# Clinical trial results:
# A Phase III Randomized, Double-blind, Placebo-controlled Trial Comparing Capecitabine Plus Sorafenib Versus Capecitabine Plus Placebo in the Treatment of Locally Advanced or Metastatic HER2-Negative Breast Cancer

## Summary

| | |
|---|---|
| EudraCT number | 2010-018501-10 |
| Trial protocol | BE DE GB AT CZ IE ES HU IT GR SE |
| Global end of trial date | 20 October 2017 |

### Results information

| | |
|---|---|
| Result version number | v2 |
| This version publication date | 01 September 2016 |
| First version publication date | 28 May 2015 |
| Version creation reason | • New data added to full data set<br>• Correction of full data set<br>Bayer sponsor contact information to be updated |

## Trial information

### Trial identification

| | |
|---|---|
| Sponsor protocol code | BAY43-9006/12444 |

### Additional study identifiers

| | |
|---|---|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT01234337 |
| WHO universal trial number (UTN) | - |

Notes:

### Sponsors

| | |
|---|---|
| Sponsor organisation name | Bayer AG |
| Sponsor organisation address | Kaiser-Wilhelm-Allee, Leverkusen, Germany, D-51368 |
| Public contact | Therapeutic Area Head, Bayer AG, clinical-trials-contact@bayer.com |
| Scientific contact | Therapeutic Area Head, Bayer AG, clinical-trials-contact@bayer.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 | Interim |
| Date of interim/final analysis | 12 May 2014 |
| Is this the analysis of the primary completion data? | No |

| | |
|---|---|
| Global end of trial reached? | Yes |
| Global end of trial date | 20 October 2017 |
| Was the trial ended prematurely? | No |

Notes:

## General information about the trial

Main objective of the trial:

The primary efficacy endpoint was to compare the Progression Free Survival (PFS) as assessed by the independent review panel according to Response Evaluation Criteria for Solid Tumors (RECIST) 1.1 between the treatment groups (sorafenib in combination of capecitabine versus placebo in combination of capecitabine).

Protection of trial subjects:

The conduct of this clinical study met all local legal and regulatory requirements. The study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and the International Conference on Harmonization guideline E6: Good Clinical Practice. Before entering the study, the informed consent form was read by and explained to all subjects. Participating subjects signed informed consent form and could withdraw from the study at any time without any disadvantage and without having to provide a reason for this decision. Only investigators qualified by training and experience were selected as appropriate experts to investigate the study drug.

Background therapy:

Capecitabine was administered orally at a dose of 1,000 milligram per square meter (mg/m^2) twice daily (12 hours apart) on Days 1 through 14 of each 21-day cycle. Capecitabine dose was escalated to 1,250 mg/m^2 twice daily if fatigue, dermatologic toxicities, and/or gastrointestinal toxicities in a prior cycle in which the subject received sorafenib at a total daily dose of 800 mg/4 tablets (400 mg/2 tablets, twice daily) were Grade 1 or less as per the common terminology criteria for adverse events version 4.0 (CTCAE v4.0).

Evidence for comparator: -

| | |
|---|---|
| Actual start date of recruitment | 21 February 2011 |
| Long term follow-up planned | Yes |
| Long term follow-up rationale | Efficacy |
| Long term follow-up duration | 39 Months |
| Independent data monitoring committee (IDMC) involvement? | Yes |

Notes:

## Population of trial subjects

### Subjects enrolled per country

| | |
|---|---|
| Country: Number of subjects enrolled | Poland: 8 |
| Country: Number of subjects enrolled | Sweden: 9 |
| Country: Number of subjects enrolled | United Kingdom: 13 |
| Country: Number of subjects enrolled | Austria: 4 |
| Country: Number of subjects enrolled | Belgium: 20 |
| Country: Number of subjects enrolled | Czech Republic: 23 |
| Country: Number of subjects enrolled | France: 21 |
| Country: Number of subjects enrolled | Germany: 12 |
| Country: Number of subjects enrolled | Greece: 15 |

| | |
|---|---|
| Country: Number of subjects enrolled | Hungary: 28 |
| Country: Number of subjects enrolled | Ireland: 17 |
| Country: Number of subjects enrolled | Italy: 40 |
| Country: Number of subjects enrolled | Argentina: 5 |
| Country: Number of subjects enrolled | Australia: 21 |
| Country: Number of subjects enrolled | Canada: 6 |
| Country: Number of subjects enrolled | China: 34 |
| Country: Number of subjects enrolled | Israel: 19 |
| Country: Number of subjects enrolled | Japan: 62 |
| Country: Number of subjects enrolled | Russian Federation: 13 |
| Country: Number of subjects enrolled | United States: 43 |
| Country: Number of subjects enrolled | Spain: 111 |
| Country: Number of subjects enrolled | South Africa: 13 |
| Worldwide total number of subjects | 537 |
| EEA total number of subjects | 321 |

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) | 447 |
| From 65 to 84 years | 90 |
| 85 years and over | 0 |

## Subject disposition

### Recruitment

Recruitment details:

At 154 sites in 22 countries, subjects with histologically or cytologically confirmed human epidermal growth factor receptor 2 (HER2)-negative adenocarcinoma of the breast, and locally advanced or metastatic disease, were screened.

### Pre-assignment

Screening details:

Of 707 subjects screened, 537 subjects were randomized and 527 subjects received at least 1 dose of study treatment. The reasons for 170 screen failures were adverse event in 21 subjects, disease progression, recurrence or relapse in 2, consent withdrawn in 16, death in 4, and protocol violation in 127 subjects.

### Period 1

| | |
|---|---|
| Period 1 title | Overall trial (overall period) |
| Is this the baseline period? | Yes |
| Allocation method | Randomised - controlled |
| Blinding used | Double blind |
| Roles blinded | Investigator, Carer, Assessor, Subject |

Blinding implementation details:

In compliance with applicable regulations, in the event of a suspected unexpected serious adverse reaction (SUSARs) that was considered to be related to the blinded treatment, the subject's treatment code was usually unblinded before reporting to the health authorities, ethic committees, and investigators. Unblinding occurred for emergency purposes only.

### Arms

| | |
|---|---|
| Are arms mutually exclusive? | Yes |
| **Arm title** | Sorafenib (Nexavar, BAY43-9006) + Capecitabine |

Arm description:

Capecitabine was administered orally at a dose of 1,000 mg/m^2 twice daily (12 hours apart) on Days 1 through 14 of each 21-day cycle. Sorafenib was administered orally at a dose of 600 mg (200 mg in the morning, 400 mg in the evening) daily, continuously (that is, Days 1 to 21, inclusive). A treatment cycle consisted of 21 days. If tolerability criteria were met for a subject, capecitabine dose was escalated to 1,250 mg/m^2 twice daily and sorafenib dose to a total daily dose of 800 mg for that subject.

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | Capecitabine |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Capecitabine was administered orally at a dose of 1,000 mg/m^2 twice daily (12 hours apart) on Days 1 through 14 of each 21-day cycle. Capecitabine dose was escalated to 1,250 mg/m^2 twice daily if fatigue, dermatologic toxicities, and/or gastrointestinal toxicities in a prior cycle in which the subject received sorafenib at a dose of 800 mg (400 mg twice daily) were Grade 1 or less as per the CTCAE v4.0.

| | |
|---|---|
| Investigational medicinal product name | Sorafenib |
| Investigational medicinal product code | BAY43-9006 |
| Other name | Nexavar |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Sorafenib was administered orally at a dose of 600 mg (200 mg in the morning, 400 mg in the evening) daily, continuously (that is, Days 1 to 21, inclusive). Sorafenib dose was escalated to 800 mg (400 mg twice daily) in Cycle 2 or beyond if fatigue, dermatologic toxicities, and/or gastrointestinal toxicities in a

prior cycle in which the subject received sorafenib at a total daily dose of 600 mg were Grade 1 or less as per CTCAE v4.0.

| **Arm title** | Placebo + Capecitabine |
|---|---|

Arm description:

Capecitabine was administered orally at a dose of 1,000 mg/m^2 twice daily (12 hours apart) on Days 1 through 14 of each 21-day cycle. Placebo matching to sorafenib was administered orally, 3 tablets (1 tablet in the morning, 2 tablets in the evening) daily, continuously (that is, Days 1 to 21, inclusive). A treatment cycle consisted of 21 days. If tolerability criteria were met for a subject, capecitabine dose was escalated to 1,250 mg/m^2 twice daily and placebo dose to a total daily dose of 4 tablets (2 tablets twice daily) for that subject.

| | |
|---|---|
| Arm type | Placebo |
| Investigational medicinal product name | Capecitabine |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Capecitabine was administered orally at a dose of 1,000 mg/m^2 twice daily (12 hours apart) on Days 1 through 14 of each 21-day cycle. Capecitabine dose was escalated to 1,250 mg/m^2 twice daily if fatigue, dermatologic toxicities, and/or gastrointestinal toxicities in a prior cycle in which the subject received placebo at a dose of 4 tablets (2 tablets twice daily) were Grade 1 or less as per the CTCAE v4.0.

| | |
|---|---|
| Investigational medicinal product name | Placebo |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Placebo matching to sorafenib was administered orally, 3 tablets (1 tablet in the morning, 2 tablets in the evening) daily, continuously (that is, Days 1 to 21, inclusive). Placebo dose was escalated to 4 tablets (2 tablets twice daily) in Cycle 2 or beyond if fatigue, dermatologic toxicities, and/or gastrointestinal toxicities in a prior cycle in which the subject received placebo at a total daily dose of 3 tablets were Grade 1 or less as per CTCAE v4.0.

| **Number of subjects in period 1** | Sorafenib (Nexavar, BAY43-9006) + Capecitabine | Placebo + Capecitabine |
|---|---|---|
| Started | 266 | 271 |
| Subjects received treatment | 260 | 267 |
| Completed | 0 | 0 |
| Not completed | 266 | 271 |
| Disease progression/recurrence/relapse | 181 | 223 |
| Consent withdrawn by subject | 11 | 9 |
| Adverse event, non-fatal | 58 | 21 |
| Randomized but not treated | 6 | 4 |
| Non-compliant with study medication | 3 | 2 |

| | | |
|---|---|---|
| Death | - | 1 |
| Switch to commercial drug | - | 1 |
| Investi. decision not protocol driven | 5 | 6 |
| Lost to follow-up | - | 1 |
| Protocol deviation | 2 | 3 |

## Baseline characteristics

| Reporting groups | |
|---|---|
| Reporting group title | Sorafenib (Nexavar, BAY43-9006) + Capecitabine |
| Reporting group description: | |
| Capecitabine was administered orally at a dose of 1,000 mg/m^2 twice daily (12 hours apart) on Days 1 through 14 of each 21-day cycle. Sorafenib was administered orally at a dose of 600 mg (200 mg in the morning, 400 mg in the evening) daily, continuously (that is, Days 1 to 21, inclusive). A treatment cycle consisted of 21 days. If tolerability criteria were met for a subject, capecitabine dose was escalated to 1,250 mg/m^2 twice daily and sorafenib dose to a total daily dose of 800 mg for that subject. | |
| Reporting group title | Placebo + Capecitabine |
| Reporting group description: | |
| Capecitabine was administered orally at a dose of 1,000 mg/m^2 twice daily (12 hours apart) on Days 1 through 14 of each 21-day cycle. Placebo matching to sorafenib was administered orally, 3 tablets (1 tablet in the morning, 2 tablets in the evening) daily, continuously (that is, Days 1 to 21, inclusive). A treatment cycle consisted of 21 days. If tolerability criteria were met for a subject, capecitabine dose was escalated to 1,250 mg/m^2 twice daily and placebo dose to a total daily dose of 4 tablets (2 tablets twice daily) for that subject. | |

| **Reporting group values** | Sorafenib (Nexavar, BAY43-9006) + Capecitabine | Placebo + Capecitabine | Total |
|---|---|---|---|
| Number of subjects | 266 | 271 | 537 |
| Age categorical<br>Units: Subjects | | | |
| Age continuous<br>Units: years | | | |
| arithmetic mean | 53.3 | 54.4 | |
| standard deviation | ± 10.2 | ± 10.9 | - |
| Gender categorical<br>Units: Subjects | | | |
| Female | 265 | 268 | 533 |
| Male | 1 | 3 | 4 |
| Race<br>Units: Subjects | | | |
| White | 205 | 212 | 417 |
| Black | 7 | 4 | 11 |
| Asian | 50 | 50 | 100 |
| Hispanic | 4 | 5 | 9 |
| Region | | | |
| Other countries in the below category included Argentina, Australia, China, Israel and Japan. | | | |
| Units: Subjects | | | |
| Europe | 166 | 168 | 334 |
| North America | 23 | 26 | 49 |
| Other | 77 | 77 | 154 |
| Baseline performance status (Eastern Cooperative Oncology Group [ECOG])<br>Units: Subjects | | | |
| ECOG status=0 | 152 | 161 | 313 |
| ECOG status=1 | 114 | 110 | 224 |
| Number of prior chemotherapies for metastatic disease | | | |

| | | | |
|---|---|---|---|
| Assessed by Interactive voice response system (IVRS). Subjects with more than 1 actual number of prior chemotherapies were combined with subjects with 1 prior chemotherapy. | | | |
| Units: Subjects | | | |
| Prior chemotherapies=0 | 114 | 118 | 232 |
| Prior chemotherapies=1 | 152 | 153 | 305 |
| Hormone receptor status | | | |
| The hormone receptor status was assessed by IVRS, and considered as follows: in case, the tumor expressed estrogen and/or progesterone receptor, the subject was considered to have positive hormone receptor status. Otherwise, if both receptors were not expressed, then subject was considered to have a negative hormone receptor status. | | | |
| Units: Subjects | | | |
| Negative | 83 | 84 | 167 |
| Positive | 183 | 187 | 370 |
| Visceral disease at baseline<br>Units: Subjects | | | |
| Missing | 1 | 1 | 2 |
| No | 66 | 57 | 123 |
| Yes | 199 | 213 | 412 |

## End points

### End points reporting groups

| Reporting group title | Sorafenib (Nexavar, BAY43-9006) + Capecitabine |
|---|---|

Reporting group description:

Capecitabine was administered orally at a dose of 1,000 mg/m^2 twice daily (12 hours apart) on Days 1 through 14 of each 21-day cycle. Sorafenib was administered orally at a dose of 600 mg (200 mg in the morning, 400 mg in the evening) daily, continuously (that is, Days 1 to 21, inclusive). A treatment cycle consisted of 21 days. If tolerability criteria were met for a subject, capecitabine dose was escalated to 1,250 mg/m^2 twice daily and sorafenib dose to a total daily dose of 800 mg for that subject.

| Reporting group title | Placebo + Capecitabine |
|---|---|

Reporting group description:

Capecitabine was administered orally at a dose of 1,000 mg/m^2 twice daily (12 hours apart) on Days 1 through 14 of each 21-day cycle. Placebo matching to sorafenib was administered orally, 3 tablets (1 tablet in the morning, 2 tablets in the evening) daily, continuously (that is, Days 1 to 21, inclusive). A treatment cycle consisted of 21 days. If tolerability criteria were met for a subject, capecitabine dose was escalated to 1,250 mg/m^2 twice daily and placebo dose to a total daily dose of 4 tablets (2 tablets twice daily) for that subject.

| Subject analysis set title | Full analysis set (FAS) |
|---|---|
| Subject analysis set type | Full analysis |

Subject analysis set description:

FAS (also considered the Intent-to-treat (ITT) analysis set) population (N=537) was defined as all randomized subjects. Subjects were analyzed as randomized, that is, even if a subject was randomized and received no drug or if randomized and initially received incorrect drug prior to switching to correct study drug, these subjects were still analyzed for efficacy under FAS, as randomized.

| Subject analysis set title | Pharmacokinetic analysis set (PKS) |
|---|---|
| Subject analysis set type | Sub-group analysis |

Subject analysis set description:

PKS (N=182) included all subjects with a valid pharmacokinetic profile of capecitabine.

| Subject analysis set title | Safety analysis set (SAF) |
|---|---|
| Subject analysis set type | Safety analysis |

Subject analysis set description:

SAF (N=527) was comprised of all randomized subjects who received at least one dose of study medication (sorafenib, placebo or capecitabine). Subjects were analyzed as treated.

### Primary: Progression-free Survival (PFS) Assessed by the Independent Review Panel According to Response Evaluation Criteria for Solid Tumors (RECIST) 1.1

| End point title | Progression-free Survival (PFS) Assessed by the Independent Review Panel According to Response Evaluation Criteria for Solid Tumors (RECIST) 1.1 |
|---|---|

End point description:

PFS was defined as the time from date of randomization to disease progression, radiological or death due to any cause, whichever occurs first. Subjects without progression or death at the time of analysis were censored at their last date of evaluable tumor evaluation. Median and other 95% CIs computed using Kaplan-Meier estimates.

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

End point timeframe:

From randomization of the first subject until approximately 3 years or until disease radiological progression

| End point values | Sorafenib (Nexavar, BAY43-9006) + Capecitabine | Placebo + Capecitabine | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 266[1] | 271[2] | | |
| Units: days | | | | |
| median (confidence interval 95%) | 166 (131 to 206) | 165 (126 to 204) | | |

Notes:

[1] - FAS.

[2] - FAS.

## Statistical analyses

| Statistical analysis title | PFS by central review panel |
|---|---|

Statistical analysis description:

PFS was compared using a stratified log-rank test with a one-sided alpha of 0.005, stratified by region, hormone receptor status, number of previous chemotherapies for metastatic disease. The hazard ratio (sorafenib + capecitabine / placebo + capecitabine) and its 95 percent (%) confidence intervals (CIs) were calculated using the Cox model, stratified by the above factors.

| Comparison groups | Sorafenib (Nexavar, BAY43-9006) + Capecitabine v Placebo + Capecitabine |
|---|---|
| Number of subjects included in analysis | 537 |
| Analysis specification | Pre-specified |
| Analysis type | superiority[3] |
| P-value | = 0.405618 [4] |
| Method | Logrank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.973 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.779 |
| upper limit | 1.217 |

Notes:

[3] - A Hazard ratio of less than (<) 1 indicates superiority of Sorafenib + Capecitabine over Placebo + Capecitabine.

[4] - One-sided p-value from log rank test (stratified per randomization as in interactive voice response system [IVRS]).

## Secondary: Overall Survival (OS)

| End point title | Overall Survival (OS) |
|---|---|

End point description:

OS was defined as the time from date of randomization to death due to any cause. Subjects still alive at the time of analysis were censored at their last known alive date. Median and other 95% CIs computed using Kaplan-Meier estimates.

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

End point timeframe:

From randomization of the first subject until approximately 3 years later

| End point values | Sorafenib (Nexavar, BAY43-9006) + Capecitabine | Placebo + Capecitabine | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 266[5] | 271[6] | | |
| Units: days | | | | |
| median (confidence interval 95%) | 575 (467 to 645) | 616 (546 to 687) | | |

Notes:

[5] - FAS

[6] - FAS

### Statistical analyses

| Statistical analysis title | Statistical analysis for Overall Survival |
|---|---|

Statistical analysis description:

At the time of PFS final analysis, it was OS interim analysis (IA) with 285 total death events. According to protocol specified O'Brien-Fleming type alpha spending function and 285 death events at IA, the pre-specified alpha for this analysis was 0.0075 (one-sided).The hazard ratio (sorafenib + capecitabine / placebo + capecitabine) and its 95% CIs were calculated using the Cox model, stratified by randomization factors.

| Comparison groups | Sorafenib (Nexavar, BAY43-9006) + Capecitabine v Placebo + Capecitabine |
|---|---|
| Number of subjects included in analysis | 537 |
| Analysis specification | Pre-specified |
| Analysis type | superiority[7] |
| P-value | = 0.930088 [8] |
| Method | Logrank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 1.195 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.943 |
| upper limit | 1.513 |

Notes:

[7] - A Hazard ratio < 1 indicates superiority of Sorafenib+Capecitabine over Placebo+Capecitabine.

[8] - One-sided p-value from log rank test (stratified per randomization as in IVRS). OS was compared using a stratified log-rank test, stratified by region, hormone receptor status, number of previous chemotherapies for metastatic disease.

### Secondary: Time to Progression (TTP) by Central Review

| End point title | Time to Progression (TTP) by Central Review |
|---|---|

End point description:

TTP was defined as the time from date of randomization to disease radiological progression by central review. Subjects without progression at the time of analysis were censored at their last evaluable tumor assessment date. Median and its 95% CIs were computed using Kaplan-Meier estimates.

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

End point timeframe:

From randomization of the first subject until approximately 3 years later or until disease radiological progression

| End point values | Sorafenib (Nexavar, BAY43-9006) + Capecitabine | Placebo + Capecitabine | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 266[9] | 271[10] | | |
| Units: days | | | | |
| median (confidence interval 95%) | 168 (139 to 215) | 165 (127 to 208) | | |

Notes:

[9] - FAS

[10] - FAS

## Statistical analyses

| Statistical analysis title | TTP by central review panel |
|---|---|

Statistical analysis description:

TTP was compared using a stratified log-rank test with a one-sided alpha of 0.025, stratified by region, hormone receptor status, number of previous chemotherapies for metastatic disease. The hazard ratio (sorafenib + capecitabine / placebo + capecitabine) and its 95% CIs were calculated using the Cox model, stratified by the above factors.

| Comparison groups | Sorafenib (Nexavar, BAY43-9006) + Capecitabine v Placebo + Capecitabine |
|---|---|
| Number of subjects included in analysis | 537 |
| Analysis specification | Pre-specified |
| Analysis type | superiority[11] |
| P-value | = 0.2105 [12] |
| Method | Logrank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.91 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.723 |
| upper limit | 1.146 |

Notes:

[11] - A Hazard ratio <1 indicates superiority of Sorafenib+Capecitabine over Placebo+Capecitabine.

[12] - One-sided p-value from log rank test (stratified per randomization as in IVRS).

## Secondary: Objective Response Rate (ORR) by Central Review

| End point title | Objective Response Rate (ORR) by Central Review |
|---|---|

End point description:

ORR was defined as the best tumor response (Complete Response [CR] or Partial Response [PR]) observed during treatment or within 30 days after termination of study treatment, assessed according to the Response Evaluation Criteria in Solid Tumors (RECIST) criteria 1.1. CR and PR needed to be confirmed by another scan at least 4 weeks later.

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

End point timeframe:

From randomization of the first subject until approximately 3 years later or until disease radiological progression

| End point values | Sorafenib (Nexavar, BAY43-9006) + Capecitabine | Placebo + Capecitabine | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 266[13] | 271[14] | | |
| Units: percentage (%) of subjects | | | | |
| number (confidence interval 95%) | 13.5 (9.7 to 18.2) | 15.5 (11.4 to 20.4) | | |

Notes:

[13] - FAS

[14] - FAS

## Statistical analyses

| Statistical analysis title | Statistical Analysis for Objective Tumor Response |
|---|---|

Statistical analysis description:

ORR and 95% CI based on Cochran Mantel-Haenszel Test stratified by region, hormone receptor status, number of previous chemotherapies for metastatic disease. Difference = (Placebo + Capecitabine) - (Sorafenib + Capecitabine).

| Comparison groups | Placebo + Capecitabine v Sorafenib (Nexavar, BAY43-9006) + Capecitabine |
|---|---|
| Number of subjects included in analysis | 537 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.257412 [15] |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Percent Difference |
| Point estimate | 1.93 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -3.9 |
| upper limit | 7.77 |

Notes:

[15] - One-sided p-value from Cochran-Mantel-Haenszel test (stratified per randomization as in IVRS)

## Secondary: Disease Control Rate (DCR) by Central Review

| End point title | Disease Control Rate (DCR) by Central Review |
|---|---|

End point description:

Disease control rate (DCR) was defined as the proportion of subjects whose best response was complete response (CR), partial response (PR), stable disease (SD) or Non CR/Non progressive disease (PD). CR and PR needed to be confirmed by another scan at least 4 weeks later. SD and Non CR/Non PD had to be documented at least 6 weeks after randomization.

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

End point timeframe:

From randomization of the first subject until approximately 3 years later or until disease radiological progression

| End point values | Sorafenib (Nexavar, BAY43-9006) + Capecitabine | Placebo + Capecitabine | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 266[16] | 271[17] | | |
| Units: percentage (%) of subjects | | | | |
| number (confidence interval 95%) | 60.5 (54.4 to 66.4) | 58.3 (52.2 to 64.2) | | |

Notes:

[16] - FAS

[17] - FAS

### Statistical analyses

| Statistical analysis title | Statistical Analysis for Disease Control Rate |
|---|---|

Statistical analysis description:

DCR and 95% CI based on "general association Cochran-Mantel-Haenszel statistic" with one-sided alpha of 0.025 stratified by number of prior chemotherapies for metastatic disease, hormone receptor status, and region.
Difference = Placebo + Capecitabine - Sorafenib + Capecitabine.

| Comparison groups | Placebo + Capecitabine v Sorafenib (Nexavar, BAY43-9006) + Capecitabine |
|---|---|
| Number of subjects included in analysis | 537 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.284674 [18] |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Percent Difference |
| Point estimate | -2.34 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -10.4 |
| upper limit | 5.72 |

Notes:

[18] - One-sided p-value from Cochran-Mantel-Haenszel test (stratified per randomization as in IVRS).

### Secondary: Duration of Response (DOR) by Central Reader

| End point title | Duration of Response (DOR) by Central Reader |
|---|---|

End point description:

DOR was defined as the time from date of first response (CR or PR) to the date when Progressive Disease (PD) is first documented, or to the date of death, whichever occurred first according to RECIST version 1.1. Subjects still having CR or PR and have not died at the time of analysis were censored at their last date of tumor evaluation. Duration of response defined for confirmed responders only (that is, CR or PR). '99999' indicates that value could not be estimated due to censored data. Median and 95% CIs were computed using Kaplan-Meier estimates.

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

End point timeframe:

From randomization of the first subject until approximately 3 years later or until disease radiological progression

| End point values | Sorafenib (Nexavar, BAY43-9006) + Capecitabine | Placebo + Capecitabine | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 36[19] | 42[20] | | |
| Units: days | | | | |
| median (confidence interval 95%) | 313 (209 to 99999) | 290 (169 to 99999) | | |

Notes:

[19] - Only responders in FAS

[20] - Only responders in FAS

### Statistical analyses

No statistical analyses for this end point

### Other pre-specified: Patient Reported Outcomes: Functional Assessment of Cancer Therapy-Breast Symptom Index (8 item) (FBSI-8)

| End point title | Patient Reported Outcomes: Functional Assessment of Cancer Therapy-Breast Symptom Index (8 item) (FBSI-8) |
|---|---|

End point description:

The FBSI-8 was an 8-item questionnaire. Subjects responded to each item using a 5-point Likert-type scale ranging from 0 (not at all) to 4 (very much). A total scale score was calculated (range from 0 to 32), with higher scores indicating low symptomatology and reflecting a better Health-Related Quality of Life (HRQoL). The results on the analysis of covariance (ANCOVA) of time-adjusted area under curve (AUC) for the FBSI-8 score were reported. Only subjects with a baseline assessment and at least one post-baseline assessment during the study were used for the AUC-based analyses.
Please find the statistical analyses in the attachment below.

| End point type | Other pre-specified |
|---|---|

End point timeframe:

Day 1 of Cycles 1, 3, 5, 7, 9, 11, 13, 16, 19, 22, 25, 28, 31, 34, 37, and end of treatment (EOT, 21 days after last dose of study drug)

| End point values | Sorafenib (Nexavar, BAY43-9006) + Capecitabine | Placebo + Capecitabine | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 233[21] | 243[22] | | |
| Units: Scores on a scale | | | | |
| least squares mean (confidence interval 95%) | 20.915 (20.459 to 21.37) | 21.356 (20.911 to 21.801) | | |

Notes:

[21] - FAS

[22] - FAS

| Attachments (see zip file) | Statistical Analyses_Other_FBSI-8/12444_Statistical |
|---|---|

### Statistical analyses

No statistical analyses for this end point

## Other pre-specified: Patient Reported Outcomes: Euroqol-5 Dimensions (EQ-5D) - Index Score

| End point title | Patient Reported Outcomes: Euroqol-5 Dimensions (EQ-5D) - Index Score |
|---|---|

End point description:

The EQ-5D was a generic Quality of life (QoL) preference based instrument and has been validated in the cancer populations. EQ-5D questionnaire contained a 5-item descriptive system of health states (mobility, self-care, usual activities, pain/discomfort, anxiety/depression) and a visual analogue scale (VAS). From the answers to these 5 health states a single HRQoL score ranging from -0.59 to 1 were generated according to the standard scoring algorithm developed by the EuroQoL Group for the instrument. This single score was referred to as the EQ-5D index score. For the EQ-5D, higher scores represented better health status. A change of at least 0.10 to 0.12 points on the EQ-5D index is considered clinically meaningful. The results on ANCOVA of time-adjusted AUC were reported. Only subjects with a baseline assessment and at least one post-baseline assessment during the study were used for the AUC-based analyses.
Please find the statistical analyses in the attachment below.

| End point type | Other pre-specified |
|---|---|

End point timeframe:

Day 1 of Cycles 1, 3, 5, 7, 9, 11, 13, 16, 19, 22, 25, 28, and EOT (21 days after last dose of study drug)

| **End point values** | Sorafenib (Nexavar, BAY43-9006) + Capecitabine | Placebo + Capecitabine | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 236[23] | 247[24] | | |
| Units: Scores on a scale | | | | |
| least squares mean (confidence interval 95%) | 0.665 (0.641 to 0.688) | 0.69 (0.667 to 0.713) | | |

Notes:

[23] - FAS

[24] - FAS

| **Attachments (see zip file)** | 12444_Statistical Analyses_Other_EQ-5D |
|---|---|

### Statistical analyses

No statistical analyses for this end point

## Other pre-specified: Patient Reported Outcomes: Euroqol-5 Dimensions (EQ-5D) - Visual Analogue Scale (VAS) Score

| End point title | Patient Reported Outcomes: Euroqol-5 Dimensions (EQ-5D) - Visual Analogue Scale (VAS) Score |
|---|---|

End point description:

The EQ-5D was a generic QoL preference based instrument and has been validated in the cancer populations. VAS was generated from 0 (worst imaginable health state) to 100 (best imaginable health state). This VAS score was referred to as the EQ-5D self-reported health status score. The results on ANCOVA of time-adjusted AUC were reported. Only subjects with a baseline assessment and at least one post-baseline assessment during the study were used for the AUC-based analyses.
Please find the statistical analyses in the attachment below.

| End point type | Other pre-specified |
|---|---|

End point timeframe:

Day 1 of Cycles 1, 3, 5, 7, 9, 11, 13, 16, 19, 22, 25, 28, and EOT (21 days after last dose of study drug)

| End point values | Sorafenib (Nexavar, BAY43-9006) + Capecitabine | Placebo + Capecitabine | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 235[25] | 244[26] | | |
| Units: Scores on a scale | | | | |
| least squares mean (confidence interval 95%) | 67.532 (65.87 to 69.19) | 69.228 (67.6 to 70.86) | | |

Notes:

[25] - FAS

[26] - FAS

| Attachments (see zip file) | Statistical Analyses_Other_EQ-5D-VAS/12444_Statistical |
|---|---|

### Statistical analyses

No statistical analyses for this end point

### Other pre-specified: Maximum Observed Drug Concentration (Cmax) of Capecitabine and 5-fluorouracil

| End point title | Maximum Observed Drug Concentration (Cmax) of Capecitabine and 5-fluorouracil |
|---|---|

End point description:

Maximum observed drug concentration, directly taken from analytical data.
Geometric mean and percentage geometric coefficient of variation (%CV) were reported.
In the listed categories below, 'N' signifies the number of evaluable subjects for the drug administered.
Please find the statistical analyses in the attachments below.

| End point type | Other pre-specified |
|---|---|

End point timeframe:

Pre-dose and 0.5, 1, 2, and 4 hours after capecitabine dosing at Cycle 2, Day 14

| End point values | Sorafenib (Nexavar, BAY43-9006) + Capecitabine | Placebo + Capecitabine | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 78[27] | 104[28] | | |
| Units: milligram per liter | | | | |
| geometric mean (geometric coefficient of variation) | | | | |
| Capecitabine (N=56, 84) | 6.05 (± 79) | 4.68 (± 72) | | |
| 5-fluorouracil (N=51, 84) | 0.434 (± 105) | 0.382 (± 67) | | |

Notes:

[27] - PKS

[28] - PKS

| | |
|---|---|
| **Attachments (see zip file)** | 12444_Statistical Analyses_Other_Cmax of 5-<br>12444_Statistical Analyses_Other_Cmax of |

### Statistical analyses

No statistical analyses for this end point

## Other pre-specified: Area Under Curve From Time Zero to Last Quantifiable Concentration (AUC[0-tlast]) of Capecitabine and 5-fluorouracil

| | |
|---|---|
| End point title | Area Under Curve From Time Zero to Last Quantifiable Concentration (AUC[0-tlast]) of Capecitabine and 5-fluorouracil |

End point description:

AUC(0-tlast) is defined as AUC from time 0 to the last data point, calculated up by linear trapezoidal rule, down by logarithmic trapezoidal rule. Geometric mean and percentage geometric coefficient of variation (%CV) were reported. In the listed categories below, 'N' signifies the number of evaluable subjects for the drug administered.
Please find the statistical analyses in the attachments below.

| | |
|---|---|
| End point type | Other pre-specified |

End point timeframe:

Pre-dose and 0.5, 1, 2, and 4 hours after capecitabine dosing at Cycle 2, Day 14

| **End point values** | Sorafenib (Nexavar, BAY43-9006) + Capecitabine | Placebo + Capecitabine | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 78[29] | 104[30] | | |
| Units: milligram*hour per liter | | | | |
| geometric mean (geometric coefficient of variation) | | | | |
| Capecitabine (N=56, 84) | 7.12 (± 50) | 5.13 (± 48) | | |
| 5-fluorouracil (N=51, 84) | 0.621 (± 71) | 0.557 (± 47) | | |

Notes:

[29] - PKS

[30] - PKS

| | |
|---|---|
| **Attachments (see zip file)** | 12444_Statistical Analyses_Other_AUC(0-tlast) 5-<br>12444_Statistical Analyses_Other_AUC(0-tlast) of |

### Statistical analyses

No statistical analyses for this end point

## Other pre-specified: Number of Subjects With Treatment-emergent Grade 3 and 4 Laboratory Abnormalities

| | |
|---|---|
| End point title | Number of Subjects With Treatment-emergent Grade 3 and 4 Laboratory Abnormalities |

End point description:

Hematological (anemia, hemoglobin, international normalized ratio [INR], lymphocyte, neutrophil, platelet, white blood cell [WBC]), biochemical (ALT [alanine aminotransferase], AST [aspartate aminotransferase], GGT [gamma-glutamyl-transferase], lipase, hypoalbuminemia, hypocalcemia, hyperglycemia, hyperuricemia) evaluations were done. Common terminology criteria for adverse events

(CTCAE) version 4-Grade 3: Severe or medically significant; hospitalization or prolongation of hospitalization and CTCAE version 4-Grade 4: life-threatening consequences; urgent intervention were indicated. '99999' in the below table indicates that the lab parameter has no grade 4 (hemoglobin) or grade 3 (uric acid).

| End point type | Other pre-specified |
|---|---|

End point timeframe:

From the start of study treatment up to 30 days after the last dose

| **End point values** | Sorafenib (Nexavar, BAY43-9006) + Capecitabine | Placebo + Capecitabine | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 260[31] | 267[32] | | |
| Units: Subjects | | | | |
| Anemia (grade 3) | 12 | 7 | | |
| Hemoglobin increased (grade 3) | 0 | 3 | | |
| INR increased (grade 3) | 9 | 9 | | |
| Lymphocyte count decreased (grade 3) | 20 | 17 | | |
| Neutrophil count decreased (grade 3) | 11 | 19 | | |
| Platelet count decreased (grade 3) | 6 | 2 | | |
| WBC decreased (grade 3) | 15 | 13 | | |
| ALT increased (grade 3) | 4 | 5 | | |
| AST increased (grade 3) | 10 | 5 | | |
| Alkaline phosphatase increased (grade 3) | 12 | 13 | | |
| Bilirubin increased (grade 3) | 9 | 1 | | |
| GGT increased (grade 3) | 22 | 21 | | |
| Lipase increased (grade 3) | 19 | 12 | | |
| Serum amylase increased (grade 3) | 8 | 4 | | |
| Hypoalbuminemia (grade 3) | 4 | 2 | | |
| Hypocalcemia (grade 3) | 9 | 6 | | |
| Hypokalemia (grade 3) | 20 | 11 | | |
| Hyponatremia (grade 3) | 9 | 7 | | |
| Hypophosphatemia (grade 3) | 47 | 15 | | |
| Hyperglycemia (grade 3) | 9 | 10 | | |
| Lymphocyte count decreased (grade 4) | 3 | 2 | | |
| Neutrophil count decreased (grade 4) | 7 | 7 | | |
| Platelet count decreased (grade 4) | 1 | 7 | | |
| WBC decreased (grade 4) | 2 | 3 | | |
| ALT increased (grade 4) | 3 | 0 | | |
| GGT increased (grade 4) | 6 | 2 | | |
| Lipase increased (grade 4) | 5 | 1 | | |
| Hypokalemia (grade 4) | 2 | 4 | | |
| Hyponatremia (grade 4) | 4 | 0 | | |
| Hypophosphatemia (grade 4) | 5 | 0 | | |
| Hyperuricemia (grade 4) | 5 | 0 | | |

Notes:

[31] - Safety Analysis Set (SAF)

[32] - Safety Analysis Set (SAF)

## Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

From start of study drug administration until 30 days after the last dose of study medication intake.

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

### Dictionary used

| | |
|---|---|
| Dictionary name | MedDRA |
| Dictionary version | 20.1 |

### Reporting groups

| | |
|---|---|
| Reporting group title | Sorafenib (Nexavar, BAY43-9006) + Capecitabine |

Reporting group description:

Sorafenib tablets were administered orally continuously at a total daily dose of 600 mg (200 mg in the morning, 400 mg in the evening) in a 3-week cycle. Capecitabine was administered orally at a total daily dose of 2,000 mg/m^2 (1,000 mg/m^2 twice daily, 12 hours apart). If tolerability criteria were met for a subject, capecitabine dose was escalated to 2,500 mg/m^2 total daily dose (1,250 mg/m^2 twice daily) and sorafenib dose to a total daily dose of 800 mg for that subject.

| | |
|---|---|
| Reporting group title | Placebo + Capecitabine |

Reporting group description:

Placebo tablets matching with sorafenib were administered orally continuously (1 tablet in the morning, 2 tablets in the evening) in a 3-week cycle. Capecitabine was administered orally at a total daily dose of 2,000 mg/m^2 (1,000 mg/m^2 twice daily, 12 hours apart). If tolerability criteria were met for a subject, capecitabine dose was escalated to 2,500 mg/m^2 total daily dose (1,250 mg/m^2 twice daily) and placebo dose to a total daily dose of 4 tablets (2 tablets twice daily) for that subject.

| **Serious adverse events** | Sorafenib (Nexavar, BAY43-9006) + Capecitabine | Placebo + Capecitabine | |
|---|---|---|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 80 / 260 (30.77%) | 71 / 267 (26.59%) | |
| number of deaths (all causes) | 159 | 154 | |
| number of deaths resulting from adverse events | 16 | 12 | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Breast cancer | | | |
| subjects affected / exposed | 0 / 260 (0.00%) | 1 / 267 (0.37%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Malignant pleural effusion | | | |
| subjects affected / exposed | 1 / 260 (0.38%) | 0 / 267 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Metastases to liver | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 260 (0.00%) | 1 / 267 (0.37%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Metastases to spine | | | |
| subjects affected / exposed | 0 / 260 (0.00%) | 1 / 267 (0.37%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Metastases to meninges | | | |
| subjects affected / exposed | 0 / 260 (0.00%) | 1 / 267 (0.37%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Tumour associated fever | | | |
| subjects affected / exposed | 1 / 260 (0.38%) | 0 / 267 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Breast cancer metastatic | | | |
| subjects affected / exposed | 1 / 260 (0.38%) | 2 / 267 (0.75%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 2 | |
| Cancer pain | | | |
| subjects affected / exposed | 1 / 260 (0.38%) | 0 / 267 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Metastases to central nervous system | | | |
| subjects affected / exposed | 1 / 260 (0.38%) | 0 / 267 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vascular disorders | | | |
| Lymphoedema | | | |
| subjects affected / exposed | 1 / 260 (0.38%) | 0 / 267 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Superior vena cava syndrome | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 260 (0.38%) | 0 / 267 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Deep vein thrombosis | | | |
| subjects affected / exposed | 1 / 260 (0.38%) | 3 / 267 (1.12%) | |
| occurrences causally related to treatment / all | 1 / 1 | 1 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Peripheral artery occlusion | | | |
| subjects affected / exposed | 1 / 260 (0.38%) | 0 / 267 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Venous thrombosis limb | | | |
| subjects affected / exposed | 0 / 260 (0.00%) | 1 / 267 (0.37%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Surgical and medical procedures | | | |
| Cholecystectomy | | | |
| subjects affected / exposed | 0 / 260 (0.00%) | 1 / 267 (0.37%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hysterectomy | | | |
| subjects affected / exposed | 1 / 260 (0.38%) | 0 / 267 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pleurodesis | | | |
| subjects affected / exposed | 2 / 260 (0.77%) | 0 / 267 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Central venous catheterisation | | | |
| subjects affected / exposed | 1 / 260 (0.38%) | 0 / 267 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hepatectomy | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 260 (0.38%) | 0 / 267 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Axillary lymphadenectomy | | | |
| subjects affected / exposed | 1 / 260 (0.38%) | 0 / 267 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cancer surgery | | | |
| subjects affected / exposed | 0 / 260 (0.00%) | 1 / 267 (0.37%) | |
| 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 | | | |
| Death | | | |
| subjects affected / exposed | 2 / 260 (0.77%) | 1 / 267 (0.37%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 2 | 0 / 1 | |
| Fatigue | | | |
| subjects affected / exposed | 2 / 260 (0.77%) | 2 / 267 (0.75%) | |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Mucosal inflammation | | | |
| subjects affected / exposed | 1 / 260 (0.38%) | 0 / 267 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pain | | | |
| subjects affected / exposed | 2 / 260 (0.77%) | 0 / 267 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pyrexia | | | |
| subjects affected / exposed | 0 / 260 (0.00%) | 3 / 267 (1.12%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| General physical health deterioration | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 3 / 260 (1.15%) | 3 / 267 (1.12%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 3 | 0 / 2 | |
| Reproductive system and breast disorders | | | |
| Menorrhagia | | | |
| subjects affected / exposed | 1 / 260 (0.38%) | 0 / 267 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Asphyxia | | | |
| subjects affected / exposed | 1 / 260 (0.38%) | 0 / 267 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bronchospasm | | | |
| subjects affected / exposed | 1 / 260 (0.38%) | 0 / 267 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Dyspnoea | | | |
| subjects affected / exposed | 8 / 260 (3.08%) | 3 / 267 (1.12%) | |
| occurrences causally related to treatment / all | 1 / 9 | 0 / 5 | |
| deaths causally related to treatment / all | 0 / 2 | 0 / 0 | |
| Haemoptysis | | | |
| subjects affected / exposed | 0 / 260 (0.00%) | 1 / 267 (0.37%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pleural effusion | | | |
| subjects affected / exposed | 6 / 260 (2.31%) | 11 / 267 (4.12%) | |
| occurrences causally related to treatment / all | 0 / 6 | 0 / 11 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 1 | |
| Pneumonitis | | | |
| subjects affected / exposed | 1 / 260 (0.38%) | 0 / 267 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|---|---|---|
| Pneumothorax | | | |
| subjects affected / exposed | 1 / 260 (0.38%) | 3 / 267 (1.12%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pulmonary embolism | | | |
| subjects affected / exposed | 3 / 260 (1.15%) | 4 / 267 (1.50%) | |
| occurrences causally related to treatment / all | 1 / 3 | 2 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pulmonary microemboli | | | |
| subjects affected / exposed | 1 / 260 (0.38%) | 0 / 267 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory failure | | | |
| subjects affected / exposed | 3 / 260 (1.15%) | 0 / 267 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 3 | 0 / 0 | |
| Tracheal obstruction extrinsic | | | |
| subjects affected / exposed | 1 / 260 (0.38%) | 0 / 267 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Psychiatric disorders | | | |
| Confusional state | | | |
| subjects affected / exposed | 1 / 260 (0.38%) | 0 / 267 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Investigations | | | |
| Biopsy lung | | | |
| subjects affected / exposed | 1 / 260 (0.38%) | 0 / 267 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Blood bilirubin increased | | | |
| subjects affected / exposed | 0 / 260 (0.00%) | 1 / 267 (0.37%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|---|---|---|
| White blood cell count decreased | | | |
| subjects affected / exposed | 1 / 260 (0.38%) | 0 / 267 (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 | | | |
| Femoral neck fracture | | | |
| subjects affected / exposed | 1 / 260 (0.38%) | 0 / 267 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Femur fracture | | | |
| subjects affected / exposed | 1 / 260 (0.38%) | 1 / 267 (0.37%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hip fracture | | | |
| subjects affected / exposed | 0 / 260 (0.00%) | 1 / 267 (0.37%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Humerus fracture | | | |
| subjects affected / exposed | 0 / 260 (0.00%) | 1 / 267 (0.37%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Tendon rupture | | | |
| subjects affected / exposed | 0 / 260 (0.00%) | 1 / 267 (0.37%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Wrist fracture | | | |
| subjects affected / exposed | 1 / 260 (0.38%) | 0 / 267 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Congenital, familial and genetic disorders | | | |
| Aplasia | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 260 (0.00%) | 1 / 267 (0.37%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac disorders | | | |
| Bundle branch block right | | | |
| subjects affected / exposed | 0 / 260 (0.00%) | 1 / 267 (0.37%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pericardial effusion | | | |
| subjects affected / exposed | 0 / 260 (0.00%) | 5 / 267 (1.87%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 6 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiopulmonary failure | | | |
| subjects affected / exposed | 0 / 260 (0.00%) | 1 / 267 (0.37%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Nervous system disorders | | | |
| Disturbance in attention | | | |
| subjects affected / exposed | 1 / 260 (0.38%) | 0 / 267 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Dizziness | | | |
| subjects affected / exposed | 0 / 260 (0.00%) | 1 / 267 (0.37%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Epilepsy | | | |
| subjects affected / exposed | 1 / 260 (0.38%) | 0 / 267 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Facial paralysis | | | |
| subjects affected / exposed | 0 / 260 (0.00%) | 1 / 267 (0.37%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Headache | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 2 / 260 (0.77%) | 1 / 267 (0.37%) | |
| occurrences causally related to treatment / all | 2 / 2 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hepatic encephalopathy | | | |
| subjects affected / exposed | 1 / 260 (0.38%) | 1 / 267 (0.37%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 1 | |
| Lethargy | | | |
| subjects affected / exposed | 0 / 260 (0.00%) | 1 / 267 (0.37%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Neuralgia | | | |
| subjects affected / exposed | 1 / 260 (0.38%) | 0 / 267 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Presyncope | | | |
| subjects affected / exposed | 1 / 260 (0.38%) | 0 / 267 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Sciatica | | | |
| subjects affected / exposed | 1 / 260 (0.38%) | 0 / 267 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Spinal cord compression | | | |
| subjects affected / exposed | 0 / 260 (0.00%) | 1 / 267 (0.37%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Brain oedema | | | |
| subjects affected / exposed | 0 / 260 (0.00%) | 1 / 267 (0.37%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Central nervous system mass | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 260 (0.00%) | 1 / 267 (0.37%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cytotoxic oedema | | | |
| subjects affected / exposed | 1 / 260 (0.38%) | 0 / 267 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 2 / 260 (0.77%) | 2 / 267 (0.75%) | |
| occurrences causally related to treatment / all | 2 / 2 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Febrile neutropenia | | | |
| subjects affected / exposed | 0 / 260 (0.00%) | 1 / 267 (0.37%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Neutropenia | | | |
| subjects affected / exposed | 2 / 260 (0.77%) | 0 / 267 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Thrombocytopenia | | | |
| subjects affected / exposed | 0 / 260 (0.00%) | 1 / 267 (0.37%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Eye disorders | | | |
| Eye symptom | | | |
| subjects affected / exposed | 1 / 260 (0.38%) | 0 / 267 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal disorders | | | |
| Abdominal discomfort | | | |
| subjects affected / exposed | 0 / 260 (0.00%) | 1 / 267 (0.37%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|---|---|---|
| Abdominal pain | | | |
| subjects affected / exposed | 2 / 260 (0.77%) | 1 / 267 (0.37%) | |
| occurrences causally related to treatment / all | 0 / 2 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Acute abdomen | | | |
| subjects affected / exposed | 1 / 260 (0.38%) | 0 / 267 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ascites | | | |
| subjects affected / exposed | 1 / 260 (0.38%) | 2 / 267 (0.75%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 7 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Colitis | | | |
| subjects affected / exposed | 1 / 260 (0.38%) | 2 / 267 (0.75%) | |
| occurrences causally related to treatment / all | 1 / 1 | 2 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Constipation | | | |
| subjects affected / exposed | 1 / 260 (0.38%) | 0 / 267 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Diarrhoea | | | |
| subjects affected / exposed | 3 / 260 (1.15%) | 8 / 267 (3.00%) | |
| occurrences causally related to treatment / all | 3 / 3 | 5 / 8 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Enteritis | | | |
| subjects affected / exposed | 0 / 260 (0.00%) | 1 / 267 (0.37%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Melaena | | | |
| subjects affected / exposed | 1 / 260 (0.38%) | 0 / 267 (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 | 3 / 260 (1.15%) | 2 / 267 (0.75%) | |
| occurrences causally related to treatment / all | 1 / 3 | 1 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Oesophageal stenosis | | | |
| subjects affected / exposed | 1 / 260 (0.38%) | 0 / 267 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pancreatitis | | | |
| subjects affected / exposed | 1 / 260 (0.38%) | 0 / 267 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Swollen tongue | | | |
| subjects affected / exposed | 1 / 260 (0.38%) | 0 / 267 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vomiting | | | |
| subjects affected / exposed | 7 / 260 (2.69%) | 1 / 267 (0.37%) | |
| occurrences causally related to treatment / all | 5 / 7 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Duodenal stenosis | | | |
| subjects affected / exposed | 1 / 260 (0.38%) | 0 / 267 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Subileus | | | |
| subjects affected / exposed | 0 / 260 (0.00%) | 1 / 267 (0.37%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Neutropenic colitis | | | |
| subjects affected / exposed | 0 / 260 (0.00%) | 3 / 267 (1.12%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Hepatobiliary disorders | | | |
| Gallbladder pain | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 260 (0.38%) | 0 / 267 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hepatic failure | | | |
| subjects affected / exposed | 2 / 260 (0.77%) | 1 / 267 (0.37%) | |
| occurrences causally related to treatment / all | 2 / 2 | 0 / 1 | |
| deaths causally related to treatment / all | 1 / 1 | 0 / 1 | |
| Hyperbilirubinaemia | | | |
| subjects affected / exposed | 1 / 260 (0.38%) | 0 / 267 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Jaundice cholestatic | | | |
| subjects affected / exposed | 1 / 260 (0.38%) | 0 / 267 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Skin and subcutaneous tissue disorders | | | |
| Erythema multiforme | | | |
| subjects affected / exposed | 1 / 260 (0.38%) | 0 / 267 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Palmar-plantar erythrodysaesthesia syndrome | | | |
| subjects affected / exposed | 0 / 260 (0.00%) | 1 / 267 (0.37%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Rash | | | |
| subjects affected / exposed | 1 / 260 (0.38%) | 0 / 267 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal and urinary disorders | | | |
| Hydronephrosis | | | |
| subjects affected / exposed | 1 / 260 (0.38%) | 1 / 267 (0.37%) | |
| occurrences causally related to treatment / all | 0 / 1 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

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|---|---|---|---|
| Renal colic | | | |
| subjects affected / exposed | 1 / 260 (0.38%) | 0 / 267 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Acute kidney injury | | | |
| subjects affected / exposed | 1 / 260 (0.38%) | 0 / 267 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Musculoskeletal and connective tissue disorders | | | |
| Arthralgia | | | |
| subjects affected / exposed | 3 / 260 (1.15%) | 1 / 267 (0.37%) | |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Back pain | | | |
| subjects affected / exposed | 2 / 260 (0.77%) | 0 / 267 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bone pain | | | |
| subjects affected / exposed | 0 / 260 (0.00%) | 1 / 267 (0.37%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Musculoskeletal pain | | | |
| subjects affected / exposed | 0 / 260 (0.00%) | 1 / 267 (0.37%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Myopathy | | | |
| subjects affected / exposed | 1 / 260 (0.38%) | 0 / 267 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Mobility decreased | | | |
| subjects affected / exposed | 0 / 260 (0.00%) | 1 / 267 (0.37%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

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|---|---|---|---|
| Musculoskeletal chest pain | | | |
| subjects affected / exposed | 1 / 260 (0.38%) | 0 / 267 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infections and infestations | | | |
| Bronchitis | | | |
| subjects affected / exposed | 1 / 260 (0.38%) | 0 / 267 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastroenteritis viral | | | |
| subjects affected / exposed | 1 / 260 (0.38%) | 0 / 267 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumonia | | | |
| subjects affected / exposed | 2 / 260 (0.77%) | 0 / 267 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Sepsis | | | |
| subjects affected / exposed | 2 / 260 (0.77%) | 0 / 267 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Urinary tract infection | | | |
| subjects affected / exposed | 2 / 260 (0.77%) | 1 / 267 (0.37%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cytomegalovirus enterocolitis | | | |
| subjects affected / exposed | 1 / 260 (0.38%) | 0 / 267 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lung infection | | | |
| subjects affected / exposed | 2 / 260 (0.77%) | 0 / 267 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Metabolism and nutrition disorders | | | |

| | | | |
|---|---|---|---|
| Dehydration | | | |
| subjects affected / exposed | 2 / 260 (0.77%) | 0 / 267 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypercalcaemia | | | |
| subjects affected / exposed | 0 / 260 (0.00%) | 2 / 267 (0.75%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hyperglycaemia | | | |
| subjects affected / exposed | 0 / 260 (0.00%) | 1 / 267 (0.37%) | |
| 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 / 260 (0.00%) | 1 / 267 (0.37%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypokalaemia | | | |
| subjects affected / exposed | 1 / 260 (0.38%) | 4 / 267 (1.50%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hyponatraemia | | | |
| subjects affected / exposed | 1 / 260 (0.38%) | 0 / 267 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypophosphataemia | | | |
| subjects affected / exposed | 0 / 260 (0.00%) | 1 / 267 (0.37%) | |
| 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** | Sorafenib (Nexavar, BAY43-9006) + Capecitabine | Placebo + Capecitabine | |
|---|---|---|---|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 256 / 260 (98.46%) | 248 / 267 (92.88%) | |
| Vascular disorders | | | |
| Hypertension | | | |
| subjects affected / exposed | 69 / 260 (26.54%) | 16 / 267 (5.99%) | |
| occurrences (all) | 92 | 21 | |
| General disorders and administration site conditions | | | |
| Asthenia | | | |
| subjects affected / exposed | 49 / 260 (18.85%) | 51 / 267 (19.10%) | |
| occurrences (all) | 67 | 69 | |
| Fatigue | | | |
| subjects affected / exposed | 79 / 260 (30.38%) | 81 / 267 (30.34%) | |
| occurrences (all) | 101 | 102 | |
| Influenza like illness | | | |
| subjects affected / exposed | 5 / 260 (1.92%) | 15 / 267 (5.62%) | |
| occurrences (all) | 9 | 19 | |
| Mucosal inflammation | | | |
| subjects affected / exposed | 39 / 260 (15.00%) | 19 / 267 (7.12%) | |
| occurrences (all) | 49 | 20 | |
| Oedema peripheral | | | |
| subjects affected / exposed | 9 / 260 (3.46%) | 23 / 267 (8.61%) | |
| occurrences (all) | 10 | 29 | |
| Pyrexia | | | |
| subjects affected / exposed | 28 / 260 (10.77%) | 32 / 267 (11.99%) | |
| occurrences (all) | 31 | 39 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Cough | | | |
| subjects affected / exposed | 25 / 260 (9.62%) | 23 / 267 (8.61%) | |
| occurrences (all) | 25 | 25 | |
| Dyspnoea | | | |
| subjects affected / exposed | 32 / 260 (12.31%) | 41 / 267 (15.36%) | |
| occurrences (all) | 34 | 47 | |
| Psychiatric disorders | | | |

| | | | |
|---|---|---|---|
| Anxiety | | | |
| subjects affected / exposed | 19 / 260 (7.31%) | 12 / 267 (4.49%) | |
| occurrences (all) | 19 | 12 | |
| Insomnia | | | |
| subjects affected / exposed | 16 / 260 (6.15%) | 12 / 267 (4.49%) | |
| occurrences (all) | 16 | 12 | |
| Investigations | | | |
| Alanine aminotransferase increased | | | |
| subjects affected / exposed | 27 / 260 (10.38%) | 21 / 267 (7.87%) | |
| occurrences (all) | 34 | 24 | |
| Aspartate aminotransferase increased | | | |
| subjects affected / exposed | 27 / 260 (10.38%) | 23 / 267 (8.61%) | |
| occurrences (all) | 32 | 26 | |
| Blood bilirubin increased | | | |
| subjects affected / exposed | 19 / 260 (7.31%) | 17 / 267 (6.37%) | |
| occurrences (all) | 27 | 26 | |
| Gamma-glutamyltransferase increased | | | |
| subjects affected / exposed | 14 / 260 (5.38%) | 4 / 267 (1.50%) | |
| occurrences (all) | 14 | 4 | |
| Lipase increased | | | |
| subjects affected / exposed | 13 / 260 (5.00%) | 5 / 267 (1.87%) | |
| occurrences (all) | 15 | 5 | |
| Neutrophil count decreased | | | |
| subjects affected / exposed | 14 / 260 (5.38%) | 10 / 267 (3.75%) | |
| occurrences (all) | 27 | 22 | |
| Weight decreased | | | |
| subjects affected / exposed | 28 / 260 (10.77%) | 12 / 267 (4.49%) | |
| occurrences (all) | 28 | 13 | |
| White blood cell count decreased | | | |
| subjects affected / exposed | 17 / 260 (6.54%) | 12 / 267 (4.49%) | |
| occurrences (all) | 23 | 23 | |
| Nervous system disorders | | | |
| Dizziness | | | |
| subjects affected / exposed | 21 / 260 (8.08%) | 22 / 267 (8.24%) | |
| occurrences (all) | 26 | 26 | |
| Dysgeusia | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 12 / 260 (4.62%) | 20 / 267 (7.49%) | |
| occurrences (all) | 13 | 20 | |
| Headache | | | |
| subjects affected / exposed | 35 / 260 (13.46%) | 36 / 267 (13.48%) | |
| occurrences (all) | 49 | 45 | |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 31 / 260 (11.92%) | 32 / 267 (11.99%) | |
| occurrences (all) | 37 | 37 | |
| Neutropenia | | | |
| subjects affected / exposed | 12 / 260 (4.62%) | 24 / 267 (8.99%) | |
| occurrences (all) | 22 | 46 | |
| Eye disorders | | | |
| Lacrimation increased | | | |
| subjects affected / exposed | 0 / 260 (0.00%) | 16 / 267 (5.99%) | |
| occurrences (all) | 0 | 21 | |
| Gastrointestinal disorders | | | |
| Abdominal pain | | | |
| subjects affected / exposed | 33 / 260 (12.69%) | 28 / 267 (10.49%) | |
| occurrences (all) | 40 | 41 | |
| Abdominal pain upper | | | |
| subjects affected / exposed | 35 / 260 (13.46%) | 19 / 267 (7.12%) | |
| occurrences (all) | 44 | 22 | |
| Constipation | | | |
| subjects affected / exposed | 53 / 260 (20.38%) | 33 / 267 (12.36%) | |
| occurrences (all) | 67 | 36 | |
| Diarrhoea | | | |
| subjects affected / exposed | 123 / 260 (47.31%) | 98 / 267 (36.70%) | |
| occurrences (all) | 291 | 190 | |
| Dyspepsia | | | |
| subjects affected / exposed | 16 / 260 (6.15%) | 25 / 267 (9.36%) | |
| occurrences (all) | 19 | 31 | |
| Nausea | | | |
| subjects affected / exposed | 101 / 260 (38.85%) | 97 / 267 (36.33%) | |
| occurrences (all) | 166 | 150 | |
| Stomatitis | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 45 / 260 (17.31%) | 24 / 267 (8.99%) | |
| occurrences (all) | 54 | 29 | |
| Vomiting | | | |
| subjects affected / exposed | 65 / 260 (25.00%) | 53 / 267 (19.85%) | |
| occurrences (all) | 118 | 83 | |
| Skin and subcutaneous tissue disorders | | | |
| Alopecia | | | |
| subjects affected / exposed | 44 / 260 (16.92%) | 6 / 267 (2.25%) | |
| occurrences (all) | 49 | 6 | |
| Dry skin | | | |
| subjects affected / exposed | 19 / 260 (7.31%) | 17 / 267 (6.37%) | |
| occurrences (all) | 23 | 19 | |
| Palmar-plantar erythrodysaesthesia syndrome | | | |
| subjects affected / exposed | 206 / 260 (79.23%) | 158 / 267 (59.18%) | |
| occurrences (all) | 288 | 228 | |
| Rash | | | |
| subjects affected / exposed | 48 / 260 (18.46%) | 22 / 267 (8.24%) | |
| occurrences (all) | 58 | 29 | |
| Musculoskeletal and connective tissue disorders | | | |
| Arthralgia | | | |
| subjects affected / exposed | 35 / 260 (13.46%) | 27 / 267 (10.11%) | |
| occurrences (all) | 54 | 33 | |
| Back pain | | | |
| subjects affected / exposed | 33 / 260 (12.69%) | 33 / 267 (12.36%) | |
| occurrences (all) | 39 | 34 | |
| Muscle spasms | | | |
| subjects affected / exposed | 17 / 260 (6.54%) | 6 / 267 (2.25%) | |
| occurrences (all) | 24 | 6 | |
| Musculoskeletal pain | | | |
| subjects affected / exposed | 9 / 260 (3.46%) | 17 / 267 (6.37%) | |
| occurrences (all) | 9 | 21 | |
| Pain in extremity | | | |
| subjects affected / exposed | 23 / 260 (8.85%) | 21 / 267 (7.87%) | |
| occurrences (all) | 32 | 28 | |
| Infections and infestations | | | |

| | | | |
|---|---|---|---|
| Nasopharyngitis | | | |
| subjects affected / exposed | 24 / 260 (9.23%) | 23 / 267 (8.61%) | |
| occurrences (all) | 35 | 28 | |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 15 / 260 (5.77%) | 11 / 267 (4.12%) | |
| occurrences (all) | 15 | 12 | |
| Urinary tract infection | | | |
| subjects affected / exposed | 16 / 260 (6.15%) | 15 / 267 (5.62%) | |
| occurrences (all) | 21 | 16 | |
| Metabolism and nutrition disorders | | | |
| Hypokalaemia | | | |
| subjects affected / exposed | 22 / 260 (8.46%) | 15 / 267 (5.62%) | |
| occurrences (all) | 24 | 19 | |
| Hypophosphataemia | | | |
| subjects affected / exposed | 16 / 260 (6.15%) | 4 / 267 (1.50%) | |
| occurrences (all) | 22 | 5 | |
| Decreased appetite | | | |
| subjects affected / exposed | 53 / 260 (20.38%) | 38 / 267 (14.23%) | |
| occurrences (all) | 63 | 40 | |

## More information

## Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|---|---|
| 29 December 2010 | 1. Several changes were made to the inclusion criterion concerning subjects who were (1) resistant to or failed prior taxane and an anthracycline OR (2) resistant to or failed prior taxane and for whom further anthracycline therapy was not indicated<br>2. Clarification of Consent to Long-Term Follow-up as information on overall survival (a secondary study objective) must be collected for all subjects<br>3. Subjects in the Long-term Follow-up Period should have regular computed tomography (CT) scans/magnetic resonance images (MRIs) until disease progression is documented<br>4. The IVRS used in this study has a built-in 3-day time period for the screening phase<br>5. Participation in the pharmacokinetics part of the study is not mandatory<br>6. To allow collection of pharmacokinetic samples at the scheduled Day 15 visit of appropriate cycles rather than Day 14 to enhance subject convenience by eliminating the need for this additional Day-14 visit<br>7. Anti-cancer drugs or device therapy for the treatment of breast cancer was prohibited within 4 weeks (28 days) or 5 half-lives, whichever was longer, prior to randomization<br>8. Allowed for the use of hematopoietic growth factor (only cycles subsequent to Cycle 1) in study subjects at the discretion of the investigator<br>9. To emphasize that a subject may decline to participate in the optional genetic biomarker study and yet still participate in the study trial. |
| 03 May 2011 | 1. Clarifications on inclusion criteria regarding radiological evaluations, dose range of doxorubicin equivalents, eligibility following taxane and anthracycline therapy, discontinuation of prior chemotherapy, and pregnancy test<br>2. Clarifications on exclusion criteria regarding testing of subjects with unknown HER2 status, breast cancer types, subjects with brain metastases, baseline infections, prior radiation, excluded therapies, hemorrhage/bleeding events<br>3. To allow dose re-escalation of sorafenib/placebo only under the specific circumstances that are clearly defined in protocol<br>4. Included detailed guidelines on dose modifications, dose interruptions, and criteria for reintroduction of study medications in response to hematologic toxicities<br>5. To allow subjects for collection of pharmacokinetic samples, to attend their weekly clinic visit scheduled for Cycle 2/Day 15 to be conducted on Cycle 2/Day 14<br>6. To state that, if 10 slides are not available, fewer slides may be accepted for formalin-fixed paraffin embedded biopsy after discussion and agreement with the sponsor<br>7. In the interest of increasing the subject safety the protocol was modified to specify that subjects should undergo electrocardiograms (ECGs) on Day 1 of each cycle in addition to previously specified baseline, end-of-treatment, and as-required ECGs<br>8. The text on excluded concurrent therapies was clarified for consistency with the remainder of the protocol<br>9. The inclusion criterion regarding cancer-evaluation imaging at baseline was amended to allow a bone scan to be conducted up to 8 weeks before randomization to be used as the baseline scan<br>10. Screening study assessments should be performed within specified time periods relative to randomization<br>11. The instructions regarding HER2 status determination were changed in order to reflect the current practices regarding laboratory accreditation and usage of testing kits. |

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| 26 January 2012 | Amendment 6 modified inclusion criteria defining the specification for prior treatment with taxane and anthracycline therapy in subjects who relapsed over 12 months following the end of treatment and clarifications were made.<br>1. The inclusion criterion regarding baseline cancer evaluation imaging was amended to allow the baseline bone scan to have been conducted up to 12 weeks before randomization<br>2. Detailed guidelines on baseline criteria for laboratory evaluations were provided.<br>3. Re-screening was permitted in cases in which the subject's eligibility for the study depended on the completion of further treatment, or to allow protocol compliant time lines for assessment or washout periods<br>4. Detailed guidelines on dose modifications, dose interruptions, and criteria for re-introduction of study medications in response to hematologic toxicities based on the CTCAE v4.0 grade of events |
| 03 September 2013 | 1. The original assumption of a 1-sided alpha of 0.025, power of 98% and a randomization ratio of 1:1 between treatments for 363 PFS events (for progression events based on central radiology review) to detect a 66.7% increase in PFS was amended to an assumption of a 1-sided alpha of 0.025, power of 92.8% and a randomization ratio of 1:1 between treatments for 250 PFS events (including progression events based on central radiology review and death, if death occurs before disease progression) to detect a 66.7% increase in PFS<br>2. The following statement: "assuming a median OS of 12 months for the control group, approximately 270 deaths would be expected at the time of the PFS analysis. For the final analysis of OS, 405 deaths are projected to occur by approximately 43.3 months after the first subject is randomized" was amended to "assuming a median of 12 months for the control group, approximately 270 deaths would be expected at the time of the PFS analysis. However, at the time approximately 250 PFS events are reached, if the observed number of deaths is less than approximately 270, the trial will continue and remain blinded until approximately 270 deaths are observed. In such a case, the analysis of PFS will include all PFS data up to the later data cutoff date for approximately 270 deaths. For the final analysis of OS, and based on actual events, 405 deaths are projected to occur by approximately 56.2 months after the first subject was randomized."<br>3. DCR was added as a secondary end-point. |

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.

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| Results of exploratory analysis of biomarkers are anticipated in the month of February, 2016.<br>Occurrence of "±" in relation with geometric CV (%) is auto-generated and cannot be deleted. |

Notes: