Clinical trial results:
A phase II trial to evaluate efficacy and safety of crizotinib treatment in advanced adenocarcinoma of the lung harbouring ROS1 translocations

Summary

EudraCT number	2013-002737-38
Trial protocol	DE AT
Global end of trial date	29 February 2020

Results information

Result version number	v1 (current)
This version publication date	28 April 2021
First version publication date	28 April 2021
Summary attachment (see zip file)	Prefinal analysis publication 2019 (Michels_EUCROSS_2019.pdf) Prefinal analysis publication 2019 supplement (Supplementary.pdf)

Trial information

Trial identification

Sponsor protocol code	EUCROSS

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02183870
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	University of Cologne
Sponsor organisation address	Albertus-Magnus-Platz, Köln, Germany, 50923
Public contact	Lung Cancer Group Cologne, Lung Cancer Group Cologne, 0049 22147887008, juergen.wolf@uk-koeln.de
Scientific contact	Lung Cancer Group Cologne, Lung Cancer Group Cologne, 0049 22147887008, juergen.wolf@uk-koeln.de

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	31 January 2020
Is this the analysis of the primary completion data?	Yes
Primary completion date	31 January 2020
Global end of trial reached?	Yes
Global end of trial date	29 February 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate efficacy of crizotinib treatment in advanced adenocarcinoma of the lung harbouring ROS1 fusion genes as assessed by central testing; primary endpoint: objective response rate (ORR); evaluation criteria: investigator assessed RECIST v.1.1 analysis

Protection of trial subjects:

Measures were prespecified for interruption of treatment and/or dose reduction if specific toxicities at specific grades occur.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	28 April 2014
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Spain: 9
Country: Number of subjects enrolled	Germany: 25
Worldwide total number of subjects	34
EEA total number of subjects	34

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	25
From 65 to 84 years	9
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Recuitment from May 2014 to December 2015 in Germany and Spain.

Pre-assignment

Screening details:

Patients 18 years of age or older with locally advanced or metastatic histologically confirmed NSCLC and ROS1 rearrangement in local testing were allowed to enter screening after written informed consent, independent of the number of prior therapies.

Period 1

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

Arms

Arm title	Crizotinib

Arm description:

Experimental study medication

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

Dosage and administration details:

250mg twice a day, will be administered orally at approximately the same time each day on a continuous daily dosing schedule, beginning at d1. Crizotinib can be dosed without regard to meals.

Number of subjects in period 1	Crizotinib
Started	34
Completed	34

Baseline characteristics

Reporting groups

Reporting group title	baseline and treatment

Reporting group description: -

Reporting group values	baseline and treatment	Total	
Number of subjects	34	34	
Age categorical			
Age at informed consent			
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)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	25	25	
From 65-84 years	9	9	
85 years and over	0	0	
Adults 18-64	0	0	
Adults 65-84	0	0	
Age continuous			
Age Median (Range)			
Units: years			
median	56		
full range (min-max)	33 to 84	-	
Gender categorical			
Units: Subjects			
Female	19	19	
Male	15	15	
ECOG			
ECOG Score			
Units: Subjects			
Score 0	12	12	
Score 1	20	20	
Score 2	2	2	
Ethnic group			
Ethnic group			
Units: Subjects			
Caucasian	31	31	
Asian	2	2	
other	1	1	

Subject analysis sets

Subject analysis set title	Response-evaluable
Subject analysis set type	Per protocol

Subject analysis set description:

The response-evaluable population will include all patients who are eligible and received at least one dose of study medication, who have an adequate baseline tumor assessment and whose NSCLC was ROS1 positive by FISH testing as assessed by the central laboratory selected by the sponsor. The response-evaluable population will be the primary population for the efficacy endpoints ORR, DCR, DR, TTR, PFS and OS.

Subject analysis set title	Valid-for-safety
Subject analysis set type	Intention-to-treat

Subject analysis set description:

The vaild-for-safety analysis population will include all enrolled patients who received at least one dose of study medication. The vaild-for-safety analysis population will be the primary population for evaluating patient characteristics, treatment administration/compliance, toxicity and adverse events.

Reporting group values	Response-evaluable	Valid-for-safety	
Number of subjects	30	34	
Age categorical			
Age at informed consent			
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)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	21	25	
From 65-84 years	9	9	
85 years and over	0	0	
Adults 18-64	0	0	
Adults 65-84	0	0	
Age continuous			
Age Median (Range)			
Units: years			
median	60	56	
full range (min-max)	33 to 84	33 to 84	
Gender categorical			
Units: Subjects			
Female	17	19	
Male	13	15	
ECOG			
ECOG Score			
Units: Subjects			
Score 0	12	12	
Score 1	17	20	
Score 2	1	2	
Ethnic group			
Ethnic group			
Units: Subjects			
Caucasian	27	31	

Asian	2	2	
other	1	1	

End points

End points reporting groups

Reporting group title	Crizotinib
Reporting group description: Experimental study medication	
Subject analysis set title	Response-evaluable
Subject analysis set type	Per protocol
Subject analysis set description: The response-evaluable population will include all patients who are eligible and received at least one dose of study medication, who have an adequate baseline tumor assessment and whose NSCLC was ROS1 positive by FISH testing as assessed by the central laboratory selected by the sponsor. The response-evaluable population will be the primary population for the efficacy endpoints ORR, DCR, DR, TTR, PFS and OS.	
Subject analysis set title	Valid-for-safety
Subject analysis set type	Intention-to-treat
Subject analysis set description: The vaild-for-safety analysis population will include all enrolled patients who received at least one dose of study medication. The vaild-for-safety analysis population will be the primary population for evaluating patient characteristics, treatment administration/compliance, toxicity and adverse events.	

Primary: Overall response rate (local)

End point title	Overall response rate (local)[1]
End point description: ORR is defined as the percentage of patients with CR or PR according to investigator assessed RECIST v.1.1 evaluation.	
End point type	Primary
End point timeframe: During study 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: Single-arm trial - no statistical testing

End point values	Response-evaluable	Valid-for-safety		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	30	34		
Units: percent				
number (confidence interval 95%)	70 (51 to 85)	71 (53 to 85)		

Statistical analyses

No statistical analyses for this end point

Secondary: Progression-free survival (local)

End point title	Progression-free survival (local)
End point description: PFS is defined as the time from the date of first dose to first documentation of objective disease progression (local evaluation) or to death on study due to any cause, whichever occurs first.	
End point type	Secondary

End point timeframe:

During study treatment plus 28 days (deaths up to 14 weeks after end of study treatment)

End point values	Response-evaluable	Valid-for-safety		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	30	34		
Units: months				
median (confidence interval 95%)	19.4 (10.1 to 32.2)	19.4 (9.6 to 32.2)		

Statistical analyses

No statistical analyses for this end point

Secondary: Overall survival at 24 months

End point title	Overall survival at 24 months

End point description:

OS is defined as the time from date of first dose to the date of death to any cause.

End point type	Secondary

End point timeframe:

Durngi study treatment and follow-up

End point values	Response-evaluable	Valid-for-safety		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	30	34		
Units: percent				
number (confidence interval 95%)	64 (47 to 82)	64 (47 to 80)		

Statistical analyses

No statistical analyses for this end point

Secondary: Overall survival at 36 months

End point title	Overall survival at 36 months

End point description:

OS is defined as the time from date of first dose to the date of death to any cause.

End point type	Secondary

End point timeframe:

During studytreatment and follow-up

End point values	Response-evaluable	Valid-for-safety		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	30	34		
Units: percent				
number (confidence interval 95%)	64 (47 to 82)	64 (47 to 80)		

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of response

End point title	Duration of response

End point description:

DR is defined as the time from the first documentation of objective tumor response (CR or PR) that is subsequently confirmed to the first documentation of objective disease progression or to death due to any cause, whichever occurs first. DR will be calculated for the response evaluable population in the subgroup of patients with a confirmed objective response.

End point type	Secondary

End point timeframe:

During study treatment vand follow-up

End point values	Response-evaluable			
Subject group type	Subject analysis set			
Number of subjects analysed	30			
Units: months				
median (confidence interval 95%)	21 (8.3 to 99999)			

Statistical analyses

No statistical analyses for this end point

Secondary: Overall response rate (central blind review)

End point title	Overall response rate (central blind review)

End point description:

Calculated based on all patients in the response-evaluable population. ORR is defined as the percentage of patients with CR or PR according to central blind RECIST v.1.1 evaluation.

End point type	Secondary

End point timeframe:

During study treatment

End point values	Response-evaluable	Valid-for-safety		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	30	34		
Units: percent				
number (confidence interval 95%)	73 (54 to 88)	74 (56 to 87)		

Statistical analyses

No statistical analyses for this end point

Secondary: Disease control rate (local)

End point title	Disease control rate (local)

End point description:

DCR is defined as the percentage of patients with CR, PR or SD according to RECIST v.1.1 (investigator assessed)

End point type	Secondary

End point timeframe:

During study treatment.

End point values	Response-evaluable	Valid-for-safety		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	30	34		
Units: percent				
number (confidence interval 95%)	90 (74 to 98)	88 (73 to 97)		

Statistical analyses

No statistical analyses for this end point

Secondary: Progression free survival (central blind review)

End point title	Progression free survival (central blind review)

End point description:

PFS is defined as the time from the date of first dose to first documentation of objective disease progression (central blind review evaluation) or to death on study due to any cause, whichever occurs first.

End point type	Secondary

End point timeframe:

During study treatment plus 28 days (deaths up to 14 weeks after end of study treatment)

End point values	Response-evaluable			
Subject group type	Subject analysis set			
Number of subjects analysed	30			
Units: months				
median (confidence interval 95%)	20.0 (9.6 to 99999)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Timeframe for AE

Adverse event reporting additional description:

AE additional description

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	19.0

Reporting groups

Reporting group title	Valid-for-Safety

Reporting group description: -

Serious adverse events	Valid-for-Safety		
Total subjects affected by serious adverse events			
subjects affected / exposed	21 / 34 (61.76%)		
number of deaths (all causes)	15		
number of deaths resulting from adverse events	7		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Neoplasm progression	Additional description: Neoplasm progression		
subjects affected / exposed	2 / 34 (5.88%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 1		
Injury, poisoning and procedural complications			
Vascular access complication	Additional description: Vascular access complication		
subjects affected / exposed	1 / 34 (2.94%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Haematoma	Additional description: Haematoma		
subjects affected / exposed	1 / 34 (2.94%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pulmonary embolism and thrombosis	Additional description: Pulmonary embolism and thrombosis		

subjects affected / exposed	3 / 34 (8.82%)		
occurrences causally related to treatment / all	1 / 3		
deaths causally related to treatment / all	1 / 2		
Cardiac disorders			
Bradycardia	Additional description: Bradycardia		
subjects affected / exposed	1 / 34 (2.94%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Dizziness	Additional description: Dizziness		
subjects affected / exposed	1 / 34 (2.94%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Epilepsy	Additional description: Epilepsy		
subjects affected / exposed	1 / 34 (2.94%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Seizure	Additional description: Seizure		
subjects affected / exposed	1 / 34 (2.94%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Blood and lymphatic system disorders			
Thrombocytopenia	Additional description: Thrombocytopenia		
subjects affected / exposed	1 / 34 (2.94%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Chest pain	Additional description: Chest pain		
subjects affected / exposed	1 / 34 (2.94%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General physical health deterioration	Additional description: General physical health deterioration		

subjects affected / exposed	1 / 34 (2.94%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Eye disorders			
Visual disturbances	Additional description: Visual disturbances		
subjects affected / exposed	1 / 34 (2.94%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Abdominal pain	Additional description: Abdominal pain		
subjects affected / exposed	1 / 34 (2.94%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Diarrhoea	Additional description: Diarrhoea		
subjects affected / exposed	2 / 34 (5.88%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Vomiting	Additional description: Vomiting		
subjects affected / exposed	1 / 34 (2.94%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Dyspnoea	Additional description: Dyspnoea		
subjects affected / exposed	2 / 34 (5.88%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Haemoptysis	Additional description: Haemoptysis		
subjects affected / exposed	1 / 34 (2.94%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pleural effusion	Additional description: Pleural effusion		
subjects affected / exposed	3 / 34 (8.82%)		
occurrences causally related to treatment / all	0 / 6		
deaths causally related to treatment / all	0 / 0		

Pneumonitis	Additional description: Pneumonitis		
subjects affected / exposed	1 / 34 (2.94%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Pneumothorax	Additional description: Pneumothorax		
subjects affected / exposed	1 / 34 (2.94%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Renal cyst	Additional description: Renal cyst		
subjects affected / exposed	1 / 34 (2.94%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Erysipelas	Additional description: Erysipelas		
subjects affected / exposed	1 / 34 (2.94%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Lung abscess	Additional description: Lung abscess		
subjects affected / exposed	1 / 34 (2.94%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Pneumonia	Additional description: Pneumonia		
subjects affected / exposed	2 / 34 (5.88%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 1		
Respiratory tract infection	Additional description: Respiratory tract infection		
subjects affected / exposed	1 / 34 (2.94%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Viral infection	Additional description: Viral infection		
subjects affected / exposed	1 / 34 (2.94%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Valid-for-Safety		
Total subjects affected by non-serious adverse events subjects affected / exposed	33 / 34 (97.06%)		
Vascular disorders			
Deep vein thrombosis	Additional description: Deep vein thrombosis		
subjects affected / exposed	3 / 34 (8.82%)		
occurrences (all)	3		
Hypotension	Additional description: Hypotension		
subjects affected / exposed	2 / 34 (5.88%)		
occurrences (all)	2		
Orthostatic hypotension	Additional description: Orthostatic hypotension		
subjects affected / exposed	2 / 34 (5.88%)		
occurrences (all)	2		
Pulmonary embolism and thrombosis	Additional description: Pulmonary embolism and thrombosis		
subjects affected / exposed	2 / 34 (5.88%)		
occurrences (all)	2		
General disorders and administration site conditions			
Asthenia and fatigue	Additional description: Asthenia and fatigue		
subjects affected / exposed	11 / 34 (32.35%)		
occurrences (all)	13		
Chest pain	Additional description: Chest pain		
subjects affected / exposed	4 / 34 (11.76%)		
occurrences (all)	4		
Mucosal inflammation	Additional description: Mucosal inflammation		
subjects affected / exposed	3 / 34 (8.82%)		
occurrences (all)	4		
Oedema	Additional description: Oedema		
subjects affected / exposed	22 / 34 (64.71%)		
occurrences (all)	35		
Pyrexia	Additional description: Pyrexia		

subjects affected / exposed	3 / 34 (8.82%)		
occurrences (all)	3		
Immune system disorders			
Seasonal allergy	Additional description: Seasonal allergy		
subjects affected / exposed	2 / 34 (5.88%)		
occurrences (all)	3		
Respiratory, thoracic and mediastinal disorders			
Cough	Additional description: Cough		
subjects affected / exposed	8 / 34 (23.53%)		
occurrences (all)	12		
Dyspnoea	Additional description: Dyspnoea		
subjects affected / exposed	6 / 34 (17.65%)		
occurrences (all)	6		
Investigations			
Alanine aminotransferase increased	Additional description: Alanine aminotransferase increased		
subjects affected / exposed	12 / 34 (35.29%)		
occurrences (all)	27		
Aspartate aminotransferase increased	Additional description: Aspartate aminotransferase increased		
subjects affected / exposed	9 / 34 (26.47%)		
occurrences (all)	24		
Blood albumin decreased and protein total decreased	Additional description: Blood albumin decreased and protein total decreased		
subjects affected / exposed	4 / 34 (11.76%)		
occurrences (all)	11		
Blood alkaline phosphatase increased	Additional description: Blood alkaline phosphatase increased		
subjects affected / exposed	4 / 34 (11.76%)		
occurrences (all)	10		
Blood creatinine increased	Additional description: Blood creatinine increased		
subjects affected / exposed	9 / 34 (26.47%)		
occurrences (all)	20		
Blood magnesium decreased	Additional description: Blood magnesium decreased		
subjects affected / exposed	3 / 34 (8.82%)		
occurrences (all)	6		
Blood phosphorus decreased	Additional description: Blood phosphorus decreased		
subjects affected / exposed	5 / 34 (14.71%)		
occurrences (all)	8		

Blood potassium increased	Additional description: Blood potassium increased		
subjects affected / exposed	3 / 34 (8.82%)		
occurrences (all)	10		
Blood sodium decreased	Additional description: Blood sodium decreased		
subjects affected / exposed	4 / 34 (11.76%)		
occurrences (all)	4		
Gamma-glutamyltransferase increased	Additional description: Gamma-glutamyltransferase increased		
subjects affected / exposed	3 / 34 (8.82%)		
occurrences (all)	5		
Cardiac disorders			
Bradycardia	Additional description: Bradycardia		
subjects affected / exposed	17 / 34 (50.00%)		
occurrences (all)	44		
Nervous system disorders			
Dizziness	Additional description: Dizziness		
subjects affected / exposed	10 / 34 (29.41%)		
occurrences (all)	11		
Dysgeusia	Additional description: Dysgeusia		
subjects affected / exposed	3 / 34 (8.82%)		
occurrences (all)	3		
Headache	Additional description: Headache		
subjects affected / exposed	5 / 34 (14.71%)		
occurrences (all)	6		
Neuropathy peripheral	Additional description: Neuropathy peripheral		
subjects affected / exposed	4 / 34 (11.76%)		
occurrences (all)	8		
Blood and lymphatic system disorders			
Anaemia	Additional description: Anaemia		
subjects affected / exposed	10 / 34 (29.41%)		
occurrences (all)	18		
Leukopenia/neutropenia	Additional description: Leukopenia/neutropenia		
subjects affected / exposed	11 / 34 (32.35%)		
occurrences (all)	31		
Thrombocytopenia	Additional description: Thrombocytopenia		
subjects affected / exposed	4 / 34 (11.76%)		
occurrences (all)	6		

Ear and labyrinth disorders			
Vertigo	Additional description: Vertigo		
subjects affected / exposed	3 / 34 (8.82%)		
occurrences (all)	4		
Eye disorders			
Eye pain	Additional description: Eye pain		
subjects affected / exposed	2 / 34 (5.88%)		
occurrences (all)	2		
Visual disturbances	Additional description: Visual disturbances		
subjects affected / exposed	22 / 34 (64.71%)		
occurrences (all)	26		
Gastrointestinal disorders			
Abdominal pain	Additional description: Abdominal pain		
subjects affected / exposed	6 / 34 (17.65%)		
occurrences (all)	8		
Constipation	Additional description: Constipation		
subjects affected / exposed	9 / 34 (26.47%)		
occurrences (all)	10		
Diarrhoea	Additional description: Diarrhoea		
subjects affected / exposed	20 / 34 (58.82%)		
occurrences (all)	28		
Dyspepsia	Additional description: Dyspepsia		
subjects affected / exposed	5 / 34 (14.71%)		
occurrences (all)	5		
Nausea	Additional description: Nausea		
subjects affected / exposed	16 / 34 (47.06%)		
occurrences (all)	22		
Stomatitis	Additional description: Stomatitis		
subjects affected / exposed	2 / 34 (5.88%)		
occurrences (all)	3		
Vomiting	Additional description: Vomiting		
subjects affected / exposed	12 / 34 (35.29%)		
occurrences (all)	14		
Skin and subcutaneous tissue disorders			
Eczema	Additional description: Eczema		
subjects affected / exposed	2 / 34 (5.88%)		
occurrences (all)	2		

Nail disorders	Additional description: Nail disorders		
subjects affected / exposed	2 / 34 (5.88%)		
occurrences (all)	2		
Rash	Additional description: Rash		
subjects affected / exposed	4 / 34 (11.76%)		
occurrences (all)	5		
Musculoskeletal and connective tissue disorders			
Arthralgia	Additional description: Arthralgia		
subjects affected / exposed	4 / 34 (11.76%)		
occurrences (all)	4		
Muscle cramps	Additional description: Muscle cramps		
subjects affected / exposed	5 / 34 (14.71%)		
occurrences (all)	6		
Musculoskeletal pain	Additional description: Musculoskeletal pain		
subjects affected / exposed	13 / 34 (38.24%)		
occurrences (all)	17		
Musculoskeletal chest pain	Additional description: Musculoskeletal chest pain		
subjects affected / exposed	2 / 34 (5.88%)		
occurrences (all)	2		
Infections and infestations			
Gastroenteritis	Additional description: Gastroenteritis		
subjects affected / exposed	2 / 34 (5.88%)		
occurrences (all)	4		
Influenza	Additional description: Influenza		
subjects affected / exposed	3 / 34 (8.82%)		
occurrences (all)	3		
Respiratory tract infection	Additional description: Respiratory tract infection		
subjects affected / exposed	14 / 34 (41.18%)		
occurrences (all)	21		
Urinary tract infection	Additional description: Urinary tract infection		
subjects affected / exposed	6 / 34 (17.65%)		
occurrences (all)	6		
Metabolism and nutrition disorders			
Decreased appetite	Additional description: Decreased appetite		
subjects affected / exposed	5 / 34 (14.71%)		
occurrences (all)	5		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
01 August 2015	Amendment 2: Clarification of primary objectives and addition of secondary objectives; implementation of patient diary.
15 March 2016	Amendment 3: New definition of "end of study"; implementation of an additional blood sample collection for ctDNA analysis; extension of the intervals for tumour assessment in the efficacy follow-up; implementation of a pre-final analysis.
04 April 2018	Amendment 5: Premature termination of trial therapy and new definition of "end of study".
04 September 2019	Amendment 6: Termination of the trial; Survival follow-up will be performed not later than January 31st 2020. The study data base will be closed and the study will be terminated on February 29th 2020

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/30978502