Clinical trial results:
TRastuzumab in HER2-negative Early breast cancer as Adjuvant Treatment for Circulating Tumor Cells (CTC) ("Treat CTC" trial)

Summary

EudraCT number	2009-017485-23
Trial protocol	BE FR GB DE GR AT
Global end of trial date	22 August 2018

Results information

Result version number	v1 (current)
This version publication date	07 September 2019
First version publication date	07 September 2019

Trial information

Trial identification

Sponsor protocol code	EORTC 90091-10093

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01548677
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	EORTC
Sponsor organisation address	Avenue E Mounier 83/11, Brussels, Belgium, 1200
Public contact	Regulatory department, EORTC, +32 27741613, regulatory@eortc.be
Scientific contact	Regulatory department, EORTC, +32 27741613, 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	13 April 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	03 April 2017
Global end of trial reached?	Yes
Global end of trial date	22 August 2018
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

To evaluate whether trastuzumab decreases the detection rate of CTC in patients with HER2-negative primary BC by comparing the trastuzumab treated arm to the observation arm.

Protection of trial subjects:

The responsible investigator ensured that this study was 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 had been written, and the study was 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 was approved by the competent ethics committee(s) as required by the applicable national legislation.

Background therapy:

Not applicable

Evidence for comparator:

Subjects with HER2-negative early BC still relapse and die from BC despite optimal locoregional treatment (surgery and radiotherapy if indicated) and optimal systemic treatment (adjuvant chemotherapy and / or hormonal therapy). Relapse is considered to be due to the micrometastatic cells that are undetectable by the classical imaging and laboratory studies (minimal residual disease) after completing standard locoregional and systemic treatment. Circulating Tumor Cells (CTC) are considered as a surrogate marker of minimal residual disease.
Detection of CTC before or after the administration of adjuvant chemotherapy has been suggested to be a prognostic factor associated with poor clinical outcome in early BC subjects treated with adjuvant chemotherapy with or without hormonotherapy. The above studies suggest that adjuvant chemotherapy with or without hormonotherapy may not eradicate CTC.
In a small pilot study, a short course of trastuzumab eliminated peripheral blood CK19mRNA and HER2mRNA in 2/3 subjects with BC.
A subset analysis of the NSABP B-31 trial suggests that benefit from adjuvant trastuzumab may not be confined to subjects with IHC3+ or FISH-positive primary tumors.
Since currently it is not known how many HER2 receptors per tumor cell are necessary to elicit an immune response by trastuzumab, in the "Treat CTC study", we hypothesize that patients with HER2-negative non-metastatic BC and detectable CTC (irrespective of HER2 overexpression), may benefit from trastuzumab through immune related clearance of minimal residual disease.

Actual start date of recruitment	15 March 2013
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	United Kingdom: 1
Country: Number of subjects enrolled	Austria: 10

Country: Number of subjects enrolled	Belgium: 220
Country: Number of subjects enrolled	France: 505
Country: Number of subjects enrolled	Germany: 581
Worldwide total number of subjects	1317
EEA total number of subjects	1317

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)	1122
From 65 to 84 years	195
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The first patient was screened on April 30, 2013. On October 17, 2016, when accrual to the study was closed, 1317 patients were registered in the study by 70 sites in 5 countries.
Of the 1317 patients who were screened and registered, 63 (4.8%) were randomized.

Pre-assignment

Screening details:

Age ≥ 18 years
≥ 1 CTC/15mL of blood by CellSearch® by the national lab and CTC image confirmed by at least two other central labs
Centrally confirmed HER2-negative primary BC. A HER2-negative primary BC sample eligible for randomization should have HER2 IHC scores of 0 or 1+ or 2+ AND should be HER2 FISH negative in central testing

Pre-assignment period milestones

Number of subjects started	1317
Number of subjects completed	63

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Ineligible at randomization: 1244
Reason: Number of subjects	Consent withdrawn by subject: 10

Period 1

Period 1 title	Post-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	Observation

Arm description:

Wait and see

Arm type	No intervention

No investigational medicinal product assigned in this arm

Arm title	Trastuzumab

Arm description:

Trastuzumab

Arm type	Experimental
Investigational medicinal product name	Trastuzumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

Patients in the trastuzumab arm will receive 8 mg/kg of loading dose IV over 90 minutes for the first cycle (week 0), followed by 6 mg/kg IV over 30 minutes every 3 weeks (weeks 3, 6, 9, 12, 15) for the 5 subsequent cycles, if the initial dose was well tolerated.

Number of subjects in period 1[1]	Observation	Trastuzumab
Started	32	31
Completed	28	27
Not completed	4	4
Adverse event, serious fatal	-	1
Patient decision	1	-
Progressive disease	2	3
Protocol deviation	1	-

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: The worldwide number of patients enrolled refers to the number of patients in the pre-assignment period who were screened before entering the study.
Only the patients who were enrolled/randomized contribute to the baseline period.

Baseline characteristics

Reporting groups	
Reporting group title	Observation
Reporting group description: Wait and see	
Reporting group title	Trastuzumab
Reporting group description: Trastuzumab	

Reporting group values	Observation	Trastuzumab	Total
Number of subjects	32	31	63
Age categorical Units: Subjects			
Adults (18-64 years)	28	26	54
From 65-84 years	4	5	9
Gender categorical Units: Subjects			
Female	32	31	63
Male	0	0	0
ER status			
Stratification factor			
Units: Subjects			
Positive	21	21	42
Negative	11	10	21
Chemotherapy setting			
Chemotherapy setting prior to randomization: stratification factor			
Units: Subjects			
Neo-adjuvant	14	17	31
Adjuvant, node positive	17	14	31
Adjuvant, node negative	1	0	1
Performance status			
WHO Performance status			
Units: Subjects			
PS 0	25	25	50
PS 1	7	6	13
Synchronous breast cancer Units: Subjects			
Unifocal unilateral	24	22	46
Multifocal unilateral	4	4	8
Unknown	4	5	9
Tumor histology Units: Subjects			
Ductal	20	18	38
Lobular	5	8	13
Mixed	1	2	3
Other	4	3	7
Unknown	2	0	2

Tumor grade Units: Subjects			
Well differentiated	2	0	2
Moderately differentiated	17	12	29
Poorly differentiated	10	18	28
Undifferentiated	1	0	1
Unknown	2	1	3
Pathological tumor size Units: mm			
median	24	25	
full range (min-max)	4 to 840	7 to 180	-

End points

End points reporting groups	
Reporting group title	Observation
Reporting group description: Wait and see	
Reporting group title	Trastuzumab
Reporting group description: Trastuzumab	

Primary: Central review of CTC test at week 18	
End point title	Central review of CTC test at week 18
End point description: - CTC Blood Test: A blood test (2 x 7.5 mL) for the detection of peripheral blood nucleated cell lacking CD45, expressing cytokeratin 8,18,19 - Evaluable CTC Blood Test (see chapter 10.3.1): The blood (total 15 mL) has been successfully processed from a technical point of view and a negative or positive result can be delivered. At least 1 of the 2 tubes needs to have an evaluable test result - CTC Blood Test positive: at least 1 CTC / 15mL of peripheral blood analyzed - CTC Blood Test negative: No CTC / 15 mL of peripheral blood analyzed - The positive CTC Blood Test will be centrally reviewed based on images.	
End point type	Primary
End point timeframe: Test at week 18	

End point values	Observation	Trastuzumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	32	31		
Units: Subjects				
Positive	4	5		
Negative	25	24		
Missing (no blood sample)	3	2		

Statistical analyses

Statistical analysis title	Primary analysis
Statistical analysis description: The comparison for the primary endpoint will be performed on the per protocol population (patients as randomized with evaluable test at week 18) using a one-sided test with overall alpha of 0.1. The odds ratio and its confidence interval will be estimated using a logistic regression model.	
Comparison groups	Observation v Trastuzumab

Number of subjects included in analysis	63
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.765 [1]
Method	Fisher exact
Parameter estimate	Odds ratio (OR)
Point estimate	1.3
Confidence interval	
level	90 %
sides	1-sided
upper limit	3.32

Notes:

[1] - Note that the conditional power, given the current observed data, to obtain statistical significance at the end of the study (as designed) is 0.493.

Statistical analysis title	Primary analysis - sensitivity analysis

Statistical analysis description:

A sensitivity analysis of the primary test was planned per protocol considering patients who went off treatment without an evaluable CTC blood test performed at treatment discontinuation as having an event at week 18. This applies to the patients without CTC test at week 18 (due to progressive disease (2), death before the test could be done (1), the scheduling issue (1) and the starting of new treatment before performing the test (1)).

Comparison groups	Observation v Trastuzumab
Number of subjects included in analysis	63
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.644
Method	Fisher exact
Parameter estimate	Odds ratio (OR)
Point estimate	1.04
Confidence interval	
level	90 %
sides	1-sided
upper limit	2.26

Secondary: Recurrence free interval

End point title	Recurrence free interval

End point description:

The Recurrence Free Interval (RFI) is calculated as the time between randomization and recurrence of disease, including any invasive ipsilateral breast tumor, local/regional invasive relapse, distant recurrence, and death from breast cancer documented with an imaging study or biopsy (Hudis et al., Ref. 60). Death documented from other causes than breast cancer will be analyzed as competing risk. Patients who did not experience any of these will be censored at the time of their last follow-up.
Due to the limited follow-up in the study, the median is not reached for this endpoint. Therefore, the result reported is the recurrence free rate at 1 year.

End point type	Secondary

End point timeframe:

The Recurrence Free Interval (RFI) is calculated from randomization to end of follow-up.

End point values	Observation	Trastuzumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	32	31		
Units: % at 1 year				
number (confidence interval 95%)	93.8 (77.3 to 98.4)	87.6 (65.3 to 96.0)		

Attachments (see zip file)	RFI.gif

Statistical analyses

No statistical analyses for this end point

Secondary: Invasive Disease Free Survival

End point title	Invasive Disease Free Survival

End point description:

Invasive Disease Free Survival (IDFS) (Ref. 60) is calculated as the time between randomization and the occurrence of an invasive disease recurrence (including any invasive ipsilateral breast tumor, local/regional invasive relapse, distant recurrence, invasive contralateral breast cancer, second primary invasive cancer (non-breast)), or death (any cause). Patients who did not experience any of these will be censored at the time of their last follow-up.

Due to the limited follow-up, the median is not reached for this endpoint. Therefore, the invasive disease free rate at 1 year is reported.

End point type	Secondary

End point timeframe:

From randomization till end of follow-up

End point values	Observation	Trastuzumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	32	31		
Units: % at 1 year				
number (confidence interval 95%)	93.8 (77.3 to 98.4)	84.8 (63.4 to 94.2)		

Attachments (see zip file)	IDFS.gif

Statistical analyses

No statistical analyses for this end point

Secondary: Disease free survival

End point title	Disease free survival

End point description:

Disease Free Survival (DFS) (Ref. 60) is determined as the time from randomization to either the date

of disease progression or the date of death (any cause). Disease progression for this end-point is defined as any invasive ipsilateral breast tumor, local/regional invasive relapse, distant recurrence, invasive contralateral breast cancer, ipsilateral or contralateral DCIS or second primary invasive cancer (incl. non-breast). Patients who did not experience any of these will be censored at the time of their last follow-up.

Due to limited follow-up in this study, the median is not reached. Therefore, only the disease free survival rate at 1 year is reported.

End point type	Secondary

End point timeframe:

From randomization till end of follow-up.

End point values	Observation	Trastuzumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	32	31		
Units: % at 1 year				
number (confidence interval 95%)	93.8 (77.3 to 98.4)	84.8 (63.4 to 94.2)		

Attachments (see zip file)	DFS.gif

Statistical analyses

No statistical analyses for this end point

Secondary: Overal survival

End point title	Overal survival

End point description:

Overall Survival (OS) is calculated as the time from randomization to the date of death (any cause). Patients alive at the time of analysis will be censored at the last time they are known to be alive.

Due to limited follow-up in this study, the median is not reached. Therefore, only the survival rate at 1 year is reported.

End point type	Secondary

End point timeframe:

From randomization till end of follow-up.

End point values	Observation	Trastuzumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	32	31		
Units: % at 1 year				
number (confidence interval 95%)	100 (0 to 100)	83.1 (59.9 to 93.5)		

Attachments (see zip file)	OS.gif

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events were collected at registration, at the end of each cycle (experimental arm only) and at the end of the observation period (week 18, observational arm only).

Adverse event reporting additional description:

CRF for AEs contains pre-specified items + additional boxes for all "other" AEs. (4% AEs are reported as "other" and are not reported as not available from the list of SOC).
Note that AEs related to hematology and biochemistry lab values were not specifically collected and are not included in the table below

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	22

Reporting groups

Reporting group title	Trastuzumab
Reporting group description: -	
Reporting group title	Observation
Reporting group description:	
Observation	

Serious adverse events	Trastuzumab	Observation	
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 31 (12.90%)	0 / 32 (0.00%)	
number of deaths (all causes)	4	2	
number of deaths resulting from adverse events	0	0	
Vascular disorders			
LYMPHOEDEMA			
alternative dictionary used: MedDRA 22			
subjects affected / exposed	1 / 31 (3.23%)	0 / 32 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
SYNCOPE			
alternative dictionary used: MedDRA 22			
subjects affected / exposed	1 / 31 (3.23%)	0 / 32 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			

PYREXIA			
alternative dictionary used: MedDRA 22			
subjects affected / exposed	1 / 31 (3.23%)	0 / 32 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
PNEUMONITIS			
alternative dictionary used: MedDRA 22			
subjects affected / exposed	1 / 31 (3.23%)	0 / 32 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
RESPIRATORY DISTRESS			
alternative dictionary used: MedDRA 22			
subjects affected / exposed	1 / 31 (3.23%)	0 / 32 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Infections and infestations			
PNEUMONIA			
alternative dictionary used: MedDRA 22			
subjects affected / exposed	1 / 31 (3.23%)	0 / 32 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
SEPSIS			
alternative dictionary used: MedDRA 22			
subjects affected / exposed	1 / 31 (3.23%)	0 / 32 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	

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

Non-serious adverse events	Trastuzumab	Observation	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	26 / 31 (83.87%)	17 / 32 (53.13%)	

Vascular disorders			
FLUSHING			
alternative dictionary used: MedDRA 22			
subjects affected / exposed	0 / 31 (0.00%)	1 / 32 (3.13%)	
occurrences (all)	0	1	
HOT FLASHES			
alternative dictionary used: MedDRA 22			
subjects affected / exposed	5 / 31 (16.13%)	2 / 32 (6.25%)	
occurrences (all)	6	2	
HYPERTENSION			
alternative dictionary used: MedDRA 22			
subjects affected / exposed	2 / 31 (6.45%)	2 / 32 (6.25%)	
occurrences (all)	5	5	
LYMPHOCELE			
alternative dictionary used: MedDRA 22			
subjects affected / exposed	1 / 31 (3.23%)	0 / 32 (0.00%)	
occurrences (all)	1	0	
General disorders and administration site conditions			
CHILLS			
alternative dictionary used: MedDRA 22			
subjects affected / exposed	3 / 31 (9.68%)	0 / 32 (0.00%)	
occurrences (all)	4	0	
EDEMA LIMBS			
alternative dictionary used: MedDRA 22			
subjects affected / exposed	2 / 31 (6.45%)	2 / 32 (6.25%)	
occurrences (all)	5	3	
FATIGUE			
alternative dictionary used: MedDRA 22			
subjects affected / exposed	10 / 31 (32.26%)	2 / 32 (6.25%)	
occurrences (all)	36	2	
FEVER			
alternative dictionary used: MedDRA 22			
subjects affected / exposed	3 / 31 (9.68%)	1 / 32 (3.13%)	
occurrences (all)	4	1	
FLU LIKE SYMPTOMS			

alternative dictionary used: MedDRA 22			
subjects affected / exposed	2 / 31 (6.45%)	0 / 32 (0.00%)	
occurrences (all)	3	0	
GEN OTH ASTHENIA			
alternative dictionary used: MedDRA 22			
subjects affected / exposed	1 / 31 (3.23%)	0 / 32 (0.00%)	
occurrences (all)	1	0	
NON-CARDIAC CHEST PAIN			
alternative dictionary used: MedDRA 22			
subjects affected / exposed	0 / 31 (0.00%)	2 / 32 (6.25%)	
occurrences (all)	0	2	
PAIN			
alternative dictionary used: MedDRA 22			
subjects affected / exposed	0 / 31 (0.00%)	1 / 32 (3.13%)	
occurrences (all)	0	1	
Reproductive system and breast disorders			
IRREGULAR MENSTRUATION			
alternative dictionary used: MedDRA 22			
subjects affected / exposed	1 / 31 (3.23%)	0 / 32 (0.00%)	
occurrences (all)	2	0	
Respiratory, thoracic and mediastinal disorders			
BRONCHIAL OBSTRUCTION			
alternative dictionary used: MedDRA 22			
subjects affected / exposed	0 / 31 (0.00%)	1 / 32 (3.13%)	
occurrences (all)	0	1	
COUGH			
alternative dictionary used: MedDRA 22			
subjects affected / exposed	5 / 31 (16.13%)	1 / 32 (3.13%)	
occurrences (all)	6	1	
DYSPNEA			
alternative dictionary used: MedDRA 22			
subjects affected / exposed	3 / 31 (9.68%)	0 / 32 (0.00%)	
occurrences (all)	14	0	
MUS OTH RESTLESS LEGS SYMPTOM			

alternative dictionary used: MedDRA 22			
subjects affected / exposed	1 / 31 (3.23%)	0 / 32 (0.00%)	
occurrences (all)	1	0	
PARESTHESIA			
alternative dictionary used: MedDRA 22			
subjects affected / exposed	2 / 31 (6.45%)	0 / 32 (0.00%)	
occurrences (all)	3	0	
PNEUMONITIS			
alternative dictionary used: MedDRA 22			
subjects affected / exposed	2 / 31 (6.45%)	0 / 32 (0.00%)	
occurrences (all)	2	0	
RES OTH ACUTE RESPIRATORY DISTRESS			
alternative dictionary used: MedDRA 22			
subjects affected / exposed	1 / 31 (3.23%)	0 / 32 (0.00%)	
occurrences (all)	1	0	
RES OTH NASAL MUCOSITIS			
alternative dictionary used: MedDRA 22			
subjects affected / exposed	0 / 31 (0.00%)	1 / 32 (3.13%)	
occurrences (all)	0	1	
SNEEZING			
alternative dictionary used: MedDRA 22			
subjects affected / exposed	1 / 31 (3.23%)	0 / 32 (0.00%)	
occurrences (all)	5	0	
UPPER RESPIRATORY INFECTION			
alternative dictionary used: MedDRA 22			
subjects affected / exposed	1 / 31 (3.23%)	0 / 32 (0.00%)	
occurrences (all)	1	0	
Psychiatric disorders			
ANXIETY			
alternative dictionary used: MedDRA 22			
subjects affected / exposed	2 / 31 (6.45%)	0 / 32 (0.00%)	
occurrences (all)	2	0	
DEPRESSION			
alternative dictionary used: MedDRA 22			

subjects affected / exposed	1 / 31 (3.23%)	0 / 32 (0.00%)	
occurrences (all)	1	0	
INSOMNIA			
alternative dictionary used: MedDRA 22			
subjects affected / exposed	1 / 31 (3.23%)	0 / 32 (0.00%)	
occurrences (all)	1	0	
Investigations			
CD4 LYMPHOCYTES DECREASED			
alternative dictionary used: MedDRA 22			
subjects affected / exposed	0 / 31 (0.00%)	2 / 32 (6.25%)	
occurrences (all)	0	2	
WEIGHT GAIN			
alternative dictionary used: MedDRA 22			
subjects affected / exposed	2 / 31 (6.45%)	0 / 32 (0.00%)	
occurrences (all)	4	0	
WEIGHT LOSS			
alternative dictionary used: MedDRA 22			
subjects affected / exposed	2 / 31 (6.45%)	0 / 32 (0.00%)	
occurrences (all)	3	0	
Injury, poisoning and procedural complications			
DERMATITIS RADIATION			
alternative dictionary used: MedDRA 22			
subjects affected / exposed	4 / 31 (12.90%)	2 / 32 (6.25%)	
occurrences (all)	7	2	
Cardiac disorders			
CAR TACHYCARDIA			
alternative dictionary used: MedDRA 22			
subjects affected / exposed	1 / 31 (3.23%)	0 / 32 (0.00%)	
occurrences (all)	1	0	
Nervous system disorders			
AMNESIA			
alternative dictionary used: MedDRA 22			
subjects affected / exposed	1 / 31 (3.23%)	0 / 32 (0.00%)	
occurrences (all)	1	0	
DYSGEUSIA			

alternative dictionary used: MedDRA 22			
subjects affected / exposed	1 / 31 (3.23%)	0 / 32 (0.00%)	
occurrences (all)	1	0	
HEADACHE			
alternative dictionary used: MedDRA 22			
subjects affected / exposed	4 / 31 (12.90%)	2 / 32 (6.25%)	
occurrences (all)	8	3	
MUS GENERALIZED MUSCLES WEAKNESS			
alternative dictionary used: MedDRA 22			
subjects affected / exposed	1 / 31 (3.23%)	0 / 32 (0.00%)	
occurrences (all)	1	0	
NER OTH LIGHTHEADEDNESS			
alternative dictionary used: MedDRA 22			
subjects affected / exposed	1 / 31 (3.23%)	0 / 32 (0.00%)	
occurrences (all)	1	0	
NEURALGIA			
alternative dictionary used: MedDRA 22			
subjects affected / exposed	3 / 31 (9.68%)	0 / 32 (0.00%)	
occurrences (all)	6	0	
PARESTHESIA			
alternative dictionary used: MedDRA 22			
subjects affected / exposed	1 / 31 (3.23%)	0 / 32 (0.00%)	
occurrences (all)	1	0	
PERIPHERAL MOTOR NEUROPATHY			
alternative dictionary used: MedDRA 22			
subjects affected / exposed	0 / 31 (0.00%)	1 / 32 (3.13%)	
occurrences (all)	0	1	
PERIPHERAL SENSORY NEUROPATHY			
alternative dictionary used: MedDRA 22			
subjects affected / exposed	0 / 31 (0.00%)	2 / 32 (6.25%)	
occurrences (all)	0	2	
SYNCOPE			
alternative dictionary used: MedDRA 22			

subjects affected / exposed	1 / 31 (3.23%)	0 / 32 (0.00%)	
occurrences (all)	1	0	
VASOVAGAL REACTION			
alternative dictionary used: MedDRA 22			
subjects affected / exposed	1 / 31 (3.23%)	0 / 32 (0.00%)	
occurrences (all)	1	0	
Blood and lymphatic system disorders			
ANEMIA			
alternative dictionary used: MedDRA 22			
subjects affected / exposed	1 / 31 (3.23%)	0 / 32 (0.00%)	
occurrences (all)	1	0	
Ear and labyrinth disorders			
TINNITUS			
alternative dictionary used: MedDRA 22			
subjects affected / exposed	1 / 31 (3.23%)	1 / 32 (3.13%)	
occurrences (all)	1	2	
Eye disorders			
BLURRED VISION			
alternative dictionary used: MedDRA 22			
subjects affected / exposed	1 / 31 (3.23%)	0 / 32 (0.00%)	
occurrences (all)	5	0	
EYE OTH LOSING EYELASHES			
alternative dictionary used: MedDRA 22			
subjects affected / exposed	1 / 31 (3.23%)	0 / 32 (0.00%)	
occurrences (all)	1	0	
Gastrointestinal disorders			
ABDOMINAL DISTENSION			
alternative dictionary used: MedDRA 22			
subjects affected / exposed	1 / 31 (3.23%)	0 / 32 (0.00%)	
occurrences (all)	1	0	
DYSPHAGIA			
alternative dictionary used: MedDRA 22			
subjects affected / exposed	1 / 31 (3.23%)	0 / 32 (0.00%)	
occurrences (all)	1	0	
GAS OTH STOMATITIS			
alternative dictionary used: MedDRA 22			

subjects affected / exposed	1 / 31 (3.23%)	0 / 32 (0.00%)	
occurrences (all)	1	0	
MUCOSITIS ORAL			
alternative dictionary used: MedDRA 22			
subjects affected / exposed	1 / 31 (3.23%)	0 / 32 (0.00%)	
occurrences (all)	1	0	
NAUSEA			
alternative dictionary used: MedDRA 22			
subjects affected / exposed	1 / 31 (3.23%)	0 / 32 (0.00%)	
occurrences (all)	1	0	
Hepatobiliary disorders			
HEPATIC FAILURE			
alternative dictionary used: MedDRA 22			
subjects affected / exposed	1 / 31 (3.23%)	0 / 32 (0.00%)	
occurrences (all)	1	0	
Skin and subcutaneous tissue disorders			
ALOPECIA			
alternative dictionary used: MedDRA 22			
subjects affected / exposed	1 / 31 (3.23%)	1 / 32 (3.13%)	
occurrences (all)	1	1	
NAIL LOSS			
alternative dictionary used: MedDRA 22			
subjects affected / exposed	1 / 31 (3.23%)	1 / 32 (3.13%)	
occurrences (all)	4	1	
PRURITUS			
alternative dictionary used: MedDRA 22			
subjects affected / exposed	3 / 31 (9.68%)	0 / 32 (0.00%)	
occurrences (all)	5	0	
RASH ACNEIFORM			
alternative dictionary used: MedDRA 22			
subjects affected / exposed	1 / 31 (3.23%)	0 / 32 (0.00%)	
occurrences (all)	2	0	
Endocrine disorders			
END HOT FLUSHES			
alternative dictionary used: MedDRA 22			

subjects affected / exposed	0 / 31 (0.00%)	1 / 32 (3.13%)	
occurrences (all)	0	1	
Musculoskeletal and connective tissue disorders			
ARTHRALGIA			
alternative dictionary used: MedDRA 22			
subjects affected / exposed	8 / 31 (25.81%)	5 / 32 (15.63%)	
occurrences (all)	23	6	
BACK PAIN			
alternative dictionary used: MedDRA 22			
subjects affected / exposed	2 / 31 (6.45%)	0 / 32 (0.00%)	
occurrences (all)	2	0	
JOINT RANGE OF MOTION DECREASED			
alternative dictionary used: MedDRA 22			
subjects affected / exposed	1 / 31 (3.23%)	0 / 32 (0.00%)	
occurrences (all)	1	0	
MYALGIA			
alternative dictionary used: MedDRA 22			
subjects affected / exposed	4 / 31 (12.90%)	0 / 32 (0.00%)	
occurrences (all)	19	0	
PAIN IN EXTREMITY			
alternative dictionary used: MedDRA 22			
subjects affected / exposed	2 / 31 (6.45%)	1 / 32 (3.13%)	
occurrences (all)	2	2	
Infections and infestations			
BRONCHIAL INFECTION			
alternative dictionary used: MedDRA 22			
subjects affected / exposed	1 / 31 (3.23%)	0 / 32 (0.00%)	
occurrences (all)	2	0	
INF OTH COMMON COLD			
alternative dictionary used: MedDRA 22			
subjects affected / exposed	0 / 31 (0.00%)	1 / 32 (3.13%)	
occurrences (all)	0	1	
LARYNGITIS			
alternative dictionary used: MedDRA 22			

subjects affected / exposed	1 / 31 (3.23%)	0 / 32 (0.00%)	
occurrences (all)	1	0	
LUNG INFECTION			
alternative dictionary used: MedDRA 22			
subjects affected / exposed	1 / 31 (3.23%)	0 / 32 (0.00%)	
occurrences (all)	1	0	
MUCOSAL INFECTION			
alternative dictionary used: MedDRA 22			
subjects affected / exposed	1 / 31 (3.23%)	0 / 32 (0.00%)	
occurrences (all)	1	0	
PHARYNGITIS			
alternative dictionary used: MedDRA 22			
subjects affected / exposed	1 / 31 (3.23%)	0 / 32 (0.00%)	
occurrences (all)	1	0	
SEPSIS			
alternative dictionary used: MedDRA 22			
subjects affected / exposed	1 / 31 (3.23%)	0 / 32 (0.00%)	
occurrences (all)	1	0	
SINUSITIS			
alternative dictionary used: MedDRA 22			
subjects affected / exposed	1 / 31 (3.23%)	0 / 32 (0.00%)	
occurrences (all)	1	0	
UPPER RESPIRATORY INFECTION			
alternative dictionary used: MedDRA 22			
subjects affected / exposed	1 / 31 (3.23%)	0 / 32 (0.00%)	
occurrences (all)	1	0	
Metabolism and nutrition disorders			
HYPERGLYCEMIA			
alternative dictionary used: MedDRA 22			
subjects affected / exposed	1 / 31 (3.23%)	1 / 32 (3.13%)	
occurrences (all)	2	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
02 February 2012	Major changes included: 1. Initially, our assumptions for the "TREAT CTC" trial were that after (neo)adjuvant chemotherapy CTC detection rate would be 20% and HER2-positive CTC detection rate would be 15%. A pilot feasibility study was done and we found that CTC detection rate either before or after (neo)adjuvant chemotherapy was 11.9%. We also observed that 40% of the women with HER2-negative early breast cancer and detectable CTC had at least 1 HER2-positive CTC. In two other reported studies CTC detection rate after neoadjuvant chemotherapy was 17% and 10.6%, respectively. As the above mentioned research has shown a lower detection rate of CTC and of HER2-positive CTC, the design was changed to measure CTC rather than HER2-positive CTC. Furthermore in the new "TREAT CTC" design we assume a very conservative CTC detection rate after (neo) adjuvant chemotherapy of 8%. In addition to adjusting the design for the new validated CTC detection rate, strong safeguards have been built into the protocol covering feasibility, patient safety and early stopping mechanisms. Three interim analyses were planned. The first 2 are dedicated to assessing feasibility, the level of detection of CTC, the level of test failures and checking the assumptions. These analyses will be performed after 150 and/or 300 patients (depending on the accrual rate) have been screened. The third interim analysis will be performed at 50% randomisation for assessing test superiority and futility as well as feasibility. 2. The number of patients to be randomized between trastuzumab and observation increased from 80 to 174 in order to increase the power of the study to detect a 15% difference in CTC detection rate at week 18 between the two arms. 3. Several secondary clinical endpoints were added, including the comparison of the recurrence free interval between the trastuzumab and observation arm.
03 December 2013	The PS in the selection criteria has been described, selection criteria were expanded to allow the inclusion of male breast cancer and all invasive breast cancer grades and sizes (i.e. we now include grade 1 tumors and tumors < 1cm), unifocal or multifocal unilateral or unifocal or multifocal synchronous bilateral BC if all foci are HER-2 negative and patients with previous history of DCIS because it increases the screening population and leaving We have removed the exclusion for prior use of bisphosphonate treatment or denosumab therapy because some patients could have started the above therapy for ostheoporosis treatment or previously enrolled in a clinical trial, we are however excluding the concomitant administration. We have clarified the confirmation of CTC testing will be done in one national reference lab and image confirmation by two central labs. This is as requested by the original guidelines from Veridex ® decreasing the possibilities of false positives. Timelines have been extended from surgery or last dose of chemotherapy to registration from 12 to 24 weeks to facilitate patient screening and inclusion. We also updated pre-clinical information in the rationale. We added additional information regarding trastuzumab, packaging and reconciliation, as requested by French authorities. We added additional information regarding trastuzumab the duration of administration after the first dose and monitoring in the rationale and changes. The end of study definition is now aligned to our standard wording and SOP. The text of PIS/IC has been clarified and now 4 questions have been summarized in 2 questions. We strongly believe that this amendment will facilitate the accrual of this relative rare population, without jeopardizing their safety. Additional administrative corrections and updates have been implemented.

16 March 2015	This amendment is considered scientific because, among other changes, it proposes a modification of the inclusion criteria. In the previous version of the protocol, the patient population was limited to patients who had completed either - adjuvant chemotherapy for node-positive disease (pN ≥ 1, macrometastasis only) or - neoadjuvant chemotherapy; in this case residual invasive disease in breast or lymph nodes is required. These criteria were devised to identify a high risk population, partially to allow sufficient events for a timely analysis of the secondary endpoint recurrence free interval (RFI). Due to increased mammographic screening, node-negative patients are becoming more prevalent as compared to node-positive patients. Furthermore, a considerable proportion of women receiving adjuvant chemotherapy for early breast cancer have high risk node-negative disease. Considering these basically we allow node- negative patients to be included in this study. The implications this amendment may have on the design parameters are the following. Given the currently observed CTC detection rate (approx. 15%) and the results summarized above for the series of 2026 patients, this modification is expected to slightly reduce the overall CTC detection rate, albeit still within the limits expected within the protocol. Therefore, as - the end of accrual is mainly driven by the number of patients randomized and not by the number of patients screened (with upper limit of 2175), - we do not expect that including CTC positive patients with node negative disease will impact the assumed CTC detection rate at week 18 in the observation arm, there would be no need to update the design of the study in terms of number of patients to be randomized or screened.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

The trial was closed early on the grounds of futility as pre-specified in the interim analysis

Notes:

Online references

http://www.ncbi.nlm.nih.gov/pubmed/29893791