



Clinical trial results:

DETECT III – A multicenter, randomized, phase III study to compare standard therapy alone versus standard therapy plus Lapatinib in patients with initially HER2-negative metastatic breast cancer and HER2-positive circulating tumor cells

Summary

EudraCT number	2010-024238-46
Trial protocol	DE
Global end of trial date	20 January 2023

Results information

Result version number	v1 (current)
This version publication date	10 May 2024
First version publication date	10 May 2024
Summary attachment (see zip file)	Müller et al. 2021_ESMO_prognostic relevance of HER2 status (Müller et al. 2021 - prognostic relevance of CTCs in MBC DETECT study program.pdf) Fehm et. al_ClinChem_2024 (Fehm_etal-01_2024-Efficacy of Lapatinib-DETECTIII-ClinChem.pdf)

Trial information

Trial identification

Sponsor protocol code	D-III
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01619111
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Universitätsklinik Ulm
Sponsor organisation address	Albert-Einstein-Allee 29, Ulm, Germany, 89075
Public contact	Studienzentrale , Universitätsklinikum Ulm - Klinik für Frauenheilkunde und Geburtshilfe, 0049 73150058652, Studienzentrale.UFK@uniklinik-ulm.de
Scientific contact	Prof. Wolfgang Janni, Universitätsklinikum Ulm - Klinik für Frauenheilkunde und Geburtshilfe, 3150058652 73150058652, Studienzentrale.UFK@uniklinik-ulm.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	20 January 2023
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	20 January 2023
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of the trial was to prove the clinical efficacy of lapatinib (as assessed by the CTC clearance rate) in patients with metastasizing breast cancer who exhibit HER2-positive circulating tumor cells (CTC) although the primary tumor tissue and/or biopsies from metastatic sites were investigated for HER2 status and showed HER2-negativity.

Protection of trial subjects:

Safety and tolerability were assessed by evaluation of adverse event (AE) and serious adverse event (SAE) reports using the international Common Terminology Criteria for Adverse Events (CTCAE), version 4.0. The safety population (which is equivalent to mITT population) comprised all randomized subjects who received at least one dose of the respective study treatment.

Background therapy:

Reference therapy was standard therapy, to be selected from the mono-chemotherapies or endocrine therapies

Evidence for comparator: -

Actual start date of recruitment	01 April 2012
Long term follow-up planned	Yes
Long term follow-up rationale	Efficacy, Safety
Long term follow-up duration	24 Months
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Germany: 101
Worldwide total number of subjects	101
EEA total number of subjects	101

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)	101
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Patients with HER2-neg. metastatic breast cancer,

Pre-assignment

Screening details:

positive HER2-status of circulating tumor cells (CTCs)

Pre-assignment period milestones

Number of subjects started	101
Number of subjects completed	101

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Standard Therapy plus Lapatinib

Arm description:

Lapatinib was administered to patients randomized to a treatment with lapatinib in addition to a standard chemo (docetaxel, paclitaxel, capecitabine, vinorelbine, NPLD) - or endocrine therapy (aromatase inhibitor Exemestan, letrozol, anastrozol).

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

Dosage and administration details:

daily dose of lapatinib may have been adjusted dependent on the dose regimen of the standard chemo- or endocrine therapy and on the occurrence of adverse events.

In any case, the maximum daily dose was 1500 mg, the minimum daily dose was 750 mg. Duration of lapatinib therapy was 12 months

Arm title	Standard therapy
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Arm description:

During the randomized treatment period all patients received a standard chemo- or endocrine therapy whether they were allocated to lapatinib treatment or not

Arm type	Standard therapy
No investigational medicinal product assigned in this arm	

Number of subjects in period 1	Standard Therapy plus Lapatinib	Standard therapy
Started	53	48
Completed	53	48

Baseline characteristics

Reporting groups

Reporting group title	Standard Therapy plus Lapatinib
Reporting group description:	
Lapatinib was administered to patients randomized to a treatment with lapatinib in addition to a standard chemo (docetaxel, paclitaxel, capecitabine, vinorelbine, NPLD) - or endocrine therapy (aromatase inhibitor Exemestan, letrozol, anastrozol).	
Reporting group title	Standard therapy
Reporting group description:	
During the randomized treatment period all patients received a standard chemo- or endocrine therapy whether they were allocated to lapatinib treatment or not	

Reporting group values	Standard Therapy plus Lapatinib	Standard therapy	Total
Number of subjects	53	48	101
Age categorical			
total iTT population n = 101 median age 59 (26-80)			
Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	53	48	101
From 65-84 years	0	0	0
85 years and over	0	0	0
Age continuous			
Units: years			
median	59	58	
standard deviation	± 0	± 0	-
Gender categorical			
Units: Subjects			
Female	53	48	101
Male	0	0	0
CTC clearance rate (at the time of first CTC assessment and survival)			
CTC clearance rates at the time of first CTC assessment and survival			
Units: Subjects			
CTC clearance	53	48	101
CTC clearance rate (after study treatment and survival)			
Units: Subjects			
CTC clearance	53	48	101
PFS			
PFS was calculated as the time interval from randomization until progressive disease (PD), and patients without known progression were censored at the last date they had a documented tumor staging without evidence of progressive disease. Because of incomplete documentation of tumor staging, PFS data were not available for all patients.			

Units: month			
median	7.2	4.1	
full range (min-max)	0 to 9.4	2.2 to 5.9	-
Survival according to randomization arm			
Units: month			
median	23.2	9.1	
full range (min-max)	14 to 32.3	8.3 to 9.9	-

Subject analysis sets

Subject analysis set title	Randomized ITT population
Subject analysis set type	Intention-to-treat

Subject analysis set description:

All randomized subjects who received at least one dose of the respective study treatment (chemotherapy or endocrine therapy alone; chemotherapy or endocrine therapy + lapatinib).

Reporting group values	Randomized ITT population		
Number of subjects	101		
Age categorical			
total iTT population n = 101 median age 59 (26-80)			
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)	101		
From 65-84 years	0		
85 years and over	0		
Age continuous			
Units: years			
median	59		
standard deviation	± 0		
Gender categorical			
Units: Subjects			
Female	101		
Male	0		
CTC clearance rate (at the time of first CTC assessment and survival)			
CTC clearance rates at the time of first CTC assessment and survival			
Units: Subjects			
CTC clearance	101		
CTC clearance rate (after study treatment and survival)			
Units: Subjects			
CTC clearance	101		
PFS			
PFS was calculated as the time interval from randomization until progressive disease (PD), and patients without known progression were censored at the last date they had a documented tumor staging without evidence of progressive disease. Because of incomplete documentation of tumor staging, PFS			

data were not available for all patients.			
Units: month			
median	4.6		
full range (min-max)	0 to 22		
Survival according to randomization arm			
Units: month			
median	21.1		
full range (min-max)	0 to 21.1		

End points

End points reporting groups

Reporting group title	Standard Therapy plus Lapatinib
Reporting group description: Lapatinib was administered to patients randomized to a treatment with lapatinib in addition to a standard chemo (docetaxel, paclitaxel, capecitabine, vinorelbine, NPLD) - or endocrine therapy (aromatase inhibitor Exemestan, letrozol, anastrozol).	
Reporting group title	Standard therapy
Reporting group description: During the randomized treatment period all patients received a standard chemo- or endocrine therapy whether they were allocated to lapatinib treatment or not	
Subject analysis set title	Randomized ITT population
Subject analysis set type	Intention-to-treat
Subject analysis set description: All randomized subjects who received at least one dose of the respective study treatment (chemotherapy or endocrine therapy alone; chemotherapy or endocrine therapy + lapatinib).	

Primary: CTC clearance rates at the time of first CTC assessment

End point title	CTC clearance rates at the time of first CTC assessment
End point description: A first follow-up CTC assessment could be performed in 69 patients (30 and 39 patients in the standard and lapatinib arms, respectively) after a median time of 73 days (interquartile range 64–87 days, range 22–215 days). CTC clearance was observed in 8 (26.7%, 95% CI 10.8% - 42.5%) patients in the standard arm and in 12 (30.8%, 95% CI 16.3% - 45.3%) patients in the lapatinib arm; the difference was not statistically significant (p = 0.710;	
End point type	Primary
End point timeframe: CTC clearance rates at the time of first CTC assessment	

End point values	Standard Therapy plus Lapatinib	Standard therapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	12	8		
Units: %				
median (confidence interval 95%)	30.8 (16.3 to 45.3)	26.7 (10.8 to 42.5)		

Attachments (see zip file)	ctc clearance rate after first assessment/ctc clearance rate
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Statistical analyses

Statistical analysis title	non-parametric
Comparison groups	Standard Therapy plus Lapatinib v Standard therapy

Number of subjects included in analysis	20
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.71
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)

Primary: CTC clearance rates after study treatment

End point title	CTC clearance rates after study treatment
End point description:	
The primary endpoint, i.e., the CTC clearance rate, was calculated as the proportion of patients with at least one CTC detected in 7.5 ml of peripheral blood drawn before treatment that showed no evidence of CTCs in the blood after study treatment (i.e., at the time of the closure visit, which took place either after a patient had received one year of study treatment or at the time the study treatment had to be stopped because of progress, toxicity or patient wish).	
End point type	Primary
End point timeframe:	
A first follow-up CTC assessment after study treatment	

End point values	Standard Therapy plus Lapatinib	Standard therapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	27	22		
Units: %				
median (confidence interval 95%)	14.8 (1.4 to 28.2)	31.8 (12.4 to 51.3)		

Attachments (see zip file)	ctc clearance rate after study treatment/ctc clearance rate after
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Statistical analyses

Statistical analysis title	non-parametric
Comparison groups	Standard Therapy plus Lapatinib v Standard therapy
Number of subjects included in analysis	49
Analysis specification	Pre-specified
Analysis type	other ^[1]
P-value	= 0.156 ^[2]
Method	Chi-squared

Notes:

[1] - The primary endpoint CTC clearance rate will be evaluated using non-parametric statistical methods appropriate for the analysis of frequencies and rates (i.e. Chi-square tests and modifications thereof). The proportion of patients that show no evidence of CTCs in the blood after the study treatment will be compared between the two treatment arms, and relative risks, odds ratios and their 95% confidence intervals will be reported.

[2] - All p values will be two-sided if not stated otherwise. The statistical methods described in this

section are suited for the data and distributions usually expected in this type of trials. The suitability will be checked after data entry. If necessary

Secondary: OS

End point title	OS
End point description: Patients with no evidence of CTCs at the first follow-up CTC assessment (i.e., patients with CTC clearance at the first follow-up) showed better OS than patients with CTCs (CTC clearance: median OS 42.4 months; no CTC clearance: median OS 14.1 months; HR 0.34; 95% CI 0.16–0.70; p = 0.004; Figure 5). Patients showing CTC clearance at the first follow-up CTC assessment also had numerically longer PFS, but the difference was not significant (CTC clearance: median PFS 10.1 months; no CTC clearance: median PFS 6.2 months; HR 0.56; 95% CI 0.29–1.07; p = 0.078).	
End point type	Secondary
End point timeframe: overall survival according to CTC clearance at the time of first follow-up CTC assessment.	

End point values	Randomized ITT population			
Subject group type	Subject analysis set			
Number of subjects analysed	69			
Units: month				
median (confidence interval 95%)				
ctc clearance	42.4 (0 to 42.4)			
no ctc clearance	14.1 (0 to 14.1)			

Attachments (see zip file)	overall survival OS-CTC clearance.pptx
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Statistical analyses

No statistical analyses for this end point

Secondary: PFS

End point title	PFS
End point description: progression-free survival according to randomization arm	
End point type	Secondary
End point timeframe: progression-free survival according to randomization arm	

End point values	Standard Therapy plus Lapatinib	Standard therapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	47	40		
Units: month				
median (confidence interval 95%)	7.2 (5.0 to 9.4)	4.1 (2.2 to 5.9)		

Attachments (see zip file)	PFS randomization arm/PFS-randomization arm.pptx
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Statistical analyses

Statistical analysis title	PFS
Comparison groups	Standard Therapy plus Lapatinib v Standard therapy
Number of subjects included in analysis	87
Analysis specification	Pre-specified
Analysis type	other ^[3]
P-value	= 0.092
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.67
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.42
upper limit	1.07
Variability estimate	Standard deviation

Notes:

[3] - PFS data were available for 87 patients. The median PFS follow-up time for patients without progression was 4.6 months. Progressive disease occurred in 34 of 40 patients in the standard arm and in 36 of 47 patients in the lapatinib arm. Patients in the lapatinib arm showed a numerically but not significantly better PFS than patients in the standard arm

Secondary: OS according to randomization

End point title	OS according to randomization
End point description:	
Survival according to randomization arm	
End point type	Secondary
End point timeframe:	
End of study	

End point values	Standard Therapy plus Lapatinib	Standard therapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	53	48		
Units: month				
median (confidence interval 95%)	23.2 (14 to 32.3)	9.1 (8.3 to 9.9)		

Attachments (see zip file)	OS randomization arm/overall survival OS-randomization arm.
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Statistical analyses

Statistical analysis title	OS randomization arm
Comparison groups	Standard Therapy plus Lapatinib v Standard therapy
Number of subjects included in analysis	101
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.008 ^[4]
Method	Regression, Cox

Notes:

[4] - This was evident based on univariable Cox regression analysis (HR 0.53; 95% CI 0.33–0.84; p = 0.008) and multivariable Cox regression analysis adjusted for the metastasis-free interval (<12 months, >12 months), type of metastases (visceral, non-visce

Adverse events

Adverse events information

Timeframe for reporting adverse events:

start of study - first dose of study treatment until end of study

Adverse event reporting additional description:

The safety evaluation was performed in the Safety Population, defined as all randomized patients who received at least one dose of the respective study treatment (chemotherapy or endocrine therapy alone; chemotherapy or endocrine therapy + lapatinib). The safety set comprised 101 patients (48 patients in the standard arm, 53 patients in the lapatinib arm).

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	20.0
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Reporting groups

Reporting group title	Standard arm
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Reporting group description:

In conclusion, types and frequencies of adverse events observed in the DETECT III study were as expected for the treatments given in this study, with diarrhea in the lapatinib arm being the most common side effect observed.

Reporting group title	Lapatinib arm
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Reporting group description: -

Serious adverse events	Standard arm	Lapatinib arm	
Total subjects affected by serious adverse events			
subjects affected / exposed	21 / 48 (43.75%)	36 / 53 (67.92%)	
number of deaths (all causes)	40	33	
number of deaths resulting from adverse events	0	0	
Cardiac disorders			
Dyspnoea			
subjects affected / exposed	4 / 48 (8.33%)	5 / 53 (9.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
anemia			
subjects affected / exposed	10 / 48 (20.83%)	5 / 53 (9.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenia			

subjects affected / exposed	4 / 48 (8.33%)	5 / 53 (9.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Leukopenia			
subjects affected / exposed	5 / 48 (10.42%)	6 / 53 (11.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
diarrhea			
subjects affected / exposed	0 / 48 (0.00%)	13 / 53 (24.53%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Standard arm	Lapatinib arm	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	32 / 48 (66.67%)	53 / 53 (100.00%)	
Blood and lymphatic system disorders			
anemia			
subjects affected / exposed	23 / 48 (47.92%)	15 / 53 (28.30%)	
occurrences (all)	0	0	
Leukopenia			
subjects affected / exposed	7 / 48 (14.58%)	11 / 53 (20.75%)	
occurrences (all)	0	0	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	19 / 48 (39.58%)	22 / 53 (41.51%)	
occurrences (all)	0	0	
Gastrointestinal disorders			
diarrhea			
subjects affected / exposed	10 / 48 (20.83%)	38 / 53 (71.70%)	
occurrences (all)	0	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
25 October 2012	Change of sponsor from University Hospital Düsseldorf to University Hospital Ulm
30 September 2014	Subsequent changes in protocol
09 June 2015	Administrative changes in the protocol
16 March 2016	Acknowledgement of administrative changes in the trial protocol and patient information

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported