (all)	3	0	0
Creatinine renal clearance increased			
subjects affected / exposed	1 / 4 (25.00%)	0 / 1 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Gamma-glutamyltransferase increased			
subjects affected / exposed	2 / 4 (50.00%)	1 / 1 (100.00%)	1 / 5 (20.00%)
occurrences (all)	2	1	1
Lipase increased			
subjects affected / exposed	1 / 4 (25.00%)	0 / 1 (0.00%)	1 / 5 (20.00%)
occurrences (all)	1	0	1
Weight decreased			

subjects affected / exposed	0 / 4 (0.00%)	0 / 1 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	1
Injury, poisoning and procedural complications			
Cartilage injury			
subjects affected / exposed	0 / 4 (0.00%)	0 / 1 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	1
Cardiac disorders			
Bradycardia			
subjects affected / exposed	0 / 4 (0.00%)	0 / 1 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Sinus bradycardia			
subjects affected / exposed	1 / 4 (25.00%)	0 / 1 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Tachycardia			
subjects affected / exposed	0 / 4 (0.00%)	0 / 1 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	1
Nervous system disorders			
Aphasia			
subjects affected / exposed	0 / 4 (0.00%)	0 / 1 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Cognitive disorder			
subjects affected / exposed	0 / 4 (0.00%)	0 / 1 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Depressed level of consciousness			
subjects affected / exposed	0 / 4 (0.00%)	0 / 1 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Dizziness			
subjects affected / exposed	0 / 4 (0.00%)	0 / 1 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Headache			
subjects affected / exposed	0 / 4 (0.00%)	0 / 1 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Hemiparesis			
subjects affected / exposed	0 / 4 (0.00%)	0 / 1 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Somnolence			

subjects affected / exposed	0 / 4 (0.00%)	0 / 1 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	2 / 4 (50.00%)	0 / 1 (0.00%)	3 / 5 (60.00%)
occurrences (all)	3	0	3
Leukocytosis			
subjects affected / exposed	1 / 4 (25.00%)	0 / 1 (0.00%)	0 / 5 (0.00%)
occurrences (all)	2	0	0
Lymphopenia			
subjects affected / exposed	2 / 4 (50.00%)	0 / 1 (0.00%)	0 / 5 (0.00%)
occurrences (all)	2	0	0
Neutropenia			
subjects affected / exposed	0 / 4 (0.00%)	0 / 1 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Thrombocytopenia			
subjects affected / exposed	0 / 4 (0.00%)	0 / 1 (0.00%)	2 / 5 (40.00%)
occurrences (all)	0	0	2
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	2 / 4 (50.00%)	1 / 1 (100.00%)	2 / 5 (40.00%)
occurrences (all)	2	1	2
Abdominal pain upper			
subjects affected / exposed	1 / 4 (25.00%)	0 / 1 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Constipation			
subjects affected / exposed	2 / 4 (50.00%)	0 / 1 (0.00%)	0 / 5 (0.00%)
occurrences (all)	2	0	0
Diarrhoea			
subjects affected / exposed	3 / 4 (75.00%)	1 / 1 (100.00%)	2 / 5 (40.00%)
occurrences (all)	4	2	3
Eructation			
subjects affected / exposed	0 / 4 (0.00%)	0 / 1 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	1
Flatulence			

subjects affected / exposed	0 / 4 (0.00%)	0 / 1 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 4 (0.00%)	0 / 1 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Nausea			
subjects affected / exposed	3 / 4 (75.00%)	1 / 1 (100.00%)	3 / 5 (60.00%)
occurrences (all)	6	1	4
Stomatitis			
subjects affected / exposed	1 / 4 (25.00%)	0 / 1 (0.00%)	0 / 5 (0.00%)
occurrences (all)	2	0	0
Vomiting			
subjects affected / exposed	2 / 4 (50.00%)	1 / 1 (100.00%)	4 / 5 (80.00%)
occurrences (all)	2	1	6
Skin and subcutaneous tissue disorders			
Dermatitis acneiform			
subjects affected / exposed	0 / 4 (0.00%)	0 / 1 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Dermatitis bullous			
subjects affected / exposed	1 / 4 (25.00%)	0 / 1 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Palmar-plantar erythrodysaesthesia syndrome			
subjects affected / exposed	1 / 4 (25.00%)	0 / 1 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Photosensitivity reaction			
subjects affected / exposed	1 / 4 (25.00%)	0 / 1 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Pruritus			
subjects affected / exposed	1 / 4 (25.00%)	0 / 1 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Rash			
subjects affected / exposed	1 / 4 (25.00%)	1 / 1 (100.00%)	1 / 5 (20.00%)
occurrences (all)	1	1	1
Skin toxicity			

subjects affected / exposed	1 / 4 (25.00%)	0 / 1 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Renal and urinary disorders			
Haematuria			
subjects affected / exposed	0 / 4 (0.00%)	0 / 1 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Renal failure			
subjects affected / exposed	0 / 4 (0.00%)	0 / 1 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 4 (0.00%)	0 / 1 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	1
Back pain			
subjects affected / exposed	0 / 4 (0.00%)	0 / 1 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Muscular weakness			
subjects affected / exposed	0 / 4 (0.00%)	0 / 1 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	1
Musculoskeletal pain			
subjects affected / exposed	0 / 4 (0.00%)	0 / 1 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	1
Infections and infestations			
Bronchitis			
subjects affected / exposed	0 / 4 (0.00%)	0 / 1 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Candiduria			
subjects affected / exposed	0 / 4 (0.00%)	0 / 1 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	1
Catheter site cellulitis			
subjects affected / exposed	0 / 4 (0.00%)	0 / 1 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Genital herpes			
subjects affected / exposed	0 / 4 (0.00%)	0 / 1 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Influenza			

subjects affected / exposed	1 / 4 (25.00%)	0 / 1 (0.00%)	0 / 5 (0.00%)
occurrences (all)	2	0	0
Paronychia			
subjects affected / exposed	0 / 4 (0.00%)	0 / 1 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Pyelonephritis			
subjects affected / exposed	1 / 4 (25.00%)	0 / 1 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Urinary tract infection			
subjects affected / exposed	0 / 4 (0.00%)	0 / 1 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Uterine infection			
subjects affected / exposed	0 / 4 (0.00%)	0 / 1 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	2 / 4 (50.00%)	0 / 1 (0.00%)	1 / 5 (20.00%)
occurrences (all)	2	0	1
Dehydration			
subjects affected / exposed	0 / 4 (0.00%)	0 / 1 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Hypercalcaemia			
subjects affected / exposed	1 / 4 (25.00%)	0 / 1 (0.00%)	1 / 5 (20.00%)
occurrences (all)	1	0	1
Hyperglycaemia			
subjects affected / exposed	0 / 4 (0.00%)	0 / 1 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Hyperkalaemia			
subjects affected / exposed	1 / 4 (25.00%)	0 / 1 (0.00%)	0 / 5 (0.00%)
occurrences (all)	2	0	0
Hypernatraemia			
subjects affected / exposed	0 / 4 (0.00%)	0 / 1 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Hyperuricaemia			
subjects affected / exposed	0 / 4 (0.00%)	0 / 1 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0

Hypokalaemia			
subjects affected / exposed	2 / 4 (50.00%)	0 / 1 (0.00%)	1 / 5 (20.00%)
occurrences (all)	4	0	1
Hypomagnesaemia			
subjects affected / exposed	0 / 4 (0.00%)	0 / 1 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	1
Increased appetite			
subjects affected / exposed	0 / 4 (0.00%)	0 / 1 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0

Non-serious adverse events	All Subjects	Glioblastoma	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	22 / 22 (100.00%)	12 / 12 (100.00%)	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	5 / 22 (22.73%)	1 / 12 (8.33%)	
occurrences (all)	5	1	
Fatigue			
subjects affected / exposed	6 / 22 (27.27%)	5 / 12 (41.67%)	
occurrences (all)	6	5	
Gait disturbance			
subjects affected / exposed	1 / 22 (4.55%)	1 / 12 (8.33%)	
occurrences (all)	1	1	
Oedema			
subjects affected / exposed	1 / 22 (4.55%)	0 / 12 (0.00%)	
occurrences (all)	1	0	
Oedema peripheral			
subjects affected / exposed	3 / 22 (13.64%)	3 / 12 (25.00%)	
occurrences (all)	3	3	
Pain			
subjects affected / exposed	1 / 22 (4.55%)	0 / 12 (0.00%)	
occurrences (all)	1	0	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	1 / 22 (4.55%)	0 / 12 (0.00%)	
occurrences (all)	1	0	

Dyspnoea			
subjects affected / exposed	1 / 22 (4.55%)	1 / 12 (8.33%)	
occurrences (all)	1	1	
Epistaxis			
subjects affected / exposed	1 / 22 (4.55%)	1 / 12 (8.33%)	
occurrences (all)	1	1	
Lung disorder			
subjects affected / exposed	1 / 22 (4.55%)	0 / 12 (0.00%)	
occurrences (all)	1	0	
Respiratory disorder			
subjects affected / exposed	1 / 22 (4.55%)	1 / 12 (8.33%)	
occurrences (all)	1	1	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	2 / 22 (9.09%)	1 / 12 (8.33%)	
occurrences (all)	2	1	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	7 / 22 (31.82%)	2 / 12 (16.67%)	
occurrences (all)	8	2	
Amylase increased			
subjects affected / exposed	2 / 22 (9.09%)	0 / 12 (0.00%)	
occurrences (all)	4	0	
Aspartate aminotransferase increased			
subjects affected / exposed	5 / 22 (22.73%)	0 / 12 (0.00%)	
occurrences (all)	11	0	
Blood alkaline phosphatase increased			
subjects affected / exposed	4 / 22 (18.18%)	0 / 12 (0.00%)	
occurrences (all)	5	0	
Blood bilirubin abnormal			
subjects affected / exposed	1 / 22 (4.55%)	0 / 12 (0.00%)	
occurrences (all)	2	0	
Blood bilirubin increased			
subjects affected / exposed	1 / 22 (4.55%)	0 / 12 (0.00%)	
occurrences (all)	2	0	
Blood creatinine increased			

subjects affected / exposed	2 / 22 (9.09%)	0 / 12 (0.00%)	
occurrences (all)	3	0	
Creatinine renal clearance increased			
subjects affected / exposed	1 / 22 (4.55%)	0 / 12 (0.00%)	
occurrences (all)	1	0	
Gamma-glutamyltransferase increased			
subjects affected / exposed	4 / 22 (18.18%)	0 / 12 (0.00%)	
occurrences (all)	4	0	
Lipase increased			
subjects affected / exposed	2 / 22 (9.09%)	0 / 12 (0.00%)	
occurrences (all)	2	0	
Weight decreased			
subjects affected / exposed	2 / 22 (9.09%)	1 / 12 (8.33%)	
occurrences (all)	2	1	
Injury, poisoning and procedural complications			
Cartilage injury			
subjects affected / exposed	1 / 22 (4.55%)	0 / 12 (0.00%)	
occurrences (all)	1	0	
Cardiac disorders			
Bradycardia			
subjects affected / exposed	1 / 22 (4.55%)	1 / 12 (8.33%)	
occurrences (all)	1	1	
Sinus bradycardia			
subjects affected / exposed	1 / 22 (4.55%)	0 / 12 (0.00%)	
occurrences (all)	1	0	
Tachycardia			
subjects affected / exposed	1 / 22 (4.55%)	0 / 12 (0.00%)	
occurrences (all)	1	0	
Nervous system disorders			
Aphasia			
subjects affected / exposed	2 / 22 (9.09%)	2 / 12 (16.67%)	
occurrences (all)	2	2	
Cognitive disorder			
subjects affected / exposed	1 / 22 (4.55%)	1 / 12 (8.33%)	
occurrences (all)	1	1	
Depressed level of consciousness			

subjects affected / exposed	1 / 22 (4.55%)	1 / 12 (8.33%)	
occurrences (all)	1	1	
Dizziness			
subjects affected / exposed	1 / 22 (4.55%)	1 / 12 (8.33%)	
occurrences (all)	2	2	
Headache			
subjects affected / exposed	3 / 22 (13.64%)	3 / 12 (25.00%)	
occurrences (all)	3	3	
Hemiparesis			
subjects affected / exposed	1 / 22 (4.55%)	1 / 12 (8.33%)	
occurrences (all)	1	1	
Somnolence			
subjects affected / exposed	2 / 22 (9.09%)	2 / 12 (16.67%)	
occurrences (all)	2	2	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	5 / 22 (22.73%)	0 / 12 (0.00%)	
occurrences (all)	6	0	
Leukocytosis			
subjects affected / exposed	1 / 22 (4.55%)	0 / 12 (0.00%)	
occurrences (all)	2	0	
Lymphopenia			
subjects affected / exposed	3 / 22 (13.64%)	1 / 12 (8.33%)	
occurrences (all)	3	1	
Neutropenia			
subjects affected / exposed	2 / 22 (9.09%)	2 / 12 (16.67%)	
occurrences (all)	2	2	
Thrombocytopenia			
subjects affected / exposed	5 / 22 (22.73%)	3 / 12 (25.00%)	
occurrences (all)	5	3	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	5 / 22 (22.73%)	0 / 12 (0.00%)	
occurrences (all)	5	0	
Abdominal pain upper			

subjects affected / exposed	1 / 22 (4.55%)	0 / 12 (0.00%)	
occurrences (all)	1	0	
Constipation			
subjects affected / exposed	4 / 22 (18.18%)	2 / 12 (16.67%)	
occurrences (all)	4	2	
Diarrhoea			
subjects affected / exposed	13 / 22 (59.09%)	7 / 12 (58.33%)	
occurrences (all)	17	8	
Eructation			
subjects affected / exposed	1 / 22 (4.55%)	0 / 12 (0.00%)	
occurrences (all)	1	0	
Flatulence			
subjects affected / exposed	1 / 22 (4.55%)	1 / 12 (8.33%)	
occurrences (all)	1	1	
Gastrooesophageal reflux disease			
subjects affected / exposed	1 / 22 (4.55%)	1 / 12 (8.33%)	
occurrences (all)	1	1	
Nausea			
subjects affected / exposed	13 / 22 (59.09%)	6 / 12 (50.00%)	
occurrences (all)	17	6	
Stomatitis			
subjects affected / exposed	3 / 22 (13.64%)	2 / 12 (16.67%)	
occurrences (all)	5	3	
Vomiting			
subjects affected / exposed	11 / 22 (50.00%)	4 / 12 (33.33%)	
occurrences (all)	15	6	
Skin and subcutaneous tissue disorders			
Dermatitis acneiform			
subjects affected / exposed	1 / 22 (4.55%)	1 / 12 (8.33%)	
occurrences (all)	1	1	
Dermatitis bullous			
subjects affected / exposed	1 / 22 (4.55%)	0 / 12 (0.00%)	
occurrences (all)	1	0	
Palmar-plantar erythrodysaesthesia syndrome			

subjects affected / exposed	1 / 22 (4.55%)	0 / 12 (0.00%)	
occurrences (all)	1	0	
Photosensitivity reaction			
subjects affected / exposed	1 / 22 (4.55%)	0 / 12 (0.00%)	
occurrences (all)	1	0	
Pruritus			
subjects affected / exposed	1 / 22 (4.55%)	0 / 12 (0.00%)	
occurrences (all)	1	0	
Rash			
subjects affected / exposed	3 / 22 (13.64%)	0 / 12 (0.00%)	
occurrences (all)	3	0	
Skin toxicity			
subjects affected / exposed	1 / 22 (4.55%)	0 / 12 (0.00%)	
occurrences (all)	1	0	
Renal and urinary disorders			
Haematuria			
subjects affected / exposed	1 / 22 (4.55%)	1 / 12 (8.33%)	
occurrences (all)	1	1	
Renal failure			
subjects affected / exposed	1 / 22 (4.55%)	1 / 12 (8.33%)	
occurrences (all)	1	1	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	2 / 22 (9.09%)	1 / 12 (8.33%)	
occurrences (all)	2	1	
Back pain			
subjects affected / exposed	3 / 22 (13.64%)	3 / 12 (25.00%)	
occurrences (all)	3	3	
Muscular weakness			
subjects affected / exposed	1 / 22 (4.55%)	0 / 12 (0.00%)	
occurrences (all)	1	0	
Musculoskeletal pain			
subjects affected / exposed	1 / 22 (4.55%)	0 / 12 (0.00%)	
occurrences (all)	1	0	
Infections and infestations			

Bronchitis			
subjects affected / exposed	1 / 22 (4.55%)	1 / 12 (8.33%)	
occurrences (all)	1	1	
Candiduria			
subjects affected / exposed	1 / 22 (4.55%)	0 / 12 (0.00%)	
occurrences (all)	1	0	
Catheter site cellulitis			
subjects affected / exposed	1 / 22 (4.55%)	1 / 12 (8.33%)	
occurrences (all)	1	1	
Genital herpes			
subjects affected / exposed	1 / 22 (4.55%)	1 / 12 (8.33%)	
occurrences (all)	1	1	
Influenza			
subjects affected / exposed	1 / 22 (4.55%)	0 / 12 (0.00%)	
occurrences (all)	2	0	
Paronychia			
subjects affected / exposed	1 / 22 (4.55%)	1 / 12 (8.33%)	
occurrences (all)	1	1	
Pyelonephritis			
subjects affected / exposed	1 / 22 (4.55%)	0 / 12 (0.00%)	
occurrences (all)	1	0	
Urinary tract infection			
subjects affected / exposed	2 / 22 (9.09%)	2 / 12 (16.67%)	
occurrences (all)	2	2	
Uterine infection			
subjects affected / exposed	1 / 22 (4.55%)	1 / 12 (8.33%)	
occurrences (all)	1	1	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	3 / 22 (13.64%)	0 / 12 (0.00%)	
occurrences (all)	3	0	
Dehydration			
subjects affected / exposed	1 / 22 (4.55%)	1 / 12 (8.33%)	
occurrences (all)	1	1	
Hypercalcaemia			

subjects affected / exposed	2 / 22 (9.09%)	0 / 12 (0.00%)	
occurrences (all)	2	0	
Hyperglycaemia			
subjects affected / exposed	2 / 22 (9.09%)	2 / 12 (16.67%)	
occurrences (all)	2	2	
Hyperkalaemia			
subjects affected / exposed	1 / 22 (4.55%)	0 / 12 (0.00%)	
occurrences (all)	2	0	
Hypernatraemia			
subjects affected / exposed	1 / 22 (4.55%)	1 / 12 (8.33%)	
occurrences (all)	1	1	
Hyperuricaemia			
subjects affected / exposed	1 / 22 (4.55%)	1 / 12 (8.33%)	
occurrences (all)	1	1	
Hypokalaemia			
subjects affected / exposed	3 / 22 (13.64%)	0 / 12 (0.00%)	
occurrences (all)	5	0	
Hypomagnesaemia			
subjects affected / exposed	1 / 22 (4.55%)	0 / 12 (0.00%)	
occurrences (all)	1	0	
Increased appetite			
subjects affected / exposed	1 / 22 (4.55%)	1 / 12 (8.33%)	
occurrences (all)	1	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
30 November 2015	Clarified the inclusion criteria 2 for ALK positivity. A subject was to have a histologically or cytologically confirmed diagnosis of one of the tumors that was ALK- positive. The ALK test results were to be available at the Investigator site before the first dose of the study drug. The tumor types are described below: ALCL: local confirmation of diagnosis of ALK+ ALCL was sufficient for eligibility. IMT: local confirmation of translocation involving the ALK gene. GBM, IBC and any other locally documented ALK+ tumor were to carry a locally documented genetic alteration of ALK. Provided follow up evaluations for hepatic toxicities and work-up guidelines for potential Drug Induced Liver Injury (DILI) cases. Updated the exclusion criteria for contraception use. Dose guidance modification for QTcF text was updated to provide clarification on monitoring procedure.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported