# Clinical trial results:
# Multicentre, randomised, double-blind, Phase III trial to investigate the efficacy and safety of oral BIBF 1120 plus standard docetaxel therapy compared to placebo plus standard docetaxel therapy in patients with stage IIIB/IV or recurrent non small cell lung cancer after failure of first line chemotherapy (LUME Lung 1).

## Summary

| | |
|---|---|
| EudraCT number | 2007-004803-36 |
| Trial protocol | DE BE CZ AT DK LT ES SK GB FR PT BG IT GR |
| Global end of trial date | 13 November 2017 |

**Results information**

| | |
|---|---|
| Result version number | v2 (current) |
| This version publication date | 14 November 2021 |
| First version publication date | 25 November 2018 |
| Version creation reason | |

## Trial information

**Trial identification**

| | |
|---|---|
| Sponsor protocol code | 1199.13 |

**Additional study identifiers**

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

Notes:

**Sponsors**

| | |
|---|---|
| Sponsor organisation name | Boehringer Ingelheim |
| Sponsor organisation address | Binger Strasse 173, Ingelheim am Rhein, Germany, 55216 |
| Public contact | QRPE Processes and Systems Coordination Clinical Trial Information Disclosure, Boehringer Ingelheim, 001 8002430127, clintriage.rdg@boehringer-ingelheim.com |
| Scientific contact | QRPE Processes and Systems Coordination Clinical Trial Information Disclosure, Boehringer Ingelheim, 001 8002430127, clintriage.rdg@boehringer-ingelheim.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 | 11 December 2017 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 02 November 2010 |
| Global end of trial reached? | Yes |
| Global end of trial date | 13 November 2017 |
| Was the trial ended prematurely? | No |

Notes:

## General information about the trial

Main objective of the trial:

To investigate the efficacy and safety of nintedanib as compared to matching placebo in patients with stage IIIB/IV or recurrent non small cell lung cancer (NSCLC) treated with standard therapy of docetaxel after failure of first line chemotherapy

Protection of trial subjects:

Only subjects that met all the study inclusion and none of the exclusion criteria were entered in the study. All subjects were free to withdraw from the clinical trial at any time for any reason given. Close monitoring of all subjects was adhered to throughout the trial conduct

Background therapy: -

Evidence for comparator: -

| | |
|---|---|
| Actual start date of recruitment | 03 December 2008 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | Yes |

Notes:

## Population of trial subjects

### Subjects enrolled per country

| | |
|---|---|
| Country: Number of subjects enrolled | China: 224 |
| Country: Number of subjects enrolled | Korea, Republic of: 24 |
| Country: Number of subjects enrolled | India: 158 |
| Country: Number of subjects enrolled | South Africa: 43 |
| Country: Number of subjects enrolled | Austria: 6 |
| Country: Number of subjects enrolled | Belgium: 19 |
| Country: Number of subjects enrolled | Bulgaria: 37 |
| Country: Number of subjects enrolled | Belarus: 53 |
| Country: Number of subjects enrolled | Switzerland: 5 |
| Country: Number of subjects enrolled | Czechia: 15 |
| Country: Number of subjects enrolled | Germany: 204 |
| Country: Number of subjects enrolled | Denmark: 22 |
| Country: Number of subjects enrolled | Spain: 40 |
| Country: Number of subjects enrolled | France: 60 |
| Country: Number of subjects enrolled | Georgia: 35 |
| Country: Number of subjects enrolled | Greece: 35 |
| Country: Number of subjects enrolled | Croatia: 12 |

| | |
|---|---|
| Country: Number of subjects enrolled | Italy: 42 |
| Country: Number of subjects enrolled | Israel: 48 |
| Country: Number of subjects enrolled | Lithuania: 20 |
| Country: Number of subjects enrolled | Portugal: 44 |
| Country: Number of subjects enrolled | Poland: 149 |
| Country: Number of subjects enrolled | Russian Federation: 176 |
| Country: Number of subjects enrolled | Romania: 105 |
| Country: Number of subjects enrolled | Slovakia: 1 |
| Country: Number of subjects enrolled | Ukraine: 177 |
| Country: Number of subjects enrolled | United Kingdom: 19 |
| Worldwide total number of subjects | 1773 |
| EEA total number of subjects | 811 |

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) | 1229 |
| From 65 to 84 years | 543 |
| 85 years and over | 1 |

## Subject disposition

### Recruitment

Recruitment details:

Two-arm, randomised, double-blind, placebo-controlled, parallel-group comparison of nintedanib versus matching placebo. In this study,1773 subjects were enrolled, 1314 subjects were randomised and entered and 1307 subjects were treated.

### Pre-assignment

Screening details:

All subjects were screened for eligibility to participate in trial. Subjects attended specialist sites to ensure that they (the subjects) met all implemented inclusion/exclusion criteria. Subjects were not to be randomised to trial drug if any of the specific entry criteria was violated.

### Period 1

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

Blinding implementation details:

The trial had a parallel-group, double-blind, placebo-controlled design.

### Arms

| | |
|---|---|
| Are arms mutually exclusive? | Yes |
| **Arm title** | Nintedanib plus docetaxel |

Arm description:

Nintedanib 200 mg twice daily administered orally in the form of a soft gelatin capsule plus docetaxel 75 milligram (mg)/square meter (m2) once every 3 weeks administered via intravenous infusion over 1 hour (h).

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | docetaxel |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Concentrate for solution for injection |
| Routes of administration | Intravenous use |

Dosage and administration details:

docetaxel 75 mg/m2 once every 3 weeks administered via intravenous infusion over 1 hour (h) with dose reduction to 60 mg/m2 if required.

| | |
|---|---|
| Investigational medicinal product name | Nintedanib |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Capsule, soft |
| Routes of administration | Oral use |

Dosage and administration details:

Nintedanib 200 mg twice daily administered orally in the form of a soft gelatin capsule with dose reduction to 150 mg b.i.d. or 100 mg twice daily (b.i.d.) (according to the protocol-defined dose reduction scheme) if required. No dose increase was allowed after a dose reduction.

| | |
|---|---|
| **Arm title** | Placebo plus docetaxel |

Arm description:

Placebo soft gelatin capsule matching that of nintedanib 2 times daily plus docetaxel 75 mg/m2 once every 3 weeks administered via intravenous infusion over 1 hour (h).

| | |
|---|---|
| Arm type | Placebo |

| | |
|---|---|
| Investigational medicinal product name | matching placebo to nintedanib |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Capsule, soft |
| Routes of administration | Oral use |

Dosage and administration details:

matching placebo to nintedanib twice daily administered orally in a form of a soft gelatin capsule.

| | |
|---|---|
| Investigational medicinal product name | docetaxel |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Concentrate for solution for injection |
| Routes of administration | Intravenous use |

Dosage and administration details:

docetaxel 75 mg/m2 once every 3 weeks administered via intravenous infusion over 1 hour (h) with dose reduction to 60 mg/m2 if required.

| **Number of subjects in period 1[1]** | Nintedanib plus docetaxel | Placebo plus docetaxel |
|---|---|---|
| Started | 655 | 659 |
| Completed | 6 | 5 |
| Not completed | 649 | 654 |
| Other AE - Non−Fatal event | 54 | 50 |
| Progressive disease (modified RECIST) | 404 | 435 |
| Consent withdrawn by subject | 60 | 42 |
| Other AE - Fatal event | 30 | 23 |
| Worsening or AE of underlying disease | 64 | 70 |
| Lost to follow-up | 5 | 5 |
| Protocol deviation | 9 | 9 |
| Reasons other than stated above | 20 | 16 |
| Not treated | 3 | 4 |

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: Not all enrolled subjects were randomized in the baseline period.

## Baseline characteristics

| Reporting groups | |
|---|---|
| Reporting group title | Nintedanib plus docetaxel |
| Reporting group description: | |
| Nintedanib 200 mg twice daily administered orally in the form of a soft gelatin capsule plus docetaxel 75 milligram (mg)/square meter (m2) once every 3 weeks administered via intravenous infusion over 1 hour (h). | |
| Reporting group title | Placebo plus docetaxel |
| Reporting group description: | |
| Placebo soft gelatin capsule matching that of nintedanib 2 times daily plus docetaxel 75 mg/m2 once every 3 weeks administered via intravenous infusion over 1 hour (h). | |

| Reporting group values | Nintedanib plus docetaxel | Placebo plus docetaxel | Total |
|---|---|---|---|
| Number of subjects | 655 | 659 | 1314 |
| Age categorical<br>Units: Subjects | | | |
| Age Continuous | | | |
| Randomised Set (RS)- Includes all randomised patients, whether patients had received study treatment or not | | | |
| Units: years | | | |
| arithmetic mean | 59.7 | 59.8 | |
| standard deviation | ± 9.7 | ± 9.0 | - |
| Sex: Female, Male | | | |
| Randomised Set | | | |
| Units: Subjects | | | |
| Female | 179 | 180 | 359 |
| Male | 476 | 479 | 955 |
| Tumour histology | | | |
| Randomised Set | | | |
| Units: Subjects | | | |
| Adenocarcinoma | 322 | 336 | 658 |
| Squamous cell carcinoma | 276 | 279 | 555 |
| Other | 57 | 44 | 101 |
| Number of patients with adenocarcinoma and time since first line therapy in categories | | | |
| Randomised Set | | | |
| Units: Subjects | | | |
| <9 month | 206 | 199 | 405 |
| >=9 month | 112 | 134 | 246 |
| Missing | 4 | 3 | 7 |
| No tumour histology of adenocarcinoma | 333 | 323 | 656 |

## End points

### End points reporting groups

| | |
|---|---|
| Reporting group title | Nintedanib plus docetaxel |
| Reporting group description: | |
| Nintedanib 200 mg twice daily administered orally in the form of a soft gelatin capsule plus docetaxel 75 milligram (mg)/square meter (m2) once every 3 weeks administered via intravenous infusion over 1 hour (h). | |
| Reporting group title | Placebo plus docetaxel |
| Reporting group description: | |
| Placebo soft gelatin capsule matching that of nintedanib 2 times daily plus docetaxel 75 mg/m2 once every 3 weeks administered via intravenous infusion over 1 hour (h). | |
| Subject analysis set title | Nitedanib 200 mg bid plus docetaxel |
| Subject analysis set type | Intention-to-treat |
| Subject analysis set description: | |
| Nintedanib 200 mg twice daily administered orally in the form of a soft gelatin capsule plus docetaxel 75 mg/m2 once every 3 weeks administered via intravenous infusion over 1 hour (h). | |
| Subject analysis set title | Nintedanib 150 bid mg plus docetaxel |
| Subject analysis set type | Intention-to-treat |
| Subject analysis set description: | |
| Nintedanib 150 mg twice daily administered orally in the form of a soft gelatin capsule plus docetaxel 75 mg/m2 once every 3 weeks administered via intravenous infusion over 1 hour (h). | |

### Primary: Progression Free Survival (PFS) as assessed by central independent review

| | |
|---|---|
| End point title | Progression Free Survival (PFS) as assessed by central independent review |
| End point description: | |
| Progression Free Survival (PFS) as assessed by central independent review according to the modified Response Evaluation Criteria In Solid Tumors Criteria (RECIST) (version 1.0) criteria. Progression free survival (PFS) is defined as the duration of time from date of randomisation to date of progression or death (whatever occurs earlier). Median, 25th and 75th percentiles are calculated from an unadjusted Kaplan-Meier curve. | |
| End point type | Primary |
| End point timeframe: | |
| From randomisation until cut-off date 2 November 2010 (when 713 PFS events were observed) | |

| End point values | Nintedanib plus docetaxel | Placebo plus docetaxel | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 565[1] | 569[2] | | |
| Units: months | | | | |
| median (inter-quartile range (Q1-Q3)) | 3.4 (1.5 to 5.7) | 2.7 (1.4 to 4.6) | | |

Notes:

[1] - Randomised Set

[2] - Randomised Set

### Statistical analyses

| | |
|---|---|
| **Statistical analysis title** | Statistical Analysis 1 |
| Comparison groups | Nintedanib plus docetaxel v Placebo plus docetaxel |

| | |
|---|---|
| Number of subjects included in analysis | 1134 |
| Analysis specification | Pre-specified |
| Analysis type | superiority[3] |
| P-value | = 0.0019 [4] |
| Method | Regression, Cox |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.79 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.68 |
| upper limit | 0.92 |

Notes:

[3] - HR below 1 favors nintedanib

[4] - HR, CI and p-value obtained from the proportional hazards model stratified by baseline ECOG PS (0 vs 1), tumour histology (squamous vs non-squamous), brain metastases at baseline (yes vs no) and prior treatment with bevacizumab (yes vs no)

## Secondary: Overall Survival (Key secondary endpoint)

| | |
|---|---|
| End point title | Overall Survival (Key secondary endpoint) |

End point description:

Overall Survival (OS) defined as the duration from randomisation to death (irrespective of the reason of death). Median, 25th and 75th percentiles are calculated from an unadjusted Kaplan-Meier curve. A fixed-sequence-testing was implemented for key secondary endpoint if both the primary and the follow-up analysis showed a treatment benefit (P<0.05) of nintedanib over placebo. In this case, the OS would be tested using hierarchical testing of statistical hypotheses in (1) patients with adenocarcinoma and <9 months since start of first-line therapy, (2) patients with adenocarcinoma, and (3) all patients. Each hypothesis could be only tested at the pre-specified alpha level if the previous null hypothesis in the testing sequence had been.

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

End point timeframe:

From randomisation until cut-off date 15 February 2013 (approximately 48 months or 1151 deaths among all patients )

| **End point values** | Nintedanib plus docetaxel | Placebo plus docetaxel | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 655[5] | 659[6] | | |
| Units: months | | | | |
| median (inter-quartile range (Q1-Q3)) | | | | |
| Adenocarcinoma and <9 months\| | 10.9 (5.1 to 21.9) | 7.9 (4.5 to 14.5) | | |
| Adenocarcinoma\| | 12.6 (5.5 to 24.2) | 10.3 (5.5 to 19.9) | | |
| All patients\| | 10.1 (5.0 to 19.4) | 9.1 (4.8 to 17.2) | | |

Notes:

[5] - Randomised Set

[6] - Randomised Set

## Statistical analyses

| **Statistical analysis title** | Statistical Analysis 1 |
|---|---|

Statistical analysis description:

Hierarchical testing was tested in a fixed sequence of statistical hypotheses in (1) patients with adenocarcinoma and <9 months since start of first-line therapy, (2) patients with adenocarcinoma, and (3) all patients. Each hypothesis could be only tested at the pre-specified alpha level if the previous null hypothesis in the testing sequence had been rejected. Overall survival for patients with adenocarcinoma and <9 months since start of first line therapy.

| | |
|---|---|
| Comparison groups | Nintedanib plus docetaxel v Placebo plus docetaxel |
| Number of subjects included in analysis | 1314 |
| Analysis specification | Pre-specified |
| Analysis type | superiority[7] |
| P-value | = 0.0073 [8] |
| Method | Regression, Cox |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.75 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.6 |
| upper limit | 0.92 |

Notes:

[7] - The overall alpha level followed a Lan-DeMets spending function with O'Brien-Fleming shape parameter to preserve an overall 2-sided alpha level of 0.05. HR below 1 favors nintedanib
[8] - HR, CI and p-value obtained from the prop. hazards model stratified by baseline ECOG PS (0 vs 1 - one pat. had 2), brain metastases at baseline (yes vs no) and prior treatment with bevacizumab (yes vs no)

| **Statistical analysis title** | Statistical Analysis 2 |
|---|---|

Statistical analysis description:

Hierarchical testing was tested in a fixed sequence of statistical hypotheses in (1) patients with adenocarcinoma and <9 months since start of first-line therapy, (2) patients with adenocarcinoma, and (3) all patients. Each hypothesis could be only tested at the pre-specified alpha level if the previous null hypothesis in the testing sequence had been rejected. Overall survival for patients with adenocarcinoma.

| | |
|---|---|
| Comparison groups | Nintedanib plus docetaxel v Placebo plus docetaxel |
| Number of subjects included in analysis | 1314 |
| Analysis specification | Pre-specified |
| Analysis type | superiority[9] |
| P-value | = 0.0359 [10] |
| Method | Regression, Cox |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.83 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.7 |
| upper limit | 0.99 |

Notes:

[9] - The overall alpha level followed a Lan-DeMets spending function with O'Brien-Fleming shape parameter to preserve an overall 2-sided alpha level of 0.05. HR below 1 favors nintedanib
[10] - HR, CI and p-value obtained from the prop. hazards model stratified by baseline ECOG PS (0 vs 1 - one pat. had 2), brain metastases at baseline (yes vs no) and prior treatment with bevacizumab (yes vs no)

| **Statistical analysis title** | Statistical Analysis 3 |
|---|---|

Statistical analysis description:

Hierarchical testing was tested in a fixed sequence of statistical hypotheses in (1) patients with

adenocarcinoma and <9 months since start of first-line therapy, (2) patients with adenocarcinoma, and (3) all patients. Each hypothesis could be only tested at the pre-specified alpha level if the previous null hypothesis in the testing sequence had been rejected. Overall survival for all patients.

| | |
|---|---|
| Comparison groups | Nintedanib plus docetaxel v Placebo plus docetaxel |
| Number of subjects included in analysis | 1314 |
| Analysis specification | Pre-specified |
| Analysis type | superiority[11] |
| P-value | = 0.272 [12] |
| Method | Regression, Cox |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.94 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.83 |
| upper limit | 1.05 |

Notes:

[11] - The overall alpha level followed a Lan-DeMets spending function with O'Brien-Fleming shape parameter to preserve an overall 2-sided alpha level of 0.05. HR below 1 favors nintedanib

[12] - HR, CI and p-value obtained from the prop. hazards model stratified by baseline ECOG PS (0 vs 1 - one pat. had 2), tumour histology (squamous vs non-squamous), brain metastases at baseline (yes vs no) and prior treatment with bevacizumab (yes vs no)

## Secondary: Follow-up analysis of Progression Free Survival (PFS) as Assessed by Central Independent Review

| | |
|---|---|
| End point title | Follow-up analysis of Progression Free Survival (PFS) as Assessed by Central Independent Review |

End point description:

Follow-up analysis was conducted at the time of overall survival analysis. Progression Free Survival (PFS) as assessed by central independent review according to the modified RECIST (version 1.0) criteria. Median, 25th and 75th percentiles are calculated from an unadjusted Kaplan-Meier curve.

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

End point timeframe:

From randomisation until cut-off date 15 February 2013

| End point values | Nintedanib plus docetaxel | Placebo plus docetaxel | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 655[13] | 659[14] | | |
| Units: months | | | | |
| median (inter-quartile range (Q1-Q3)) | 3.5 (1.5 to 5.7) | 2.7 (1.4 to 5.5) | | |

Notes:

[13] - Randomised Set

[14] - Randomised Set

## Statistical analyses

| Statistical analysis title | Statistical Analysis 1 |
|---|---|
| Comparison groups | Nintedanib plus docetaxel v Placebo plus docetaxel |

| | |
|---|---|
| Number of subjects included in analysis | 1314 |
| Analysis specification | Pre-specified |
| Analysis type | superiority[15] |
| P-value | = 0.007 [16] |
| Method | Regression, Cox |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.85 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.75 |
| upper limit | 0.96 |

Notes:

[15] - HR below 1 favors nintedanib

[16] - HR, CI and p-value obtained from the proportional hazards model stratified by baseline ECOG PS (0 vs 1), tumour histology (squamous vs non-squamous), brain metastases at baseline (yes vs no) and prior treatment with bevacizumab (yes vs no)

## Secondary: Follow-up analysis of Progression Free Survival (PFS) as Assessed by investigator

| | |
|---|---|
| End point title | Follow-up analysis of Progression Free Survival (PFS) as Assessed by investigator |

End point description:

Follow-up analysis was conducted at the time of overall survival analysis. Progression Free Survival (PFS) as assessed by investigator according to the modified RECIST (version 1.0) criteria. Median, 25th and 75th percentiles are calculated from an unadjusted Kaplan-Meier curve.

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

End point timeframe:

From randomisation until cut-off date 15 February 2013

| End point values | Nintedanib plus docetaxel | Placebo plus docetaxel | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 655[17] | 659[18] | | |
| Units: months | | | | |
| median (inter-quartile range (Q1-Q3)) | 4.2 (2.1 to 7.1) | 3.0 (1.4 to 5.7) | | |

Notes:

[17] - Randomised Set

[18] - Randomised Set

## Statistical analyses

| Statistical analysis title | Statistical Analysis 1 |
|---|---|
| Comparison groups | Nintedanib plus docetaxel v Placebo plus docetaxel |
| Number of subjects included in analysis | 1314 |
| Analysis specification | Pre-specified |
| Analysis type | superiority[19] |
| P-value | = 0.0012 [20] |
| Method | Regression, Cox |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.82 |

| | |
|---|---|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.73 |
| upper limit | 0.93 |

Notes:

[19] - HR below 1 favors nintedanib

[20] - HR, CI and p-value obtained from the proportional hazards model stratified by baseline ECOG PS (0 vs 1), tumour histology (squamous vs non-squamous), brain metastases at baseline (yes vs no) and prior treatment with bevacizumab (yes vs no)

## Secondary: Objective Tumour Response

| | |
|---|---|
| End point title | Objective Tumour Response |

End point description:

Confirmed objective response is defined as confirmed Complete Response (CR) and Partial Response (PR) and evaluated according to the modified RECIST criteria version 1.0. As per RECIST v1.0, Complete Response (CR), disappearance of all target lesions; Partial Response (PR), >=30% decrease in the sum of the longest diameter of target lesions. This endpoint was analysed based on the central independent reviewer as well as the investigator.

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

End point timeframe:

From randomisation until cut-off date 15 February 2013

| **End point values** | Nintedanib plus docetaxel | Placebo plus docetaxel | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 655[21] | 659[22] | | |
| Units: % of participants | | | | |
| number (not applicable) | | | | |
| central independent reviewer\| | 4.4 | 3.3 | | |
| investigator assessment\| | 10.4 | 7.6 | | |

Notes:

[21] - Randomised Set

[22] - Randomised Set

## Statistical analyses

| **Statistical analysis title** | Statistical Analysis 1 |
|---|---|

Statistical analysis description:

Analysis based on the central independent review

| | |
|---|---|
| Comparison groups | Nintedanib plus docetaxel v Placebo plus docetaxel |
| Number of subjects included in analysis | 1314 |
| Analysis specification | Pre-specified |
| Analysis type | superiority[23] |
| P-value | = 0.3067 [24] |
| Method | Regression, Logistic |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 1.34 |

| | |
|---|---|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.76 |
| upper limit | 2.39 |

Notes:

[23] - An odds ratio >1 indicates a benefit to nintedanib

[24] - Odds ratio and p-value are obtained from logistic regression model adjusted for baseline ECOG PS (0 vs 1)

| **Statistical analysis title** | Statistical Analysis 2 |
|---|---|

Statistical analysis description:

Analysis based on the investigator's assessment

| | |
|---|---|
| Comparison groups | Nintedanib plus docetaxel v Placebo plus docetaxel |
| Number of subjects included in analysis | 1314 |
| Analysis specification | Pre-specified |
| Analysis type | superiority[25] |
| P-value | = 0.0761 [26] |
| Method | Regression, Logistic |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 1.41 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.96 |
| upper limit | 2.08 |

Notes:

[25] - An odds ratio >1 indicates a benefit to nintedanib

[26] - Odds ratio and p-value are obtained from logistic regression model adjusted for baseline ECOG PS (0 vs 1)

## Secondary: Duration of confirmed objective tumour response

| | |
|---|---|
| End point title | Duration of confirmed objective tumour response |

End point description:

The duration of objective response is the time from first documented (CR) or (PR) to the time of progression or death and evaluated according to the modified RECIST criteria version 1.0. As per RECIST v1.0, Complete Response (CR), disappearance of all target lesions; Partial Response (PR), >=30% decrease in the sum of the longest diameter of target lesions. Median, 25th and 75th percentiles are calculated from an unadjusted Kaplan-Meier curve. This endpoint was analysed based on the central independent reviewer as well as the investigator.

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

End point timeframe:

From randomisation until cut-off date 15 February 2013

| **End point values** | Nintedanib plus docetaxel | Placebo plus docetaxel | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 655[27] | 659[28] | | |
| Units: months | | | | |
| median (inter-quartile range (Q1-Q3)) | | | | |
| central independent reviewer\| | 4.3 (3.0 to 5.7) | 4.3 (2.8 to 8.5) | | |

| | | | | |
|---|---|---|---|---|
| investigator assessment\| | 5.7 (4.1 to 10.0) | 5.5 (3.9 to 9.6) | | |

Notes:

[27] - Randomised Set

[28] - Randomised Set

### Statistical analyses

No statistical analyses for this end point

## Secondary: Time to Confirmed Objective Tumour Response

| End point title | Time to Confirmed Objective Tumour Response |
|---|---|

End point description:

Time to confirmed objective response is defined as time from randomisation to the date of first documented (CR) or (PR) and evaluated according to the modified RECIST criteria version 1.0. Median, 25th and 75th percentiles are calculated from an unadjusted Kaplan-Meier curve. This endpoint was analysed based on the central independent reviewer as well as the investigator.

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

End point timeframe:

From randomisation until cut-off date 15 February 2013

| End point values | Nintedanib plus docetaxel | Placebo plus docetaxel | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 655[29] | 659[30] | | |
| Units: months | | | | |
| median (inter-quartile range (Q1-Q3)) | | | | |
| central independent reviewer\| | 1.5 (1.4 to 3.0) | 2.9 (1.4 to 5.6) | | |
| investigator assessment\| | 2.6 (1.4 to 4.0) | 2.7 (1.4 to 4.1) | | |

Notes:

[29] - Randomised Set

[30] - Randomised Set

### Statistical analyses

No statistical analyses for this end point

## Secondary: Disease Control

| End point title | Disease Control |
|---|---|

End point description:

Disease control was defined as a best overall response of Complete Response (CR), Partial Response (PR), or Stable Disease (SD) and evaluated according to the modified RECIST criteria version 1.0. As per RECIST v1.0 for target lesions : Complete Response (CR), disappearance of all target lesions; Partial Response (PR), >=30% decrease in the sum of the longest diameter of target lesions; progression, as a 20% increase in the sum of the longest diameter of target lesions, or a measurable increase in a non-target lesion, or the appearance of new lesions; Stable Disease (SD), neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for disease progression. This endpoint was analysed based on the central independent reviewer as well as the investigator.

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

End point timeframe:

From randomisation until cut-off date 15 February 2013

| End point values | Nintedanib plus docetaxel | Placebo plus docetaxel | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 655[31] | 659[32] | | |
| Units: % of participants | | | | |
| number (not applicable) | | | | |
| central independent reviewer\| | 54.0 | 41.3 | | |
| investigator assessment\| | 63.4 | 51.4 | | |

Notes:

[31] - Randomised Set

[32] - Randomised Set

## Statistical analyses

| Statistical analysis title | Statistical Analysis 1 |
|---|---|

Statistical analysis description:

Analysis based on the central independent review

| | |
|---|---|
| Comparison groups | Nintedanib plus docetaxel v Placebo plus docetaxel |
| Number of subjects included in analysis | 1314 |
| Analysis specification | Pre-specified |
| Analysis type | superiority[33] |
| P-value | < 0.0001 [34] |
| Method | Regression, Logistic |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 1.68 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 1.35 |
| upper limit | 2.09 |

Notes:

[33] - An odds ratio >1 indicates a benefit to nintedanib

[34] - Odds ratio and p-value are obtained from logistic regression model adjusted for baseline ECOG PS (0 vs 1)

| Statistical analysis title | Statistical Analysis 2 |
|---|---|

Statistical analysis description:

Analysis based on investigator's assessment

| | |
|---|---|
| Comparison groups | Nintedanib plus docetaxel v Placebo plus docetaxel |
| Number of subjects included in analysis | 1314 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | < 0.0001 [35] |
| Method | Regression, Logistic |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 1.64 |

| Confidence interval | |
|---|---|
| level | 95 % |
| sides | 2-sided |
| lower limit | 1.31 |
| upper limit | 2.05 |

Notes:

[35] - Odds ratio and p-value are obtained from logistic regression model adjusted for baseline ECOG PS (0 vs 1)

## Secondary: Duration of Disease Control

| End point title | Duration of Disease Control |
|---|---|

End point description:

The duration of disease control was defined as the time from randomisation to the date of disease progression or death (which ever occurs first) for patients with disease control. Median, 25th and 75th percentiles are calculated from an unadjusted Kaplan-Meier curve. This endpoint was analysed based on the central independent reviewer as well as the investigator.

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

End point timeframe:

From randomisation until cut-off date 15 February 2013

| End point values | Nintedanib plus docetaxel | Placebo plus docetaxel | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 655[36] | 659[37] | | |
| Units: months | | | | |
| median (inter-quartile range (Q1-Q3)) | | | | |
| central independent reviewer\| | 5.6 (4.1 to 7.1) | 5.6 (4.0 to 8.2) | | |
| investigator assessment\| | 5.7 (4.2 to 8.4) | 5.6 (4.1 to 8.5) | | |

Notes:

[36] - Randomised Set

[37] - Randomised Set

### Statistical analyses

No statistical analyses for this end point

## Secondary: Change from baseline in tumour size

| End point title | Change from baseline in tumour size |
|---|---|

End point description:

Percentage change from baseline in tumour size is defined as decrease in the sum of the longest diameter of the target lesion. Presented means are in fact adjusted best means percentage changes generated from ANOVA model adjusted for baseline ECOG PS (0 vs. 1), tumour histology (squamous vs non-squamous), brain metastases at baseline (yes vs no) and prior treatment with bevacizumab (yes vs no) This endpoint was analysed based on the central independent reviewer as well as the investigator.

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

End point timeframe:

From randomisation until cut-off date 15 February 2013

| End point values | Nintedanib plus docetaxel | Placebo plus docetaxel | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 655[38] | 659[39] | | |
| Units: percentage of change in tumor size in mm | | | | |
| arithmetic mean (confidence interval 95%) | | | | |
| central independent reviewer\| | -4.87 (-6.62 to -3.12) | 0.58 (-1.19 to 2.35) | | |
| investigator assessment\| | -10.34 (-12.58 to -8.11) | -2.14 (-4.39 to 0.10) | | |

Notes:

[38] - Randomised Set

[39] - Randomised Set

## Statistical analyses

| Statistical analysis title | Statistical Analysis 1 |
|---|---|

Statistical analysis description:

Analysis based on the central independent review

| Comparison groups | Nintedanib plus docetaxel v Placebo plus docetaxel |
|---|---|
| Number of subjects included in analysis | 1314 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 [40] |
| Method | ANOVA |

Notes:

[40] - P-value generated from ANOVA model adjusted for baseline ECOG PS (0 vs. 1), tumour histology (squamous vs non-squamous), brain metastases at baseline (yes vs no) and prior treatment with bevacizumab (yes vs no)

| Statistical analysis title | Statistical Analysis 2 |
|---|---|

Statistical analysis description:

Analysis based on the investigator's assessment

| Comparison groups | Nintedanib plus docetaxel v Placebo plus docetaxel |
|---|---|
| Number of subjects included in analysis | 1314 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 [41] |
| Method | ANOVA |

Notes:

[41] - P-value generated from ANOVA model adjusted for baseline ECOG PS (0 vs. 1), tumour histology (squamous vs non-squamous), brain metastases at baseline (yes vs no) and prior treatment with bevacizumab (yes vs no)

## Secondary: Clinical improvement

| End point title | Clinical improvement |
|---|---|

End point description:

Clinical improvement was defined as the time from randomisation to deterioration in body weight and/or Eastern Cooperative Oncology group performance score (ECOG PS) whichever occurred first. Median, 25th and 75th percentiles are calculated from an unadjusted Kaplan-Meier curve.

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

End point timeframe:

From randomisation until cut-off date 15 February 2013

| End point values | Nintedanib plus docetaxel | Placebo plus docetaxel | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 655[42] | 659[43] | | |
| Units: months | | | | |
| median (inter-quartile range (Q1-Q3)) | 5.9 (2.1 to 22.7) | 5.2 (2.1 to 19.2) | | |

Notes:

[42] - Randomised set

[43] - Randomised set

## Statistical analyses

| Statistical analysis title | Statistical Analysis 1 |
|---|---|
| Comparison groups | Nintedanib plus docetaxel v Placebo plus docetaxel |
| Number of subjects included in analysis | 1314 |
| Analysis specification | Pre-specified |
| Analysis type | superiority[44] |
| P-value | = 0.7282 [45] |
| Method | Regression, Cox |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 1.03 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.87 |
| upper limit | 1.21 |

Notes:

[44] - HR below 1 favors nintedanib

[45] - HR, CI and p-value obtained from the prop. hazards model stratified by baseline ECOG PS (0 vs 1 - one pat.had 2), tumour histology (squamous vs non-squamous), brain metastases at baseline (yes vs no) and prior treatment with bevacizumab (yes vs no)

## Secondary: Quality of life (QoL)

| End point title | Quality of life (QoL) |
|---|---|

End point description:

QoL was measured by standardised questionnaires (EQ-5D, EORTC QLQ-C30, EORTC QLQ-LC13). The EORTC QLQ-C30 comprises of 30 questions, using both multi-item scales and single-item measures. EORTC LC-13 comprises of 13 questions incorporating 1 multi-item scale and a series of single items. The following were the main points of interest: Time to deterioration of cough (QLQ-LC13 question 1), Time to deterioration of dyspnoea (QLQ-LC13, composite of questions 3 to 5), Time to deterioration of pain (QLQ- C30, composite of questions 9 and 19). Time to deterioration of cough, dyspnoea and pain was defined as the time to a 10-point increase from the baseline score. Median, 25th and 75th percentiles are calculated from an unadjusted Kaplan-Meier curve

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

End point timeframe:

From randomisation until cut-off date 15 February 2013

| End point values | Nintedanib plus docetaxel | Placebo plus docetaxel | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 655[46] | 659[47] | | |
| Units: months | | | | |
| median (inter-quartile range (Q1-Q3)) | | | | |
| Time to deterioration of cough\| | 4.3 (1.6 to 11.8) | 3.5 (1.5 to 12.6) | | |
| Time to deterioration of dyspnoea\| | 2.0 (0.8 to 4.2) | 2.1 (0.8 to 4.5) | | |
| Time to deterioration of pain\| | 2.8 (1.1 to 6.5) | 2.6 (0.8 to 5.8) | | |

Notes:

[46] - Randomised set

[47] - Randomised set

## Statistical analyses

| Statistical analysis title | Statistical Analysis 1 |
|---|---|
| Statistical analysis description: | |
| Analysis evaluating the time to deterioration of cough | |
| Comparison groups | Nintedanib plus docetaxel v Placebo plus docetaxel |
| Number of subjects included in analysis | 1314 |
| Analysis specification | Pre-specified |
| Analysis type | superiority[48] |
| P-value | = 0.1858 [49] |
| Method | Regression, Cox |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.9 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.77 |
| upper limit | 1.05 |

Notes:

[48] - HR below 1 favors nintedanib

[49] - HR, CI and p-value obtained from the prop. hazards model stratified by baseline ECOG PS (0 vs >=1), tumour histology (squamous vs non-squamous), brain metastases at baseline (yes vs no) and prior treatment with bevacizumab (yes vs no)

| Statistical analysis title | Statistical Analysis 2 |
|---|---|
| Statistical analysis description: | |
| Analysis evaluating the time to deterioration of dyspnoea | |
| Comparison groups | Nintedanib plus docetaxel v Placebo plus docetaxel |
| Number of subjects included in analysis | 1314 |
| Analysis specification | Pre-specified |
| Analysis type | superiority[50] |
| P-value | = 0.5203 [51] |
| Method | Regression, Cox |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 1.05 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.91 |
| upper limit | 1.2 |

Notes:

[50] - HR below 1 favors nintedanib

[51] - HR, CI and p-value obtained from the prop. hazards model stratified by baseline ECOG PS (0 vs >=1), tumour histology (squamous vs non-squamous), brain metastases at baseline (yes vs no) and prior treatment with bevacizumab (yes vs no)

| **Statistical analysis title** | Statistical Analysis 3 |
|---|---|

Statistical analysis description:

Analysis evaluating the time to deterioration of pain

| | |
|---|---|
| Comparison groups | Nintedanib plus docetaxel v Placebo plus docetaxel |
| Number of subjects included in analysis | 1314 |
| Analysis specification | Pre-specified |
| Analysis type | superiority[52] |
| P-value | = 0.4373 [53] |
| Method | Regression, Cox |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.95 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.82 |
| upper limit | 1.09 |

Notes:

[52] - HR below 1 favors nintedanib

[53] - HR, CI and p-value obtained from the prop. hazards model stratified by baseline ECOG PS (0 vs >= 1), tumour histology (squamous vs non-squamous), brain metastases at baseline (yes vs no) and prior treatment with bevacizumab (yes vs no)

## Secondary: Dose normalised predose plasma concentration at steady state (Cpre,ss,norm) of nintedanib and of its metabolites BIBF 1202 and BIBF 1202

| End point title | Dose normalised predose plasma concentration at steady state (Cpre,ss,norm) of nintedanib and of its metabolites BIBF 1202 and BIBF 1202 glucuronide |
|---|---|

End point description:

Geometric mean of dose normalised predose plasma concentration (Cpre,ss,norm) of nintedanib and of its metabolites BIBF 1202 and BIBF 1202 glucuronide evaluated at steady state based on course 2 and 3. If only one value was available and valid, then this value was used for calculation of Cpre,ss,norm.

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

End point timeframe:

Before the administration of nintedanib or placebo and between a window of 30 mins to an hour after administration of trial drug during Course 2 and between 1 and 3 hours after administration of trial drug during Course 3

| **End point values** | Nitedanib 200 mg bid plus docetaxel | Nintedanib 150 bid mg plus docetaxel | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 454 | 38 | | |
| Units: ng/mL/mg | | | | |
| geometric mean (geometric coefficient of variation) | | | | |
| nintedanib\| | 0.0707 (± 77.7) | 0.106 (± 52.6) | | |
| metabolite BIBF 1202\| | 0.0907 (± 127) | 0.190 (± 152) | | |

| | | | | |
|---|---|---|---|---|
| metabolite BIBF 1202 glucuronide\| | 1.04 (± 153) | 1.94 (± 135) | | |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Incidence and intensity of adverse events

| End point title | Incidence and intensity of adverse events |
|---|---|

End point description:

Incidence and intensity of adverse events according to the Common Terminology Criteria for Adverse Events (CTCAE) version 3.0. The worst CTCAE grade per patient is reported and MedDRA version 15.1 used. Serious signs and symptoms of progressive disease were reported as an adverse event in analysis of this endpoint. Treated set- all randomised patients who were documented to have taken at least 1 dose of study medication . Patients were allocated to the treatment groups according to the treatment actually received.

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

End point timeframe:

From the first drug administration until 28 days after the last drug administration, up to 42 months

| End point values | Nintedanib plus docetaxel | Placebo plus docetaxel | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 655[54] | 659[55] | | |
| Units: % of participants | | | | |
| number (not applicable) | | | | |
| Grade 1 | 5.7 | 8.2 | | |
| Grade 2 | 16.6 | 20.5 | | |
| Grade 3 | 21.2 | 21.2 | | |
| Grade 4 | 33.7 | 31.3 | | |
| Grade 5 | 16.4 | 11.8 | | |

Notes:

[54] - Treated set

[55] - Treated set

## Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

From the first drug administration until 28 days after the last drug administration, up to 42 months.

Adverse event reporting additional description:

Number of participants at risk corresponds to all randomised patients who were documented to have taken at least 1 dose of study medication . Patients were allocated to the treatment groups according to the treatment actually received.

| | |
|---|---|
| Assessment type | Systematic |

### Dictionary used

| | |
|---|---|
| Dictionary name | MedDRA |
| Dictionary version | 15.1 |

### Reporting groups

| | |
|---|---|
| Reporting group title | Placebo plus docetaxel |

Reporting group description:

Placebo soft gelatin capsule matching that of nintedanib 2 times daily plus docetaxel 75 mg/m2 once every 3 weeks administered via intravenous infusion over 1 hour (h).

| | |
|---|---|
| Reporting group title | Nintedanib plus docetaxel |

Reporting group description:

Nintedanib 200 mg twice daily administered orally in the form of a soft gelatin capsule plus docetaxel 75 mg/m2 once every 3 weeks administered via intravenous infusion over 1 hour (h).

| Serious adverse events | Placebo plus docetaxel | Nintedanib plus docetaxel | |
|---|---|---|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 206 / 655 (31.45%) | 224 / 652 (34.36%) | |
| number of deaths (all causes) | 562 | 565 | |
| number of deaths resulting from adverse events | 77 | 107 | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Hepatic cancer metastatic | | | |
| subjects affected / exposed | 0 / 655 (0.00%) | 1 / 652 (0.15%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Malignant neoplasm progression | | | |
| subjects affected / exposed | 17 / 655 (2.60%) | 25 / 652 (3.83%) | |
| occurrences causally related to treatment / all | 0 / 17 | 1 / 25 | |
| deaths causally related to treatment / all | 0 / 15 | 1 / 25 | |
| Metastases to central nervous system | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 2 / 655 (0.31%) | 2 / 652 (0.31%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 1 | |
| Metastases to chest wall | | | |
| subjects affected / exposed | 0 / 655 (0.00%) | 1 / 652 (0.15%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Metastases to kidney | | | |
| subjects affected / exposed | 1 / 655 (0.15%) | 0 / 652 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Metastases to meninges | | | |
| subjects affected / exposed | 0 / 655 (0.00%) | 3 / 652 (0.46%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 3 | |
| Metastases to skin | | | |
| subjects affected / exposed | 1 / 655 (0.15%) | 0 / 652 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Metastatic neoplasm | | | |
| subjects affected / exposed | 1 / 655 (0.15%) | 0 / 652 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Metastatic pain | | | |
| subjects affected / exposed | 1 / 655 (0.15%) | 0 / 652 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Tumour necrosis | | | |
| subjects affected / exposed | 1 / 655 (0.15%) | 0 / 652 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Tumour pain | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 2 / 655 (0.31%) | 1 / 652 (0.15%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vascular disorders | | | |
| Circulatory collapse | | | |
| subjects affected / exposed | 1 / 655 (0.15%) | 0 / 652 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Deep vein thrombosis | | | |
| subjects affected / exposed | 1 / 655 (0.15%) | 3 / 652 (0.46%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Haemorrhage | | | |
| subjects affected / exposed | 2 / 655 (0.31%) | 1 / 652 (0.15%) | |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 1 | |
| deaths causally related to treatment / all | 1 / 2 | 0 / 1 | |
| Hypotension | | | |
| subjects affected / exposed | 1 / 655 (0.15%) | 3 / 652 (0.46%) | |
| occurrences causally related to treatment / all | 0 / 1 | 1 / 3 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Peripheral ischaemia | | | |
| subjects affected / exposed | 1 / 655 (0.15%) | 0 / 652 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Subclavian artery thrombosis | | | |
| subjects affected / exposed | 1 / 655 (0.15%) | 0 / 652 (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 / 655 (0.15%) | 1 / 652 (0.15%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Thrombosis | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 655 (0.15%) | 0 / 652 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Venous thrombosis | | | |
| subjects affected / exposed | 0 / 655 (0.00%) | 1 / 652 (0.15%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Venous thrombosis limb | | | |
| subjects affected / exposed | 0 / 655 (0.00%) | 1 / 652 (0.15%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| General disorders and administration site conditions | | | |
| Asthenia | | | |
| subjects affected / exposed | 4 / 655 (0.61%) | 7 / 652 (1.07%) | |
| occurrences causally related to treatment / all | 0 / 4 | 1 / 8 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 2 | |
| Chest discomfort | | | |
| subjects affected / exposed | 1 / 655 (0.15%) | 1 / 652 (0.15%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Chest pain | | | |
| subjects affected / exposed | 8 / 655 (1.22%) | 7 / 652 (1.07%) | |
| occurrences causally related to treatment / all | 1 / 8 | 0 / 7 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 2 | |
| Condition aggravated | | | |
| subjects affected / exposed | 0 / 655 (0.00%) | 1 / 652 (0.15%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Death | | | |
| subjects affected / exposed | 1 / 655 (0.15%) | 2 / 652 (0.31%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 2 | |
| Device occlusion | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 655 (0.15%) | 0 / 652 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Extravasation | | | |
| subjects affected / exposed | 1 / 655 (0.15%) | 0 / 652 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Fatigue | | | |
| subjects affected / exposed | 1 / 655 (0.15%) | 7 / 652 (1.07%) | |
| occurrences causally related to treatment / all | 1 / 1 | 5 / 7 | |
| deaths causally related to treatment / all | 0 / 0 | 1 / 1 | |
| Feeling abnormal | | | |
| subjects affected / exposed | 1 / 655 (0.15%) | 0 / 652 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| General physical health deterioration | | | |
| subjects affected / exposed | 8 / 655 (1.22%) | 11 / 652 (1.69%) | |
| occurrences causally related to treatment / all | 2 / 8 | 4 / 12 | |
| deaths causally related to treatment / all | 0 / 6 | 0 / 8 | |
| Malaise | | | |
| subjects affected / exposed | 0 / 655 (0.00%) | 1 / 652 (0.15%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Mucosal inflammation | | | |
| subjects affected / exposed | 1 / 655 (0.15%) | 1 / 652 (0.15%) | |
| occurrences causally related to treatment / all | 0 / 1 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Multi-organ failure | | | |
| subjects affected / exposed | 1 / 655 (0.15%) | 2 / 652 (0.31%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 2 | |
| Oedema peripheral | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 655 (0.00%) | 1 / 652 (0.15%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Organ failure | | | |
| subjects affected / exposed | 0 / 655 (0.00%) | 1 / 652 (0.15%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Pain | | | |
| subjects affected / exposed | 0 / 655 (0.00%) | 1 / 652 (0.15%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Performance status decreased | | | |
| subjects affected / exposed | 0 / 655 (0.00%) | 1 / 652 (0.15%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pyrexia | | | |
| subjects affected / exposed | 9 / 655 (1.37%) | 7 / 652 (1.07%) | |
| occurrences causally related to treatment / all | 3 / 11 | 3 / 7 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Immune system disorders | | | |
| Drug hypersensitivity | | | |
| subjects affected / exposed | 2 / 655 (0.31%) | 2 / 652 (0.31%) | |
| occurrences causally related to treatment / all | 0 / 2 | 3 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypersensitivity | | | |
| subjects affected / exposed | 3 / 655 (0.46%) | 0 / 652 (0.00%) | |
| occurrences causally related to treatment / all | 3 / 3 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Acute respiratory distress syndrome | | | |
| subjects affected / exposed | 0 / 655 (0.00%) | 2 / 652 (0.31%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |

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|---|---|---|---|
| Acute respiratory failure | | | |
| subjects affected / exposed | 1 / 655 (0.15%) | 3 / 652 (0.46%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 2 | |
| Alveolitis | | | |
| subjects affected / exposed | 0 / 655 (0.00%) | 1 / 652 (0.15%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Atelectasis | | | |
| subjects affected / exposed | 1 / 655 (0.15%) | 2 / 652 (0.31%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 1 | |
| Bronchial haemorrhage | | | |
| subjects affected / exposed | 0 / 655 (0.00%) | 1 / 652 (0.15%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bronchial secretion retention | | | |
| subjects affected / exposed | 1 / 655 (0.15%) | 0 / 652 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bronchostenosis | | | |
| subjects affected / exposed | 1 / 655 (0.15%) | 1 / 652 (0.15%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Chronic obstructive pulmonary disease | | | |
| subjects affected / exposed | 2 / 655 (0.31%) | 1 / 652 (0.15%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Cough | | | |
| subjects affected / exposed | 2 / 655 (0.31%) | 3 / 652 (0.46%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Dysphonia | | | |

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|---|---|---|---|
| subjects affected / exposed | 0 / 655 (0.00%) | 1 / 652 (0.15%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Dyspnoea | | | |
| subjects affected / exposed | 30 / 655 (4.58%) | 24 / 652 (3.68%) | |
| occurrences causally related to treatment / all | 2 / 33 | 1 / 25 | |
| deaths causally related to treatment / all | 1 / 12 | 0 / 15 | |
| Haemoptysis | | | |
| subjects affected / exposed | 7 / 655 (1.07%) | 6 / 652 (0.92%) | |
| occurrences causally related to treatment / all | 1 / 7 | 0 / 8 | |
| deaths causally related to treatment / all | 0 / 2 | 0 / 4 | |
| Hypoxia | | | |
| subjects affected / exposed | 0 / 655 (0.00%) | 1 / 652 (0.15%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Interstitial lung disease | | | |
| subjects affected / exposed | 0 / 655 (0.00%) | 1 / 652 (0.15%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lung disorder | | | |
| subjects affected / exposed | 1 / 655 (0.15%) | 1 / 652 (0.15%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lung infiltration | | | |
| subjects affected / exposed | 1 / 655 (0.15%) | 0 / 652 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Obstructive airways disorder | | | |
| subjects affected / exposed | 0 / 655 (0.00%) | 1 / 652 (0.15%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Oropharyngeal pain | | | |

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|---|---|---|---|
| subjects affected / exposed | 1 / 655 (0.15%) | 0 / 652 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pleural effusion | | | |
| subjects affected / exposed | 8 / 655 (1.22%) | 8 / 652 (1.23%) | |
| occurrences causally related to treatment / all | 0 / 9 | 0 / 9 | |
| deaths causally related to treatment / all | 0 / 2 | 0 / 2 | |
| Pleuritic pain | | | |
| subjects affected / exposed | 0 / 655 (0.00%) | 1 / 652 (0.15%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumonitis | | | |
| subjects affected / exposed | 0 / 655 (0.00%) | 1 / 652 (0.15%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumothorax | | | |
| subjects affected / exposed | 1 / 655 (0.15%) | 3 / 652 (0.46%) | |
| 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 | 6 / 655 (0.92%) | 4 / 652 (0.61%) | |
| occurrences causally related to treatment / all | 2 / 6 | 2 / 4 | |
| deaths causally related to treatment / all | 1 / 3 | 0 / 0 | |
| Pulmonary fibrosis | | | |
| subjects affected / exposed | 0 / 655 (0.00%) | 1 / 652 (0.15%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pulmonary haemorrhage | | | |
| subjects affected / exposed | 3 / 655 (0.46%) | 5 / 652 (0.77%) | |
| occurrences causally related to treatment / all | 1 / 3 | 1 / 5 | |
| deaths causally related to treatment / all | 1 / 3 | 0 / 3 | |
| Respiratory depression | | | |

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|---|---|---|---|
| subjects affected / exposed | 1 / 655 (0.15%) | 0 / 652 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Respiratory failure | | | |
| subjects affected / exposed | 2 / 655 (0.31%) | 8 / 652 (1.23%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 8 | |
| deaths causally related to treatment / all | 0 / 2 | 0 / 8 | |
| Stridor | | | |
| subjects affected / exposed | 1 / 655 (0.15%) | 0 / 652 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Tracheal stenosis | | | |
| subjects affected / exposed | 1 / 655 (0.15%) | 0 / 652 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Psychiatric disorders | | | |
| Confusional state | | | |
| subjects affected / exposed | 2 / 655 (0.31%) | 0 / 652 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Depression | | | |
| subjects affected / exposed | 0 / 655 (0.00%) | 4 / 652 (0.61%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Disorientation | | | |
| subjects affected / exposed | 3 / 655 (0.46%) | 0 / 652 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Mental disorder due to a general medical condition | | | |
| subjects affected / exposed | 1 / 655 (0.15%) | 1 / 652 (0.15%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Panic attack | | | |

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|---|---|---|---|
| subjects affected / exposed | 0 / 655 (0.00%) | 1 / 652 (0.15%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Personality change | | | |
| subjects affected / exposed | 0 / 655 (0.00%) | 1 / 652 (0.15%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Psychotic disorder | | | |
| subjects affected / exposed | 1 / 655 (0.15%) | 0 / 652 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Investigations | | | |
| Alanine aminotransferase increased | | | |
| subjects affected / exposed | 0 / 655 (0.00%) | 2 / 652 (0.31%) | |
| occurrences causally related to treatment / all | 0 / 0 | 2 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Aspartate aminotransferase increased | | | |
| subjects affected / exposed | 0 / 655 (0.00%) | 2 / 652 (0.31%) | |
| occurrences causally related to treatment / all | 0 / 0 | 2 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Blood creatinine increased | | | |
| subjects affected / exposed | 1 / 655 (0.15%) | 1 / 652 (0.15%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Haemoglobin decreased | | | |
| subjects affected / exposed | 2 / 655 (0.31%) | 3 / 652 (0.46%) | |
| occurrences causally related to treatment / all | 0 / 2 | 1 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hepatic enzyme increased | | | |
| subjects affected / exposed | 0 / 655 (0.00%) | 1 / 652 (0.15%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Liver function test abnormal | | | |

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|---|---|---|---|
| subjects affected / exposed | 1 / 655 (0.15%) | 0 / 652 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Neutrophil count decreased | | | |
| subjects affected / exposed | 3 / 655 (0.46%) | 6 / 652 (0.92%) | |
| occurrences causally related to treatment / all | 3 / 3 | 5 / 6 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Weight decreased | | | |
| subjects affected / exposed | 1 / 655 (0.15%) | 0 / 652 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| White blood cell count decreased | | | |
| subjects affected / exposed | 2 / 655 (0.31%) | 3 / 652 (0.46%) | |
| occurrences causally related to treatment / all | 2 / 2 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Injury, poisoning and procedural complications | | | |
| Acetabulum fracture | | | |
| subjects affected / exposed | 1 / 655 (0.15%) | 0 / 652 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Alcohol poisoning | | | |
| subjects affected / exposed | 1 / 655 (0.15%) | 0 / 652 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Femoral neck fracture | | | |
| subjects affected / exposed | 0 / 655 (0.00%) | 1 / 652 (0.15%) | |
| 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 | 1 / 655 (0.15%) | 0 / 652 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Post procedural haemorrhage | | | |

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|---|---|---|---|
| subjects affected / exposed | 1 / 655 (0.15%) | 0 / 652 (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 | 0 / 655 (0.00%) | 1 / 652 (0.15%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac disorders | | | |
| Acute myocardial infarction | | | |
| subjects affected / exposed | 1 / 655 (0.15%) | 0 / 652 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Angina pectoris | | | |
| subjects affected / exposed | 1 / 655 (0.15%) | 0 / 652 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Atrial fibrillation | | | |
| subjects affected / exposed | 2 / 655 (0.31%) | 5 / 652 (0.77%) | |
| occurrences causally related to treatment / all | 1 / 2 | 1 / 5 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Atrial flutter | | | |
| subjects affected / exposed | 2 / 655 (0.31%) | 1 / 652 (0.15%) | |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Atrioventricular block second degree | | | |
| subjects affected / exposed | 0 / 655 (0.00%) | 1 / 652 (0.15%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac arrest | | | |
| subjects affected / exposed | 0 / 655 (0.00%) | 1 / 652 (0.15%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Cardiac failure | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 655 (0.15%) | 0 / 652 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac failure acute | | | |
| subjects affected / exposed | 2 / 655 (0.31%) | 1 / 652 (0.15%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 1 | |
| Cardio-respiratory arrest | | | |
| subjects affected / exposed | 2 / 655 (0.31%) | 1 / 652 (0.15%) | |
| occurrences causally related to treatment / all | 0 / 2 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 2 | 0 / 0 | |
| Cardiopulmonary failure | | | |
| subjects affected / exposed | 2 / 655 (0.31%) | 1 / 652 (0.15%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 2 | 0 / 1 | |
| Coronary artery disease | | | |
| subjects affected / exposed | 1 / 655 (0.15%) | 0 / 652 (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 | 3 / 655 (0.46%) | 1 / 652 (0.15%) | |
| occurrences causally related to treatment / all | 1 / 3 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Pericardial effusion | | | |
| subjects affected / exposed | 0 / 655 (0.00%) | 4 / 652 (0.61%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Pericarditis | | | |
| subjects affected / exposed | 0 / 655 (0.00%) | 1 / 652 (0.15%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Tachyarrhythmia | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 655 (0.00%) | 2 / 652 (0.31%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ventricular arrhythmia | | | |
| subjects affected / exposed | 0 / 655 (0.00%) | 1 / 652 (0.15%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nervous system disorders | | | |
| Aphasia | | | |
| subjects affected / exposed | 1 / 655 (0.15%) | 0 / 652 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Brain oedema | | | |
| subjects affected / exposed | 2 / 655 (0.31%) | 1 / 652 (0.15%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Cerebral infarction | | | |
| subjects affected / exposed | 0 / 655 (0.00%) | 1 / 652 (0.15%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cerebrovascular accident | | | |
| subjects affected / exposed | 2 / 655 (0.31%) | 0 / 652 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Cognitive disorder | | | |
| subjects affected / exposed | 0 / 655 (0.00%) | 1 / 652 (0.15%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Coma | | | |
| subjects affected / exposed | 0 / 655 (0.00%) | 1 / 652 (0.15%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Convulsion | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 655 (0.00%) | 4 / 652 (0.61%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Depressed level of consciousness | | | |
| subjects affected / exposed | 1 / 655 (0.15%) | 0 / 652 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Diplegia | | | |
| subjects affected / exposed | 0 / 655 (0.00%) | 1 / 652 (0.15%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Dizziness | | | |
| subjects affected / exposed | 2 / 655 (0.31%) | 1 / 652 (0.15%) | |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Encephalopathy | | | |
| subjects affected / exposed | 1 / 655 (0.15%) | 0 / 652 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Epiduritis | | | |
| subjects affected / exposed | 1 / 655 (0.15%) | 0 / 652 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Facial paresis | | | |
| subjects affected / exposed | 0 / 655 (0.00%) | 1 / 652 (0.15%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Headache | | | |
| subjects affected / exposed | 1 / 655 (0.15%) | 0 / 652 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hemiplegia | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 655 (0.15%) | 0 / 652 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypoaesthesia | | | |
| subjects affected / exposed | 1 / 655 (0.15%) | 0 / 652 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Intracranial pressure increased | | | |
| subjects affected / exposed | 2 / 655 (0.31%) | 1 / 652 (0.15%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 2 | 0 / 1 | |
| Ischaemic stroke | | | |
| subjects affected / exposed | 0 / 655 (0.00%) | 1 / 652 (0.15%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 1 / 1 | |
| Lethargy | | | |
| subjects affected / exposed | 0 / 655 (0.00%) | 1 / 652 (0.15%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Loss of consciousness | | | |
| subjects affected / exposed | 0 / 655 (0.00%) | 2 / 652 (0.31%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Monoparesis | | | |
| subjects affected / exposed | 1 / 655 (0.15%) | 0 / 652 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nervous system disorder | | | |
| subjects affected / exposed | 1 / 655 (0.15%) | 0 / 652 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Neuralgia | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 655 (0.00%) | 1 / 652 (0.15%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Neuropathy peripheral | | | |
| subjects affected / exposed | 0 / 655 (0.00%) | 1 / 652 (0.15%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Paraesthesia | | | |
| subjects affected / exposed | 0 / 655 (0.00%) | 1 / 652 (0.15%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Paraparesis | | | |
| subjects affected / exposed | 1 / 655 (0.15%) | 0 / 652 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Restless legs syndrome | | | |
| subjects affected / exposed | 1 / 655 (0.15%) | 0 / 652 (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 | 2 / 655 (0.31%) | 0 / 652 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Syncope | | | |
| subjects affected / exposed | 2 / 655 (0.31%) | 1 / 652 (0.15%) | |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Transient ischaemic attack | | | |
| subjects affected / exposed | 2 / 655 (0.31%) | 1 / 652 (0.15%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |

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|---|---|---|---|
| subjects affected / exposed | 6 / 655 (0.92%) | 2 / 652 (0.31%) | |
| occurrences causally related to treatment / all | 3 / 6 | 1 / 3 | |
| deaths causally related to treatment / all | 1 / 1 | 0 / 0 | |
| Disseminated intravascular coagulation | | | |
| subjects affected / exposed | 0 / 655 (0.00%) | 1 / 652 (0.15%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Febrile neutropenia | | | |
| subjects affected / exposed | 19 / 655 (2.90%) | 30 / 652 (4.60%) | |
| occurrences causally related to treatment / all | 12 / 20 | 27 / 34 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Leukopenia | | | |
| subjects affected / exposed | 2 / 655 (0.31%) | 1 / 652 (0.15%) | |
| occurrences causally related to treatment / all | 1 / 2 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Neutropenia | | | |
| subjects affected / exposed | 21 / 655 (3.21%) | 21 / 652 (3.22%) | |
| occurrences causally related to treatment / all | 20 / 24 | 18 / 21 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pancytopenia | | | |
| subjects affected / exposed | 0 / 655 (0.00%) | 2 / 652 (0.31%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Thrombocytopenia | | | |
| subjects affected / exposed | 2 / 655 (0.31%) | 0 / 652 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ear and labyrinth disorders | | | |
| Vertigo | | | |
| subjects affected / exposed | 2 / 655 (0.31%) | 0 / 652 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Eye disorders | | | |

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|---|---|---|---|
| Diplopia | | | |
| subjects affected / exposed | 0 / 655 (0.00%) | 1 / 652 (0.15%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Gastrointestinal disorders | | | |
| Abdominal pain | | | |
| subjects affected / exposed | 4 / 655 (0.61%) | 2 / 652 (0.31%) | |
| occurrences causally related to treatment / all | 2 / 4 | 2 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Abdominal pain upper | | | |
| subjects affected / exposed | 2 / 655 (0.31%) | 0 / 652 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Diarrhoea | | | |
| subjects affected / exposed | 13 / 655 (1.98%) | 16 / 652 (2.45%) | |
| occurrences causally related to treatment / all | 11 / 13 | 13 / 16 | |
| deaths causally related to treatment / all | 0 / 0 | 1 / 1 | |
| Diverticulum intestinal | | | |
| subjects affected / exposed | 0 / 655 (0.00%) | 1 / 652 (0.15%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 1 / 1 | |
| Duodenal ulcer haemorrhage | | | |
| subjects affected / exposed | 0 / 655 (0.00%) | 1 / 652 (0.15%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Dysphagia | | | |
| subjects affected / exposed | 2 / 655 (0.31%) | 0 / 652 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Enteritis | | | |
| subjects affected / exposed | 0 / 655 (0.00%) | 1 / 652 (0.15%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastric perforation | | | |

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|---|---|---|---|
| subjects affected / exposed | 1 / 655 (0.15%) | 0 / 652 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastritis erosive | | | |
| subjects affected / exposed | 1 / 655 (0.15%) | 0 / 652 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal necrosis | | | |
| subjects affected / exposed | 1 / 655 (0.15%) | 0 / 652 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Haematochezia | | | |
| subjects affected / exposed | 0 / 655 (0.00%) | 1 / 652 (0.15%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Haemorrhoidal haemorrhage | | | |
| subjects affected / exposed | 1 / 655 (0.15%) | 0 / 652 (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 | 0 / 655 (0.00%) | 1 / 652 (0.15%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Intestinal perforation | | | |
| subjects affected / exposed | 1 / 655 (0.15%) | 0 / 652 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Large intestine perforation | | | |
| subjects affected / exposed | 1 / 655 (0.15%) | 1 / 652 (0.15%) | |
| occurrences causally related to treatment / all | 0 / 1 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 1 | 1 / 1 | |
| Nausea | | | |

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|---|---|---|---|
| subjects affected / exposed | 1 / 655 (0.15%) | 0 / 652 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Neutropenic colitis | | | |
| subjects affected / exposed | 0 / 655 (0.00%) | 1 / 652 (0.15%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pancreatitis | | | |
| subjects affected / exposed | 0 / 655 (0.00%) | 2 / 652 (0.31%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pancreatitis acute | | | |
| subjects affected / exposed | 0 / 655 (0.00%) | 1 / 652 (0.15%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Stomatitis | | | |
| subjects affected / exposed | 3 / 655 (0.46%) | 1 / 652 (0.15%) | |
| occurrences causally related to treatment / all | 3 / 4 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vomiting | | | |
| subjects affected / exposed | 7 / 655 (1.07%) | 8 / 652 (1.23%) | |
| occurrences causally related to treatment / all | 3 / 7 | 5 / 8 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hepatobiliary disorders | | | |
| Bile duct obstruction | | | |
| subjects affected / exposed | 1 / 655 (0.15%) | 1 / 652 (0.15%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cholecystocholangitis | | | |
| subjects affected / exposed | 0 / 655 (0.00%) | 1 / 652 (0.15%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cholestasis | | | |

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|---|---|---|---|
| subjects affected / exposed | 1 / 655 (0.15%) | 2 / 652 (0.31%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hepatic failure | | | |
| subjects affected / exposed | 0 / 655 (0.00%) | 1 / 652 (0.15%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Hepatic function abnormal | | | |
| subjects affected / exposed | 0 / 655 (0.00%) | 1 / 652 (0.15%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Jaundice cholestatic | | | |
| subjects affected / exposed | 0 / 655 (0.00%) | 1 / 652 (0.15%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal and urinary disorders | | | |
| Bladder perforation | | | |
| subjects affected / exposed | 0 / 655 (0.00%) | 1 / 652 (0.15%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Haematuria | | | |
| subjects affected / exposed | 0 / 655 (0.00%) | 1 / 652 (0.15%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal failure acute | | | |
| subjects affected / exposed | 1 / 655 (0.15%) | 1 / 652 (0.15%) | |
| occurrences causally related to treatment / all | 0 / 1 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Urinary incontinence | | | |
| subjects affected / exposed | 0 / 655 (0.00%) | 1 / 652 (0.15%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Urinary retention | | | |

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|---|---|---|---|
| subjects affected / exposed | 2 / 655 (0.31%) | 0 / 652 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Musculoskeletal and connective tissue disorders | | | |
| Back pain | | | |
| subjects affected / exposed | 0 / 655 (0.00%) | 1 / 652 (0.15%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bone pain | | | |
| subjects affected / exposed | 2 / 655 (0.31%) | 0 / 652 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Flank pain | | | |
| subjects affected / exposed | 0 / 655 (0.00%) | 1 / 652 (0.15%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Haemarthrosis | | | |
| subjects affected / exposed | 1 / 655 (0.15%) | 0 / 652 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Muscular weakness | | | |
| subjects affected / exposed | 0 / 655 (0.00%) | 2 / 652 (0.31%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Myalgia | | | |
| subjects affected / exposed | 1 / 655 (0.15%) | 0 / 652 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Musculoskeletal chest pain | | | |
| subjects affected / exposed | 0 / 655 (0.00%) | 1 / 652 (0.15%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pain in extremity | | | |

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|---|---|---|---|
| subjects affected / exposed | 1 / 655 (0.15%) | 1 / 652 (0.15%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pathological fracture | | | |
| subjects affected / exposed | 1 / 655 (0.15%) | 1 / 652 (0.15%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infections and infestations | | | |
| Abscess rupture | | | |
| subjects affected / exposed | 0 / 655 (0.00%) | 1 / 652 (0.15%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Appendicitis | | | |
| subjects affected / exposed | 1 / 655 (0.15%) | 0 / 652 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bronchitis | | | |
| subjects affected / exposed | 4 / 655 (0.61%) | 1 / 652 (0.15%) | |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bronchopneumonia | | | |
| subjects affected / exposed | 1 / 655 (0.15%) | 0 / 652 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Cellulitis | | | |
| subjects affected / exposed | 0 / 655 (0.00%) | 1 / 652 (0.15%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Empyema | | | |
| subjects affected / exposed | 1 / 655 (0.15%) | 1 / 652 (0.15%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Erysipelas | | | |

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|---|---|---|---|
| subjects affected / exposed | 0 / 655 (0.00%) | 1 / 652 (0.15%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Febrile infection | | | |
| subjects affected / exposed | 1 / 655 (0.15%) | 0 / 652 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Folliculitis | | | |
| subjects affected / exposed | 0 / 655 (0.00%) | 1 / 652 (0.15%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastroenteritis | | | |
| subjects affected / exposed | 2 / 655 (0.31%) | 0 / 652 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 3 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal infection | | | |
| subjects affected / exposed | 0 / 655 (0.00%) | 1 / 652 (0.15%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| H1N1 influenza | | | |
| subjects affected / exposed | 1 / 655 (0.15%) | 0 / 652 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infection | | | |
| subjects affected / exposed | 2 / 655 (0.31%) | 0 / 652 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Infectious pleural effusion | | | |
| subjects affected / exposed | 1 / 655 (0.15%) | 2 / 652 (0.31%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Influenza | | | |

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|---|---|---|---|
| subjects affected / exposed | 0 / 655 (0.00%) | 1 / 652 (0.15%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Laryngitis | | | |
| subjects affected / exposed | 0 / 655 (0.00%) | 1 / 652 (0.15%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lower respiratory tract infection | | | |
| subjects affected / exposed | 3 / 655 (0.46%) | 4 / 652 (0.61%) | |
| occurrences causally related to treatment / all | 1 / 3 | 0 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 2 | |
| Lung abscess | | | |
| subjects affected / exposed | 0 / 655 (0.00%) | 1 / 652 (0.15%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Lung infection | | | |
| subjects affected / exposed | 0 / 655 (0.00%) | 1 / 652 (0.15%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Neutropenic infection | | | |
| subjects affected / exposed | 0 / 655 (0.00%) | 1 / 652 (0.15%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 1 / 1 | |
| Neutropenic sepsis | | | |
| subjects affected / exposed | 1 / 655 (0.15%) | 0 / 652 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Opportunistic infection | | | |
| subjects affected / exposed | 1 / 655 (0.15%) | 0 / 652 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Oral candidiasis | | | |

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|---|---|---|---|
| subjects affected / exposed | 0 / 655 (0.00%) | 1 / 652 (0.15%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Perirectal abscess | | | |
| subjects affected / exposed | 0 / 655 (0.00%) | 1 / 652 (0.15%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pharyngitis | | | |
| subjects affected / exposed | 0 / 655 (0.00%) | 2 / 652 (0.31%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumonia | | | |
| subjects affected / exposed | 26 / 655 (3.97%) | 17 / 652 (2.61%) | |
| occurrences causally related to treatment / all | 8 / 28 | 2 / 17 | |
| deaths causally related to treatment / all | 2 / 8 | 0 / 3 | |
| Pulmonary tuberculosis | | | |
| subjects affected / exposed | 1 / 655 (0.15%) | 0 / 652 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory tract infection | | | |
| subjects affected / exposed | 3 / 655 (0.46%) | 1 / 652 (0.15%) | |
| occurrences causally related to treatment / all | 2 / 5 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory tract infection bacterial | | | |
| subjects affected / exposed | 1 / 655 (0.15%) | 0 / 652 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Sepsis | | | |
| subjects affected / exposed | 3 / 655 (0.46%) | 7 / 652 (1.07%) | |
| occurrences causally related to treatment / all | 0 / 3 | 4 / 7 | |
| deaths causally related to treatment / all | 0 / 1 | 3 / 5 | |
| Septic shock | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 655 (0.00%) | 2 / 652 (0.31%) | |
| occurrences causally related to treatment / all | 0 / 0 | 2 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 2 / 2 | |
| Streptococcal infection | | | |
| subjects affected / exposed | 1 / 655 (0.15%) | 0 / 652 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Tuberculosis | | | |
| subjects affected / exposed | 0 / 655 (0.00%) | 1 / 652 (0.15%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Urinary tract infection | | | |
| subjects affected / exposed | 2 / 655 (0.31%) | 1 / 652 (0.15%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 3 / 655 (0.46%) | 1 / 652 (0.15%) | |
| occurrences causally related to treatment / all | 1 / 3 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Metabolism and nutrition disorders | | | |
| Decreased appetite | | | |
| subjects affected / exposed | 1 / 655 (0.15%) | 1 / 652 (0.15%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Dehydration | | | |
| subjects affected / exposed | 1 / 655 (0.15%) | 5 / 652 (0.77%) | |
| occurrences causally related to treatment / all | 1 / 1 | 4 / 6 | |
| deaths causally related to treatment / all | 0 / 0 | 1 / 1 | |
| Hypercalcaemia | | | |
| subjects affected / exposed | 0 / 655 (0.00%) | 1 / 652 (0.15%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hyperglycaemia | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 655 (0.15%) | 1 / 652 (0.15%) | |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hyperuricaemia | | | |
| subjects affected / exposed | 0 / 655 (0.00%) | 1 / 652 (0.15%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypoalbuminaemia | | | |
| subjects affected / exposed | 0 / 655 (0.00%) | 1 / 652 (0.15%) | |
| 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 / 655 (0.00%) | 1 / 652 (0.15%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypokalaemia | | | |
| subjects affected / exposed | 2 / 655 (0.31%) | 1 / 652 (0.15%) | |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hyponatraemia | | | |
| subjects affected / exposed | 0 / 655 (0.00%) | 4 / 652 (0.61%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

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

| **Non-serious adverse events** | Placebo plus docetaxel | Nintedanib plus docetaxel | |
|---|---|---|---|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 547 / 655 (83.51%) | 569 / 652 (87.27%) | |
| Investigations | | | |
| Alanine aminotransferase increased | | | |
| subjects affected / exposed | 55 / 655 (8.40%) | 186 / 652 (28.53%) | |
| occurrences (all) | 76 | 320 | |
| Aspartate aminotransferase | | | |

| | | | |
|---|---|---|---|
| increased | | | |
| subjects affected / exposed | 43 / 655 (6.56%) | 146 / 652 (22.39%) | |
| occurrences (all) | 53 | 242 | |
| Blood alkaline phosphatase increased | | | |
| subjects affected / exposed | 9 / 655 (1.37%) | 38 / 652 (5.83%) | |
| occurrences (all) | 9 | 43 | |
| Haemoglobin decreased | | | |
| subjects affected / exposed | 79 / 655 (12.06%) | 71 / 652 (10.89%) | |
| occurrences (all) | 103 | 99 | |
| Neutrophil count decreased | | | |
| subjects affected / exposed | 234 / 655 (35.73%) | 237 / 652 (36.35%) | |
| occurrences (all) | 574 | 682 | |
| White blood cell count decreased | | | |
| subjects affected / exposed | 160 / 655 (24.43%) | 158 / 652 (24.23%) | |
| occurrences (all) | 402 | 476 | |
| Nervous system disorders | | | |
| Dizziness | | | |
| subjects affected / exposed | 35 / 655 (5.34%) | 31 / 652 (4.75%) | |
| occurrences (all) | 38 | 34 | |
| Dysgeusia | | | |
| subjects affected / exposed | 34 / 655 (5.19%) | 31 / 652 (4.75%) | |
| occurrences (all) | 43 | 35 | |
| Headache | | | |
| subjects affected / exposed | 42 / 655 (6.41%) | 39 / 652 (5.98%) | |
| occurrences (all) | 44 | 41 | |
| Peripheral sensory neuropathy | | | |
| subjects affected / exposed | 47 / 655 (7.18%) | 40 / 652 (6.13%) | |
| occurrences (all) | 51 | 45 | |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 43 / 655 (6.56%) | 33 / 652 (5.06%) | |
| occurrences (all) | 49 | 40 | |
| Neutropenia | | | |
| subjects affected / exposed | 78 / 655 (11.91%) | 77 / 652 (11.81%) | |
| occurrences (all) | 193 | 142 | |
| General disorders and administration site conditions | | | |

| | | | |
|---|---|---|---|
| Asthenia | | | |
| subjects affected / exposed | 61 / 655 (9.31%) | 52 / 652 (7.98%) | |
| occurrences (all) | 77 | 58 | |
| Chest pain | | | |
| subjects affected / exposed | 57 / 655 (8.70%) | 49 / 652 (7.52%) | |
| occurrences (all) | 71 | 52 | |
| Fatigue | | | |
| subjects affected / exposed | 175 / 655 (26.72%) | 192 / 652 (29.45%) | |
| occurrences (all) | 231 | 252 | |
| Oedema peripheral | | | |
| subjects affected / exposed | 42 / 655 (6.41%) | 35 / 652 (5.37%) | |
| occurrences (all) | 52 | 38 | |
| Pyrexia | | | |
| subjects affected / exposed | 92 / 655 (14.05%) | 77 / 652 (11.81%) | |
| occurrences (all) | 129 | 108 | |
| Gastrointestinal disorders | | | |
| Abdominal pain | | | |
| subjects affected / exposed | 37 / 655 (5.65%) | 35 / 652 (5.37%) | |
| occurrences (all) | 45 | 41 | |
| Constipation | | | |
| subjects affected / exposed | 76 / 655 (11.60%) | 35 / 652 (5.37%) | |
| occurrences (all) | 97 | 43 | |
| Diarrhoea | | | |
| subjects affected / exposed | 134 / 655 (20.46%) | 267 / 652 (40.95%) | |
| occurrences (all) | 196 | 518 | |
| Nausea | | | |
| subjects affected / exposed | 118 / 655 (18.02%) | 158 / 652 (24.23%) | |
| occurrences (all) | 172 | 231 | |
| Stomatitis | | | |
| subjects affected / exposed | 56 / 655 (8.55%) | 62 / 652 (9.51%) | |
| occurrences (all) | 67 | 78 | |
| Vomiting | | | |
| subjects affected / exposed | 56 / 655 (8.55%) | 102 / 652 (15.64%) | |
| occurrences (all) | 96 | 152 | |
| Respiratory, thoracic and mediastinal disorders | | | |

| | | | |
|---|---|---|---|
| Cough | | | |
| subjects affected / exposed | 108 / 655 (16.49%) | 97 / 652 (14.88%) | |
| occurrences (all) | 126 | 110 | |
| Dyspnoea | | | |
| subjects affected / exposed | 83 / 655 (12.67%) | 102 / 652 (15.64%) | |
| occurrences (all) | 98 | 111 | |
| Skin and subcutaneous tissue disorders | | | |
| Alopecia | | | |
| subjects affected / exposed | 119 / 655 (18.17%) | 107 / 652 (16.41%) | |
| occurrences (all) | 121 | 107 | |
| Psychiatric disorders | | | |
| Insomnia | | | |
| subjects affected / exposed | 38 / 655 (5.80%) | 31 / 652 (4.75%) | |
| occurrences (all) | 43 | 35 | |
| Musculoskeletal and connective tissue disorders | | | |
| Arthralgia | | | |
| subjects affected / exposed | 46 / 655 (7.02%) | 40 / 652 (6.13%) | |
| occurrences (all) | 52 | 55 | |
| Back pain | | | |
| subjects affected / exposed | 44 / 655 (6.72%) | 27 / 652 (4.14%) | |
| occurrences (all) | 53 | 34 | |
| Myalgia | | | |
| subjects affected / exposed | 45 / 655 (6.87%) | 40 / 652 (6.13%) | |
| occurrences (all) | 64 | 53 | |
| Pain in extremity | | | |
| subjects affected / exposed | 41 / 655 (6.26%) | 31 / 652 (4.75%) | |
| occurrences (all) | 45 | 39 | |
| Metabolism and nutrition disorders | | | |
| Decreased appetite | | | |
| subjects affected / exposed | 102 / 655 (15.57%) | 145 / 652 (22.24%) | |
| occurrences (all) | 115 | 173 | |

## More information

## Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|---|---|
| 15 May 2009 | With Protocol Amendment 1, Revise typing errors that were detected in the original protocol. Addition of a statement with regard to the tasks and members of the Data Monitoring Committee (DMC), addition of a statement concerning docetaxel hypersensitivity, addition of an additional safety laboratory test in case of bilirubin increase, addition of food intake on the days of and the days preceding pharmacokinetic blood sampling, clarification of one exclusion criterion, allow extension of screening period in exceptional situations |
| 12 February 2014 | Prior to the amendment, patients who had stopped active treatment were to be followed-up until death or lost to follow-up. Since the analysis of the key secondary end point OS was complete, the follow-up period for patients who had stopped active treatment was reduced to 28 days which was the reporting period for AEs (after last administration of trial medication). With Protocol Amendment 2, the end of the trial was redefined. The clinical trial was considered completed as soon as the last patient had completed the first follow-up visit which was recommended to take place at least 28 days after end of active treatment (EOT). It was clarified that data collected after the cut-off date of the final OS analysis will be reported in a revision of the CTR. |
| 16 April 2015 | The European Commission granted marketing authorisation for nintedanib (Vargatef®) in combination with docetaxel for the treatment of patients with locally advanced, metastatic or recurrent NSCLC of adenocarcinoma tumour histology after first-line chemotherapy on 21 November 2014. With Protocol Amendment 3, all patients still on treatment were unblinded; patients in the placebo arm were given the opportunity to be treated with BIBF1120 and patients in the active arm were allowed to continue to be treated with BIBF1120. Since the trial was complete and no further cumulative data analyses were planned, efficacy assessment were to be done according to standard practice but were no longer collected in the CRF. Safety assessments were to be done as clinically indicated. Adverse events (AEs) were still reported in the CRF. Reporting requirements for SAEs remained the same. All sections f the clinical trial protocol affected by unblinding of the remaining patients, the switch from placebo to BIBF 1120, and the new procedures regarding data collection were revised. It was clarified that only clinically significant physical examination findings were to be reported in the CRF as an AE. New packaging of BIBF 1120 and a new distribution process were described. It was clarified that placebo was no longer provided to patients. The end of the trial was redefined. The clinical trial was considered completed as soon as the last patient was transferred to another programme or had completed the first follow-up visit which was recommended to take place 28 days after end of active treatment. |

Notes:

## Interruptions (globally)

Were there any global interruptions to the trial? No

## Limitations and caveats

None reported