# 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 |

**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 >=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 wthout 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 tretament: 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) |

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 |

| | |
|---|---|
| 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 tretament: 12 weeks (4 cycles 1 q22) EC, if response than 12 weeks (4 cycles 1 q22) with T.

| **Arm title** | ECH-TH (Setting III) |
|---|---|

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) |
|---|---|

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 randomszed 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 patinets (pts) enrolled in the trial icluded 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)<br>All enrolled HER2-negative patients were randomly assigned in 1:1 ratio to receive Epirubicin-Cyclophosphamide-Docetaxel with Bevacizumab (ECB-TB) or wthout 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.<br>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<br>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)<br>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).<br>The dose of docetaxel was increased from 75 mg/m2 to 100 mg/m2 (Amendment 1).<br>The dose of lapatinib was reduced from 1250 mg daily to 1000 mg daily (Amendment 2).<br>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)<br>Epirubicin-Cyclophosphamide-Docetaxel + Lapatinib (ECL-TL), for more details see arm ECH-TH.<br>A total of 311 patients were randomszed 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-cyclophopshamide 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) |
|---|---|

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 wthout 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/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) |
|---|---|

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 randomszed 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) |
|---|---|
| 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-cyclophopshamide 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).

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

| End point title | pathological complete response (pCR=ypT0 ypN0) all settings |
|---|---|

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 |
|---|---|

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) |
|---|---|

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) |
|---|---|

| 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 ration (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.<br>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 |
|---|---|

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 |
|---|---|

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) |
|---|---|

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) |
|---|---|

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 |
|---|---|

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 |
|---|---|

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 armswas 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) edpoint 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 teratment 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 teratment 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 teratment 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) edpoint 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 longrank 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 |

### Dictionary used

| | |
|---|---|
| Dictionary name | n.a. |
| Dictionary version | n.a. |

### Reporting groups

| | |
|---|---|
| Reporting group title | ECB-TB (Setting I) |

Reporting group description:

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

| | |
|---|---|
| Reporting group title | EC-T (Setting I) |

Reporting group description:

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

| | |
|---|---|
| Reporting group title | Pw (Setting II) |

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) |

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) |

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) |

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

| | | | |
|---|---|---|---|
| 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 disordes | | | |
| 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 | 214 / 956 (22.38%) | 208 / 969 (21.47%) | 36 / 198 (18.18%) |
| occurrences (all) | 214 | 208 | 36 |
| Skin and subcutaneous tissue disorders | | | |
| Alopecia | | | |
| subjects affected / exposed | 909 / 956 (95.08%) | 913 / 969 (94.22%) | 169 / 198 (85.35%) |
| occurrences (all) | 909 | 913 | 169 |
| Palmar-plantar erythrodysesthesia | Additional description: Hand-foot syndrome any grade | | |
| subjects affected / exposed | 438 / 956 (45.82%) | 300 / 969 (30.96%) | 45 / 198 (22.73%) |
| occurrences (all) | 438 | 300 | 45 |
| Rash acneiform | | | |
| subjects affected / exposed | 273 / 956 (28.56%) | 257 / 969 (26.52%) | 36 / 198 (18.18%) |
| occurrences (all) | 273 | 257 | 36 |
| Nail changes | | | |
| subjects affected / exposed | 418 / 956 (43.72%) | 347 / 969 (35.81%) | 69 / 198 (34.85%) |
| occurrences (all) | 418 | 347 | 69 |
| Infections and infestations | | | |
| Conjunctivitis | | | |
| subjects affected / exposed | 347 / 956 (36.30%) | 278 / 969 (28.69%) | 23 / 198 (11.62%) |
| occurrences (all) | 347 | 278 | 23 |
| Infection | | | |
| subjects affected / exposed | 449 / 956 (46.97%) | 343 / 969 (35.40%) | 45 / 198 (22.73%) |
| occurrences (all) | 449 | 343 | 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 | 88 / 197 (44.67%) | 138 / 307 (44.95%) | 138 / 308 (44.81%) |
| occurrences (all) | 88 | 138 | 138 |
| Alanine aminotransferase | | | |
| subjects affected / exposed | 105 / 197 (53.30%) | 178 / 307 (57.98%) | 173 / 308 (56.17%) |
| occurrences (all) | 105 | 178 | 173 |
| Vascular disorders | | | |
| Hot flashes | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 61 / 197 (30.96%) | 105 / 307 (34.20%) | 92 / 308 (29.87%) |
| occurrences (all) | 61 | 105 | 92 |
| Nervous system disorders | | | |
| Peripheral sensory neuropathy | Additional description: Sensory neuropathy | | |
| subjects affected / exposed | 106 / 197 (53.81%) | 175 / 307 (57.00%) | 155 / 308 (50.32%) |
| occurrences (all) | 106 | 175 | 155 |
| Blood and lymphatic system disorders | | | |
| Leukopenia | | | |
| subjects affected / exposed | 178 / 197 (90.36%) | 288 / 307 (93.81%) | 286 / 308 (92.86%) |
| occurrences (all) | 178 | 288 | 286 |
| Neutropenia | | | |
| subjects affected / exposed | 113 / 197 (57.36%) | 269 / 307 (87.62%) | 250 / 308 (81.17%) |
| occurrences (all) | 113 | 269 | 250 |
| Febrile neutropenia | | | |
| subjects affected / exposed | 3 / 197 (1.52%) | 22 / 307 (7.17%) | 30 / 308 (9.74%) |
| occurrences (all) | 3 | 22 | 30 |
| Thrombocytopenia | | | |
| subjects affected / exposed | 31 / 197 (15.74%) | 91 / 307 (29.64%) | 101 / 308 (32.79%) |
| occurrences (all) | 31 | 91 | 101 |
| Anemia | | | |
| subjects affected / exposed | 172 / 197 (87.31%) | 292 / 307 (95.11%) | 288 / 308 (93.51%) |
| occurrences (all) | 172 | 292 | 288 |
| General disorders and administration site conditions | | | |
| Fatigue | | | |
| subjects affected / exposed | 134 / 197 (68.02%) | 244 / 307 (79.48%) | 244 / 308 (79.22%) |
| occurrences (all) | 134 | 244 | 244 |
| Edema | | | |
| subjects affected / exposed | 51 / 197 (25.89%) | 119 / 307 (38.76%) | 88 / 308 (28.57%) |
| occurrences (all) | 51 | 119 | 88 |
| Gastrointestinal disorders | | | |
| Nausea | | | |
| subjects affected / exposed | 48 / 197 (24.37%) | 221 / 307 (71.99%) | 221 / 308 (71.75%) |
| occurrences (all) | 48 | 221 | 221 |
| Vomiting | | | |
| subjects affected / exposed | 17 / 197 (8.63%) | 104 / 307 (33.88%) | 125 / 308 (40.58%) |
| occurrences (all) | 17 | 104 | 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 | Protocol amendment 1 included the following changes:<br>• General abolition of capecitabine for all study patients and all corresponding chapters and mentions were removed<br>• 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)<br>• Supportive treatment for lapatinib was updated<br>• 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 | Protocol amendment 2 included the following changes:<br>• Information on Anthracycline combined with Taxanes, Trastuzumab, Bevacizumab and Taxanes, and RAD001 and Paclitaxel treatments were updated<br>• Information on expected toxicities for RAD001 and lapatinib was updated. The dose of lapatinib was reduced from 1250 mg daily to 1000 mg daily<br>• Rationale of the GeparQuinto Trial was updated: The MRT-PREDICT substudy will compare the molecular changes with changes revealed by MR imaging<br>• 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<br>• 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<br>• Text editing of inclusion criteria No 7 and exclusion criteria No 9<br>• 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<br>• Supportive treatment with pegfilgrastim and loperamide was updated<br>• Toxicities (Clinically relevant cardiac events) at Follow-up evaluation had to be reported<br>• 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 | Protocol amendment 3 included the following changes:<br>• 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<br>• 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 occoured 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 α=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

http://www.ncbi.nlm.nih.gov/pubmed/24136883

http://www.ncbi.nlm.nih.gov/pubmed/25223482