



Clinical trial results:

A Randomized, Open Label, Multicenter Phase IIIb Study Comparing Two Trastuzumab Dosing Regimens, Each in Combination With Cisplatin/Capecitabine Chemotherapy, as First-Line Therapy in Patients With HER2-Positive Metastatic Gastric or Gastro-Esophageal Junction Adenocarcinoma Who Have Not Received Prior Treatment for Metastatic Disease

Summary

| | |
|--------------------------|-------------------------|
| EudraCT number | 2011-001526-19 |
| Trial protocol | DE ES GB IT CZ HU PT PL |
| Global end of trial date | 25 August 2015 |

Results information

| | |
|--------------------------------|-----------------|
| Result version number | v1 (current) |
| This version publication date | 22 October 2016 |
| First version publication date | 22 October 2016 |

Trial information

Trial identification

| | |
|-----------------------|---------|
| Sponsor protocol code | BO27798 |
|-----------------------|---------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT01450696 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|--|
| Sponsor organisation name | F. Hoffmann-La Roche AG |
| Sponsor organisation address | Grenzacherstrasse 124, Basel, Switzerland, CH-4070 |
| Public contact | Roche Trial Information Hotline, F. Hoffmann-La Roche AG, +41 61 6878333, global.trial_information@roche.com |
| Scientific contact | Roche Trial Information Hotline, F. Hoffmann-La Roche AG, +41 61 6878333, global.trial_information@roche.com |

Notes:

Paediatric regulatory details

| | |
|--|----|
| Is trial part of an agreed paediatric investigation plan (PIP) | No |
| Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial? | No |
| Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial? | No |

Notes:

Results analysis stage

| | |
|--|----------------|
| Analysis stage | Final |
| Date of interim/final analysis | 25 August 2015 |
| Is this the analysis of the primary completion data? | No |
| Global end of trial reached? | Yes |
| Global end of trial date | 25 August 2015 |
| Was the trial ended prematurely? | Yes |

Notes:

General information about the trial

Main objective of the trial:

This study was designed to evaluate the effect of Herceptin (trastuzumab) administered at a loading dose of 8 milligrams per kilogram (mg/kg) followed by 6 mg/kg every three weeks (q3w) as standard of care versus a loading dose of Herceptin at 8 mg/kg followed by 10 mg/kg along with cisplatin and capecitabine, to test whether it produced higher trastuzumab exposure and might have resulted in improved survival duration.

Protection of trial subjects:

The study was conducted in accordance with the principles of the "Declaration of Helsinki" and Good Clinical Practice (GCP).

Background therapy: -

Evidence for comparator: -

| | |
|---|------------------|
| Actual start date of recruitment | 29 December 2011 |
| Long term follow-up planned | Yes |
| Long term follow-up rationale | Safety, Efficacy |
| Long term follow-up duration | 24 Months |
| Independent data monitoring committee (IDMC) involvement? | Yes |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|--|
| Country: Number of subjects enrolled | Poland: 6 |
| Country: Number of subjects enrolled | Portugal: 1 |
| Country: Number of subjects enrolled | Spain: 5 |
| Country: Number of subjects enrolled | United Kingdom: 1 |
| Country: Number of subjects enrolled | Czech Republic: 14 |
| Country: Number of subjects enrolled | Germany: 2 |
| Country: Number of subjects enrolled | Hungary: 3 |
| Country: Number of subjects enrolled | Italy: 7 |
| Country: Number of subjects enrolled | Australia: 2 |
| Country: Number of subjects enrolled | Bosnia and Herzegovina: 16 |
| Country: Number of subjects enrolled | Brazil: 13 |
| Country: Number of subjects enrolled | Chile: 8 |
| Country: Number of subjects enrolled | China: 77 |
| Country: Number of subjects enrolled | Korea, Democratic People's Republic of: 13 |
| Country: Number of subjects enrolled | Mexico: 6 |
| Country: Number of subjects enrolled | New Zealand: 2 |
| Country: Number of subjects enrolled | Peru: 7 |

| | |
|--------------------------------------|------------------------|
| Country: Number of subjects enrolled | South Africa: 3 |
| Country: Number of subjects enrolled | Russian Federation: 30 |
| Country: Number of subjects enrolled | Serbia: 10 |
| Country: Number of subjects enrolled | Turkey: 38 |
| Country: Number of subjects enrolled | Ukraine: 26 |
| Country: Number of subjects enrolled | United States: 6 |
| Worldwide total number of subjects | 296 |
| EEA total number of subjects | 39 |

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) | 170 |
| From 65 to 84 years | 125 |
| 85 years and over | 1 |

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

A total of 248 participants (124 participants per group) were randomized in the study up to data cutoff date of 13 February 2015, and 48 additional participants (24 participants per group) were randomized between data cutoff date of 13 February 2015 and end of study (25 August 2015) for additional safety data.

Period 1

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

Arms

| | |
|------------------------------|--|
| Are arms mutually exclusive? | Yes |
| Arm title | Capecitabine + Cisplatin + Herceptin (6 mg/kg) |

Arm description:

Participants received Herceptin at a loading dose of 8 mg/kg on Day 1 of Cycle 1 followed by 6 mg/kg every three weeks (q3w) as standard of care from Day 1 of Cycle 2 until disease progression, occurrence of unacceptable toxicity, or withdrawal from the study for another reason (cycle length = 21 days). Participants also received cisplatin 80 milligrams per meter-squared (mg/m²) intravenously q3w plus capecitabine 800 mg/m² orally twice daily for 14 days q3w for up to 6 treatment cycles (Cycles 1 to 6).

| | |
|--|--|
| Arm type | Active comparator |
| Investigational medicinal product name | Herceptin |
| Investigational medicinal product code | |
| Other name | Trastuzumab |
| Pharmaceutical forms | Powder for concentrate for solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

Herceptin was administered IV at a loading dose of 8 mg/kg on Day 1 of Cycle 1 followed by 6 mg/kg or 10 mg/kg (depending upon treatment assignment) q3w from Day 1 of Cycle 2 until disease progression, occurrence of unacceptable toxicity, or withdrawal from the study for another reason.

| | |
|------------------|---|
| Arm title | Capecitabine + Cisplatin + Herceptin (10 mg/kg) |
|------------------|---|

Arm description:

Participants received Herceptin at a loading dose of 8 mg/kg on Day 1 of Cycle 1 followed by 10 mg/kg q3w from Day 1 of Cycle 2 until disease progression, occurrence of unacceptable toxicity, or withdrawal from the study for another reason (cycle length = 21 days). Participants also received cisplatin 80 mg/m² intravenously q3w plus capecitabine 800 mg/m² orally twice daily for 14 days q3w for up to 6 treatment cycles (Cycles 1 to 6).

| | |
|--|--|
| Arm type | Experimental |
| Investigational medicinal product name | Herceptin |
| Investigational medicinal product code | |
| Other name | Trastuzumab |
| Pharmaceutical forms | Powder for concentrate for solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

Herceptin was administered IV at a loading dose of 8 mg/kg on Day 1 of Cycle 1 followed by 6 mg/kg or 10 mg/kg (depending upon treatment assignment) q3w from Day 1 of Cycle 2 until disease progression, occurrence of unacceptable toxicity, or withdrawal from the study for another reason.

| Number of subjects in period 1 | Capecitabine + Cisplatin + Herceptin (6 mg/kg) | Capecitabine + Cisplatin + Herceptin (10 mg/kg) |
|---------------------------------------|--|---|
| Started | 148 | 148 |
| Treated (Safety Population) | 147 | 147 |
| Completed | 0 | 0 |
| Not completed | 148 | 148 |
| Consent withdrawn by subject | 13 | 2 |
| Study terminated by Sponsor | 53 | 58 |
| Death | 77 | 84 |
| Non-compliance | 1 | - |
| Never treated | 1 | 1 |
| Lost to follow-up | 3 | 3 |

Baseline characteristics

Reporting groups

| | |
|---|---|
| Reporting group title | Capecitabine + Cisplatin + Herceptin (6 mg/kg) |
| Reporting group description: Participants received Herceptin at a loading dose of 8 mg/kg on Day 1 of Cycle 1 followed by 6 mg/kg every three weeks (q3w) as standard of care from Day 1 of Cycle 2 until disease progression, occurrence of unacceptable toxicity, or withdrawal from the study for another reason (cycle length = 21 days). Participants also received cisplatin 80 milligrams per meter-squared (mg/m ²) intravenously q3w plus capecitabine 800 mg/m ² orally twice daily for 14 days q3w for up to 6 treatment cycles (Cycles 1 to 6). | |
| Reporting group title | Capecitabine + Cisplatin + Herceptin (10 mg/kg) |
| Reporting group description: Participants received Herceptin at a loading dose of 8 mg/kg on Day 1 of Cycle 1 followed by 10 mg/kg q3w from Day 1 of Cycle 2 until disease progression, occurrence of unacceptable toxicity, or withdrawal from the study for another reason (cycle length = 21 days). Participants also received cisplatin 80 mg/m ² intravenously q3w plus capecitabine 800 mg/m ² orally twice daily for 14 days q3w for up to 6 treatment cycles (Cycles 1 to 6). | |

| Reporting group values | Capecitabine + Cisplatin + Herceptin (6 mg/kg) | Capecitabine + Cisplatin + Herceptin (10 mg/kg) | Total |
|---|--|---|-------|
| Number of subjects | 148 | 148 | 296 |
| Age categorical Units: Subjects | | | |
| Age continuous Units: years arithmetic mean standard deviation | 59.5 ± 10.6 | 62.4 ± 10.7 | - |
| Gender categorical Units: Subjects | | | |
| Female | 32 | 37 | 69 |
| Male | 116 | 111 | 227 |

End points

End points reporting groups

| | |
|---|---|
| Reporting group title | Capecitabine + Cisplatin + Herceptin (6 mg/kg) |
| Reporting group description: Participants received Herceptin at a loading dose of 8 mg/kg on Day 1 of Cycle 1 followed by 6 mg/kg every three weeks (q3w) as standard of care from Day 1 of Cycle 2 until disease progression, occurrence of unacceptable toxicity, or withdrawal from the study for another reason (cycle length = 21 days). Participants also received cisplatin 80 milligrams per meter-squared (mg/m ²) intravenously q3w plus capecitabine 800 mg/m ² orally twice daily for 14 days q3w for up to 6 treatment cycles (Cycles 1 to 6). | |
| Reporting group title | Capecitabine + Cisplatin + Herceptin (10 mg/kg) |
| Reporting group description: Participants received Herceptin at a loading dose of 8 mg/kg on Day 1 of Cycle 1 followed by 10 mg/kg q3w from Day 1 of Cycle 2 until disease progression, occurrence of unacceptable toxicity, or withdrawal from the study for another reason (cycle length = 21 days). Participants also received cisplatin 80 mg/m ² intravenously q3w plus capecitabine 800 mg/m ² orally twice daily for 14 days q3w for up to 6 treatment cycles (Cycles 1 to 6). | |

Primary: Percentage of Participants Who Died - Full Analysis Set (FAS)

| | |
|---|--|
| End point title | Percentage of Participants Who Died - Full Analysis Set (FAS) ^[1] |
| End point description: The percentage of participants who died as of the analysis data cutoff date of 13 February 2015 was reported among participants from the FAS with available data. The FAS population included all participants who were randomized in this study. Here, number of subjects analyzed reflects the number of participants who were evaluable for this endpoint. | |
| End point type | Primary |
| End point timeframe: From date of randomization until death or premature withdrawal (up to approximately 31 months or data cutoff date of 13 February 2015) | |
| Notes: [1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point. Justification: No statistical analysis was planned for this endpoint. | |

| End point values | Capecitabine + Cisplatin + Herceptin (6 mg/kg) | Capecitabine + Cisplatin + Herceptin (10 mg/kg) | | |
|-----------------------------------|--|---|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 124 | 124 | | |
| Units: percentage of participants | | | | |
| number (not applicable) | 46.8 | 54 | | |

Statistical analyses

No statistical analyses for this end point

Primary: Overall Survival - FAS

| | |
|-----------------|------------------------|
| End point title | Overall Survival - FAS |
|-----------------|------------------------|

End point description:

Overall survival was defined as the time from the date of randomization to the date of death from any cause. Overall survival was estimated among participants from the FAS using the Kaplan-Meier approach. The 95 percent (%) confidence interval (CI) for median was computed using the method of Brookmeyer and Crowley. FAS population. Here, number of participants analyzed reflects the number of participants who were evaluable for this outcome measure.

| | |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

From date of randomization until death or premature withdrawal (up to approximately 31 months or data cutoff date of 13 February 2015)

| End point values | Capecitabine + Cisplatin + Herceptin (6 mg/kg) | Capecitabine + Cisplatin + Herceptin (10 mg/kg) | | |
|----------------------------------|---|--|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 124 | 124 | | |
| Units: months | | | | |
| median (confidence interval 95%) | 12.485 (10.086 to 13.864) | 10.612 (9.363 to 12.419) | | |

Statistical analyses

| | |
|-----------------------------------|---------------------|
| Statistical analysis title | Stratified Analysis |
|-----------------------------------|---------------------|

Statistical analysis description:

Stratified analysis included stratum of creatinine clearance (45 to 59 milliliters per minute [mL/min] and greater than or equal to \geq 60 mL/min). Hazard ratio was estimated by Cox regression.

| | |
|---|--|
| Comparison groups | Capecitabine + Cisplatin + Herceptin (6 mg/kg) v Capecitabine + Cisplatin + Herceptin (10 mg/kg) |
| Number of subjects included in analysis | 248 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.2401 |
| Method | Logrank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 1.24 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.86 |
| upper limit | 1.78 |

| | |
|-----------------------------------|-----------------------|
| Statistical analysis title | Unstratified Analysis |
|-----------------------------------|-----------------------|

Statistical analysis description:

Unstratified analysis. Hazard ratio was estimated by Cox regression.

| | |
|-------------------|--|
| Comparison groups | Capecitabine + Cisplatin + Herceptin (6 mg/kg) v Capecitabine + Cisplatin + Herceptin (10 mg/kg) |
|-------------------|--|

| | |
|---|-------------------|
| Number of subjects included in analysis | 248 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.1285 |
| Method | Logrank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 1.32 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.92 |
| upper limit | 1.88 |

Secondary: Percentage of Participants Who Died - Per Protocol Set (PPS)

| | |
|---|--|
| End point title | Percentage of Participants Who Died - Per Protocol Set (PPS) |
| End point description: | |
| The percentage of participants who died as of the analysis data cutoff date of 13 February 2015 was reported among participants from the PPS. The PPS included all participants who were found to have a trastuzumab minimum plasma concentration (Cmin) less than (<) 12 micrograms per milliliter (µg/mL) on treatment Day 21 of Cycle 1 following the initial loading dose of 8 mg/kg. | |
| End point type | Secondary |
| End point timeframe: | |
| From date of randomization until death or premature withdrawal (up to approximately 31 months or data cutoff date of 13 February 2015) | |

| End point values | Capecitabine + Cisplatin + Herceptin (6 mg/kg) | Capecitabine + Cisplatin + Herceptin (10 mg/kg) | | |
|-----------------------------------|---|--|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 33 | 32 | | |
| Units: percentage of participants | | | | |
| number (not applicable) | 51.5 | 59.4 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival - PPS

| | |
|---|------------------------|
| End point title | Overall Survival - PPS |
| End point description: | |
| Overall survival was defined as the time from the date of randomization to the date of death from any cause. Overall survival was estimated among participants from the PPS using the Kaplan-Meier approach. The 95% CI for median was computed using the method of Brookmeyer and Crowley. PPS population. | |
| End point type | Secondary |

End point timeframe:

From date of randomization until death or premature withdrawal (up to approximately 31 months or data cutoff date of 13 February 2015)

| End point values | Capecitabine + Cisplatin + Herceptin (6 mg/kg) | Capecitabine + Cisplatin + Herceptin (10 mg/kg) | | |
|----------------------------------|--|---|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 33 | 32 | | |
| Units: months | | | | |
| median (confidence interval 95%) | 10.809 (8.082 to 14.752) | 9.363 (5.552 to 14.357) | | |

Statistical analyses

| Statistical analysis title | Stratified Analysis |
|----------------------------|---------------------|
|----------------------------|---------------------|

Statistical analysis description:

Stratified analysis included stratum of creatinine clearance (45 to 59 mL/min and ≥ 60 mL/min). Hazard ratio was estimated by Cox regression.

| | |
|---|--|
| Comparison groups | Capecitabine + Cisplatin + Herceptin (6 mg/kg) v Capecitabine + Cisplatin + Herceptin (10 mg/kg) |
| Number of subjects included in analysis | 65 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.9931 |
| Method | Logrank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 1 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.49 |
| upper limit | 2.04 |

| Statistical analysis title | Unstratified Analysis |
|----------------------------|-----------------------|
|----------------------------|-----------------------|

Statistical analysis description:

Unstratified analysis. Hazard ratio was estimated by Cox regression.

| | |
|-------------------|--|
| Comparison groups | Capecitabine + Cisplatin + Herceptin (6 mg/kg) v Capecitabine + Cisplatin + Herceptin (10 mg/kg) |
|-------------------|--|

| | |
|---|-------------------|
| Number of subjects included in analysis | 65 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.9458 |
| Method | Logrank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 1.02 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.52 |
| upper limit | 2.02 |

Secondary: Percentage of Participants With Disease Progression or Death - PPS

| | |
|-----------------|--|
| End point title | Percentage of Participants With Disease Progression or Death - PPS |
|-----------------|--|

End point description:

Disease progression was defined by Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1 as a $\geq 20\%$ increase in the sum of diameters of target lesions, taking as reference the smallest sum on study including Baseline (nadir). In addition to the relative increase of 20%, the sum was also required to demonstrate an absolute increase of ≥ 5 millimeters (mm). The percentage of participants who died or experienced disease progression as of the analysis data cutoff date of 13 February 2015 was reported among participants from the PPS. PPS population.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

From date of randomization until first occurrence of disease progression or death; assessed every 6 weeks (up to approximately 31 months or data cutoff date of 13 February 2015)

| End point values | Capecitabine + Cisplatin + Herceptin (6 mg/kg) | Capecitabine + Cisplatin + Herceptin (10 mg/kg) | | |
|-----------------------------------|--|---|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 33 | 32 | | |
| Units: percentage of participants | | | | |
| number (not applicable) | 75.8 | 81.3 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Progression-Free Survival - PPS

| | |
|-----------------|---------------------------------|
| End point title | Progression-Free Survival - PPS |
|-----------------|---------------------------------|

End point description:

Progression-free survival was defined as the time between the day of randomization and the date of first documentation of disease progression or date of death, whichever occurred first, measured following RECIST Version 1.1 criteria. Disease progression was defined as a $\geq 20\%$ increase in the sum of

diameters of target lesions, taking as reference the smallest sum on study including Baseline (nadir). In addition to the relative increase of 20%, the sum was also required to demonstrate an absolute increase of ≥ 5 mm. The 95% CI for median was computed using the method of Brookmeyer and Crowley. PPS population.

| | |
|---|-----------|
| End point type | Secondary |
| End point timeframe: | |
| From date of randomization until first occurrence of disease progression or death; assessed every 6 weeks (up to approximately 31 months or data cutoff date of 13 February 2015) | |

| | | | | |
|----------------------------------|--|---|--|--|
| End point values | Capecitabine + Cisplatin + Herceptin (6 mg/kg) | Capecitabine + Cisplatin + Herceptin (10 mg/kg) | | |
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 33 | 32 | | |
| Units: months | | | | |
| median (confidence interval 95%) | 5.388 (2.793 to 7.721) | 4.37 (2.727 to 6.834) | | |

Statistical analyses

| | |
|-----------------------------------|---------------------|
| Statistical analysis title | Stratified Analysis |
|-----------------------------------|---------------------|

Statistical analysis description:

Stratified analysis included stratum of creatinine clearance (45 to 59 mL/min and ≥ 60 mL/min). Hazard ratio was estimated by Cox regression.

| | |
|---|--|
| Comparison groups | Capecitabine + Cisplatin + Herceptin (6 mg/kg) v Capecitabine + Cisplatin + Herceptin (10 mg/kg) |
| Number of subjects included in analysis | 65 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.6759 |
| Method | Logrank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 1.13 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.63 |
| upper limit | 2.02 |

| | |
|-----------------------------------|-----------------------|
| Statistical analysis title | Unstratified Analysis |
|-----------------------------------|-----------------------|

Statistical analysis description:

Unstratified analysis. Hazard ratio was estimated by Cox regression.

| | |
|-------------------|--|
| Comparison groups | Capecitabine + Cisplatin + Herceptin (6 mg/kg) v Capecitabine + Cisplatin + Herceptin (10 mg/kg) |
|-------------------|--|

| | |
|---|-------------------|
| Number of subjects included in analysis | 65 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.5764 |
| Method | Logrank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 1.17 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.67 |
| upper limit | 2.05 |

Secondary: Percentage of Participants With Objective Response - PPS

| | |
|---|--|
| End point title | Percentage of Participants With Objective Response - PPS |
| End point description: | |
| Objective response was defined as the occurrence of either a complete response (CR) or partial response (PR) as determined by RECIST Version 1.1 based on investigator assessment. CR was defined as disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) were required to have reduction in short axis to <10 mm. PR was defined as a $\geq 30\%$ decrease in the sum of diameters of target lesions, taking as reference the Baseline sum diameters. The 95% CI was constructed using Blyth-Still-Casella method. PPS population. | |
| End point type | Secondary |
| End point timeframe: | |
| From date of randomization until first occurrence of disease progression or death; assessed every 6 weeks (up to approximately 31 months or data cutoff date of 13 February 2015) | |

| End point values | Capecitabine + Cisplatin + Herceptin (6 mg/kg) | Capecitabine + Cisplatin + Herceptin (10 mg/kg) | | |
|-----------------------------------|--|---|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 33 | 32 | | |
| Units: percentage of participants | | | | |
| number (confidence interval 95%) | 57.6 (40.12 to 73.16) | 50 (31.89 to 68.11) | | |

Statistical analyses

| | |
|--|--|
| Statistical analysis title | Difference in Response Rates |
| Statistical analysis description: | |
| The 95% CI for difference in response rates was constructed using the normal approximation to the binomial distribution. | |
| Comparison groups | Capecitabine + Cisplatin + Herceptin (6 mg/kg) v Capecitabine + Cisplatin + Herceptin (10 mg/kg) |

| | |
|---|------------------------------|
| Number of subjects included in analysis | 65 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.5402 |
| Method | Chi-squared |
| Parameter estimate | Difference in response rates |
| Point estimate | -7.58 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -31.75 |
| upper limit | 16.6 |

| | |
|---|--|
| Statistical analysis title | Odds Ratio |
| Comparison groups | Capecitabine + Cisplatin + Herceptin (6 mg/kg) v Capecitabine + Cisplatin + Herceptin (10 mg/kg) |
| Number of subjects included in analysis | 65 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 0.74 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.28 |
| upper limit | 1.96 |

Secondary: Trastuzumab Cmin on Day 21 of Cycles 1 to 11 - FAS

| | |
|--|--|
| End point title | Trastuzumab Cmin on Day 21 of Cycles 1 to 11 - FAS |
| End point description: | |
| Cmin samples were obtained in all participants randomized to receive Herceptin (FAS). The observed Cmin was recorded, averaged among all participants, and expressed in µg/mL. FAS population. Here, number of subjects analyzed reflects the number of participants who were evaluable for this endpoint. Here also, "n" reflects the number of participants who were evaluable for each category in the respective arms. | |
| End point type | Secondary |
| End point timeframe: | |
| Day 21 of Cycle 1, 2, 3, 4, 5, 7, 9, 11 (cycle length = 21 days) | |

| End point values | Capecitabine + Cisplatin + Herceptin (6 mg/kg) | Capecitabine + Cisplatin + Herceptin (10 mg/kg) | | |
|--------------------------------------|---|--|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 100 | 99 | | |
| Units: µg/mL | | | | |
| arithmetic mean (standard deviation) | | | | |
| Cycle 1 (n=100,99) | 17.1 (± 14.3) | 18.1 (± 18.1) | | |
| Cycle 2 (n=93,76) | 19.2 (± 8.8) | 35.3 (± 19.4) | | |
| Cycle 3 (n=77,71) | 23.2 (± 11.8) | 40.7 (± 20.6) | | |
| Cycle 4 (n=73,61) | 25.9 (± 12.1) | 47.6 (± 20.2) | | |
| Cycle 5 (n=70,60) | 26.7 (± 10.6) | 49.3 (± 23.2) | | |
| Cycle 7 (n=51,44) | 31.4 (± 14.2) | 58.1 (± 27.6) | | |
| Cycle 9 (n=31,24) | 33.7 (± 17.6) | 61 (± 23.9) | | |
| Cycle 11 (n=24,16) | 32.5 (± 14.7) | 68.4 (± 35.9) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Trastuzumab Serum Concentration on Day 1 of Cycle 1 - FAS

| | |
|--|---|
| End point title | Trastuzumab Serum Concentration on Day 1 of Cycle 1 - FAS |
| End point description: | |
| Trastuzumab serum concentration samples were obtained in all participants randomized to receive Herceptin (FAS). The observed concentration values were recorded, averaged among all participants, and expressed in µg/mL. FAS population. Here, number of subjects analyzed reflects the number of participants who were evaluable for this endpoint. Here also, "n" reflects the number of participants who were evaluable for each category in the respective groups. | |
| End point type | Secondary |
| End point timeframe: | |
| Pre-dose (0 minutes) and within 15 minutes after end of 2-hour Herceptin infusion on Day 1 of Cycle 1 (cycle length = 21 days) | |

| End point values | Capecitabine + Cisplatin + Herceptin (6 mg/kg) | Capecitabine + Cisplatin + Herceptin (10 mg/kg) | | |
|--------------------------------------|---|--|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 110 | 111 | | |
| Units: µg/mL | | | | |
| arithmetic mean (standard deviation) | | | | |
| Pre-dose (n=109,110) | 0.168 (± 1.69) | 0.0204 (± 0.123) | | |
| End of infusion (n=110,111) | 126 (± 59.6) | 137 (± 55.7) | | |

Statistical analyses

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From date of randomization until 6 months after last dose of study drug or end of study (up to approximately 32 months or final data collection date of 25 August 2015)

Adverse event reporting additional description:

Safety evaluable population included all participants who were randomized and received at least one dose of any component of study treatment.

| | |
|-----------------|----------------|
| Assessment type | Non-systematic |
|-----------------|----------------|

Dictionary used

| | |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

| | |
|--------------------|------|
| Dictionary version | 18.0 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|--|
| Reporting group title | Capecitabine + Cisplatin + Herceptin (6 mg/kg) |
|-----------------------|--|

Reporting group description:

Participants received Herceptin at a loading dose of 8 mg/kg on Day 1 of Cycle 1 followed by 6 mg/kg q3w as standard of care from Day 1 of Cycle 2 until disease progression, occurrence of unacceptable toxicity, or withdrawal from the study for another reason (cycle length = 21 days). Participants also received cisplatin 80 mg/m² intravenously q3w plus capecitabine 800 mg/m² orally twice daily for 14 days q3w for up to 6 treatment cycles (Cycles 1 to 6).

| | |
|-----------------------|---|
| Reporting group title | Capecitabine + Cisplatin + Herceptin (10 mg/kg) |
|-----------------------|---|

Reporting group description:

Participants received Herceptin at a loading dose of 8 mg/kg on Day 1 of Cycle 1 followed by 10 mg/kg q3w from Day 1 of Cycle 2 until disease progression, occurrence of unacceptable toxicity, or withdrawal from the study for another reason (cycle length = 21 days). Participants also received cisplatin 80 mg/m² intravenously q3w plus capecitabine 800 mg/m² orally twice daily for 14 days q3w for up to 6 treatment cycles (Cycles 1 to 6).

| Serious adverse events | Capecitabine + Cisplatin + Herceptin (6 mg/kg) | Capecitabine + Cisplatin + Herceptin (10 mg/kg) | |
|---|--|---|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 35 / 147 (23.81%) | 38 / 147 (25.85%) | |
| number of deaths (all causes) | 77 | 84 | |
| number of deaths resulting from adverse events | | | |
| Vascular disorders | | | |
| Bleeding varicose vein | | | |
| subjects affected / exposed | 0 / 147 (0.00%) | 1 / 147 (0.68%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Deep vein thrombosis | | | |
| subjects affected / exposed | 0 / 147 (0.00%) | 1 / 147 (0.68%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|--|-----------------|-----------------|--|
| Peripheral embolism | | | |
| subjects affected / exposed | 0 / 147 (0.00%) | 1 / 147 (0.68%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| General disorders and administration site conditions | | | |
| Asthenia | | | |
| subjects affected / exposed | 1 / 147 (0.68%) | 0 / 147 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Death | | | |
| subjects affected / exposed | 1 / 147 (0.68%) | 1 / 147 (0.68%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 1 | |
| Pyrexia | | | |
| subjects affected / exposed | 1 / 147 (0.68%) | 0 / 147 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Chronic obstructive pulmonary disease | | | |
| subjects affected / exposed | 0 / 147 (0.00%) | 1 / 147 (0.68%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Pneumonia aspiration | | | |
| subjects affected / exposed | 0 / 147 (0.00%) | 1 / 147 (0.68%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pulmonary embolism | | | |
| subjects affected / exposed | 1 / 147 (0.68%) | 0 / 147 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Injury, poisoning and procedural complications | | | |
| Infusion related reaction | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 147 (0.00%) | 1 / 147 (0.68%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lymphatic duct injury | | | |
| subjects affected / exposed | 1 / 147 (0.68%) | 0 / 147 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Spinal compression fracture | | | |
| subjects affected / exposed | 1 / 147 (0.68%) | 0 / 147 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac disorders | | | |
| Bradycardia | | | |
| subjects affected / exposed | 1 / 147 (0.68%) | 1 / 147 (0.68%) | |
| occurrences causally related to treatment / all | 0 / 1 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac arrest | | | |
| subjects affected / exposed | 1 / 147 (0.68%) | 1 / 147 (0.68%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 1 / 1 | 0 / 1 | |
| Cardiovascular insufficiency | | | |
| subjects affected / exposed | 1 / 147 (0.68%) | 0 / 147 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Myocardial infarction | | | |
| subjects affected / exposed | 0 / 147 (0.00%) | 1 / 147 (0.68%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Palpitations | | | |
| subjects affected / exposed | 0 / 147 (0.00%) | 1 / 147 (0.68%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Tachyarrhythmia | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 147 (0.68%) | 0 / 147 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ventricular fibrillation | | | |
| subjects affected / exposed | 0 / 147 (0.00%) | 1 / 147 (0.68%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Nervous system disorders | | | |
| Cerebral ischaemia | | | |
| subjects affected / exposed | 0 / 147 (0.00%) | 1 / 147 (0.68%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Cerebrovascular accident | | | |
| subjects affected / exposed | 1 / 147 (0.68%) | 0 / 147 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Dizziness | | | |
| subjects affected / exposed | 0 / 147 (0.00%) | 1 / 147 (0.68%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Haemorrhage intracranial | | | |
| subjects affected / exposed | 1 / 147 (0.68%) | 0 / 147 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 7 / 147 (4.76%) | 6 / 147 (4.08%) | |
| occurrences causally related to treatment / all | 0 / 8 | 1 / 8 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Febrile neutropenia | | | |
| subjects affected / exposed | 3 / 147 (2.04%) | 3 / 147 (2.04%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Neutropenia | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 147 (0.68%) | 0 / 147 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pancytopenia | | | |
| subjects affected / exposed | 0 / 147 (0.00%) | 1 / 147 (0.68%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Thrombocytopenia | | | |
| subjects affected / exposed | 0 / 147 (0.00%) | 1 / 147 (0.68%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal disorders | | | |
| Abdominal pain upper | | | |
| subjects affected / exposed | 1 / 147 (0.68%) | 0 / 147 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Constipation | | | |
| subjects affected / exposed | 1 / 147 (0.68%) | 0 / 147 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Diarrhoea | | | |
| subjects affected / exposed | 0 / 147 (0.00%) | 4 / 147 (2.72%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastric haemorrhage | | | |
| subjects affected / exposed | 2 / 147 (1.36%) | 0 / 147 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal haemorrhage | | | |
| subjects affected / exposed | 1 / 147 (0.68%) | 0 / 147 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Intestinal obstruction | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 147 (0.68%) | 0 / 147 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nausea | | | |
| subjects affected / exposed | 2 / 147 (1.36%) | 0 / 147 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Obstruction gastric | | | |
| subjects affected / exposed | 2 / 147 (1.36%) | 1 / 147 (0.68%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Odynophagia | | | |
| subjects affected / exposed | 0 / 147 (0.00%) | 1 / 147 (0.68%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Oesophageal haemorrhage | | | |
| subjects affected / exposed | 0 / 147 (0.00%) | 1 / 147 (0.68%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Upper gastrointestinal haemorrhage | | | |
| subjects affected / exposed | 0 / 147 (0.00%) | 1 / 147 (0.68%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vomiting | | | |
| subjects affected / exposed | 5 / 147 (3.40%) | 3 / 147 (2.04%) | |
| occurrences causally related to treatment / all | 0 / 5 | 1 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hepatobiliary disorders | | | |
| Drug-induced liver injury | | | |
| subjects affected / exposed | 0 / 147 (0.00%) | 1 / 147 (0.68%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal and urinary disorders | | | |

| | | | |
|---|-----------------|-----------------|--|
| Acute kidney injury | | | |
| subjects affected / exposed | 4 / 147 (2.72%) | 2 / 147 (1.36%) | |
| occurrences causally related to treatment / all | 0 / 5 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 2 | |
| Renal failure | | | |
| subjects affected / exposed | 3 / 147 (2.04%) | 0 / 147 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 3 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ureteric obstruction | | | |
| subjects affected / exposed | 0 / 147 (0.00%) | 1 / 147 (0.68%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Musculoskeletal and connective tissue disorders | | | |
| Musculoskeletal chest pain | | | |
| subjects affected / exposed | 0 / 147 (0.00%) | 1 / 147 (0.68%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infections and infestations | | | |
| Appendicitis | | | |
| subjects affected / exposed | 0 / 147 (0.00%) | 1 / 147 (0.68%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Catheter site infection | | | |
| subjects affected / exposed | 0 / 147 (0.00%) | 1 / 147 (0.68%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cellulitis | | | |
| subjects affected / exposed | 0 / 147 (0.00%) | 1 / 147 (0.68%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infective spondylitis | | | |
| subjects affected / exposed | 0 / 147 (0.00%) | 1 / 147 (0.68%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|-----------------|-----------------|--|
| Neutropenic sepsis | | | |
| subjects affected / exposed | 0 / 147 (0.00%) | 1 / 147 (0.68%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumonia | | | |
| subjects affected / exposed | 2 / 147 (1.36%) | 2 / 147 (1.36%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 2 | |
| Sepsis | | | |
| subjects affected / exposed | 2 / 147 (1.36%) | 1 / 147 (0.68%) | |
| occurrences causally related to treatment / all | 0 / 2 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Tinea pedis | | | |
| subjects affected / exposed | 0 / 147 (0.00%) | 1 / 147 (0.68%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Tooth infection | | | |
| subjects affected / exposed | 1 / 147 (0.68%) | 0 / 147 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Urinary tract infection | | | |
| subjects affected / exposed | 1 / 147 (0.68%) | 0 / 147 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Metabolism and nutrition disorders | | | |
| Decreased appetite | | | |
| subjects affected / exposed | 2 / 147 (1.36%) | 0 / 147 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Diabetes mellitus | | | |
| subjects affected / exposed | 1 / 147 (0.68%) | 1 / 147 (0.68%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Electrolyte imbalance | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 147 (0.68%) | 0 / 147 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypernatraemia | | | |
| subjects affected / exposed | 1 / 147 (0.68%) | 0 / 147 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypoalbuminaemia | | | |
| subjects affected / exposed | 0 / 147 (0.00%) | 1 / 147 (0.68%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypocalcaemia | | | |
| subjects affected / exposed | 0 / 147 (0.00%) | 1 / 147 (0.68%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypoglycaemia | | | |
| subjects affected / exposed | 0 / 147 (0.00%) | 1 / 147 (0.68%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypokalaemia | | | |
| subjects affected / exposed | 2 / 147 (1.36%) | 1 / 147 (0.68%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hyponatraemia | | | |
| subjects affected / exposed | 0 / 147 (0.00%) | 1 / 147 (0.68%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

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

| Non-serious adverse events | Capecitabine + Cisplatin + Herceptin (6 mg/kg) | Capecitabine + Cisplatin + Herceptin (10 mg/kg) | |
|---|---|--|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 123 / 147 (83.67%) | 122 / 147 (82.99%) | |
| Investigations | | | |
| Weight decreased | | | |
| subjects affected / exposed | 10 / 147 (6.80%) | 17 / 147 (11.56%) | |
| occurrences (all) | 10 | 18 | |
| Nervous system disorders | | | |
| Dizziness | | | |
| subjects affected / exposed | 8 / 147 (5.44%) | 2 / 147 (1.36%) | |
| occurrences (all) | 11 | 3 | |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 47 / 147 (31.97%) | 40 / 147 (27.21%) | |
| occurrences (all) | 62 | 55 | |
| Leukopenia | | | |
| subjects affected / exposed | 26 / 147 (17.69%) | 24 / 147 (16.33%) | |
| occurrences (all) | 49 | 61 | |
| Neutropenia | | | |
| subjects affected / exposed | 61 / 147 (41.50%) | 69 / 147 (46.94%) | |
| occurrences (all) | 109 | 142 | |
| Thrombocytopenia | | | |
| subjects affected / exposed | 14 / 147 (9.52%) | 14 / 147 (9.52%) | |
| occurrences (all) | 19 | 18 | |
| General disorders and administration site conditions | | | |
| Asthenia | | | |
| subjects affected / exposed | 16 / 147 (10.88%) | 11 / 147 (7.48%) | |
| occurrences (all) | 20 | 12 | |
| Fatigue | | | |
| subjects affected / exposed | 25 / 147 (17.01%) | 23 / 147 (15.65%) | |
| occurrences (all) | 33 | 30 | |
| Oedema peripheral | | | |
| subjects affected / exposed | 9 / 147 (6.12%) | 6 / 147 (4.08%) | |
| occurrences (all) | 10 | 8 | |
| Pyrexia | | | |

| | | | |
|--|-------------------------|------------------------|--|
| subjects affected / exposed occurrences (all) | 15 / 147 (10.20%) 19 | 14 / 147 (9.52%) 19 | |
| Gastrointestinal disorders | | | |
| Abdominal pain | | | |
| subjects affected / exposed | 8 / 147 (5.44%) | 7 / 147 (4.76%) | |
| occurrences (all) | 11 | 8 | |
| Abdominal pain upper | | | |
| subjects affected / exposed | 12 / 147 (8.16%) | 11 / 147 (7.48%) | |
| occurrences (all) | 13 | 12 | |
| Constipation | | | |
| subjects affected / exposed | 19 / 147 (12.93%) | 25 / 147 (17.01%) | |
| occurrences (all) | 24 | 35 | |
| Diarrhoea | | | |
| subjects affected / exposed | 24 / 147 (16.33%) | 30 / 147 (20.41%) | |
| occurrences (all) | 36 | 42 | |
| Nausea | | | |
| subjects affected / exposed | 55 / 147 (37.41%) | 55 / 147 (37.41%) | |
| occurrences (all) | 105 | 109 | |
| Vomiting | | | |
| subjects affected / exposed | 36 / 147 (24.49%) | 42 / 147 (28.57%) | |
| occurrences (all) | 71 | 83 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Cough | | | |
| subjects affected / exposed | 9 / 147 (6.12%) | 3 / 147 (2.04%) | |
| occurrences (all) | 10 | 3 | |
| Skin and subcutaneous tissue disorders | | | |
| Palmar-plantar erythrodysaesthesia syndrome | | | |
| subjects affected / exposed | 14 / 147 (9.52%) | 20 / 147 (13.61%) | |
| occurrences (all) | 14 | 23 | |
| Renal and urinary disorders | | | |
| Chronic kidney disease | | | |
| subjects affected / exposed | 7 / 147 (4.76%) | 13 / 147 (8.84%) | |
| occurrences (all) | 7 | 17 | |
| Renal failure | | | |
| subjects affected / exposed | 5 / 147 (3.40%) | 8 / 147 (5.44%) | |
| occurrences (all) | 7 | 8 | |

| | | | |
|------------------------------------|-------------------|-------------------|--|
| Metabolism and nutrition disorders | | | |
| Decreased appetite | | | |
| subjects affected / exposed | 32 / 147 (21.77%) | 27 / 147 (18.37%) | |
| occurrences (all) | 47 | 41 | |
| Hypoalbuminaemia | | | |
| subjects affected / exposed | 5 / 147 (3.40%) | 10 / 147 (6.80%) | |
| occurrences (all) | 8 | 14 | |
| Hypocalcaemia | | | |
| subjects affected / exposed | 9 / 147 (6.12%) | 9 / 147 (6.12%) | |
| occurrences (all) | 10 | 12 | |
| Hypokalaemia | | | |
| subjects affected / exposed | 6 / 147 (4.08%) | 15 / 147 (10.20%) | |
| occurrences (all) | 7 | 19 | |
| Hyponatraemia | | | |
| subjects affected / exposed | 3 / 147 (2.04%) | 8 / 147 (5.44%) | |
| occurrences (all) | 3 | 10 | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|----------------|--|
| 02 August 2011 | <ul style="list-style-type: none">- Clarified the instructions for collection of pharmacokinetic samples for serial measurements of trastuzumab concentrations in case of dose delay of Herceptin.- Revised actions and maximum hold times for study drug administration for non-hematological Grade 3 and Grade 4 (excluding cardiac) and hematological toxicities (neutropenia) that were not specifically attributable to one component of study treatment but related to study treatment.- Clarified instructions for the reloading dose of Herceptin in case of delayed dose beyond 7 days for the higher dose Herceptin (8 mg/kg loading dose followed by 10 mg/kg q3w) and the standard of care dose Herceptin (8 mg/kg loading dose followed by 6 mg/kg q3w) treatment arms.- Provided revised guidance for dose modifications and timeframe of dose delay due to hematological toxicity attributable to capecitabine or cisplatin and revised platelet count threshold for assessment of need for dose modification or delay of capecitabine and/or cisplatin. |
| 06 August 2013 | <ul style="list-style-type: none">- Provided clarification and updated instructions to Protocol B for the pharmacokinetic sampling schedule in case of delay of Herceptin administration.- The cardiac safety follow-up timeline was extended from 6 to 24 months.- An inclusion criterion (lung or liver plus at least one other organ in addition to the primary tumor must be involved by metastatic gastric tumor) was clarified by specifying the acceptability of metastases in other locations such as distant lymph node, peritoneum, and malignant pleural effusion as a second site of metastasis.- Updated exclusion criterion to add basal cell carcinoma of the skin within the last five years prior to enrollment was an allowed malignancy. Reporting instructions for abnormal liver function tests were included to address the identification/reporting of potential drug-induced liver injury (DILI).- Extracellular domain (ECD) analyses were included in Cycles 2 to 5 of the main study in order to ensure that a sufficient number of data were collected for the second pharmacokinetic interim analysis in order to fully understand the distribution of the shed ECD concentrations in participants with metastatic gastric cancer (MGC), and to enable an accurate assessment of whether the increase in HER2 ECD levels would have an impact on serum trastuzumab pharmacokinetics. These analyses were incorporated into the protocol to support the EMA issued Follow-Up Measure (FUM 70.1, 70.2, and 70.3) for the MGC filing in Europe (Type II Variation on EME/HC/000278/II/47). |

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.

Trial was stopped for futility based on pre-planned interim analysis results.

Notes: