Clinical trial results:
Afatinib in pretreated patients with advanced NSCLC harbouring HER2 exon 20 mutations

Summary

EudraCT number	2014-005098-35
Trial protocol	ES DE NL
Global end of trial date	15 September 2017

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_Dziadziuszko et al__J Thorac Oncol_2019_DOI: 10.1016/j.jtho.2019.02.017 (ETOP NICHE Dziadziuszko et al_2019.pdf)

Trial information

Trial identification

Sponsor protocol code	ETOP7-14 NICHE

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02369484
WHO universal trial number (UTN)	-
Other trial identifiers	Boehringer number: 1200.230

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 315119400, NICHE@etop-eu.org
Scientific contact	ETOP Coordinating Office, ETOP, +41 315119400, NICHE@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	15 September 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	15 September 2017
Global end of trial reached?	Yes
Global end of trial date	15 September 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the ability of afatinib to control disease in pretreated patients with advanced NSCLC harbouring HER2 exon 20 mutations.

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	24 June 2015
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	Netherlands: 7
Country: Number of subjects enrolled	Spain: 3
Country: Number of subjects enrolled	Germany: 3
Worldwide total number of subjects	13
EEA total number of subjects	13

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)	8
From 65 to 84 years	5
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The first patient was enrolled to the ETOP/7-14 NICHE trial on 16.09.2015, while the last one on August 2016, before accrual was suspended in October 2016. Patients were enrolled in 3 centers (Netherlands Cancer Institute of Amsterdam, Vall d' Herbon Univesity Hospital (Spain) and Universitatsklinikum Koln (Germany).

Pre-assignment

Screening details:

All 13 patients eligible for enrollment received treatment.

Period 1

Period 1 title	Overall study
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Afatinib

Arm description:

Afatinib 40 mg p.o./day until tumour progression or lack of tolerability

Arm type	Experimental
Investigational medicinal product name	Giotrif
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

40mg daily p.o. until tumor progression or lack of tolerability.
Dose reduction to 30mg, reep 20mg, if required.

Number of subjects in period 1	Afatinib
Started	13
Completed	13

Period 2

Period 2 title	Interim analysis
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Afanitib (interim)

Arm description:

Afatinib 40 mg p.o./day until tumour progression or lack of tolerability

Arm type	Experimental
Investigational medicinal product name	Giotrif
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

40mg daily p.o. until tumor progression or lack of tolerability.
Dose reduction to 30mg, reep 20mg, if required.

Number of subjects in period 2[1]	Afanitib (interim)
Started	9
Completed	9

Notes:

[1] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.
Justification: A Simon’s two-stage phase II design is adopted, with 9 patients in the 1st stage and 13 patients in the 2nd stage. The primary endpoint, disease control (DC), is evaluated at the 1st stage, after the first 9 patients have been followed for 12 weeks (interim analysis), and at the 2nd stage, approx. 40 months after inclusion of 1st patient (final analysis).

Baseline characteristics

Reporting groups	
Reporting group title	Overall study
Reporting group description:	
Afatinib 40 mg p.o./day until tumour progression or lack of tolerability	

Reporting group values	Overall study	Total	
Number of subjects	13	13	
Age categorical			
Age as continuous characteristic only			
Units: Subjects			

Age continuous			
Age of patient at enrollment			
Units: years			
median	59		
full range (min-max)	39 to 82	-	
Gender categorical			
Units: Subjects			
Female	9	9	
Male	4	4	
Smoking history			
Units: Subjects			
Current smoker	1	1	
Former smoker	4	4	
Never smoked	8	8	
Region of Enrollment			
Units: Subjects			
Netherlands	7	7	
Germany	3	3	
Spain	3	3	
ECOG Performance status			
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	7	7	
PS 1	4	4	
PS 2	2	2	
T parameter			
Primary tumor (T) TX: Main tumor cannot be measured. T0: Main tumor cannot be found. T1, T2, T3, T4: Refers to the size and/or extent of the main tumor. The higher the number after the T, the larger the tumor or the more it has grown into nearby tissues. T's may be further divided to provide more detail, such as T3a and T3b.			
Units: Subjects			

T1b	1	1	
T2a	3	3	
T3	3	3	
T4	6	6	
N parameter			
Regional lymph nodes (N) NX: Cancer in nearby lymph nodes cannot be measured. N0: There is no cancer in nearby lymph nodes. N1, N2, N3: Refers to the number and location of lymph nodes that contain cancer. The higher the number after the N, the more lymph nodes that contain cancer.			
Units: Subjects			
N0	5	5	
N2	3	3	
N3	5	5	
M parameter			
Distant metastasis (M) MX: Metastasis cannot be measured. M0: Cancer has not spread to other parts of the body. M1: Cancer has spread to other parts of the body.			
Units: Subjects			
M0	1	1	
M1a	6	6	
M1b	6	6	
TNM staging			
The TNM system is the most widely used cancer staging system. In the TNM system: The T refers to the size and extent of the main tumor. The main tumor is usually called the primary tumor. The N refers to the the number of nearby lymph nodes that have cancer. The M refers to whether the cancer has metastasized. This means that the cancer has spread from the primary tumor to other parts of the body. When your cancer is described by the TNM system, there will be numbers after each letter that give more details about the cancer—for example, T1N0MX or T3N1M0.			
Units: Subjects			
T1b-N3-M1b	1	1	
T2a-N0-M1a	1	1	
T2a-N2-M1b	1	1	
T2a-N3-M1b	1	1	
T3-N0-M1b	1	1	
T3-N2-M1a	1	1	
T3-N3-M1b	1	1	
T4-N0-M1a	3	3	
T4-N2-M0	1	1	
T4-N3-M1a	1	1	
T4-N3-M1b	1	1	
Type of prior platinum treatment Units: Subjects			
Adjuvant	2	2	
Advanced disease	11	11	

End points

End points reporting groups

Reporting group title	Afatinib
Reporting group description:	
Afatinib 40 mg p.o./day until tumour progression or lack of tolerability	
Reporting group title	Afanitib (interim)
Reporting group description:	
Afatinib 40 mg p.o./day until tumour progression or lack of tolerability	

Primary: Disease control

End point title	Disease control[1]

End point description:

Disease control (DC) is defined as complete or partial response, or disease stabilisation lasting at least 12 weeks.
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. The appearance of one or more new lesions denotes disease progression.
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	Primary

End point timeframe:

At interim (after the first 9 pts have been followed for 12 weeks) & final analysis (approx. 40 months after inclusion of first pt)

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 interim analysis, evaluating the 12-week status of the first 9 patients according to the 1st stage of Simon's two-stage optimal design, 5 patients (55.6%) had progressed by 12 weeks, and thus, the stopping threshold of at most 3 patients not achieving DC by 12 weeks was crossed. Based on these results, the trial Steering Committee decided to stop recruitment into the trial. Treatment and follow-up for the enrolled patients continued as per protocol.

End point values	Afatinib	Afanitib (interim)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	13	9		
Units: participants				
DC at 12 weeks - "Yes"	7	4		
DC at 12 weeks - "No"	6	5		

Statistical analyses

No statistical analyses for this end point

Secondary: Progression-free Survival

End point title	Progression-free Survival

End point description:

Progression-free survival (PFS) is defined as the time from date of enrollment until documented progression or death, if progression is not documented. Censoring will occur at the last tumor assessment only if patients is lost to follow-up.

End point type	Secondary

End point timeframe:

Time assessed from the date of enrollment until documented progression or death (max 36 months).

End point values	Afatinib			
Subject group type	Reporting group			
Number of subjects analysed	13			
Units: weeks				
median (confidence interval 95%)	15.9 (6.0 to 35.4)			

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival

End point title	Overall Survival

End point description:

Overall survival (OS) is defined as the time from the date of enrollment until death from any cause. Censoring will occur at the last follow-up.

End point type	Secondary

End point timeframe:

Time assessed from the date of enrollment until death (max 36 months).

End point values	Afatinib			
Subject group type	Reporting group			
Number of subjects analysed	13[2]			
Units: weeks				
median (confidence interval 95%)	56.0 (16.3 to 100)			

Notes:

[2] - Upper 95% limit is not reached, so we present the maximum value.

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 to afatinib treatment 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. The appearance of one or more new lesions denotes disease progression.
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

End point timeframe:

Assessed across all time-points during the period from enrollment to termination of trial treatment (max. 36 months).

End point values	Afatinib			
Subject group type	Reporting group			
Number of subjects analysed	13			
Units: participants				
Objective response (CR or PR)	1			
Stable disease	6			
Progressive disease	5			
Non-evaluable	1			

Statistical analyses

No statistical analyses for this end point

Secondary: Toxicities of Treatment

End point title	Toxicities of Treatment

End point description:

Adverse events classified according to NCI CTCAE version 4.

End point type	Secondary

End point timeframe:

Assessed from the date of informed consent until 90 days after the final dose of afatinib (max 18 months).

End point values	Afatinib			
Subject group type	Reporting group			
Number of subjects analysed	13			
Units: participants				
Experienced AE/SAE	13			
No AE/SAE	0			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From the date of informed consent until 90 days after the final dose of afatinib (max 18 months).

Assessment type	Systematic

Dictionary used

Dictionary name	NCI CTCAE
Dictionary version	4

Reporting groups

Reporting group title	Afatinib

Reporting group description:

Afatinib: 40 mg p.o./day until tumour progression or lack of tolerability

Serious adverse events	Afatinib		
Total subjects affected by serious adverse events			
subjects affected / exposed	5 / 13 (38.46%)		
number of deaths (all causes)	8		
number of deaths resulting from adverse events	1		
Cardiac disorders			
Pericardial effusion			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Febrile neutropenia			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Diarrhea			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Dyspnea			

subjects affected / exposed	1 / 13 (7.69%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Epistaxis			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Pleural effusion			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	1 / 1		
Musculoskeletal and connective tissue disorders			
Muscle weakness lower limb			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Afatinib		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	13 / 13 (100.00%)		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			

Tumor pain			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Vascular disorders			
Hypertension			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	3 / 13 (23.08%)		
occurrences (all)	3		
Flu like symptoms			
subjects affected / exposed	2 / 13 (15.38%)		
occurrences (all)	2		
Non-cardiac chest			
subjects affected / exposed	2 / 13 (15.38%)		
occurrences (all)	2		
Malaise			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Respiratory, thoracic and mediastinal disorders			
Dyspnea			
subjects affected / exposed	3 / 13 (23.08%)		
occurrences (all)	3		
Cough			
subjects affected / exposed	2 / 13 (15.38%)		
occurrences (all)	2		
Epistaxis			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Pleural effusion			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Investigations			
GGT increased			

subjects affected / exposed occurrences (all) Asparate aminotransferase increased subjects affected / exposed occurrences (all) Creatine increased subjects affected / exposed occurrences (all) Platelet count decreased subjects affected / exposed occurrences (all) Weight loss subjects affected / exposed occurrences (all)	2 / 13 (15.38%) 2 1 / 13 (7.69%) 1 1 / 13 (7.69%) 1 1 / 13 (7.69%) 1 1 / 13 (7.69%) 1		
Cardiac disorders Ventricular arrhythmia subjects affected / exposed occurrences (all)	 1 / 13 (7.69%) 1		
Nervous system disorders Headache subjects affected / exposed occurrences (all) Dysgeusia subjects affected / exposed occurrences (all) Peripheral sensory neuropathy subjects affected / exposed occurrences (all) Other (paraplegia from Th4) subjects affected / exposed occurrences (all)	 2 / 13 (15.38%) 1 1 / 13 (7.69%) 1 1 / 13 (7.69%) 1 1 / 13 (7.69%) 1		
Blood and lymphatic system disorders Anemia subjects affected / exposed occurrences (all)	 2 / 13 (15.38%) 2		
Eye disorders			

Dry eye subjects affected / exposed occurrences (all)	2 / 13 (15.38%) 2		
Gastrointestinal disorders Diarrhea subjects affected / exposed occurrences (all)	11 / 13 (84.62%) 11		
Mucositis oral subjects affected / exposed occurrences (all)	4 / 13 (30.77%) 4		
Abdominal pain subjects affected / exposed occurrences (all)	3 / 13 (23.08%) 3		
Vomiting subjects affected / exposed occurrences (all)	3 / 13 (23.08%) 3		
Constipation subjects affected / exposed occurrences (all)	1 / 13 (7.69%) 1		
Dry mouth subjects affected / exposed occurrences (all)	1 / 13 (7.69%) 1		
Nausea subjects affected / exposed occurrences (all)	1 / 13 (7.69%) 1		
Skin and subcutaneous tissue disorders Erythema multiforme subjects affected / exposed occurrences (all)	4 / 13 (30.77%) 4		
Rash acneiform subjects affected / exposed occurrences (all)	4 / 13 (30.77%) 4		
Dry skin subjects affected / exposed occurrences (all)	3 / 13 (23.08%) 3		
Other			

subjects affected / exposed	2 / 13 (15.38%)		
occurrences (all)	2		
Alopecia			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Renal and urinary disorders			
Cystitis noninfective			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Urinary incontinence			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Urinary track obstruction			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Musculoskeletal and connective tissue disorders			
Arthalgia			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Back pain			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Bone pain			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Myalgia			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Infections and infestations			
Paronyclia			
subjects affected / exposed	5 / 13 (38.46%)		
occurrences (all)	5		
Bladder infection			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Eye infection			

subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Sinusitis			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Tooth infection			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Urinary track infection			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Nail infection			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Papulopustular rash			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Other (tonsillitis)			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Metabolism and nutrition disorders			
Hyperkalemia			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Hypermagnesemia			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Hypoalbuminemia			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Hypomagnesemia			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Hyponatremia			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported