



Clinical trial results:

An open-label phase II trial of erlotinib and bevacizumab in patients with advanced non-small cell lung cancer and activating EGFR mutations

Summary

EudraCT number	2011-004481-15
Trial protocol	ES IE FR GR GB IT DE
Global end of trial date	31 October 2018

Results information

Result version number	v1 (current)
This version publication date	07 February 2020
First version publication date	07 February 2020
Summary attachment (see zip file)	Publication_Rosell et al_LancetRM_2017_DOI: 10.1016/S2213-2600(17)30129-7 (ETOP_BELIEF_Rosell et al LancetRM 2017.pdf)

Trial information

Trial identification

Sponsor protocol code	ETOP2-11/MO27911
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01562028
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	European Thoracic Oncology Platform (ETOP)
Sponsor organisation address	Effingerstrasse 40, Bern, Switzerland, 3008
Public contact	ETOP Coordinating Office, ETOP, +41 31 511 94 00, belief@etop-eu.org
Scientific contact	ETOP Coordinating Office, ETOP, +41 31 511 94 00, belief@etop-eu.org

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	22 March 2019
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	31 October 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To determine progression free survival (PFS) of patients with advanced non-squamous NSCLC harbouring at diagnosis EGFR mutations with and without T790M mutation, treated with the combination of erlotinib and bevacizumab.

Hypotheses of interest:

When treated with bevacizumab and erlotinib

a. Median PFS increases to 18 months for patients with EGFR T790M mutation

b. Median PFS is approximately 18 months or more in patients without EGFR T790M mutation.

Protection of trial subjects:

Trial subjects are closely monitored during the entire duration of the trial by the participating investigators. For safety purposes any adverse events occurred from enrolment of a trial subject until 30 days after treatment discontinuation need to be reported.

In case of adverse events and treatment-related toxicities management guidance have been provided in the study protocol to treat trial subjects in adequately manner.

Precautions and warnings about the use of the study drug are provided in the trial subject information sheet to ensure that study drug is correctly used in order to avoid unnecessary adverse reactions and in addition to ensure that in case of an adverse event the study patient contacts the investigator for appropriate measures.

The safety and efficacy of the trial treatment have been regularly reviewed by the ETOP IDMC (independent data monitoring committee) at their semi-annual meetings to safeguard the interest and safety of the patients in the trial and to ensure the scientific integrity of the trial. Additionally, the risk/benefit ratio have been regularly evaluated by the ETOP Steering Committee on a semi-annual basis.

Technical and organisational controls (including physical, electronic and managerial measures) are in place to protect personal data and integrity of trial subjects.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	22 May 2012
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	Switzerland: 41
Country: Number of subjects enrolled	Spain: 46
Country: Number of subjects enrolled	United Kingdom: 4
Country: Number of subjects enrolled	France: 2
Country: Number of subjects enrolled	Germany: 2
Country: Number of subjects enrolled	Greece: 3

Country: Number of subjects enrolled	Ireland: 5
Country: Number of subjects enrolled	Italy: 6
Worldwide total number of subjects	109
EEA total number of subjects	68

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)	51
From 65 to 84 years	58
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Between June 11, 2012 and Oct 28, 2014, 109 eligible patients were enrolled in 29 centers of eight European countries (Spain, Switzerland, UK, Greece, Italy, Ireland, France and Germany). All patients were included in the efficacy analysis.

Pre-assignment

Screening details:

Three patients hadn't received any dose of trial treatment. The safety analysis was conducted based on 106 patients (safety cohort).

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	T790M Positive

Arm description:

Treatment-naïve patients with advanced non-small-cell lung cancer positive for an activating EGFR mutation (exon 19 deletion or L858R mutation), with T790M, treated with erlotinib and bevacizumab.

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

Dosage and administration details:

Patients will be treated with erlotinib, 150 mg p.o., daily.

Investigational medicinal product name	Avastin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Patients will be treated with bevacizumab 15 mg/kg i.v. on day 1 of each 21 day cycle.

Arm title	T790M Negative
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Arm description:

Treatment-naïve patients with advanced non-small-cell lung cancer positive for an activating EGFR mutation (exon 19 deletion or L858R mutation), without T790M, treated with erlotinib and bevacizumab.

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

Dosage and administration details:

Patients will be treated with erlotinib, 150 mg p.o., daily.

Investigational medicinal product name	Avastin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Patients will be treated with bevacizumab 15 mg/kg i.v. on day 1 of each 21 day cycle.

Number of subjects in period 1	T790M Positive	T790M Negative
Started	37	72
Completed	34	70
Not completed	3	2
Consent withdrawn by subject	1	1
Lost to follow-up	2	1

Baseline characteristics

Reporting groups

Reporting group title	T790M Positive
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Reporting group description:

Treatment-naïve patients with advanced non-small-cell lung cancer positive for an activating EGFR mutation (exon 19 deletion or L858R mutation), with T790M, treated with erlotinib and bevacizumab.

Reporting group title	T790M Negative
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Reporting group description:

Treatment-naïve patients with advanced non-small-cell lung cancer positive for an activating EGFR mutation (exon 19 deletion or L858R mutation), without T790M, treated with erlotinib and bevacizumab.

Reporting group values	T790M Positive	T790M Negative	Total
Number of subjects	37	72	109
Age categorical			
Age as continuous characteristic only			
Units: Subjects			

Age continuous			
Units: years			
median	69.5	63	
inter-quartile range (Q1-Q3)	62.3 to 74.0	53.4 to 71.2	-
Gender categorical			
Units: Subjects			
Female	25	42	67
Male	12	30	42
Smoking status			
Units: Subjects			
Current smoker	0	7	7
Former smoker	10	20	30
Never smoked	27	45	72
Histological diagnosis			
Units: Subjects			
Adenocarcinoma	34	59	93
Adenosquamous carcinoma	1	1	2
Not otherwise specified	1	2	3
Unknown	1	10	11
ECOG performance status			
ECOG Performance status scaling: PS 0:Fully active, able to carry on all pre-disease performance without restriction. PS 1:Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light housework, office work. PS 2:Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours. PS 3:Capable of only limited self-care, confined to bed or chair more than 50% of waking hours. PS 4:Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.			
Units: Subjects			
PS 0	17	36	53
PS 1	18	32	50
PS 2	2	4	6
Brain metastasis			
Units: Subjects			

Yes	7	14	21
No	30	58	88
Type of EGFR mutation Units: Subjects			
Deletion of exon 19	23	47	70
L858R mutation in exon 21	14	25	39
BRCA1 mRNA expression Units: Subjects			
Low (<9.2)	10	13	23
High (≥9.2)	10	13	23
No material or no value	17	46	63
AEG1 mRNA expression Units: Subjects			
Low (<1)	11	20	31
High (≥1)	12	18	30
No material or no value	14	34	48

End points

End points reporting groups

Reporting group title	T790M Positive
Reporting group description: Treatment-naïve patients with advanced non-small-cell lung cancer positive for an activating EGFR mutation (exon 19 deletion or L858R mutation), with T790M, treated with erlotinib and bevacizumab.	
Reporting group title	T790M Negative
Reporting group description: Treatment-naïve patients with advanced non-small-cell lung cancer positive for an activating EGFR mutation (exon 19 deletion or L858R mutation), without T790M, treated with erlotinib and bevacizumab.	

Primary: Progression Free Survival

End point title	Progression Free Survival ^[1]
End point description: Time from the date of enrollment until an investigator-documented progression or death, whichever occurs first. Assessment of Progressive Disease (PD) is based on Response Evaluation Criteria In Solid Tumors Criteria (RECIST v1.1): at least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum recorded on study. In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm.	
End point type	Primary
End point timeframe: From the date of enrollment until documented progression or death, whichever occurs first, assessed up to 48 months.	

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: In the cohort of T790M positive pts, among the first 35 pts, 23 reached 12 months without PFS event and thus, according to Simon's two-stage design, this cohort showed that erlotinib plus bevacizumab is a promising treatment. In the cohort of T790M negative pts, median PFS was 10.5 months (95% CI: 9.4-14.2) and 12-month PFS rate 48% (95% CI: 36-59), and we could not reject the null hypothesis of 12-month PFS rate ≤ 50%, versus the alternative of rate > 50% evaluated at rate = 65% (Fleming's design).

End point values	T790M Positive	T790M Negative		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	37 ^[2]	72		
Units: months				
median (confidence interval 95%)	16 (12.7 to 16)	10.5 (9.4 to 14.2)		

Notes:

[2] - The upper 95% limit is not estimable, so indicatively we present the estimation of the median.

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival

End point title	Overall Survival
End point description: Time from the date of enrollment until death from any cause.	

End point type	Secondary
End point timeframe:	
From the date of enrollment until death, assessed up to 48 months.	

End point values	T790M Positive	T790M Negative		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	37 ^[3]	72		
Units: months				
median (confidence interval 95%)	18.6 (18.6 to 18.6)	28.2 (21.4 to 41.8)		

Notes:

[3] - Median is not reached & upper limit is not estimable, so indicatively we present the lower limit.

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Treatment Failure

End point title	Time to Treatment Failure
End point description:	
Time from the date of enrollment to discontinuation of treatment for any reason including progression of disease (based on RECIST v1.1), treatment toxicity (adverse events classified according to NCI CTCAE version 4.), refusal and death.	
End point type	Secondary
End point timeframe:	
From the date of enrollment until discontinuation of treatment, assessed up to 48 months.	

End point values	T790M Positive	T790M Negative		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	37	72		
Units: months				
median (confidence interval 95%)	13.4 (5.6 to 19.6)	8.3 (6.3 to 9.8)		

Statistical analyses

No statistical analyses for this end point

Secondary: Objective Response

End point title	Objective Response
End point description:	
Objective response is defined as best overall response (CR or PR) across all assessment time-points during the period from enrollment to termination of trial treatment. Objective response, along with	

progressive and stable disease, will be determined using RECIST 1.1 criteria:

Complete Response (CR): Disappearance of all target lesions.

Partial Response (PR): At least a 30% decrease in the sum of diameters of target lesions taking as reference the baseline sum of diameters.

Progression (PD): At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum recorded on the trial. In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm.

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD taking as reference the smallest sum of diameters recorded on the trial.

End point type	Secondary
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End point timeframe:

Assessed across all time-points from enrollment to termination of trial treatment (max 48 months).

End point values	T790M Positive	T790M Negative		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	37	72		
Units: participants				
Complete Response	3	3		
Partial Response	24	54		
Stable Disease	8	9		
Progressive Disease	1	3		
Non-Evaluable	1	3		

Statistical analyses

No statistical analyses for this end point

Secondary: Disease Control

End point title	Disease Control
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End point description:

Disease control is defined as achieving objective response (CR or PR, across all time-points from enrollment to termination of trial treatment) or stable disease for at least 6 weeks. Objective response, along with SD (disease control) and PD (no disease control), will be determined using RECIST 1.1 criteria:

Complete Response (CR): Disappearance of all target lesions. Partial Response (PR): At least a 30% decrease in the sum of diameters of target lesions taking as reference the baseline sum of diameters. Progression (PD): At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum recorded on the trial. In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD taking as reference the smallest sum of diameters recorded on the trial.

End point type	Secondary
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End point timeframe:

Assessed across all time-points from enrollment to termination of trial treatment (max 48 months).

End point values	T790M Positive	T790M Negative		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	37	72		
Units: participants				
Disease Control	35	66		
No Disease Control	2	6		

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Response

End point title	Duration of Response
End point description:	
Interval from the date of first documentation of objective response (CR or PR) to the date of first documented progression or relapse. Assessment of Objective response and Progressive Disease (PD) is based on the RECIST 1.1 criteria: Complete Response (CR): Disappearance of all target lesions. Partial Response (PR): At least a 30% decrease in the sum of diameters of target lesions taking as reference the baseline sum of diameters. Progression (PD): At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum recorded on the trial. In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm.	
End point type	Secondary
End point timeframe:	
Assessed across all time-points from enrollment to to the date of first documented progression or relapse (max 48 months).	

End point values	T790M Positive	T790M Negative		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	37 ^[4]	72		
Units: months				
median (confidence interval 95%)	14.7 (14.7 to 14.7)	12 (8.2 to 20.2)		

Notes:

[4] - Median is not reached & upper limit is not estimable, so indicatively we present the lower limit.

Statistical analyses

No statistical analyses for this end point

Secondary: Adverse Events

End point title	Adverse Events
End point description:	
Adverse events graded according to NCI CTCAE V4.	
End point type	Secondary
End point timeframe:	
Assessed across all time-points until end of treatment (30 +/-5 days following the last dose of study	

drug) (max 48 months).

End point values	T790M Positive	T790M Negative		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	36 ^[5]	70 ^[6]		
Units: participants				
Experienced AE/SAE	36	69		
No AE/SAE	0	1		
Experienced SAE	12	19		

Notes:

[5] - One patient never started treatment (lost to follow-up).

[6] - Two patients never started treatment (one due to withdrawal and one patient was lost to follow-up).

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Assessed across all time-points until end of treatment (30 +/-5 days following the last dose of study drug) (max 48 months).

Adverse event reporting additional description:

One patient from the T790 positive arm never started treatment (lost to follow-up).

Two patients from the T790 negative arm never started treatment (one lost to follow-up and one withdrawal).

Assessment type	Systematic
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Dictionary used

Dictionary name	NCI CTCAE
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Dictionary version	4
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Reporting groups

Reporting group title	T790M Positive
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Reporting group description:

Treatment-naïve patients with advanced non-small-cell lung cancer positive for an activating EGFR mutation (exon 19 deletion or L858R mutation), with T790M, treated with erlotinib (150 mg p.o., daily) and bevacizumab (15 mg/kg i.v. on day 1 of each 21 day cycle).

Reporting group title	T790M Negative
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Reporting group description:

Treatment-naïve patients with advanced non-small-cell lung cancer positive for an activating EGFR mutation (exon 19 deletion or L858R mutation), without T790M, treated with erlotinib (150 mg p.o., daily) and bevacizumab (15 mg/kg i.v. on day 1 of each 21 day cycle).

Serious adverse events	T790M Positive	T790M Negative	
Total subjects affected by serious adverse events			
subjects affected / exposed	12 / 36 (33.33%)	19 / 70 (27.14%)	
number of deaths (all causes)	13	28	
number of deaths resulting from adverse events	1	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Other			
subjects affected / exposed	0 / 36 (0.00%)	1 / 70 (1.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Thromboembolic event			
subjects affected / exposed	1 / 36 (2.78%)	3 / 70 (4.29%)	
occurrences causally related to treatment / all	1 / 1	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypotension			

subjects affected / exposed	1 / 36 (2.78%)	0 / 70 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	1 / 36 (2.78%)	0 / 70 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Fever			
subjects affected / exposed	0 / 36 (0.00%)	1 / 70 (1.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Pneumothorax			
subjects affected / exposed	0 / 36 (0.00%)	1 / 70 (1.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Other			
subjects affected / exposed	0 / 36 (0.00%)	1 / 70 (1.43%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Confusion			
subjects affected / exposed	2 / 36 (5.56%)	0 / 70 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Serum amylase increased			
subjects affected / exposed	1 / 36 (2.78%)	0 / 70 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Hip fracture			

subjects affected / exposed	1 / 36 (2.78%)	0 / 70 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute coronary syndrome			
subjects affected / exposed	0 / 36 (0.00%)	1 / 70 (1.43%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Other			
subjects affected / exposed	0 / 36 (0.00%)	2 / 70 (2.86%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cognitive disturbance			
subjects affected / exposed	1 / 36 (2.78%)	0 / 70 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dizziness			
subjects affected / exposed	0 / 36 (0.00%)	1 / 70 (1.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Seizure			
subjects affected / exposed	0 / 36 (0.00%)	1 / 70 (1.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Disseminated intravascular coagulation			
subjects affected / exposed	0 / 36 (0.00%)	1 / 70 (1.43%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal pain			

subjects affected / exposed	1 / 36 (2.78%)	1 / 70 (1.43%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colonic perforation			
subjects affected / exposed	1 / 36 (2.78%)	1 / 70 (1.43%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhea			
subjects affected / exposed	0 / 36 (0.00%)	2 / 70 (2.86%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis			
subjects affected / exposed	0 / 36 (0.00%)	2 / 70 (2.86%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anal hemorrhage			
subjects affected / exposed	1 / 36 (2.78%)	0 / 70 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis			
subjects affected / exposed	1 / 36 (2.78%)	0 / 70 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dysphagia			
subjects affected / exposed	1 / 36 (2.78%)	0 / 70 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Other			
subjects affected / exposed	0 / 36 (0.00%)	1 / 70 (1.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Other			

subjects affected / exposed	0 / 36 (0.00%)	1 / 70 (1.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Rash maculo-papular			
subjects affected / exposed	1 / 36 (2.78%)	0 / 70 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	0 / 36 (0.00%)	1 / 70 (1.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Other			
subjects affected / exposed	0 / 36 (0.00%)	1 / 70 (1.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Appendicitis			
subjects affected / exposed	0 / 36 (0.00%)	2 / 70 (2.86%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung infection			
subjects affected / exposed	0 / 36 (0.00%)	2 / 70 (2.86%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	2 / 36 (5.56%)	0 / 70 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal infection			
subjects affected / exposed	1 / 36 (2.78%)	0 / 70 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Biliary tract infection			
subjects affected / exposed	0 / 36 (0.00%)	1 / 70 (1.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bone infection			
subjects affected / exposed	0 / 36 (0.00%)	1 / 70 (1.43%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchial infection			
subjects affected / exposed	1 / 36 (2.78%)	0 / 70 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	1 / 36 (2.78%)	1 / 70 (1.43%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	2 / 36 (5.56%)	0 / 70 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 4 %

Non-serious adverse events	T790M Positive	T790M Negative	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	36 / 36 (100.00%)	69 / 70 (98.57%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	33 / 36 (91.67%)	62 / 70 (88.57%)	
occurrences (all)	33	62	
Thromboembolic event			
subjects affected / exposed	2 / 36 (5.56%)	2 / 70 (2.86%)	
occurrences (all)	2	2	
Hematoma			

subjects affected / exposed occurrences (all)	2 / 36 (5.56%) 2	3 / 70 (4.29%) 3	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	23 / 36 (63.89%)	34 / 70 (48.57%)	
occurrences (all)	23	34	
Pain			
subjects affected / exposed	10 / 36 (27.78%)	12 / 70 (17.14%)	
occurrences (all)	10	12	
Edema limbs			
subjects affected / exposed	5 / 36 (13.89%)	4 / 70 (5.71%)	
occurrences (all)	5	4	
Fever			
subjects affected / exposed	3 / 36 (8.33%)	5 / 70 (7.14%)	
occurrences (all)	3	5	
Flu like symptoms			
subjects affected / exposed	3 / 36 (8.33%)	4 / 70 (5.71%)	
occurrences (all)	3	4	
Other			
subjects affected / exposed	3 / 36 (8.33%)	3 / 70 (4.29%)	
occurrences (all)	3	3	
Non-cardiac chest pain			
subjects affected / exposed	2 / 36 (5.56%)	2 / 70 (2.86%)	
occurrences (all)	2	2	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	24 / 36 (66.67%)	30 / 70 (42.86%)	
occurrences (all)	24	30	
Epistaxis			
subjects affected / exposed	18 / 36 (50.00%)	20 / 70 (28.57%)	
occurrences (all)	18	20	
Dyspnea			
subjects affected / exposed	12 / 36 (33.33%)	18 / 70 (25.71%)	
occurrences (all)	12	18	
Other			

subjects affected / exposed occurrences (all)	4 / 36 (11.11%) 4	4 / 70 (5.71%) 4	
Voice alteration subjects affected / exposed occurrences (all)	5 / 36 (13.89%) 5	4 / 70 (5.71%) 4	
Hoarseness subjects affected / exposed occurrences (all)	3 / 36 (8.33%) 3	5 / 70 (7.14%) 5	
Psychiatric disorders Depression subjects affected / exposed occurrences (all)	2 / 36 (5.56%) 2	7 / 70 (10.00%) 7	
Anxiety subjects affected / exposed occurrences (all)	2 / 36 (5.56%) 2	3 / 70 (4.29%) 3	
Insomnia subjects affected / exposed occurrences (all)	2 / 36 (5.56%) 2	2 / 70 (2.86%) 2	
Investigations Alanine aminotransferase increase subjects affected / exposed occurrences (all)	8 / 36 (22.22%) 8	21 / 70 (30.00%) 21	
Aspartate aminotransferase increase subjects affected / exposed occurrences (all)	7 / 36 (19.44%) 7	21 / 70 (30.00%) 21	
Creatinine increased subjects affected / exposed occurrences (all)	3 / 36 (8.33%) 3	2 / 70 (2.86%) 2	
Blood bilirubin increased subjects affected / exposed occurrences (all)	1 / 36 (2.78%) 1	3 / 70 (4.29%) 3	
Cardiac disorders Chest pain - cardiac subjects affected / exposed occurrences (all)	0 / 36 (0.00%) 0	3 / 70 (4.29%) 3	
Nervous system disorders			

Headache			
subjects affected / exposed	8 / 36 (22.22%)	13 / 70 (18.57%)	
occurrences (all)	8	13	
Dysgeusia			
subjects affected / exposed	6 / 36 (16.67%)	12 / 70 (17.14%)	
occurrences (all)	6	12	
Dizziness			
subjects affected / exposed	6 / 36 (16.67%)	10 / 70 (14.29%)	
occurrences (all)	6	10	
Paresthesia			
subjects affected / exposed	3 / 36 (8.33%)	6 / 70 (8.57%)	
occurrences (all)	3	6	
Other			
subjects affected / exposed	2 / 36 (5.56%)	2 / 70 (2.86%)	
occurrences (all)	2	2	
Aphonia			
subjects affected / exposed	4 / 36 (11.11%)	0 / 70 (0.00%)	
occurrences (all)	4	0	
Peripheral sensory neuropathy			
subjects affected / exposed	1 / 36 (2.78%)	3 / 70 (4.29%)	
occurrences (all)	1	3	
Blood and lymphatic system disorders			
Anemia			
subjects affected / exposed	1 / 36 (2.78%)	4 / 70 (5.71%)	
occurrences (all)	1	4	
Other			
subjects affected / exposed	2 / 36 (5.56%)	2 / 70 (2.86%)	
occurrences (all)	2	2	
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	0 / 36 (0.00%)	4 / 70 (5.71%)	
occurrences (all)	0	4	
Eye disorders			
Conjunctivitis			
subjects affected / exposed	9 / 36 (25.00%)	9 / 70 (12.86%)	
occurrences (all)	9	9	
Other			

subjects affected / exposed occurrences (all)	5 / 36 (13.89%) 5	7 / 70 (10.00%) 7	
Dry eye subjects affected / exposed occurrences (all)	3 / 36 (8.33%) 3	5 / 70 (7.14%) 5	
Watering eyes subjects affected / exposed occurrences (all)	2 / 36 (5.56%) 2	1 / 70 (1.43%) 1	
Gastrointestinal disorders			
Diarrhea subjects affected / exposed occurrences (all)	30 / 36 (83.33%) 30	55 / 70 (78.57%) 55	
Nausea subjects affected / exposed occurrences (all)	13 / 36 (36.11%) 13	20 / 70 (28.57%) 20	
Mucositis oral subjects affected / exposed occurrences (all)	15 / 36 (41.67%) 15	15 / 70 (21.43%) 15	
Abdominal pain subjects affected / exposed occurrences (all)	4 / 36 (11.11%) 4	15 / 70 (21.43%) 15	
Constipation subjects affected / exposed occurrences (all)	8 / 36 (22.22%) 8	12 / 70 (17.14%) 12	
Vomiting subjects affected / exposed occurrences (all)	7 / 36 (19.44%) 7	1 / 70 (1.43%) 1	
Other subjects affected / exposed occurrences (all)	6 / 36 (16.67%) 6	3 / 70 (4.29%) 3	
Hemorrhoids subjects affected / exposed occurrences (all)	4 / 36 (11.11%) 4	5 / 70 (7.14%) 5	
Anal hemorrhage subjects affected / exposed occurrences (all)	4 / 36 (11.11%) 4	3 / 70 (4.29%) 3	

Dry mouth			
subjects affected / exposed	5 / 36 (13.89%)	3 / 70 (4.29%)	
occurrences (all)	5	3	
Oral hemorrhage			
subjects affected / exposed	3 / 36 (8.33%)	5 / 70 (7.14%)	
occurrences (all)	3	5	
Dysphagia			
subjects affected / exposed	4 / 36 (11.11%)	2 / 70 (2.86%)	
occurrences (all)	4	2	
Gastroesophageal reflux disease			
subjects affected / exposed	2 / 36 (5.56%)	5 / 70 (7.14%)	
occurrences (all)	2	5	
Dyspepsia			
subjects affected / exposed	1 / 36 (2.78%)	3 / 70 (4.29%)	
occurrences (all)	1	3	
Gastritis			
subjects affected / exposed	2 / 36 (5.56%)	2 / 70 (2.86%)	
occurrences (all)	2	2	
Hemorrhoidal hemorrhage			
subjects affected / exposed	2 / 36 (5.56%)	2 / 70 (2.86%)	
occurrences (all)	2	2	
Oral pain			
subjects affected / exposed	2 / 36 (5.56%)	1 / 70 (1.43%)	
occurrences (all)	2	1	
Skin and subcutaneous tissue disorders			
Rash maculo-papular			
subjects affected / exposed	28 / 36 (77.78%)	55 / 70 (78.57%)	
occurrences (all)	28	55	
Dry skin			
subjects affected / exposed	17 / 36 (47.22%)	20 / 70 (28.57%)	
occurrences (all)	17	20	
Rash acneiform			
subjects affected / exposed	10 / 36 (27.78%)	13 / 70 (18.57%)	
occurrences (all)	10	13	
Other			

subjects affected / exposed	9 / 36 (25.00%)	13 / 70 (18.57%)	
occurrences (all)	9	13	
Alopecia			
subjects affected / exposed	8 / 36 (22.22%)	11 / 70 (15.71%)	
occurrences (all)	8	11	
Pruritus			
subjects affected / exposed	10 / 36 (27.78%)	6 / 70 (8.57%)	
occurrences (all)	10	6	
Erythema multiforme			
subjects affected / exposed	6 / 36 (16.67%)	6 / 70 (8.57%)	
occurrences (all)	6	6	
Nail ridging			
subjects affected / exposed	2 / 36 (5.56%)	3 / 70 (4.29%)	
occurrences (all)	2	3	
Nail discoloration			
subjects affected / exposed	2 / 36 (5.56%)	1 / 70 (1.43%)	
occurrences (all)	2	1	
Palmar-plantar erythrodysesthesia syndrome			
subjects affected / exposed	0 / 36 (0.00%)	3 / 70 (4.29%)	
occurrences (all)	0	3	
Skin ulceration			
subjects affected / exposed	0 / 36 (0.00%)	3 / 70 (4.29%)	
occurrences (all)	0	3	
Renal and urinary disorders			
Proteinuria			
subjects affected / exposed	27 / 36 (75.00%)	34 / 70 (48.57%)	
occurrences (all)	27	34	
Hematuria			
subjects affected / exposed	1 / 36 (2.78%)	4 / 70 (5.71%)	
occurrences (all)	1	4	
Other			
subjects affected / exposed	0 / 36 (0.00%)	5 / 70 (7.14%)	
occurrences (all)	0	5	
Musculoskeletal and connective tissue disorders			

Bone pain			
subjects affected / exposed	8 / 36 (22.22%)	13 / 70 (18.57%)	
occurrences (all)	8	13	
Back pain			
subjects affected / exposed	4 / 36 (11.11%)	15 / 70 (21.43%)	
occurrences (all)	4	15	
Arthralgia			
subjects affected / exposed	7 / 36 (19.44%)	7 / 70 (10.00%)	
occurrences (all)	7	7	
Pain in extremity			
subjects affected / exposed	6 / 36 (16.67%)	8 / 70 (11.43%)	
occurrences (all)	6	8	
Myalgia			
subjects affected / exposed	2 / 36 (5.56%)	6 / 70 (8.57%)	
occurrences (all)	2	6	
Other			
subjects affected / exposed	1 / 36 (2.78%)	4 / 70 (5.71%)	
occurrences (all)	1	4	
Chest wall pain			
subjects affected / exposed	1 / 36 (2.78%)	4 / 70 (5.71%)	
occurrences (all)	1	4	
Arthritis			
subjects affected / exposed	2 / 36 (5.56%)	2 / 70 (2.86%)	
occurrences (all)	2	2	
Infections and infestations			
Paronychia			
subjects affected / exposed	8 / 36 (22.22%)	8 / 70 (11.43%)	
occurrences (all)	8	8	
Urinary tract infection			
subjects affected / exposed	6 / 36 (16.67%)	7 / 70 (10.00%)	
occurrences (all)	6	7	
Upper respiratory infection			
subjects affected / exposed	6 / 36 (16.67%)	6 / 70 (8.57%)	
occurrences (all)	6	6	
Other			

subjects affected / exposed	5 / 36 (13.89%)	5 / 70 (7.14%)	
occurrences (all)	5	5	
Nail infection			
subjects affected / exposed	3 / 36 (8.33%)	6 / 70 (8.57%)	
occurrences (all)	3	6	
Lung infection			
subjects affected / exposed	2 / 36 (5.56%)	2 / 70 (2.86%)	
occurrences (all)	2	2	
Mucosal infection			
subjects affected / exposed	3 / 36 (8.33%)	3 / 70 (4.29%)	
occurrences (all)	3	3	
Bronchial infection			
subjects affected / exposed	2 / 36 (5.56%)	2 / 70 (2.86%)	
occurrences (all)	2	2	
Rhinitis infective			
subjects affected / exposed	1 / 36 (2.78%)	3 / 70 (4.29%)	
occurrences (all)	1	3	
Lip infection			
subjects affected / exposed	0 / 36 (0.00%)	3 / 70 (4.29%)	
occurrences (all)	0	3	
Metabolism and nutrition disorders			
Anorexia			
subjects affected / exposed	10 / 36 (27.78%)	18 / 70 (25.71%)	
occurrences (all)	10	18	
Other			
subjects affected / exposed	4 / 36 (11.11%)	7 / 70 (10.00%)	
occurrences (all)	4	7	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
21 November 2013	<p>The protocol has been revised to add new safety information from the updated Investigators Brochure of bevacizumab. It also includes several other minor clarification and modifications.</p> <p>The following safety information for bevacizumab have been updated:</p> <ul style="list-style-type: none">- Addition of necrotizing fasciitis as a known adverse reaction of bevacizumab and the management of this toxicity .- Further new safety information includes detailed clinical aspects of some known adverse events of bevacizumab.- Ovarian failure/fertility and arthralgia are also considered as known adverse reactions of bevacizumab. <p>Additional modifications included in the protocol amendment 1 are:</p> <ul style="list-style-type: none">- Together with serum samples the collection of plasma samples have been added together- Additional exclusion criteria- Procedure for bevacizumab administration in case of delay- Treatment compliance for erlotinib which will be monitored by a patient diary- Additional criteria for discontinuing bevacizumab- Modified definitions of Serious Adverse Events (SAE) and of Adverse Events of Special Interest (AESI) for bevacizumab- Adapted procedure for blood collection, serum and plasma preparation- Updated baseline evaluations and evaluations after progression- Statistical update of sample size determination- Modified general criteria for termination of the trial- Clarification concerning the withdrawal of consent, quality assurance, protocol adherence, record retention and access rules to patient data

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported