



Clinical trial results:

A phase III trials program exploring the integration of Bevacizumab, Everolimus (RAD001), and Lapatinib into current neoadjuvant chemotherapy regimes for primary breast cancer

Summary

EudraCT number	2006-005834-19
Trial protocol	DE
Global end of trial date	26 February 2016

Results information

Result version number	v1 (current)
This version publication date	16 September 2021
First version publication date	16 September 2021
Summary attachment (see zip file)	GeparQuinto CSR Synopsis (GBG 44 - Gepar5_CSR_Synopsis.pdf)

Trial information

Trial identification

Sponsor protocol code	GBG44
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00567554
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	GBG Forschungs GmbH
Sponsor organisation address	Martin Behaim Str. 12, Neu-Isenburg, Germany, 63263
Public contact	Medicine and Research, GBG Forschungs GmbH, publications@gbg.de
Scientific contact	Medicine and Research, GBG Forschungs GmbH, 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	26 February 2016
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	26 February 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To compare the pCR rates of neoadjuvant treatment of epirubicin/cyclophosphamide followed by docetaxel (EC-T) with or without bevacizumab (EC-T vs ECB-TB) in patients with HER2-negative primary breast cancer (Setting I).

To compare the pCR rates of neoadjuvant treatment with weekly paclitaxel with or without Everolimus (RAD001) (Pw vs PwR) in patients with HER2-negative primary breast cancer showing no sonographic response to 4 cycles of EC+/-B (Setting II).

To compare the pCR rates of neoadjuvant treatment with epirubicin/cyclophosphamide followed by docetaxel with either trastuzumab or lapatinib (ECH-TH vs ECL-TL) in patients with HER2-positive primary breast cancer (Setting III).

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:

cyclophosphamide, docetaxel, epirubicin, paclitaxel

Evidence for comparator:

Standard of Care (SoC)

Actual start date of recruitment	07 November 2007
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: 2600
Worldwide total number of subjects	2600
EEA total number of subjects	2600

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)	2341
From 65 to 84 years	259
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Between November 2007 and August 2015, 2600 patients with breast cancer (BC) were randomised:

Setting I (HER2- BC): 1948 randomised, 1925 started treatment

Setting II (HER2- BC, non responder): 403 (371 from Setting I +32 after additional recruitment) randomised, 395 started treatment

Setting III (HER2+ BC): 620 randomised, 615 started treatment

Pre-assignment

Screening details:

Patients with unilateral or bilateral primary carcinoma of the breast confirmed histologically by core biopsy; locally advanced tumors with cT3 or cT4 or HR-negative tumours or HR-positive with cN+ (for cT2) or pN SLN+ (for cT1) tumours; known HER2 status; age ≥ 18 years; Karnofsky index $\geq 80\%$, normal cardiac function.

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	ECB-TB (Setting I)

Arm description:

HER2-negative disease (Setting I)

All enrolled HER2-negative patients were randomly assigned in 1:1 ratio to receive Epirubicin-Cyclophosphamide-Docetaxel with Bevacizumab (ECB-TB) or without Bevacizumab (EC-T). After 4 cycles of EC +/-B the sonographic evaluation of response was performed. Patients with complete or partial response continued with the assigned treatment. Patients with disease progression went off-study. Patients without response went off setting I (N=371) and were randomly assigned in 1:1 ratio to receive either Pw or PwR (Setting II); these patients were considered as treatment failures (no pCR) for setting I regardless of their actual outcome after setting II and surgery. Additional 32 were randomised in setting II. Here setting II is presented as subject analysis set 1 and 2.

A total of 974 patients were randomised to receive ECB-TB, and 956 patients started treatment (18 patient did not start treatment due to withdrawal of informed consent).

Arm type	Experimental
Investigational medicinal product name	AVASTIN® (Bevacizumab)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Dosage: 15 mg/kg BW i.v.

Duration of treatment: 12 weeks (4 cycles 1 q22) with EC, if response than 12 weeks (4 cycles 1 q 22) with T.

Arm title	EC-T (Setting I)
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Arm description:

Epirubicin-Cyclophosphamide-Docetaxel (EC-T) (Setting I), for more information see arm ECB-TB

A total of 974 patients were randomised to receive EC-T and 969 started treatment (5 patient did not start treatment due to withdrawal of informed consent).

Arm type	control arm without bevacizumab
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Investigational medicinal product name	n.a.
Investigational medicinal product code	
Other name	reference therapy: cyclophosphamide, epirubicin, docetaxel
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Dosage: cyclophosphamide (C) 600 mg/m², epirubicin (E) 90 mg/m², docetaxel (T) 100 mg/m²

Duration of treatment: 12 weeks (4 cycles 1 q22) EC, if response than 12 weeks (4 cycles 1 q22) with T.

Arm title	ECH-TH (Setting III)
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Arm description:

HER2-positive disease (Setting III)

Patients with HER2-positive tumours received chemotherapy with EC followed by T and were randomised to anti-HER2 treatment either with trastuzumab (ECH-TH) or with lapatinib (ECL-TL).

The dose of docetaxel was increased from 75 mg/m² to 100 mg/m² (Amendment 1).

The dose of lapatinib was reduced from 1250 mg daily to 1000 mg daily (Amendment 2).

A total of 309 patients were randomised to receive ECH-TH and 307 started treatment (2 patient did not start treatment due to withdrawal of informed consent).

Arm type	Experimental
Investigational medicinal product name	HERCEPTIN® (Trastuzumab)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Dosage: loading dose: 8 mg/kg BW i.v., thereafter maintenance dose: 6 mg/kg BW i.v.

Duration of treatment: 24 weeks preoperative (8 cycles 1 q 22)

Arm title	ECL-TL (Setting III)
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Arm description:

HER2-positive disease (Setting III)

Epirubicin-Cyclophosphamide-Docetaxel + Lapatinib (ECL-TL), for more details see arm ECH-TH.

A total of 311 patients were randomised to receive ECL-TL and 308 started treatment (3 patient did not start treatment due to withdrawal of informed consent).

Arm type	Active comparator
Investigational medicinal product name	TYVERB® (Lapatinib)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Oral drops
Routes of administration	Oral use

Dosage and administration details:

Dosage: 1250 mg orally, since Amendment 2: 1000 mg orally

Duration of treatment: 24 weeks (daily)

Number of subjects in period 1^[1]	ECB-TB (Setting I)	EC-T (Setting I)	ECH-TH (Setting III)
Started	956	969	307
Completed	633	637	264
Not completed	323	332	43
Adverse event, serious fatal	-	1	-
missing	-	-	5
Physician decision	21	36	9

unknown	5	1	1
Adverse event, non-fatal	94	32	13
patient wish	38	18	10
other	4	-	2
disease progression	11	23	3
switch to setting II	150	221	-

Number of subjects in period 1^[1]	ECL-TL (Setting III)
Started	308
Completed	206
Not completed	102
Adverse event, serious fatal	-
missing	1
Physician decision	17
unknown	21
Adverse event, non-fatal	39
patient wish	22
other	-
disease progression	2
switch to setting II	-

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 (pts) enrolled in the trial included all settings (2600 patients). In setting I, 1948 pts were randomised, of whom 371 pts (nonresponder) were further randomised in setting II plus 32 additionally recruited pts (total 403 pts)=subject analysis set 1 and 2. In setting III, 620 pts were randomised. A total of 2540 pts (1925 in settings I+II and 615 in setting III) who started treatment were included in the analyses (efficacy and safety analysis set).

Baseline characteristics

Reporting groups

Reporting group title	ECB-TB (Setting I)
Reporting group description:	
HER2-negative disease (Setting I)	
All enrolled HER2-negative patients were randomly assigned in 1:1 ratio to receive Epirubicin-Cyclophosphamide-Docetaxel with Bevacizumab (ECB-TB) or without Bevacizumab (EC-T). After 4 cycles of EC +/-B the sonographic evaluation of response was performed. Patients with complete or partial response continued with the assigned treatment. Patients with disease progression went off-study. Patients without response went off setting I (N=371) and were randomly assigned in 1:1 ratio to receive either Pw or PwR (Setting II); these patients were considered as treatment failures (no pCR) for setting I regardless of their actual outcome after setting II and surgery. Additional 32 were randomised in setting II. Here setting II is presented as subject analysis set 1 and 2.	
A total of 974 patients were randomised to receive ECB-TB, and 956 patients started treatment (18 patient did not start treatment due to withdrawal of informed consent).	
Reporting group title	EC-T (Setting I)
Reporting group description:	
Epirubicin-Cyclophosphamide-Docetaxel (EC-T) (Setting I), for more information see arm ECB-TB	
A total of 974 patients were randomised to receive EC-T and 969 started treatment (5 patient did not start treatment due to withdrawal of informed consent).	
Reporting group title	ECH-TH (Setting III)
Reporting group description:	
HER2-positive disease (Setting III)	
Patients with HER2-positive tumours received chemotherapy with EC followed by T and were randomised to anti-HER2 treatment either with trastuzumab (ECH-TH) or with lapatinib (ECL-TL).	
The dose of docetaxel was increased from 75 mg/m ² to 100 mg/m ² (Amendment 1).	
The dose of lapatinib was reduced from 1250 mg daily to 1000 mg daily (Amendment 2).	
A total of 309 patients were randomised to receive ECH-TH and 307 started treatment (2 patient did not start treatment due to withdrawal of informed consent).	
Reporting group title	ECL-TL (Setting III)
Reporting group description:	
HER2-positive disease (Setting III)	
Epirubicin-Cyclophosphamide-Docetaxel + Lapatinib (ECL-TL), for more details see arm ECH-TH.	
A total of 311 patients were randomised to receive ECL-TL and 308 started treatment (3 patient did not start treatment due to withdrawal of informed consent).	

Reporting group values	ECB-TB (Setting I)	EC-T (Setting I)	ECH-TH (Setting III)
Number of subjects	956	969	307
Age categorical			
age in years at baseline (Setting I)			
Units: Subjects			
Adults (18-64 years)	857	871	281
From 65-84 years	97	98	26
85 years and over	0	0	0
missing	2	0	0
Age continuous			
Units: years			
median	49	48	50
full range (min-max)	21 to 75	24 to 78	25 to 74
Gender categorical			
Only female patients were randomised			
Units: Subjects			
Female	956	969	307
Male	0	0	0

Reporting group values	ECL-TL (Setting III)	Total	
Number of subjects	308	2540	
Age categorical			
age in years at baseline (Setting I)			
Units: Subjects			
Adults (18-64 years)	277	2286	
From 65-84 years	30	251	
85 years and over	0	0	
missing	1	3	
Age continuous			
Units: years			
median	50		
full range (min-max)	21 to 73	-	
Gender categorical			
Only female patients were randomised			
Units: Subjects			
Female	308	2540	
Male	0	0	

Subject analysis sets

Subject analysis set title	PwR (Setting II)
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

HER2-negative disease without response after 4 cycles of treatment (Setting II) Patients were randomised to weekly paclitaxel plus everolimus (RAD001, PwR) or weekly paclitaxel alone (Pw). Treatment with paclitaxel started within 7-14 days after the start of RAD001. Additionally, patients with treatment of four cycles of epirubicin-cyclophosphamide outside the study were randomised into Setting II after Amendment 2 in order to fill-in this setting. A total of 202 patients were randomised to receive PwR and 197 started treatment (5 patient did not start treatment due to withdrawal of informed consent).

Subject analysis set title	Pw (Setting II)
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

Paclitaxel weekly (Setting II), for mor details see subject analysis set PwR.

A total of 201 patients were randomised to receive Pw and 198 started treatment (3 patient did not start treatment due to withdrawal of informed consent).

Reporting group values	PwR (Setting II)	Pw (Setting II)	
Number of subjects	197	198	
Age categorical			
age in years at baseline (Setting I)			
Units: Subjects			
Adults (18-64 years)	169	171	
From 65-84 years	26	25	
85 years and over	0	0	
missing	2	2	
Age continuous			
Units: years			
median	50	51	
full range (min-max)	28 to 76	27 to 75	

Gender categorical			
Only female patients were randomised			
Units: Subjects			
Female	197	198	
Male	0	0	

End points

End points reporting groups

Reporting group title	ECB-TB (Setting I)
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Reporting group description:

HER2-negative disease (Setting I)

All enrolled HER2-negative patients were randomly assigned in 1:1 ratio to receive Epirubicin-Cyclophosphamide-Docetaxel with Bevacizumab (ECB-TB) or without Bevacizumab (EC-T). After 4 cycles of EC +/-B the sonographic evaluation of response was performed. Patients with complete or partial response continued with the assigned treatment. Patients with disease progression went off-study. Patients without response went off setting I (N=371) and were randomly assigned in 1:1 ratio to receive either Pw or PwR (Setting II); these patients were considered as treatment failures (no pCR) for setting I regardless of their actual outcome after setting II and surgery. Additional 32 were randomised in setting II. Here setting II is presented as subject analysis set 1 and 2.

A total of 974 patients were randomised to receive ECB-TB, and 956 patients started treatment (18 patient did not start treatment due to withdrawal of informed consent).

Reporting group title	EC-T (Setting I)
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Reporting group description:

Epirubicin-Cyclophosphamide-Docetaxel (EC-T) (Setting I), for more information see arm ECB-TB

A total of 974 patients were randomised to receive EC-T and 969 started treatment (5 patient did not start treatment due to withdrawal of informed consent).

Reporting group title	ECH-TH (Setting III)
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Reporting group description:

HER2-positive disease (Setting III)

Patients with HER2-positive tumours received chemotherapy with EC followed by T and were randomised to anti-HER2 treatment either with trastuzumab (ECH-TH) or with lapatinib (ECL-TL).

The dose of docetaxel was increased from 75 mg/m² to 100 mg/m² (Amendment 1).

The dose of lapatinib was reduced from 1250 mg daily to 1000 mg daily (Amendment 2).

A total of 309 patients were randomised to receive ECH-TH and 307 started treatment (2 patient did not start treatment due to withdrawal of informed consent).

Reporting group title	ECL-TL (Setting III)
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Reporting group description:

HER2-positive disease (Setting III)

Epirubicin-Cyclophosphamide-Docetaxel + Lapatinib (ECL-TL), for more details see arm ECH-TH.

A total of 311 patients were randomised to receive ECL-TL and 308 started treatment (3 patient did not start treatment due to withdrawal of informed consent).

Subject analysis set title	PwR (Setting II)
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Subject analysis set type	Modified intention-to-treat
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Subject analysis set description:

HER2-negative disease without response after 4 cycles of treatment (Setting II) Patients were randomised to weekly paclitaxel plus everolimus (RAD001, PwR) or weekly paclitaxel alone (Pw). Treatment with paclitaxel started within 7-14 days after the start of RAD001. Additionally, patients with treatment of four cycles of epirubicin-cyclophosphamide outside the study were randomised into Setting II after Amendment 2 in order to fill-in this setting.

A total of 202 patients were randomised to receive PwR and 197 started treatment (5 patient did not start treatment due to withdrawal of informed consent).

Subject analysis set title	Pw (Setting II)
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Subject analysis set type	Modified intention-to-treat
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Subject analysis set description:

Paclitaxel weekly (Setting II), for more details see subject analysis set PwR.

A total of 201 patients were randomised to receive Pw and 198 started treatment (3 patient did not start treatment due to withdrawal of informed consent).

Primary: pathological complete response (pCR=ypT0 ypN0) all settings

End point title	pathological complete response (pCR=ypT0 ypN0) all settings
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End point description:

A pathological complete response was defined as pathological stage T0 and N0 (ypT0 ypN0) after neoadjuvant therapy for all settings.

Treatment groups in each setting were compared with the use of a continuity-corrected two-sided

Pearson's chi-square test and Fisher's exact test, and 95% confidence intervals were provided for the efficacy end points.

End point type	Primary
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End point timeframe:

Setting I: 24 weeks; Setting II: 12 weeks; Setting III: 24 weeks

End point values	ECB-TB (Setting I)	EC-T (Setting I)	ECH-TH (Setting III)	ECL-TL (Setting III)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	956	969	307	308
Units: percent				
number (confidence interval 95%)				
pCR	18.4 (16.0 to 21.0)	14.9 (12.7 to 17.3)	30.3 (25.2 to 35.8)	22.7 (18.2 to 27.8)

End point values	PwR (Setting II)	Pw (Setting II)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	197	198		
Units: percent				
number (confidence interval 95%)				
pCR	3.6 (1.4 to 7.2)	5.6 (2.8 to 9.7)		

Statistical analyses

Statistical analysis title	pCR -odds ratio (Setting I)
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Statistical analysis description:

Primary efficacy endpoint pCR (ypT0 ypN0) was based on the mITT set.

Comparison groups	EC-T (Setting I) v ECB-TB (Setting I)
Number of subjects included in analysis	1925
Analysis specification	Pre-specified
Analysis type	superiority ^[1]
P-value	= 0.037
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.29
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.02
upper limit	1.65

Notes:

[1] - The difference in the pCR rates between the two treatment arms was evaluated as odds ratio (ECB-TB to EC-T) and its 95% CI.

	pCR - odds ratio (Setting II)
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Statistical analysis title	
Statistical analysis description:	
Primary endpoint pCR was based on the mITT set	
Comparison groups	PwR (Setting II) v Pw (Setting II)
Number of subjects included in analysis	395
Analysis specification	Pre-specified
Analysis type	superiority ^[2]
P-value	= 0.368
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	0.63
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.24
upper limit	1.64

Notes:

[2] - pCR comparison between treatment arms - regression analysis with odds ratio (PwR vs Pw) and 95%CI

Statistical analysis title	
pCR - odds ratio (Setting III)	
Statistical analysis description:	
Primary endpoint was based on the mITT set	
Comparison groups	ECH-TH (Setting III) v ECL-TL (Setting III)
Number of subjects included in analysis	615
Analysis specification	Pre-specified
Analysis type	superiority ^[3]
P-value	= 0.034
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	0.68
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.47
upper limit	0.97

Notes:

[3] - pCR comparison between treatment arms - regression analysis with odds ratio (ECH-TH vs ECL-TL) and 95%CI

Statistical analysis title	
pCR rates - comparison (Setting I)	
Statistical analysis description:	
pCR rates between treatment groups were compared by a continuity-corrected chi-square test with 95% confidence intervals	
Comparison groups	ECB-TB (Setting I) v EC-T (Setting I)
Number of subjects included in analysis	1925
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.042
Method	Chi-squared corrected

Statistical analysis title	pCR rates - comparison (Setting II)
Statistical analysis description: pCR rates between treatment groups were compared by a continuity-corrected chi-square test with 95% confidence intervals	
Comparison groups	PwR (Setting II) v Pw (Setting II)
Number of subjects included in analysis	395
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.476
Method	Chi-squared corrected

Statistical analysis title	pCR rates - comparison (Setting III)
Statistical analysis description: pCR rates between treatment groups were compared by a continuity-corrected two-sided chi-square test with 95% confidence intervals	
Comparison groups	ECH-TH (Setting III) v ECL-TL (Setting III)
Number of subjects included in analysis	615
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.042
Method	Chi-squared corrected

Secondary: Breast conservation rates between treatment arms, all settings

End point title	Breast conservation rates between treatment arms, all settings
End point description: Breast conservation rates (Breast conserving surgery, BCS) between treatment arms in each setting were compared by a continuity-corrected two-sided chi-square test and 95% confidence intervals were provided for the BCS. For setting I BCS was not performed in 9 (2 in ECB-TB arm and 7 in EC-T arm) and for setting II in 3 (2 in PwR arm and 1 in Pw arm) patients. Data were not available (missings) in 128 patients in setting I, 32 in settings II and 57 in setting III.	
End point type	Secondary
End point timeframe: Setting I: 24 weeks; Setting II: 12 weeks; Setting III: 24 weeks	

End point values	ECB-TB (Setting I)	EC-T (Setting I)	ECH-TH (Setting III)	ECL-TL (Setting III)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	956	969	307	308
Units: percent				
number (confidence interval 95%)				
BCS	66.6 (63.4 to 69.7)	66.6 (63.4 to 69.7)	63.6 (57.6 to 69.2)	58.6 (52.6 to 64.5)

End point values	PwR (Setting II)	Pw (Setting II)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	197	198		
Units: percent				
number (confidence interval 95%)				
BCS	54.5 (46.9 to 62.1)	62.0 (54.7 to 69.0)		

Statistical analyses

No statistical analyses for this end point

Secondary: clinical/ imaging response rates between treatment arms after EC, settings I and III

End point title	clinical/ imaging response rates between treatment arms after EC, settings I and III
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End point description:

Clinical/ imaging response rates between treatment arms in each setting were compared by a continuity-corrected two-sided chi-square test and 95% confidence intervals were provided. Clinical /imaging response included 1) Complete response (CR), 2) Partial response (PR), 3) Stable disease (SD) and 4) Progressive disease (PD). ORR (overall response rate) was defined as complete or partial response of the breast. Clinical/ imaging response rates were assessed after EC treatment and before surgery. The analyses were based on the mITT set. Here are reported clinical/ imaging response rates between treatment arms in settings I and III after EC treatment.

End point type	Secondary
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End point timeframe:

after EC treatment

End point values	ECB-TB (Setting I)	EC-T (Setting I)	ECH-TH (Setting III)	ECL-TL (Setting III)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	956	969	307	308
Units: percent				
number (not applicable)				
CR	7.1	5.6	11.2	7.2
PR	74.0	65.7	70.5	76.4
ORR	81.1	71.3	81.7	83.6

SD	18.1	26.0	17.6	15.1
PD	0.8	2.7	0.7	1.4
missing	11	11	12	16

Statistical analyses

Statistical analysis title	ORR rate after EC (setting I)
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Statistical analysis description:

Comparison of ORR rate after EC between treatment arms was based on the mITT set

Comparison groups	ECB-TB (Setting I) v EC-T (Setting I)
Number of subjects included in analysis	1925
Analysis specification	Pre-specified
Analysis type	superiority ^[4]
P-value	< 0.001
Method	Chi-squared corrected

Notes:

[4] - Continuity-corrected chi-square test

Statistical analysis title	ORR rate after EC (setting IIII)
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Statistical analysis description:

Comparison of ORR rate after EC between treatment arms was based on the mITT set

Comparison groups	ECH-TH (Setting III) v ECL-TL (Setting III)
Number of subjects included in analysis	615
Analysis specification	Pre-specified
Analysis type	superiority ^[5]
P-value	= 0.587
Method	Chi-squared corrected

Notes:

[5] - Continuity-corrected chi-square test

Secondary: clinical/ imaging response rates between treatment arms before surgery, all settings

End point title	clinical/ imaging response rates between treatment arms before surgery, all settings
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End point description:

Here are reported clinical/ imaging response rates between treatment arms in each setting before surgery (for more details see clinical/ imaging response rates between treatment arms after EC treatment).

End point type	Secondary
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End point timeframe:

before surgery

End point values	ECB-TB (Setting I)	EC-T (Setting I)	ECH-TH (Setting III)	ECL-TL (Setting III)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	956	969	307	308
Units: percent				
number (not applicable)				
CR	22.1	20.1	33.0	28.5
PR	65.3	59.5	57.1	61.7
ORR	87.4	79.6	90.1	90.2
SD	10.8	15.7	7.9	7.8
PD	1.8	4.7	2.0	2.0
missings	6	6	4	13

End point values	PwR (Setting II)	Pw (Setting II)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	197	198		
Units: percent				
number (not applicable)				
CR	8.2	9.2		
PR	44.0	52.0		
ORR	52.2	61.2		
SD	41.3	33.7		
PD	6.5	5.1		
missings	13	2		

Statistical analyses

Statistical analysis title	ORR rate before surgery (setting I)
Statistical analysis description:	
Comparison of ORR rate before surgery between treatment arms was based on the mITT set.	
Comparison groups	ECB-TB (Setting I) v EC-T (Setting I)
Number of subjects included in analysis	1925
Analysis specification	Pre-specified
Analysis type	superiority ^[6]
P-value	< 0.001
Method	Chi-squared corrected

Notes:

[6] - Continuity-corrected two-sided chi-square test

Statistical analysis title	ORR rate before surgery (setting II)
Statistical analysis description:	
Comparison of ORR rate before surgery between treatment arms was based on the mITT set	
Comparison groups	PwR (Setting II) v Pw (Setting II)

Number of subjects included in analysis	395
Analysis specification	Pre-specified
Analysis type	superiority ^[7]
P-value	= 0.079
Method	Chi-squared corrected

Notes:

[7] - Continuity-corrected chi-square test

Statistical analysis title	ORR rate before surgery (setting III)
Statistical analysis description:	
Comparison of ORR rate before surgery between treatment arms was based on the mITT set	
Comparison groups	ECH-TH (Setting III) v ECL-TL (Setting III)
Number of subjects included in analysis	615
Analysis specification	Pre-specified
Analysis type	superiority ^[8]
P-value	= 1
Method	Chi-squared corrected

Notes:

[8] - Continuity-corrected chi-square test

Secondary: Time-to-event endpoint, DFS

End point title	Time-to-event endpoint, DFS
End point description:	
Long-term (time-to-event) endpoint disease-free survival (DFS) is reported between treatment arms in each setting. The settings were analysed separately.	
DFS was defined as time in months from randomisation until any invasive loco-regional (ipsilateral breast, local/regional lymph nodes) recurrence of disease, any invasive contralateral breast cancer, any distant recurrence of disease, any secondary malignancy or death due to any cause whichever occurs first. Progression under therapy was not an event for DFS. Patients without event were censored at the date of the last contact.	
For patients of setting II treated with EC outside GeparQuinto before randomisation in setting II ("setting II fill-in patients") date of diagnosis was taken instead of the randomisation date; for all other setting II patients date of randomisation into GeparQuinto study (randomisation into setting I) was taken.	
Analysis was performed on mITT set.	
End point type	Secondary
End point timeframe:	
follow-up; median follow-up was 46.5 months (0.8-71.4) for setting I, 46.0 months (4.0-71.4) for setting II and 55.0 months (0.2-79.9) for setting III.	
3 year-DFS rates are reported.	

End point values	ECB-TB (Setting I)	EC-T (Setting I)	ECH-TH (Setting III)	ECL-TL (Setting III)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	956	969	307	308
Units: percent				
number (not applicable)				
DFS (3 years)	81.5	80.0	84.8	83.7

End point values	PwR (Setting II)	Pw (Setting II)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	197	198		
Units: percent				
number (not applicable)				
DFS (3 years)	69.3	71.3		

Statistical analyses

Statistical analysis title	DFS, setting I
Statistical analysis description:	
DFS rates and hazard ratio (HR) between treatment arms in setting I	
Comparison groups	ECB-TB (Setting I) v EC-T (Setting I)
Number of subjects included in analysis	1925
Analysis specification	Pre-specified
Analysis type	other ^[9]
P-value	= 0.78 ^[10]
Method	Logrank
Parameter estimate	Cox proportional hazard
Point estimate	1.03
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.84
upper limit	1.25

Notes:

[9] - Cox regression and logrank tests

[10] - log-rank p-value

Statistical analysis title	DFS, setting II
Statistical analysis description:	
DFS rates and hazard ratio (HR) between treatment arms in setting II	
Comparison groups	PwR (Setting II) v Pw (Setting II)
Number of subjects included in analysis	395
Analysis specification	Pre-specified
Analysis type	other ^[11]
P-value	= 0.987 ^[12]
Method	Logrank
Parameter estimate	Cox proportional hazard
Point estimate	0.997
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.69
upper limit	1.44

Notes:

[11] - Cox regression and logrank tests

[12] - log-rank p-value

Statistical analysis title	DFS, setting III
Statistical analysis description: DFS rates and hazard ratio (HR) between treatment arms in setting III	
Comparison groups	ECH-TH (Setting III) v ECL-TL (Setting III)
Number of subjects included in analysis	615
Analysis specification	Pre-specified
Analysis type	other ^[13]
P-value	= 0.808 ^[14]
Method	Logrank
Parameter estimate	Cox proportional hazard
Point estimate	1.04
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.73
upper limit	1.49

Notes:

[13] - Cox regression and logrank tests

[14] - log-rank p-value

Secondary: Time-to-event endpoint, OS

End point title	Time-to-event endpoint, OS
End point description: Long-term (time-to-event) endpoint overall survival (OS) is reported between treatment arms in each setting. The settings were analysed separately. OS was defined as time in months from randomisation until death due to any cause. Patients alive were censored at the date of the last contact. For patients of setting II treated with EC outside GeparQuinto before randomisation in setting II ("setting II fill-in patients") date of diagnosis was taken instead of the randomisation date; for all other setting II patients date of randomisation into GeparQuinto study (randomisation into setting I) was taken. Analysis was performed on the mITT set.	
End point type	Secondary
End point timeframe: follow-up, 3 years OS rates are reported	

End point values	ECB-TB (Setting I)	EC-T (Setting I)	ECH-TH (Setting III)	ECL-TL (Setting III)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	956	969	307	308
Units: percent				
number (not applicable)				
OS (3 years)	92.0	90.6	91.7	93.6

End point values	PwR (Setting II)	Pw (Setting II)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	197	198		
Units: percent				

number (not applicable)				
OS (3 years)	81.4	83.4		

Statistical analyses

Statistical analysis title	OS, setting I
Statistical analysis description: OS rates and hazard ration (HR) between treatment arms in setting I	
Comparison groups	ECB-TB (Setting I) v EC-T (Setting I)
Number of subjects included in analysis	1925
Analysis specification	Pre-specified
Analysis type	other ^[15]
P-value	= 0.836 ^[16]
Method	Logrank
Parameter estimate	Cox proportional hazard
Point estimate	0.97
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.75
upper limit	1.26

Notes:

[15] - Cox regression and logrank tests

[16] - log-rank p-value

Statistical analysis title	OS, setting II
Statistical analysis description: OS rates and hazard ration (HR) between treatment arms in setting II	
Comparison groups	PwR (Setting II) v Pw (Setting II)
Number of subjects included in analysis	395
Analysis specification	Pre-specified
Analysis type	other ^[17]
P-value	= 0.658 ^[18]
Method	Logrank
Parameter estimate	Cox proportional hazard
Point estimate	1.11
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.7
upper limit	1.74

Notes:

[17] - Cox regression and logrank tests

[18] - log-rank p-value

Statistical analysis title	OS, setting III
Statistical analysis description: OS rates and hazard ration (HR) between treatment arms in setting I	

Comparison groups	ECH-TH (Setting III) v ECL-TL (Setting III)
Number of subjects included in analysis	615
Analysis specification	Pre-specified
Analysis type	other ^[19]
P-value	= 0.297 ^[20]
Method	Logrank
Parameter estimate	Cox proportional hazard
Point estimate	0.76
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.45
upper limit	1.28

Notes:

[19] - Cox regression and logrank tests

[20] - log-rank p-value

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All adverse events occurring during the study treatment period were reported.

Adverse event reporting additional description:

AEs are reported per patient during the complete treatment duration for the overall safety population. Non-serious AEs any grade per patient occurring more frequently (> 20%) in the three settings are reported. Of note, overall number of single AE occurrences per term was not assessed, only per patient; SAEs are reported regardless of causality.

Assessment type	Systematic
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Dictionary used

Dictionary name	n.a.
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Dictionary version	n.a.
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Reporting groups

Reporting group title	ECB-TB (Setting I)
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Reporting group description:

Epirubicin-Cyclophosphamide-Docetaxel in combination with bevacizumab (ECB-TB)

Reporting group title	EC-T (Setting I)
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Reporting group description:

Epirubicin-Cyclophosphamide-Docetaxel (EC-T) (Setting I)

Reporting group title	Pw (Setting II)
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Reporting group description:

HER2-negative disease without response after 4 cycles of treatment (Setting II)

Patients received weekly paclitaxel alone (Pw)

Reporting group title	PwR (Setting II)
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Reporting group description:

HER2-negative disease without response after 4 cycles of treatment (Setting II)

Patients received weekly paclitaxel plus everolimus (RAD001, PwR)

Reporting group title	ECH-TH (Setting III)
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Reporting group description:

Patients with HER2-positive tumors received chemotherapy with EC followed by T in combination with trastuzumab (ECH-TH, Setting III)

Reporting group title	ECL-TL (Setting III)
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Reporting group description:

Patients with HER2-positive tumors received chemotherapy with EC followed by T in combination with lapatinib (ECL-TL, Setting III)

Serious adverse events	ECB-TB (Setting I)	EC-T (Setting I)	Pw (Setting II)
Total subjects affected by serious adverse events			
subjects affected / exposed	274 / 956 (28.66%)	179 / 969 (18.47%)	14 / 198 (7.07%)
number of deaths (all causes)	1	1	0
number of deaths resulting from adverse events	0	0	0
Vascular disorders			
Thromboembolic event			

subjects affected / exposed	10 / 956 (1.05%)	13 / 969 (1.34%)	0 / 198 (0.00%)
occurrences causally related to treatment / all	0 / 10	0 / 13	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lymphatic disorder			
subjects affected / exposed	0 / 956 (0.00%)	1 / 969 (0.10%)	0 / 198 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
subjects affected / exposed	2 / 956 (0.21%)	3 / 969 (0.31%)	0 / 198 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	21 / 956 (2.20%)	15 / 969 (1.55%)	0 / 198 (0.00%)
occurrences causally related to treatment / all	0 / 21	0 / 15	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nausea			
subjects affected / exposed	8 / 956 (0.84%)	10 / 969 (1.03%)	0 / 198 (0.00%)
occurrences causally related to treatment / all	0 / 8	0 / 10	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Edema			
subjects affected / exposed	0 / 956 (0.00%)	5 / 969 (0.52%)	0 / 198 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 5	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fever	Additional description: Fever (without grade 3-4 neutropenia)		
subjects affected / exposed	17 / 956 (1.78%)	11 / 969 (1.14%)	1 / 198 (0.51%)
occurrences causally related to treatment / all	0 / 17	0 / 11	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pain			
subjects affected / exposed	2 / 956 (0.21%)	1 / 969 (0.10%)	0 / 198 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Other general disorders			

subjects affected / exposed	3 / 956 (0.31%)	2 / 969 (0.21%)	0 / 198 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune system disorders			
Allergic reaction			
subjects affected / exposed	2 / 956 (0.21%)	0 / 969 (0.00%)	1 / 198 (0.51%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
Reproductive disorders			
subjects affected / exposed	2 / 956 (0.21%)	4 / 969 (0.41%)	0 / 198 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 4	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Dyspnea			
subjects affected / exposed	1 / 956 (0.10%)	4 / 969 (0.41%)	1 / 198 (0.51%)
occurrences causally related to treatment / all	0 / 1	0 / 4	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Other respiratory disorders			
subjects affected / exposed	6 / 956 (0.63%)	2 / 969 (0.21%)	0 / 198 (0.00%)
occurrences causally related to treatment / all	0 / 6	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Psychiatric disorders			
subjects affected / exposed	1 / 956 (0.10%)	4 / 969 (0.41%)	0 / 198 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 4	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Injury, poisoning and procedural complications			
subjects affected / exposed	13 / 956 (1.36%)	2 / 969 (0.21%)	1 / 198 (0.51%)
occurrences causally related to treatment / all	0 / 13	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			

Hypertension			
subjects affected / exposed	6 / 956 (0.63%)	2 / 969 (0.21%)	0 / 198 (0.00%)
occurrences causally related to treatment / all	0 / 6	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac except congestive heart failure			
subjects affected / exposed	1 / 956 (0.10%)	5 / 969 (0.52%)	1 / 198 (0.51%)
occurrences causally related to treatment / all	0 / 1	0 / 5	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Heart failure	Additional description: Congestive heart failure NYHA		
subjects affected / exposed	2 / 956 (0.21%)	0 / 969 (0.00%)	0 / 198 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Peripheral sensory neuropathy			
subjects affected / exposed	2 / 956 (0.21%)	1 / 969 (0.10%)	0 / 198 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Other neurological disorders			
subjects affected / exposed	10 / 956 (1.05%)	4 / 969 (0.41%)	0 / 198 (0.00%)
occurrences causally related to treatment / all	0 / 10	0 / 4	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Headache			
subjects affected / exposed	2 / 956 (0.21%)	1 / 969 (0.10%)	0 / 198 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Leukopenia			
subjects affected / exposed	29 / 956 (3.03%)	13 / 969 (1.34%)	1 / 198 (0.51%)
occurrences causally related to treatment / all	0 / 29	0 / 13	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neutropenia			
subjects affected / exposed	94 / 956 (9.83%)	52 / 969 (5.37%)	1 / 198 (0.51%)
occurrences causally related to treatment / all	0 / 94	0 / 52	0 / 1
deaths causally related to treatment / all	0 / 0	1 / 1	0 / 0

Febrile neutropenia			
subjects affected / exposed	74 / 956 (7.74%)	36 / 969 (3.72%)	0 / 198 (0.00%)
occurrences causally related to treatment / all	0 / 74	0 / 36	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thrombocytopenia	Additional description: Thrombopenia		
subjects affected / exposed	3 / 956 (0.31%)	0 / 969 (0.00%)	0 / 198 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anemia			
subjects affected / exposed	3 / 956 (0.31%)	4 / 969 (0.41%)	3 / 198 (1.52%)
occurrences causally related to treatment / all	0 / 3	0 / 4	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Other hematological			
subjects affected / exposed	2 / 956 (0.21%)	2 / 969 (0.21%)	0 / 198 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	1 / 956 (0.10%)	0 / 969 (0.00%)	0 / 198 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ear and labyrinth disorders			
subjects affected / exposed	1 / 956 (0.10%)	1 / 969 (0.10%)	0 / 198 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
Eye disorders			
subjects affected / exposed	0 / 956 (0.00%)	1 / 969 (0.10%)	0 / 198 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Vomiting			

subjects affected / exposed	5 / 956 (0.52%)	4 / 969 (0.41%)	0 / 198 (0.00%)
occurrences causally related to treatment / all	0 / 5	0 / 4	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Other gastrointestinal disorders			
subjects affected / exposed	12 / 956 (1.26%)	6 / 969 (0.62%)	0 / 198 (0.00%)
occurrences causally related to treatment / all	0 / 12	0 / 6	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Constipation			
subjects affected / exposed	2 / 956 (0.21%)	1 / 969 (0.10%)	0 / 198 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
ASAT			
subjects affected / exposed	0 / 956 (0.00%)	1 / 969 (0.10%)	0 / 198 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
subjects affected / exposed	2 / 956 (0.21%)	1 / 969 (0.10%)	0 / 198 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Palmar-plantar erythrodysaesthesia syndrome	Additional description: Hand-foot syndrome		
subjects affected / exposed	4 / 956 (0.42%)	3 / 969 (0.31%)	0 / 198 (0.00%)
occurrences causally related to treatment / all	0 / 4	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Other skin disorders			
subjects affected / exposed	3 / 956 (0.31%)	3 / 969 (0.31%)	0 / 198 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Renal and urinary disorders			
subjects affected / exposed	0 / 956 (0.00%)	2 / 969 (0.21%)	1 / 198 (0.51%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Musculoskeletal and connective tissue disorders			
Musculoskeletal disorders			
subjects affected / exposed	7 / 956 (0.73%)	7 / 969 (0.72%)	1 / 198 (0.51%)
occurrences causally related to treatment / all	0 / 7	0 / 7	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Infection			
subjects affected / exposed	40 / 956 (4.18%)	32 / 969 (3.30%)	2 / 198 (1.01%)
occurrences causally related to treatment / all	0 / 40	0 / 32	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Diarrhoea			
subjects affected / exposed	7 / 956 (0.73%)	4 / 969 (0.41%)	0 / 198 (0.00%)
occurrences causally related to treatment / all	0 / 7	0 / 4	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Stomatitis	Additional description: Stomatitis/mucositis/esophagitis		
subjects affected / exposed	40 / 956 (4.18%)	3 / 969 (0.31%)	1 / 198 (0.51%)
occurrences causally related to treatment / all	0 / 40	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	PwR (Setting II)	ECH-TH (Setting III)	ECL-TL (Setting III)
Total subjects affected by serious adverse events			
subjects affected / exposed	22 / 197 (11.17%)	63 / 307 (20.52%)	78 / 308 (25.32%)
number of deaths (all causes)	1	0	0
number of deaths resulting from adverse events	0	0	0
Vascular disorders			
Thromboembolic event			
subjects affected / exposed	0 / 197 (0.00%)	6 / 307 (1.95%)	6 / 308 (1.95%)
occurrences causally related to treatment / all	0 / 0	0 / 6	0 / 6
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lymphatic disorder			
subjects affected / exposed	0 / 197 (0.00%)	0 / 307 (0.00%)	0 / 308 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			

subjects affected / exposed	0 / 197 (0.00%)	1 / 307 (0.33%)	0 / 308 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	2 / 197 (1.02%)	1 / 307 (0.33%)	9 / 308 (2.92%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 9
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nausea			
subjects affected / exposed	0 / 197 (0.00%)	4 / 307 (1.30%)	2 / 308 (0.65%)
occurrences causally related to treatment / all	0 / 0	0 / 4	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Edema			
subjects affected / exposed	0 / 197 (0.00%)	1 / 307 (0.33%)	0 / 308 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fever			
	Additional description: Fever (without grade 3-4 neutropenia)		
subjects affected / exposed	5 / 197 (2.54%)	5 / 307 (1.63%)	4 / 308 (1.30%)
occurrences causally related to treatment / all	0 / 5	0 / 5	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pain			
subjects affected / exposed	0 / 197 (0.00%)	0 / 307 (0.00%)	1 / 308 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Other general disorders			
subjects affected / exposed	0 / 197 (0.00%)	1 / 307 (0.33%)	0 / 308 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune system disorders			
Allergic reaction			
subjects affected / exposed	0 / 197 (0.00%)	2 / 307 (0.65%)	2 / 308 (0.65%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Reproductive system and breast disorders			
Reproductive disorders			
subjects affected / exposed	0 / 197 (0.00%)	0 / 307 (0.00%)	1 / 308 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Dyspnea			
subjects affected / exposed	1 / 197 (0.51%)	2 / 307 (0.65%)	0 / 308 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Other respiratory disorders			
subjects affected / exposed	4 / 197 (2.03%)	1 / 307 (0.33%)	0 / 308 (0.00%)
occurrences causally related to treatment / all	0 / 4	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Psychiatric disorders			
subjects affected / exposed	0 / 197 (0.00%)	1 / 307 (0.33%)	3 / 308 (0.97%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Injury, poisoning and procedural complications			
subjects affected / exposed	0 / 197 (0.00%)	1 / 307 (0.33%)	1 / 308 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Hypertension			
subjects affected / exposed	0 / 197 (0.00%)	0 / 307 (0.00%)	1 / 308 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac except congestive heart failure			
subjects affected / exposed	1 / 197 (0.51%)	4 / 307 (1.30%)	2 / 308 (0.65%)
occurrences causally related to treatment / all	0 / 1	0 / 4	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Heart failure subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	Additional description: Congestive heart failure NYHA		
	1 / 197 (0.51%)	0 / 307 (0.00%)	1 / 308 (0.32%)
	0 / 1	0 / 0	0 / 1
	0 / 0	0 / 0	0 / 0
Nervous system disorders Peripheral sensory neuropathy subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	0 / 197 (0.00%)	1 / 307 (0.33%)	0 / 308 (0.00%)
	0 / 0	0 / 1	0 / 0
	0 / 0	0 / 0	0 / 0
Other neurological disorders subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	0 / 197 (0.00%)	4 / 307 (1.30%)	3 / 308 (0.97%)
	0 / 0	0 / 4	0 / 3
	0 / 0	0 / 0	0 / 0
Headache subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	0 / 197 (0.00%)	1 / 307 (0.33%)	1 / 308 (0.32%)
	0 / 0	0 / 1	0 / 1
	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders Leukopenia subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	0 / 197 (0.00%)	2 / 307 (0.65%)	5 / 308 (1.62%)
	0 / 0	0 / 2	0 / 5
	0 / 0	0 / 0	0 / 0
Neutropenia subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	2 / 197 (1.02%)	16 / 307 (5.21%)	20 / 308 (6.49%)
	0 / 2	0 / 16	0 / 20
	0 / 0	0 / 0	0 / 0
Febrile neutropenia subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	2 / 197 (1.02%)	11 / 307 (3.58%)	17 / 308 (5.52%)
	0 / 2	0 / 11	0 / 17
	0 / 0	0 / 0	0 / 0
Thrombocytopenia subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	Additional description: Thrombopenia		
	0 / 197 (0.00%)	0 / 307 (0.00%)	0 / 308 (0.00%)
	0 / 0	0 / 0	0 / 0
	0 / 0	0 / 0	0 / 0

Anemia			
subjects affected / exposed	1 / 197 (0.51%)	1 / 307 (0.33%)	2 / 308 (0.65%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Other hematological			
subjects affected / exposed	0 / 197 (0.00%)	1 / 307 (0.33%)	2 / 308 (0.65%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	1 / 197 (0.51%)	0 / 307 (0.00%)	0 / 308 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ear and labyrinth disorders			
subjects affected / exposed	0 / 197 (0.00%)	0 / 307 (0.00%)	0 / 308 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
Eye disorders			
subjects affected / exposed	0 / 197 (0.00%)	1 / 307 (0.33%)	0 / 308 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Vomiting			
subjects affected / exposed	0 / 197 (0.00%)	2 / 307 (0.65%)	1 / 308 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Other gastrointestinal disorders			
subjects affected / exposed	4 / 197 (2.03%)	1 / 307 (0.33%)	0 / 308 (0.00%)
occurrences causally related to treatment / all	0 / 4	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Constipation			

subjects affected / exposed	0 / 197 (0.00%)	0 / 307 (0.00%)	0 / 308 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
ASAT			
subjects affected / exposed	0 / 197 (0.00%)	0 / 307 (0.00%)	0 / 308 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
subjects affected / exposed	0 / 197 (0.00%)	1 / 307 (0.33%)	0 / 308 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Palmar-plantar erythrodysaesthesia syndrome	Additional description: Hand-foot syndrome		
subjects affected / exposed	0 / 197 (0.00%)	1 / 307 (0.33%)	1 / 308 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
othe skin disorders			
subjects affected / exposed	0 / 197 (0.00%)	1 / 307 (0.33%)	4 / 308 (1.30%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Renal and urinary disorders			
subjects affected / exposed	0 / 197 (0.00%)	0 / 307 (0.00%)	0 / 308 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Musculoskeletal disorders			
subjects affected / exposed	1 / 197 (0.51%)	2 / 307 (0.65%)	7 / 308 (2.27%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 7
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Infection			

subjects affected / exposed	7 / 197 (3.55%)	12 / 307 (3.91%)	11 / 308 (3.57%)
occurrences causally related to treatment / all	0 / 7	0 / 12	0 / 11
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Diarrhoea			
subjects affected / exposed	1 / 197 (0.51%)	4 / 307 (1.30%)	7 / 308 (2.27%)
occurrences causally related to treatment / all	0 / 1	0 / 4	0 / 7
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Stomatitis	Additional description: Stomatitis/mucositis/esophagitis		
subjects affected / exposed	1 / 197 (0.51%)	1 / 307 (0.33%)	2 / 308 (0.65%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	ECB-TB (Setting I)	EC-T (Setting I)	Pw (Setting II)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	952 / 956 (99.58%)	966 / 969 (99.69%)	195 / 198 (98.48%)
Investigations			
Aspartate aminotransferase			
subjects affected / exposed	336 / 956 (35.15%)	340 / 969 (35.09%)	59 / 198 (29.80%)
occurrences (all)	336	340	59
Alanine aminotransferase			
subjects affected / exposed	456 / 956 (47.70%)	453 / 969 (46.75%)	94 / 198 (47.47%)
occurrences (all)	456	453	94
Vascular disorders			
Hot flashes			
subjects affected / exposed	328 / 956 (34.31%)	332 / 969 (34.26%)	61 / 198 (30.81%)
occurrences (all)	328	332	61
Nervous system disorders			
Peripheral sensory neuropathy	Additional description: Sensory neuropathy		
subjects affected / exposed	499 / 956 (52.20%)	485 / 969 (50.05%)	114 / 198 (57.58%)
occurrences (all)	499	485	114
Blood and lymphatic system disorders			
Leukopenia			

subjects affected / exposed	914 / 956 (95.61%)	924 / 969 (95.36%)	149 / 198 (75.25%)
occurrences (all)	914	924	149
Neutropenia			
subjects affected / exposed	842 / 956 (88.08%)	841 / 969 (86.79%)	73 / 198 (36.87%)
occurrences (all)	842	841	73
Febrile neutropenia			
subjects affected / exposed	130 / 956 (13.60%)	69 / 969 (7.12%)	0 / 198 (0.00%)
occurrences (all)	130	69	0
Thrombocytopenia			
subjects affected / exposed	353 / 956 (36.92%)	271 / 969 (27.97%)	10 / 198 (5.05%)
occurrences (all)	353	271	10
Anemia			
subjects affected / exposed	783 / 956 (81.90%)	855 / 969 (88.24%)	166 / 198 (83.84%)
occurrences (all)	783	855	166
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	771 / 956 (80.65%)	763 / 969 (78.74%)	130 / 198 (65.66%)
occurrences (all)	771	763	130
Edema			
subjects affected / exposed	199 / 956 (20.82%)	290 / 969 (29.93%)	41 / 198 (20.71%)
occurrences (all)	199	290	41
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	725 / 956 (75.84%)	706 / 969 (72.86%)	43 / 198 (21.72%)
occurrences (all)	725	706	43
Vomiting			
subjects affected / exposed	346 / 956 (36.19%)	332 / 969 (34.26%)	14 / 198 (7.07%)
occurrences (all)	346	332	14
Diarrhoea			
subjects affected / exposed	383 / 956 (40.06%)	347 / 969 (35.81%)	32 / 198 (16.16%)
occurrences (all)	383	347	32
Stomatitis	Additional description: Stomatitis/mucositis/esophagitis any grade		
subjects affected / exposed	814 / 956 (85.15%)	652 / 969 (67.29%)	106 / 198 (53.54%)
occurrences (all)	814	652	106
Respiratory, thoracic and mediastinal disorders			

Dyspnea subjects affected / exposed occurrences (all)	214 / 956 (22.38%) 214	208 / 969 (21.47%) 208	36 / 198 (18.18%) 36
Skin and subcutaneous tissue disorders			
Alopecia subjects affected / exposed occurrences (all)	909 / 956 (95.08%) 909	913 / 969 (94.22%) 913	169 / 198 (85.35%) 169
Palmar-plantar erythrodysesthesia subjects affected / exposed occurrences (all)	438 / 956 (45.82%) 438	300 / 969 (30.96%) 300	45 / 198 (22.73%) 45
Rash acneiform subjects affected / exposed occurrences (all)	273 / 956 (28.56%) 273	257 / 969 (26.52%) 257	36 / 198 (18.18%) 36
Nail changes subjects affected / exposed occurrences (all)	418 / 956 (43.72%) 418	347 / 969 (35.81%) 347	69 / 198 (34.85%) 69
Infections and infestations			
Conjunctivitis subjects affected / exposed occurrences (all)	347 / 956 (36.30%) 347	278 / 969 (28.69%) 278	23 / 198 (11.62%) 23
Infection subjects affected / exposed occurrences (all)	449 / 956 (46.97%) 449	343 / 969 (35.40%) 343	45 / 198 (22.73%) 45

Non-serious adverse events	PwR (Setting II)	ECH-TH (Setting III)	ECL-TL (Setting III)
Total subjects affected by non-serious adverse events subjects affected / exposed	196 / 197 (99.49%)	303 / 307 (98.70%)	308 / 308 (100.00%)
Investigations			
Aspartate aminotransferase subjects affected / exposed occurrences (all)	88 / 197 (44.67%) 88	138 / 307 (44.95%) 138	138 / 308 (44.81%) 138
Alanine aminotransferase subjects affected / exposed occurrences (all)	105 / 197 (53.30%) 105	178 / 307 (57.98%) 178	173 / 308 (56.17%) 173
Vascular disorders			
Hot flashes			

subjects affected / exposed occurrences (all)	61 / 197 (30.96%) 61	105 / 307 (34.20%) 105	92 / 308 (29.87%) 92
Nervous system disorders			
Peripheral sensory neuropathy	Additional description: Sensory neuropathy		
subjects affected / exposed occurrences (all)	106 / 197 (53.81%) 106	175 / 307 (57.00%) 175	155 / 308 (50.32%) 155
Blood and lymphatic system disorders			
Leukopenia			
subjects affected / exposed occurrences (all)	178 / 197 (90.36%) 178	288 / 307 (93.81%) 288	286 / 308 (92.86%) 286
Neutropenia			
subjects affected / exposed occurrences (all)	113 / 197 (57.36%) 113	269 / 307 (87.62%) 269	250 / 308 (81.17%) 250
Febrile neutropenia			
subjects affected / exposed occurrences (all)	3 / 197 (1.52%) 3	22 / 307 (7.17%) 22	30 / 308 (9.74%) 30
Thrombocytopenia			
subjects affected / exposed occurrences (all)	31 / 197 (15.74%) 31	91 / 307 (29.64%) 91	101 / 308 (32.79%) 101
Anemia			
subjects affected / exposed occurrences (all)	172 / 197 (87.31%) 172	292 / 307 (95.11%) 292	288 / 308 (93.51%) 288
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed occurrences (all)	134 / 197 (68.02%) 134	244 / 307 (79.48%) 244	244 / 308 (79.22%) 244
Edema			
subjects affected / exposed occurrences (all)	51 / 197 (25.89%) 51	119 / 307 (38.76%) 119	88 / 308 (28.57%) 88
Gastrointestinal disorders			
Nausea			
subjects affected / exposed occurrences (all)	48 / 197 (24.37%) 48	221 / 307 (71.99%) 221	221 / 308 (71.75%) 221
Vomiting			
subjects affected / exposed occurrences (all)	17 / 197 (8.63%) 17	104 / 307 (33.88%) 104	125 / 308 (40.58%) 125

Diarrhoea			
subjects affected / exposed	64 / 197 (32.49%)	144 / 307 (46.91%)	231 / 308 (75.00%)
occurrences (all)	64	144	231
Stomatitis	Additional description: Stomatitis/mucositis/esophagitis any grade		
subjects affected / exposed	131 / 197 (66.50%)	221 / 307 (71.99%)	230 / 308 (74.68%)
occurrences (all)	131	221	230
Respiratory, thoracic and mediastinal disorders			
Dyspnea			
subjects affected / exposed	48 / 197 (24.37%)	90 / 307 (29.32%)	66 / 308 (21.43%)
occurrences (all)	48	90	66
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	163 / 197 (82.74%)	290 / 307 (94.46%)	284 / 308 (92.21%)
occurrences (all)	163	290	284
Palmar-plantar erythrodysesthesia	Additional description: Hand-foot syndrome any grade		
subjects affected / exposed	44 / 197 (22.34%)	117 / 307 (38.11%)	134 / 308 (43.51%)
occurrences (all)	44	117	134
Rash acneiform			
subjects affected / exposed	73 / 197 (37.06%)	97 / 307 (31.60%)	169 / 308 (54.87%)
occurrences (all)	73	97	169
Nail changes			
subjects affected / exposed	57 / 197 (28.93%)	147 / 307 (47.88%)	128 / 308 (41.56%)
occurrences (all)	57	147	128
Infections and infestations			
Conjunctivitis			
subjects affected / exposed	22 / 197 (11.17%)	108 / 307 (35.18%)	111 / 308 (36.04%)
occurrences (all)	22	108	111
Infection			
subjects affected / exposed	75 / 197 (38.07%)	123 / 307 (40.07%)	111 / 308 (36.04%)
occurrences (all)	75	123	111

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
29 January 2008	<p>Protocol amendment 1 included the following changes:</p> <ul style="list-style-type: none"> • General abolition of capecitabine for all study patients and all corresponding chapters and mentions were removed • The dose of docetaxel was increased from 75 mg/m² to 100 mg/m²: Patients with a HER2-positive or a HER2-negative tumors and a partial or complete remission will receive thereafter 4 cycles of docetaxel 100 mg/m², day 1 q day 21 (as part of setting I or III) • Supportive treatment for lapatinib was updated • Definition of pathological response: No microscopic evidence of residual viable invasive tumor cells in all resected specimens of the breast and no microscopic evidence of residual viable tumor cells in axillary nodes
26 February 2010	<p>Protocol amendment 2 included the following changes:</p> <ul style="list-style-type: none"> • Information on Anthracycline combined with Taxanes, Trastuzumab, Bevacizumab and Taxanes, and RAD001 and Paclitaxel treatments were updated • Information on expected toxicities for RAD001 and lapatinib was updated. The dose of lapatinib was reduced from 1250 mg daily to 1000 mg daily • Rationale of the GeparQuinto Trial was updated: The MRT-PREDICT substudy will compare the molecular changes with changes revealed by MR imaging • To examine and compare pre-specified molecular markers such as Ki-67, phospho-mTOR, YB-1, COX-2, HuR, phospho-p70 S6K, p65 NF kappa B, PTEN, PI3-K, Akt, SOX-10 (a marker for stem cell like breast cancers), and biomarkers from the GeparQuattro Herceptin resistance project, Neo-PREDICT, and other ongoing translational research projects on core biopsy before and after end of chemotherapy • Biomaterial collection: Patient has consented to the biomaterial collection and the paraffin-embedded tumor tissue block of diagnostic core has been sent to central biomaterial banks • Text editing of inclusion criteria No 7 and exclusion criteria No 9 • Update of exclusion criteria No 22: Concurrent treatment with: a) oral chronic corticosteroids unless initiated > 6 months prior to study entry and at low dose (≤ 10 mg methylprednisolone or equivalent) were not allowed; b) oral contraception and hormone replacement therapy prior treatment had to be stopped before study entry • Supportive treatment with pegfilgrastim and loperamide was updated • Toxicities (Clinically relevant cardiac events) at Follow-up evaluation had to be reported • Sample Size Determination: settings will be completed independently from each other. If setting I is completed before setting II then patients pretreated with EC outside of this trial and without interim response can be randomized
13 February 2013	<p>Protocol amendment 3 included the following changes:</p> <ul style="list-style-type: none"> • Follow-up evaluation: After chemotherapy, all patients will be followed up until end of study for the occurrence of local or distant recurrence and death. Every 6 months a visit at the trial site should be performed and documented. The site of recurrence as well as the cause of death should be documented. After the end of study no study specific treatment or investigation is planned. However information on health status of the patients might be collected either based on yearly chart reviews at the sites or based on information deriving from the GBG registry of previous study participants • End of study definition and analysis after breast surgery: End of study (EOS) will be when 379 events occurred in setting I and 120 events occurred in setting III, resp. The log-rank test will then have 80% power to detect the hazard ratio (HR) of 0.75 for disease-free survival to the significance level of $\alpha=0.05$. The analysis in setting II will be performed at the same time (HR=0.6).

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.

n.a.

Notes:

Online references

<http://www.ncbi.nlm.nih.gov/pubmed/22257523>

<http://www.ncbi.nlm.nih.gov/pubmed/20624784>

<http://www.ncbi.nlm.nih.gov/pubmed/23541564>

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