Clinical trial results:
Neoadjuvant BIBW 2992 followed by surgery in squamous cell carcinoma of the head and neck: an EORTC NOCI-HNCG window study.

Summary

EudraCT number	2011-005820-17
Trial protocol	BE IT
Global end of trial date	28 April 2016

Results information

Result version number	v1 (current)
This version publication date	15 July 2017
First version publication date	15 July 2017

Trial information

Trial identification

Sponsor protocol code	90111-24111

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01538381
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	European Organisation for Research and Treatment of Cancer
Sponsor organisation address	Avenue E. Mounier 83/11, Brussels, Belgium, 1200
Public contact	Project, Budget and Regulatory Dept, European Organisation for Research and Treatment of Cancer, +32 27741062, regulatory@eortc.be
Scientific contact	Project, Budget and Regulatory Dept, European Organisation for Research and Treatment of Cancer, +32 27741062, regulatory@eortc.be

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	28 April 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	05 August 2015
Global end of trial reached?	Yes
Global end of trial date	28 April 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The general objectives are to evaluate the pre-operative activity and the safety of afatinib in head and neck cancer and to explore the different downstream molecular pathways to identify tumor response and resistance mechanisms.
The primary objective is to evaluate the pre operative activity of afatinib as assessed by Fluorodeoxyglucose – Positron emission tomography/Computed tomography (FDG-PET/CT).

Protection of trial subjects:

The responsible investigator has ensured that this study has been conducted in agreement with either the Declaration of Helsinki (available on the World Medical Association web site (http://www.wma.net)) and/or the laws and regulations of the country, whichever provides the greatest protection of the patient.
The protocol has been written, and the study has been conducted according to the ICH Harmonized Tripartite Guideline on Good Clinical Practice (ICH-GCP, available online at http://www.ema.europa.eu/pdfs/human/ich/013595en.pdf).
The protocol has been approved by the competent ethics committee(s) as required by the applicable national legislation.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	15 March 2012
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	Italy: 13
Country: Number of subjects enrolled	Belgium: 17
Worldwide total number of subjects	30
EEA total number of subjects	30

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)	19
From 65 to 84 years	11
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

A total of 36 patients were screened. A total of 30 patients were randomized, however 3 of them were later found to not meet all eligibility criteria. In addition, one patient started afatinib treatment without going through the randomization procedure.

Pre-assignment

Screening details:

- Newly diagnosed histologically proven squamous cell carcinoma of the oral cavity, oropharynx, hypopharynx or larynx
- T3 -T4 hypopharyngeal SCCHN excluded
- Selected for a primary surgical treatment
- No distant metastases
- No prior chemotherapy, radiotherapy or targeted therapy including HER inhibitors

Period 1

Period 1 title	Randomization (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Afatinib

Arm description: -

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

Dosage and administration details:

40mg orally once daily from day -15 until day -1 prior to surgery

Arm title	No treatment

Arm description: -

Arm type	No intervention

No investigational medicinal product assigned in this arm

Number of subjects in period 1	Afatinib	No treatment
Started	25	5
Completed	24	5
Not completed	1	0
Adverse event, non-fatal	1	-

Baseline characteristics

Reporting groups	
Reporting group title	Afatinib
Reporting group description: -	
Reporting group title	No treatment
Reporting group description: -	

Reporting group values	Afatinib	No treatment	Total
Number of subjects	25	5	30
Age categorical Units: Subjects			
In utero			0
Preterm newborn infants (gestational age < 37 wks)			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)			0
From 65-84 years			0
85 years and over			0
Age continuous Units: years			
median	58	69	
full range (min-max)	35 to 76	55 to 77	-
Gender categorical Units: Subjects			
Female	9	3	12
Male	16	2	18
Tumor location Units: Subjects			
Oral cavity	20	5	25
Oropharynx	5	0	5
cT Units: Subjects			
T1	2	0	2
T2	14	3	17
T3	2	0	2
T4	7	2	9
cN Units: Subjects			
N0	10	0	10
N1	5	2	7
N2	10	3	13
ECOG Performance Status Units: Subjects			
PS 0	17	2	19

PS 1	8	3	11

Subject analysis sets	
Subject analysis set title	Evaluable population
Subject analysis set type	Per protocol
Subject analysis set description:	
Evaluable population: All randomized and eligible patients	
Subject analysis set title	Safety population
Subject analysis set type	Safety analysis
Subject analysis set description:	
Safety population: All randomized patients. For the afatinib arm, the safety population is restricted to the patients who took at least one dose of afatinib.	

Reporting group values	Evaluable population	Safety population	
Number of subjects	27	30	
Age categorical Units: Subjects			
In utero Preterm newborn infants (gestational age < 37 wks) Newborns (0-27 days) Infants and toddlers (28 days-23 months) Children (2-11 years) Adolescents (12-17 years) Adults (18-64 years) From 65-84 years 85 years and over			
Age continuous Units: years			
median	59		
full range (min-max)	35 to 77		
Gender categorical Units: Subjects			
Female	10		
Male	17		
Tumor location Units: Subjects			
Oral cavity	23		
Oropharynx	4		
cT Units: Subjects			
T1	1		
T2	15		
T3	2		
T4	9		
cN Units: Subjects			
N0	8		

N1	6		
N2	13		
ECOG Performance Status Units: Subjects			
PS 0	16		
PS 1	11		

End points

End points reporting groups

Reporting group title	Afatinib
Reporting group description: -	
Reporting group title	No treatment
Reporting group description: -	
Subject analysis set title	Evaluable population
Subject analysis set type	Per protocol
Subject analysis set description:	
Evaluable population: All randomized and eligible patients	
Subject analysis set title	Safety population
Subject analysis set type	Safety analysis
Subject analysis set description:	
Safety population: All randomized patients. For the afatinib arm, the safety population is restricted to the patients who took at least one dose of afatinib.	

Primary: Metabolic response according to FDG-PET/CT

End point title	Metabolic response according to FDG-PET/CT
End point description:	
Metabolic response measured at day -1 as per FDG-PET/CT, defined as complete metabolic response (CMR) or partial metabolic response (PMR). Centrally reviewed.	
End point type	Primary
End point timeframe:	
Metabolic response measured at day -1 (day before surgery).	

End point values	Afatinib	No treatment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	23[1]	4[2]		
Units: Percent				
Complete/partial	16	0		
Stable disease	7	3		
Missing	0	1		

Notes:

[1] - Excluding ineligible patients

[2] - Excluding ineligible patients

Statistical analyses

Statistical analysis title	FDG-PET/CT response in afatinib arm
Comparison groups	No treatment v Afatinib

Number of subjects included in analysis	27
Analysis specification	Pre-specified
Analysis type	other[3]
P-value	< 0.0001
Method	Test on a single proportion
Parameter estimate	Estimated proportion
Point estimate	69.6
Confidence interval	
level	90 %
sides	1-sided
lower limit	54.1

Notes:

[3] - Test H0: response rate < 10% in afatinib arm (23 patients)

Secondary: Response according to RECIST 1.1

End point title	Response according to RECIST 1.1

End point description:

Response measured at day -1 evaluated by RECIST v1.1 (FDG-PET/CT, MRI)

End point type	Secondary

End point timeframe:

Measured at day -1 (day before surgery)

End point values	Afatinib	No treatment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	23[4]	4[5]		
Units: Percent				
Complete/partial	5	0		
Stable disease	14	2		
Missing	4	2		

Notes:

[4] - Excluding ineligible patients

[5] - Excluding ineligible patients

Statistical analyses

Statistical analysis title	RECIST response in afatinib arm
Comparison groups	Afatinib v No treatment
Number of subjects included in analysis	27
Analysis specification	Pre-specified
Analysis type	other[6]
P-value	= 0.073
Method	Test on a single proportion
Parameter estimate	Estimated proportion
Point estimate	21.7

Confidence interval	
level	90 %
sides	1-sided
lower limit	11

Notes:

[6] - Test H0: response rate < 10% in afatinib arm (23 patients)

Secondary: Surgical comorbidities

End point title	Surgical comorbidities

End point description:

Number of patients with Max grade of surgical co-morbidities

End point type	Secondary

End point timeframe:

Surgical co-morbidities evaluated up to 4 weeks after surgery

End point values	Afatinib	No treatment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	25	5		
Units: Number of patients				
Grade 1	1	1		
Grade 2	2	0		
Grade 3	1	0		
No surgical co-morbidity	21	4		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events were collected on a CRF during the 2-week period between randomization and surgery and during follow-up of 4 weeks after surgery.

Adverse event reporting additional description:

CRF for AEs contains pre-specified items + additional boxes for all "other" AEs. AEs are evaluated using CTC grading, SAEs using MedDRA. Non-SAEs has not been collected specifically, all CTC grade>=3 AEs are reported in non-SAE section.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	19

Reporting groups

Reporting group title	Afatinib

Reporting group description: -

Reporting group title	No treatment

Reporting group description:

No treatment.

Serious adverse events	Afatinib	No treatment	
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 25 (12.00%)	0 / 5 (0.00%)	
number of deaths (all causes)	2	0	
number of deaths resulting from adverse events	0	0	
Investigations			
Blood creatinine increased			
alternative dictionary used: MedDRA 19			
subjects affected / exposed	1 / 25 (4.00%)	0 / 5 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Colitis			
alternative dictionary used: MedDRA 19			
subjects affected / exposed	1 / 25 (4.00%)	0 / 5 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
alternative dictionary used: MedDRA 19			

subjects affected / exposed	1 / 25 (4.00%)	0 / 5 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal necrosis			
alternative dictionary used: MedDRA 19			
subjects affected / exposed	1 / 25 (4.00%)	0 / 5 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal ischaemia			
alternative dictionary used: MedDRA 19			
subjects affected / exposed	1 / 25 (4.00%)	0 / 5 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis acute			
alternative dictionary used: MedDRA 19			
subjects affected / exposed	1 / 25 (4.00%)	0 / 5 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Renal failure			
alternative dictionary used: MedDRA 19			
subjects affected / exposed	1 / 25 (4.00%)	0 / 5 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Sepsis			
alternative dictionary used: MedDRA 19			
subjects affected / exposed	1 / 25 (4.00%)	0 / 5 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Afatinib	No treatment	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	5 / 25 (20.00%)	1 / 5 (20.00%)	
Investigations			
GGT			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	2 / 25 (8.00%)	0 / 5 (0.00%)	
occurrences (all)	4	0	
Lymphocytes			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	0 / 25 (0.00%)	1 / 5 (20.00%)	
occurrences (all)	0	1	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Tumor pain			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	1 / 25 (4.00%)	0 / 5 (0.00%)	
occurrences (all)	1	0	
Blood and lymphatic system disorders			
Hemoglobin			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	1 / 25 (4.00%)	0 / 5 (0.00%)	
occurrences (all)	1	0	
Gastrointestinal disorders			
Abdominal pain			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	1 / 25 (4.00%)	0 / 5 (0.00%)	
occurrences (all)	1	0	
Acute pancreatitis			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	1 / 25 (4.00%)	0 / 5 (0.00%)	
occurrences (all)	1	0	
Diarrhea			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	1 / 25 (4.00%)	0 / 5 (0.00%)	
occurrences (all)	1	0	
Dysphagia			

alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	1 / 25 (4.00%)	0 / 5 (0.00%)	
occurrences (all)	1	0	
Intestinal necrosis			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	1 / 25 (4.00%)	0 / 5 (0.00%)	
occurrences (all)	1	0	
Mesenteric ischemia			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	1 / 25 (4.00%)	0 / 5 (0.00%)	
occurrences (all)	1	0	
Skin and subcutaneous tissue disorders			
Rash acneiform			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	1 / 25 (4.00%)	0 / 5 (0.00%)	
occurrences (all)	1	0	
Renal and urinary disorders			
Acute renal failure			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	1 / 25 (4.00%)	0 / 5 (0.00%)	
occurrences (all)	1	0	
Infections and infestations			
Sepsis			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	1 / 25 (4.00%)	0 / 5 (0.00%)	
occurrences (all)	1	0	
Upper respiratory infection			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	1 / 25 (4.00%)	0 / 5 (0.00%)	
occurrences (all)	1	0	
Metabolism and nutrition disorders			
Anorexia			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	1 / 25 (4.00%)	0 / 5 (0.00%)	
occurrences (all)	1	0	
Hypercalcemia			

alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	1 / 25 (4.00%)	0 / 5 (0.00%)	
occurrences (all)	1	0	
K+			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	1 / 25 (4.00%)	0 / 5 (0.00%)	
occurrences (all)	1	0	
Phosphate			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	1 / 25 (4.00%)	0 / 5 (0.00%)	
occurrences (all)	1	0	

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