Clinical trial results:
Dual blockage with Afatinib and Trastuzumab as neooadjuvant treatment for patients with lo-cally advanced or operable breast cancer receiving taxane-anthracycline containing chemo-therapy (DAFNE study).

Summary

EudraCT number	2011-004704-38
Trial protocol	DE
Global end of trial date	19 February 2014

Results information

Result version number	v1 (current)
This version publication date	14 September 2022
First version publication date	14 September 2022
Summary attachment (see zip file)	CSR Synopsis (GBG 70 - DAFNE Clinical Study Report Synopsis - Version 1 (25.09.2014).pdf)

Trial information

Trial identification

Sponsor protocol code	GBG70

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01594177
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	GBG Forschungs GmbH
Sponsor organisation address	Martin-Behaim-Straße 12, Neu-Isenburg, Germany, 63263
Public contact	Medicine & Research, GBG Forschungs GmbH, +49 610274800, publications@gbg.de
Scientific contact	Medicine & Research, GBG Forschungs GmbH, +49 610274800, publications@gbg.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	25 September 2014
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	19 February 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To determine the pathological complete response (pCR=ypT0/is ypN0) rates of neoadjuvant treatment of afatinib in combination with weekly paclitaxel + trastuzumab followed by epirubicin/cyclophosphamide/trastuzumab in patients with HER2-positive primary breast cancer.

Protection of trial subjects:

The trial protocol including amendments, the patient information and the informed consent were reviewed and approved from a properly constituted IRB/IEC for each site prior to the study start. The trial was in compliance with the International Conference on Harmonization (ICH) - Harmonized Tripartite Guideline for Good Clinical Practice (GCP) (E6), and the Commission Directives in the European Community as well as with the applicable German national laws and regulations, and with Declaration of Helsinki and its revisions in all aspects of preparation, monitoring, reporting, auditing, and archiving.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 February 2012
Long term follow-up planned	Yes
Long term follow-up rationale	Scientific research
Long term follow-up duration	10 Years
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Germany: 65
Worldwide total number of subjects	65
EEA total number of subjects	65

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)	53
From 65 to 84 years	12
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Date of the first patient enrolled: May 31st, 2012
Date of the last patient completed: February 19th, 2014
The study was conducted at 11 sites in Germany
Overall, 79 patients were screened, 65 started treatment, 47 received the planned treatment and 63 underwent surgery.

Pre-assignment

Screening details:

Patients with previously untreated, unilateral, nonmetastatic, histologically confirmed invasive breast cancer; tumors either 2 cm or bigger based on clinical or ultrasound assessment or diagnosed as inflammatory breast cancer; centrally confirmed HER2-positive status.

Period 1

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

Arms

Arm title	afatinib

Arm description:

All patients were treated for a total duration of 30 weeks (6 weeks with afatinib and trastuzumab alone, 12 weeks with weekly paclitaxel, afatinib (-1 week) and trastuzumab and 12 weeks with epirubicin/ cyclophosphamide/trastuzumab.

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

Dosage and administration details:

20 mg oral (daily).
17 weeks (daily; first two weeks: every second day).

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

Dosage and administration details:

600 mg/ m2 i.v.
12 weeks (4 cycles 1 q 22).

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

Dosage and administration details:

90 mg/m2 i.v.
12 weeks (4 cycles 1 q 22).

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

Dosage and administration details:

80 mg/m2 i.v.
12 weeks (weekly).

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

Dosage and administration details:

Loading dose 8 mg/kg body weight i.v., thereafter 6 mg/kg body weight i.v.
30 weeks (10 cycles 1 q 22).

Number of subjects in period 1	afatinib
Started	65
Completed	47
Not completed	18
Physician decision	1
Consent withdrawn by subject	2
Adverse event, non-fatal	5
Progressive disease	1
Discontinued one study treatment but next treatmen	9

Baseline characteristics

Reporting groups	
Reporting group title	Overall trial
Reporting group description:	
HER2-positive breast cancer patients were treated for 6 weeks with afatinib and trastuzumab, followed by 12-week treatment with paclitaxel (80 mg/m2), trastuzumab, and afatinib, followed by 12 weeks with epirubicin , cyclophosphamide, and trastuzumab before surgery.	

Reporting group values	Overall trial	Total	
Number of subjects	65	65	
Age categorical			
Units: Subjects			
Adults (18-64 years)	59	59	
From 65-84 years	6	6	
85 years and over	0	0	
Age continuous			
Units: years			
median	50		
full range (min-max)	29 to 73	-	
Gender categorical			
Onyl women were allowed for this trial			
Units: Subjects			
Female	65	65	
Male	0	0	

End points

End points reporting groups

Reporting group title	afatinib

Reporting group description:

All patients were treated for a total duration of 30 weeks (6 weeks with afatinib and trastuzumab alone, 12 weeks with weekly paclitaxel, afatinib (-1 week) and trastuzumab and 12 weeks with epirubicin/ cyclophosphamide/trastuzumab.

Primary: pCR (ypT0/is ypN0)

End point title	pCR (ypT0/is ypN0)[1]

End point description:

Pathological complete response rates: no microscopic evidence of residual viable tumour cells (invasive or noninvasive) in any resected specimens of the breast and axillary nodes (ypT0/is ypN0). Pathological response was assessed considering all removed breast and lymphatic tissues from all surgeries.
The analysis of the primary endpoint of the study was performed using the mITT. A two-sided one group χ2-test was performed to exclude the pCR rate of 55% or lower. Two-sided 90% confidence intervals were calculated according to Pearson and Clopper.

End point type	Primary

End point timeframe:

30 weeks

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: The Dafne study was designed as a single arm study, therefore no comparison was available. We expected a pCR rate of 70% and wanted to exclude a pCR rate of 55% or lower with α=0.1 and 1-ß=80%, this required 65 evaluable patients for two-sided one group χ2-test

End point values	afatinib			
Subject group type	Reporting group			
Number of subjects analysed	65			
Units: percent				
number (confidence interval 90%)				
pCR	49.2 (38.5 to 60.1)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Overall trial

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	nk

Reporting groups

Reporting group title	afatinib

Reporting group description:

All patients were treated for a total duration of 30 weeks (6 weeks with afatinib and trastuzumab alone, 12 weeks with weekly paclitaxel, afatinib (-1 week) and trastuzumab and 12 weeks with epirubicin/ cyclophosphamide/trastuzumab.

Serious adverse events	afatinib		
Total subjects affected by serious adverse events			
subjects affected / exposed	22 / 65 (33.85%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Vascular disorders			
Thrombophlebitis			
subjects affected / exposed	1 / 65 (1.54%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Ischaemic stroke			
subjects affected / exposed	1 / 65 (1.54%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vertebral artery dissection			
subjects affected / exposed	1 / 65 (1.54%)		
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	2 / 65 (3.08%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Leukopenia				
subjects affected / exposed	1 / 65 (1.54%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Neutropenia				
subjects affected / exposed	1 / 65 (1.54%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
General disorders and administration site conditions				
Fever				
subjects affected / exposed	1 / 65 (1.54%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal disorders				
Diarrhoea				
subjects affected / exposed	3 / 65 (4.62%)			
occurrences causally related to treatment / all	1 / 3			
deaths causally related to treatment / all	0 / 0			
Gastric ulcer perforation				
subjects affected / exposed	1 / 65 (1.54%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Vomiting				
subjects affected / exposed	1 / 65 (1.54%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Gastritis				
subjects affected / exposed	1 / 65 (1.54%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			

Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	1 / 65 (1.54%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Panic attack			
subjects affected / exposed	1 / 65 (1.54%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Renal failure			
subjects affected / exposed	2 / 65 (3.08%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
cold			
subjects affected / exposed	1 / 65 (1.54%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Erysipelas			
subjects affected / exposed	1 / 65 (1.54%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Otitis			
subjects affected / exposed	1 / 65 (1.54%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Hyponatremia			
subjects affected / exposed	1 / 65 (1.54%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	afatinib		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	65 / 65 (100.00%)		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	59 / 65 (90.77%)		
occurrences (all)	59		
Leukopenia			
subjects affected / exposed	54 / 65 (83.08%)		
occurrences (all)	54		
Neutropenia			
subjects affected / exposed	49 / 65 (75.38%)		
occurrences (all)	49		
Thrombopenia			
subjects affected / exposed	7 / 65 (10.77%)		
occurrences (all)	7		
Increased bilirubin			
subjects affected / exposed	10 / 65 (15.38%)		
occurrences (all)	10		
Increased AP			
subjects affected / exposed	14 / 65 (21.54%)		
occurrences (all)	14		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
02 October 2012	There was one protocol amendment with the following addition regarding the afatinib intake in chapter 8.1.1.2 Precautions in order to avoid reduced drug absorption and exposure in study patients: Afatinib should be taken without food (i.e. food should not be consumed for at least three hours before and at least one hour after taking afatinib).

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/25825476

http://www.ncbi.nlm.nih.gov/pubmed/27587600