Clinical trial results:
Randomized comparison of adjuvant Docetaxel / Cyclophosphamide with sequential adjuvant EC / Docetaxel chemotherapy in patients with HER2/neu negative early breast cancer – 6 x TC vs. 4 x EC -> 4 x Doc

Summary

EudraCT number	2008-004263-19
Trial protocol	DE
Global end of trial date	01 March 2017
Results information	
Result version number	v1 (current)
This version publication date	22 March 2020
First version publication date	22 March 2020
Summary attachment (see zip file)	PlanB - Clinical Study Report (PlanB_Clinical Study Report_20181218.pdf)

Trial information

Trial identification	
Sponsor protocol code	WSGAM04
Additional study identifiers	
ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01049425
WHO universal trial number (UTN)	-

Notes:

Sponsors	
Sponsor organisation name	Westdeutsche Studiengruppe
Sponsor organisation address	Wallstraße 10, Mönchengladbach, Germany,
Public contact	Studienzentrale, Westdeutsche Studiengruppe, 0049 2161566230, wsg@wsg-online.com
Scientific contact	Studienzentrale, Westdeutsche Studiengruppe, 0049 2161566230, wsg@wsg-online.com

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 May 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	01 March 2017
Global end of trial reached?	Yes
Global end of trial date	01 March 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Compare event-free survival in patients treated with either 6 cycles of Docetaxel / Cyclophosphamide chemotherapy or 4 cycles of EC followed by 4 cycles of Docetaxel as adjuvant treatment.

Protection of trial subjects:

Dose delay and dose adjustment in case of severe or unacceptable toxicity.
Patients with hormone sensitive disease (estrogen and/or progesterone receptor positive) will receive antihormonal therapy according to national standards as defined by AGO guidelines.
Supportive Treatment: Dexamethasone according to SmPC docetaxel
G-CSF according to AGO guidelines to avoid dose delay and dose adjustment due to febrile neutropenia and infection. It is highly recommended to use Neulasta® as G-CSF treatment.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	05 February 2009
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	Germany: 2449
Worldwide total number of subjects	2449
EEA total number of subjects	2449

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)	1850

From 65 to 84 years	599
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

From 2009 to 2011, 3198 patients were registered in 90 German sites. The intent-to-treat population included 2,449 patients (EC-T/TC).

Pre-assignment

Screening details:

HER2/neu negative eartly breast cancer;
The following patients will be randomised to receive chemotherapy within the planB trial:

- Patients with HR positive disease and either RS>11 and 0-3 positive nodes
- Patients with HR positive disease and 4 or more positive nodes regardless of RS
- Patients with HR negative disease

Pre-assignment period milestones

Number of subjects started	2449
Number of subjects completed	2449

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Docetaxel - Cyclophosphamide TC)

Arm description:

TC Treatment will consist of 6 cycles of docetaxel and cyclophosphamid. Docetaxel will be given first 75 mg/m² at day 1 q3w. Followed by Cyclophosphamid 600 mg/m² at day 1 q3w.

Arm type	Active comparator
Investigational medicinal product name	Docetaxel
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate and solvent for solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

75 mg/m² on day 1 q3w for 6 cycles

Investigational medicinal product name	Cyclophosphamid
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for concentrate and solution for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

600 mg/m² on day 1 q3w for 6 cycles

Arm title	EC --> DOC (EC-DOC)

Arm description:

EC treatment will consist of 4 cycles of epirubicin and cyclophosphamide. Patients will receive 4 cycles of adjuvant therapy; each cycle will last for 3 weeks. The duration of the study treatment during adjuvant therapy is 12 weeks from cycle 1 to 4.

Following completion of 4 cycles, the patient will enter the docetaxel segment for this arm of treatment. Patients will receive 4 cycles of adjuvant therapy; each cycle will last for 3 weeks. The duration of the study treatment during adjuvant therapy is 12 weeks from cycle 1 to 4.

Arm type	Active comparator
Investigational medicinal product name	Epirubicin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for solution for injection
Routes of administration	Intravenous use
Dosage and administration details: 90 mg/m² on day 1 q3w for 4 cycles	
Investigational medicinal product name	Cyclophosphamide
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for infusion
Routes of administration	Intravenous use
Dosage and administration details: 600 mg/m² on day 1 q3w for 4 cycles	
Investigational medicinal product name	Docetaxel
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for concentrate for solution for infusion
Routes of administration	Intravenous use
Dosage and administration details: Three weeks after the last cycle of Epirubicine/Cyclophosphamide, Docetaxel will be given 100 mg/m² on day 1 q3w for additional 4 cycles.	

Number of subjects in period 1	Docetaxel - Cyclophosphamide TC)	EC --> DOC (EC-DOC)
Started	1222	1227
Completed	1217	1226
Not completed	5	1
Adverse event, serious fatal	5	1

Baseline characteristics

Reporting groups

Reporting group title	Overall Trial

Reporting group description: -

Reporting group values	Overall Trial	Total	
Number of subjects	2449	2449	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	1850	1850	
From 65-84 years	599	599	
85 years and over	0	0	
Age continuous Units: years			
median	55		
full range (min-max)	25 to 77	-	
Gender categorical Units: Subjects			
Female	2449	2449	
Male	0	0	

Subject analysis sets

Subject analysis set title	IIT population
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Among patients treated with ECDoc in the NSABP B27 trial, 71.1 % of patients were disease-free at 5 years. In this study, an accrual period of 3 years and an additionally follow up of 5 years will be planed. The one–sided equivalence test will be done at the significance levels of false positive outcome = 5 % and false negative outcome = 20 % i.e. the power of the trial is set to 80 % for the difference of clinical interest. The study treatment will be regarded as equivalent to the reference treatment, if the difference in the 5 years disease-free survival between both study arms will not be greater as 4.4 %.
A total of 2x1224 = 2448 patients are necessary to have sufficient power to show equivalence between ECDoc and TC for all randomised patients, assuming an anticipated drop-out rate of 10 %.

Reporting group values	IIT population		
Number of subjects	2449		
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)	1850		
From 65-84 years	599		
85 years and over	0		
Age continuous			
Units: years			
median	55		
full range (min-max)	25 to 77		
Gender categorical			
Units: Subjects			
Female	2449		
Male	0		

End points

End points reporting groups

Reporting group title	Docetaxel - Cyclophosphamide TC)

Reporting group description:

TC Treatment will consist of 6 cycles of docetaxel and cyclophosphamid. Docetaxel will be given first 75 mg/m² at day 1 q3w. Followed by Cyclophosphamid 600 mg/m² at day 1 q3w.

Reporting group title	EC --> DOC (EC-DOC)

Reporting group description:

EC treatment will consist of 4 cycles of epirubicin and cyclophosphamide. Patients will receive 4 cycles of adjuvant therapy; each cycle will last for 3 weeks. The duration of the study treatment during adjuvant therapy is 12 weeks from cycle 1 to 4.

Following completion of 4 cycles, the patient will enter the docetaxel segment for this arm of treatment. Patients will receive 4 cycles of adjuvant therapy; each cycle will last for 3 weeks. The duration of the study treatment during adjuvant therapy is 12 weeks from cycle 1 to 4.

Subject analysis set title	IIT population
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Among patients treated with ECDoc in the NSABP B27 trial, 71.1 % of patients were disease-free at 5 years. In this study, an accrual period of 3 years and an additionally follow up of 5 years will be planed. The one–sided equivalence test will be done at the significance levels of false positive outcome = 5 % and false negative outcome = 20 % i.e. the power of the trial is set to 80 % for the difference of clinical interest. The study treatment will be regarded as equivalent to the reference treatment, if the difference in the 5 years disease-free survival between both study arms will not be greater as 4.4 %.
A total of 2x1224 = 2448 patients are necessary to have sufficient power to show equivalence between ECDoc and TC for all randomised patients, assuming an anticipated drop-out rate of 10 %.

Primary: 5 year disease-free survival

End point title	5 year disease-free survival

End point description:

End point type	Primary

End point timeframe:

date of randomization to the date of local, regional or metastaic relapse or the date of second Primary Cancer or death

End point values	Docetaxel - Cyclophosphamide TC)	EC --> DOC (EC-DOC)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1222	1227		
Units: yes vs no				
number (confidence interval 95%)	89.6 (87.8 to 91.5)	89.8 (87.9 to 91.6)		

Statistical analyses

Statistical analysis title	Statistics PlanB
Comparison groups	Docetaxel - Cyclophosphamide TC) v EC --> DOC (EC-DOC)
Number of subjects included in analysis	2449
Analysis specification	Pre-specified
Analysis type	equivalence[1]
P-value	= 0.05
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	0.8
Confidence interval	
level	95 %
sides	1-sided
lower limit	0.044
Variability estimate	Standard deviation
Dispersion value	0.1

Notes:

[1] - one-size equivalence test

Secondary: Overall Survival

End point title	Overall Survival

End point description:

End point type	Secondary

End point timeframe:

time from randomization until survial after 5 year follow-up

End point values	Docetaxel - Cyclophosphamide TC)	EC --> DOC (EC-DOC)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1222	1227		
Units: number	1149	1104		

Statistical analyses

No statistical analyses for this end point

Secondary: Safety - Dose reduction

End point title	Safety - Dose reduction

End point description:

End point type	Secondary

End point timeframe:

number of Patient with dose reduction during chemotherapy

End point values	Docetaxel - Cyclophosphamide TC)	EC --> DOC (EC-DOC)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1222	1227		
Units: number	78	230		

Statistical analyses

No statistical analyses for this end point

Secondary: Safety - Dose delay

End point title	Safety - Dose delay

End point description:

End point type	Secondary

End point timeframe:

dose delay more than 7 days during chemotherapy

End point values	Docetaxel - Cyclophosphamide TC)	EC --> DOC (EC-DOC)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1222	1227		
Units: number	47	78		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information[1]	
Timeframe for reporting adverse events: from time of ranomization until end of 5 year follow-up	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	18

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

Notes:

[1] - There are no non-serious adverse events recorded for these results. It is expected that there will be at least one non-serious adverse event reported.
Justification: Such a detailed statistical evaluation of AE results was not done. For further AE evaluation please refer to the attached Clinical Study Report.

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
22 June 2009	new protocol Version V2.0
24 May 2011	new protocol Version 3.0 and Patient Information sheet Version 3.0

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported