# Clinical trial results:
# Randomized, Double-Blind, Multicenter, Phase 3 Study Comparing Veliparib Plus Carboplatin and Paclitaxel Versus Placebo Plus Carboplatin and Paclitaxel in Previously Untreated Advanced or Metastatic Squamous Non-Small Cell Lung Cancer (NSCLC)

## Summary

| | |
|---|---|
| EudraCT number | 2013-005020-42 |
| Trial protocol | SK FI LT CZ PT HU NO SE DE AT IT IE DK NL ES GR LV PL FR HR EE |
| Global end of trial date | 20 November 2019 |

| **Results information** | |
|---|---|
| Result version number | v1 (current) |
| This version publication date | 03 December 2020 |
| First version publication date | 03 December 2020 |

## Trial information

| **Trial identification** | |
|---|---|
| Sponsor protocol code | M11-089 |

| **Additional study identifiers** | |
|---|---|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT02106546 |
| WHO universal trial number (UTN) | - |

Notes:

| **Sponsors** | |
|---|---|
| Sponsor organisation name | Abbvie Deutschland GmbH & Co.KG |
| Sponsor organisation address | AbbVie House, Vanwall Business Park, Maidenhead, Berkshire, United Kingdom, SL6-4UB |
| Public contact | Global Medical Services, AbbVie, 001 800-633-9110, abbvieclinicaltrials@abbvie.com |
| Scientific contact | Global Medical Services, AbbVie, 001 800-633-9110, abbvieclinicaltrials@abbvie.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 | 20 November 2019 |
| Is this the analysis of the primary completion data? | No |
| Global end of trial reached? | Yes |
| Global end of trial date | 20 November 2019 |
| Was the trial ended prematurely? | No |

Notes:

## General information about the trial

Main objective of the trial:

The primary objective of the study was to assess whether the addition of oral veliparib to carboplatin and paclitaxel (C/P) would improve overall survival (OS) compared to the addition of placebo to C/P in current smokers with previously untreated locally advanced and metastatic squamous NSCLC.

Protection of trial subjects:

Subject read and understood the information provided about the study and gave written permission.

Background therapy: -

Evidence for comparator: -

| | |
|---|---|
| Actual start date of recruitment | 10 April 2014 |
| Long term follow-up planned | Yes |
| Long term follow-up rationale | Efficacy |
| Long term follow-up duration | 4 Years |
| Independent data monitoring committee (IDMC) involvement? | Yes |

Notes:

## Population of trial subjects

### Subjects enrolled per country

| | |
|---|---|
| Country: Number of subjects enrolled | Slovakia: 11 |
| Country: Number of subjects enrolled | South Africa: 18 |
| Country: Number of subjects enrolled | Spain: 37 |
| Country: Number of subjects enrolled | Sweden: 8 |
| Country: Number of subjects enrolled | Switzerland: 12 |
| Country: Number of subjects enrolled | Turkey: 43 |
| Country: Number of subjects enrolled | Ukraine: 73 |
| Country: Number of subjects enrolled | United Kingdom: 44 |
| Country: Number of subjects enrolled | United States: 95 |
| Country: Number of subjects enrolled | Australia: 16 |
| Country: Number of subjects enrolled | Austria: 5 |
| Country: Number of subjects enrolled | Belarus: 45 |
| Country: Number of subjects enrolled | Brazil: 28 |
| Country: Number of subjects enrolled | Canada: 27 |
| Country: Number of subjects enrolled | Croatia: 15 |
| Country: Number of subjects enrolled | Czech Republic: 30 |
| Country: Number of subjects enrolled | Denmark: 8 |
| Country: Number of subjects enrolled | Egypt: 17 |
| Country: Number of subjects enrolled | Estonia: 5 |
| Country: Number of subjects enrolled | Finland: 6 |
| Country: Number of subjects enrolled | France: 47 |
| Country: Number of subjects enrolled | Germany: 10 |
| Country: Number of subjects enrolled | Greece: 27 |

| | |
|---|---|
| Country: Number of subjects enrolled | Hungary: 79 |
| Country: Number of subjects enrolled | Ireland: 12 |
| Country: Number of subjects enrolled | Israel: 13 |
| Country: Number of subjects enrolled | Italy: 19 |
| Country: Number of subjects enrolled | Latvia: 19 |
| Country: Number of subjects enrolled | Lithuania: 9 |
| Country: Number of subjects enrolled | Mexico: 7 |
| Country: Number of subjects enrolled | Netherlands: 23 |
| Country: Number of subjects enrolled | New Zealand: 2 |
| Country: Number of subjects enrolled | Norway: 10 |
| Country: Number of subjects enrolled | Poland: 17 |
| Country: Number of subjects enrolled | Portugal: 19 |
| Country: Number of subjects enrolled | Puerto Rico: 1 |
| Country: Number of subjects enrolled | Russian Federation: 90 |
| Country: Number of subjects enrolled | Serbia: 23 |
| Worldwide total number of subjects | 970 |
| EEA total number of subjects | 460 |

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) | 517 |
| From 65 to 84 years | 453 |
| 85 years and over | 0 |

## Subject disposition

### Recruitment

Recruitment details:

A total of 218 sites in 37 countries enrolled participants with previously untreated advanced or metastatic squamous non-small cell lung cancer (NSCLC).

### Pre-assignment

Screening details:

Participants were randomized 1:1 to 1 of 2 groups. Randomization was stratified by tumor stage (locally advanced vs metastatic), Eastern Cooperative Oncology Group performance score (0 vs 1), geographic region (Western Europe/Australia/Americas vs Eastern Europe/Russia), and smoking history (current smoker vs never smoked vs past smoker).

### 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 | Subject, Investigator, Assessor |

### Arms

| | |
|---|---|
| Are arms mutually exclusive? | Yes |
| **Arm title** | Placebo + Carboplatin + Paclitaxel |

Arm description:

Participants received placebo orally twice a day (BID) on Days -2 to 5 (7 consecutive days) of each 21-day cycle and carboplatin at an area under the concentration-time curve (AUC) 6 mg/mL/min and paclitaxel 200 mg/m² by intravenous (IV) infusion on Day 1 of each 21-day cycle for up to a maximum 6 cycles of treatment, until treatment toxicity which, in the Investigator's opinion, prohibited further therapy, or until radiographic progression.

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

Dosage and administration details:

Capsules taken orally twice a day, 12 hours apart.

| | |
|---|---|
| Investigational medicinal product name | Carboplatin |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

Carboplatin administered intravenously over approximately 15 to 30 minutes at (AUC 6 mg/mL/min) immediately following paclitaxel infusion.

| | |
|---|---|
| Investigational medicinal product name | Paclitaxel |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

Paclitaxel administered intravenously over 3 hours at a dose of 200 mg/m².

| | |
|---|---|
| **Arm title** | Veliparib + Carboplatin + Paclitaxel |

Arm description:

Participants received veliparib 120 mg orally twice daily (BID) on Days -2 to 5 (7 consecutive days) of each 21-day cycle and carboplatin at an AUC 6 mg/mL/min and paclitaxel 200 mg/m² by intravenous (IV) infusion on Day 1 of each 21-day cycle for up to a maximum 6 cycles of treatment, until treatment toxicity which, in the Investigator's opinion, prohibited further therapy, or until radiographic progression.

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | Veliparib |
| Investigational medicinal product code | |
| Other name | ABT-888 |
| Pharmaceutical forms | Capsule |
| Routes of administration | Oral use |

Dosage and administration details:

Capsules taken orally twice a day, 12 hours apart.

| | |
|---|---|
| Investigational medicinal product name | Carboplatin |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

Carboplatin administered intravenously over approximately 15 to 30 minutes at (AUC 6 mg/mL/min) immediately following paclitaxel infusion.

| | |
|---|---|
| Investigational medicinal product name | Paclitaxel |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

Paclitaxel administered intravenously over 3 hours at a dose of 200 mg/m².

| **Number of subjects in period 1** | Placebo + Carboplatin + Paclitaxel | Veliparib + Carboplatin + Paclitaxel |
|---|---|---|
| Started | 484 | 486 |
| Received Treatment | 482 | 485 |
| Completed | 268 | 288 |
| Not completed | 216 | 198 |
| Other | 9 | 7 |
| Progressive Disease | 81 | 78 |
| Adverse Event Related to Progression | 25 | 17 |
| Consent withdrawn by subject | 17 | 16 |
| Adverse Event Not Related to Progression | 82 | 80 |
| Lost to follow-up | 2 | - |

## Baseline characteristics

| Reporting groups | |
|---|---|
| Reporting group title | Placebo + Carboplatin + Paclitaxel |
| Reporting group description: | |
| Participants received placebo orally twice a day (BID) on Days -2 to 5 (7 consecutive days) of each 21-day cycle and carboplatin at an area under the concentration-time curve (AUC) 6 mg/mL/min and paclitaxel 200 mg/m² by intravenous (IV) infusion on Day 1 of each 21-day cycle for up to a maximum 6 cycles of treatment, until treatment toxicity which, in the Investigator's opinion, prohibited further therapy, or until radiographic progression. | |
| Reporting group title | Veliparib + Carboplatin + Paclitaxel |
| Reporting group description: | |
| Participants received veliparib 120 mg orally twice daily (BID) on Days -2 to 5 (7 consecutive days) of each 21-day cycle and carboplatin at an AUC 6 mg/mL/min and paclitaxel 200 mg/m² by intravenous (IV) infusion on Day 1 of each 21-day cycle for up to a maximum 6 cycles of treatment, until treatment toxicity which, in the Investigator's opinion, prohibited further therapy, or until radiographic progression. | |

| Reporting group values | Placebo + Carboplatin + Paclitaxel | Veliparib + Carboplatin + Paclitaxel | Total |
|---|---|---|---|
| Number of subjects | 484 | 486 | 970 |
| Age categorical<br>Units: Subjects | | | |
| < 65 years | 256 | 261 | 517 |
| ≥ 65 years | 228 | 225 | 453 |
| Age continuous<br>Units: years | | | |
| median | 64.0 | 64.0 | |
| full range (min-max) | 33 to 84 | 36 to 83 | - |
| Gender categorical<br>Units: Subjects | | | |
| Female | 100 | 75 | 175 |
| Male | 384 | 411 | 795 |
| Race<br>Units: Subjects | | | |
| White | 477 | 471 | 948 |
| Black | 5 | 9 | 14 |
| Asian | 0 | 5 | 5 |
| Other | 2 | 1 | 3 |
| Geographic Region<br>Units: Subjects | | | |
| Western Europe/Australia/Americas | 239 | 242 | 481 |
| Eastern Europe/Russia | 245 | 244 | 489 |
| Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) | | | |
| ECOG performance status is used by doctors and researchers to assess how a participant's disease is progressing, assess how the disease affects the daily living activities of the participant and determine appropriate treatment and prognosis.<br>0 = Fully Active (Most Favorable Activity);<br>1 = Restricted activity but ambulatory;<br>2 = Ambulatory but unable to carry out work activities;<br>3 = Limited Self-Care;<br>4 = Completely Disabled, No self-care (Least Favorable Activity) | | | |
| Units: Subjects | | | |

| | | | |
|---|---|---|---|
| Grade 0 (fully active) | 165 | 166 | 331 |
| Grade 1 (restricted but ambulatory) | 319 | 320 | 639 |
| Smoking Status<br>Units: Subjects | | | |
| Current smoker | 276 | 276 | 552 |
| Past smoker | 181 | 181 | 362 |
| Never smoked | 27 | 29 | 56 |
| Tumor Stage<br>Units: Subjects | | | |
| Locally advanced | 112 | 114 | 226 |
| Metastatic | 372 | 372 | 744 |

## End points

### End points reporting groups

| Reporting group title | Placebo + Carboplatin + Paclitaxel |
|---|---|

Reporting group description:

Participants received placebo orally twice a day (BID) on Days -2 to 5 (7 consecutive days) of each 21-day cycle and carboplatin at an area under the concentration-time curve (AUC) 6 mg/mL/min and paclitaxel 200 mg/m² by intravenous (IV) infusion on Day 1 of each 21-day cycle for up to a maximum 6 cycles of treatment, until treatment toxicity which, in the Investigator's opinion, prohibited further therapy, or until radiographic progression.

| Reporting group title | Veliparib + Carboplatin + Paclitaxel |
|---|---|

Reporting group description:

Participants received veliparib 120 mg orally twice daily (BID) on Days -2 to 5 (7 consecutive days) of each 21-day cycle and carboplatin at an AUC 6 mg/mL/min and paclitaxel 200 mg/m² by intravenous (IV) infusion on Day 1 of each 21-day cycle for up to a maximum 6 cycles of treatment, until treatment toxicity which, in the Investigator's opinion, prohibited further therapy, or until radiographic progression.

### Primary: Overall Survival in Current Smokers

| End point title | Overall Survival in Current Smokers |
|---|---|

End point description:

Overall survival (OS) was calculated as the time from the date that the participant was randomized to the date of death. All events of death were included, regardless of whether the event occurred while the participant was still taking study drug, or after the participant discontinued study drug. Participants who had not died prior to the analysis cut-off date were censored at the date they were last known to be alive, or on the cut-off date if survival data were known after the cut-off date. The distributions of OS on the two treatment arms were estimated using the Kaplan-Meier method.
The data cut-off date for the analyses of primary and secondary efficacy endpoints was pre-specified as the date of the 400th death in current smokers and 667 events in the total ITT population.
OS was analysed in the intent-to-treat (ITT) population (all randomized participants) who were current smokers

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

End point timeframe:

From randomization to the primary analysis data cut-off date in 2017.

| End point values | Placebo + Carboplatin + Paclitaxel | Veliparib + Carboplatin + Paclitaxel | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 276[1] | 276[2] | | |
| Units: months | | | | |
| median (confidence interval 95%) | 11.1 (9.6 to 12.6) | 11.9 (10.5 to 13.5) | | |

Notes:

[1] - Current smokers

[2] - Current smokers

### Statistical analyses

| Statistical analysis title | Primary Analysis of OS in Current Smokers |
|---|---|
| Comparison groups | Placebo + Carboplatin + Paclitaxel v Veliparib + Carboplatin + Paclitaxel |
| Number of subjects included in analysis | 552 |

| | |
|---|---|
| Analysis specification | Pre-specified |
| Analysis type | superiority[3] |
| P-value | = 0.266 [4] |
| Method | Stratified Log-rank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.905 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.744 |
| upper limit | 1.101 |

Notes:

[3] - Statistical significance was determined by a two-sided P-value ≤0.05. If the primary endpoint was not met, all analyses of secondary and other efficacy endpoints were to be performed in a descriptive manner and treated as exploratory, with P-values interpreted as nominal.

[4] - Log-rank test stratified by tumor staging (locally advanced vs metastatic) and ECOG performance status (0 vs 1).

## Secondary: Overall Survival in All Participants - Primary Analysis

| | |
|---|---|
| End point title | Overall Survival in All Participants - Primary Analysis |

End point description:

Overall survival was calculated as the time from the date that the participant was randomized to the date of death. All events of death were included, regardless of whether the event occurred while the participant was still taking study drug, or after the participant discontinued study drug. Participants who had not died prior to the analysis cut-off date were censored at the date they were last known to be alive, or on the cut-off date if survival data were known after the cut-off date. The distributions of OS on the two treatment arms were estimated using the Kaplan-Meier method.
The data cut-off date for the analyses of primary and secondary efficacy endpoints was pre-specified as the date of the 400th death in current smokers and 667 events in the total ITT population.

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

End point timeframe:

From randomization to the primary analysis data cut-off date in 2017.

| **End point values** | Placebo + Carboplatin + Paclitaxel | Veliparib + Carboplatin + Paclitaxel | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 484[5] | 486[6] | | |
| Units: months | | | | |
| median (confidence interval 95%) | 11.2 (10.1 to 12.6) | 12.2 (10.9 to 13.5) | | |

Notes:

[5] - Intent-to-treat population

[6] - Intent-to-treat population

### Statistical analyses

| **Statistical analysis title** | Primary Analysis of OS in All Participants |
|---|---|
| Comparison groups | Placebo + Carboplatin + Paclitaxel v Veliparib + Carboplatin + Paclitaxel |
| Number of subjects included in analysis | 970 |
| Analysis specification | Pre-specified |
| Analysis type | other[7] |
| P-value | = 0.098 [8] |

| | |
|---|---|
| Method | Stratified Log-rank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.889 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.767 |
| upper limit | 1.031 |

Notes:

[7] - If the primary endpoint was not met, all analyses of secondary and other efficacy endpoints were to be performed in a descriptive manner and treated as exploratory, with P-values interpreted as nominal.
[8] - Stratified by tumor staging (locally advanced vs metastatic), smoking status (current smokers vs past vs never smokers), and ECOG PS (0 vs 1).

## Secondary: Progression-Free Survival in Current Smokers

| | |
|---|---|
| End point title | Progression-Free Survival in Current Smokers |

End point description:

Progression-free survival (PFS) was calculated using Kaplan-Meier methods as the time from the date that the participant was randomized to the date the participant experienced an event of disease progression or to the date of death (all causes of mortality) if disease progression was not reached. Participants who did not have an event of progression or death prior to the analysis cut-off date were censored at the date of the last disease assessment before the cut-off date, or at the date of randomization if they did not have a post-baseline assessment.
Disease progression was defined according to Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1: At least a 20% increase in the sum of the longest diameter (LD) of target lesions, taking as reference the smallest sum LD recorded since the treatment started (baseline or after) with an absolute increase of at least 5 mm, unequivocal progression of existing non-target lesions, or the appearance of any new lesions.

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

End point timeframe:

From randomization to the primary analysis data cut-off date in 2017

| **End point values** | Placebo + Carboplatin + Paclitaxel | Veliparib + Carboplatin + Paclitaxel | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 276[9] | 276[10] | | |
| Units: months | | | | |
| median (confidence interval 95%) | 5.6 (5.4 to 5.7) | 5.6 (5.5 to 5.8) | | |

Notes:

[9] - Current smokers

[10] - Current smokers

## Statistical analyses

| **Statistical analysis title** | Analysis of PFS in Current Smokers |
|---|---|
| Comparison groups | Placebo + Carboplatin + Paclitaxel v Veliparib + Carboplatin + Paclitaxel |
| Number of subjects included in analysis | 552 |
| Analysis specification | Pre-specified |
| Analysis type | other[11] |
| P-value | = 0.376 [12] |
| Method | Stratified Log-rank |

| | |
|---|---|
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.918 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.763 |
| upper limit | 1.105 |

Notes:

[11] - If the primary endpoint was not met, all analyses of secondary and other efficacy endpoints were to be performed in a descriptive manner and treated as exploratory, with P-values interpreted as nominal.

[12] - Log-rank test stratified by tumor staging (locally advanced vs metastatic) and ECOG performance status (0 vs 1).

## Secondary: Progression-Free Survival in All Participants - Primary Analysis

| | |
|---|---|
| End point title | Progression-Free Survival in All Participants - Primary Analysis |

End point description:

Progression-free survival (PFS) was calculated using Kaplan-Meier methods as the time from the date that the participant was randomized to the date the participant experienced an event of disease progression or to the date of death (all causes of mortality) if disease progression was not reached. Participants who did not have an event of progression or death prior to the analysis cut-off date were censored at the date of the last disease assessment before the cut-off date, or at the date of randomization if they did not have a post-baseline assessment.
Disease progression was defined according to Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1: At least a 20% increase in the sum of the longest diameter (LD) of target lesions, taking as reference the smallest sum LD recorded since the treatment started (baseline or after) with an absolute increase of at least 5 mm, unequivocal progression of existing non-target lesions, or the appearance of any new lesions.

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

End point timeframe:

From randomization to the primary analysis data cut-off date in 2017.

| **End point values** | Placebo + Carboplatin + Paclitaxel | Veliparib + Carboplatin + Paclitaxel | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 484[13] | 486[14] | | |
| Units: months | | | | |
| median (confidence interval 95%) | 5.6 (5.5 to 5.7) | 5.6 (5.6 to 5.8) | | |

Notes:

[13] - Intent-to-treat population

[14] - Intent-to-treat population

### Statistical analyses

| **Statistical analysis title** | Primary Analysis of PFS in All Participants |
|---|---|
| Comparison groups | Placebo + Carboplatin + Paclitaxel v Veliparib + Carboplatin + Paclitaxel |
| Number of subjects included in analysis | 970 |
| Analysis specification | Pre-specified |
| Analysis type | other[15] |
| P-value | = 0.132 [16] |
| Method | Stratified Log-rank |
| Parameter estimate | Hazard ratio (HR) |

| | |
|---|---|
| Point estimate | 0.895 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.778 |
| upper limit | 1.031 |

Notes:

[15] - If the primary endpoint was not met, all analyses of secondary and other efficacy endpoints were to be performed in a descriptive manner and treated as exploratory, with P-values interpreted as nominal.

[16] - Stratified by tumor staging (locally advanced vs metastatic), smoking status (current smokers vs past vs never smokers), and ECOG PS (0 vs 1).

## Secondary: Objective Response Rate in Current Smokers

| | |
|---|---|
| End point title | Objective Response Rate in Current Smokers |

End point description:

Disease assessments were made using computed tomography (CT) scans of the full chest and abdomen and assessed by the investigator according to the Response Evaluation Criteria in Solid Tumors (RECIST) v1.1.
Objective response rate (ORR) is defined as the percentage of participants a with complete or partial response, confirmed 4 weeks after the first documentation.
Complete Response (CR): The disappearance of all target and non-target lesions, and no new lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to < 10 mm.
Partial Response (PR): At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters, persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits, or any new lesions.

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

End point timeframe:

Tumor assessments were performed on Day 1 of Cycle 3 and Cycle 5, every 6 weeks until 1 year after starting treatment, and then every 12 weeks until radiographic progression, additional cancer treatment, or death; median time on follow-up was 20 months.

| **End point values** | Placebo + Carboplatin + Paclitaxel | Veliparib + Carboplatin + Paclitaxel | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 276[17] | 276[18] | | |
| Units: percentage of participants | | | | |
| number (confidence interval 95%) | 34.8 (29.2 to 40.7) | 34.4 (28.8 to 40.4) | | |

Notes:

[17] - Current smokers

[18] - Current smokers

## Statistical analyses

| **Statistical analysis title** | Analysis of ORR in Current Smokers |
|---|---|
| Comparison groups | Placebo + Carboplatin + Paclitaxel v Veliparib + Carboplatin + Paclitaxel |
| Number of subjects included in analysis | 552 |
| Analysis specification | Pre-specified |
| Analysis type | other[19] |
| P-value | = 0.92 [20] |
| Method | Cochran-Mantel-Haenszel |

Notes:

[19] - If the primary endpoint was not met, all analyses of secondary and other efficacy endpoints were to be performed in a descriptive manner and treated as exploratory, with P-values interpreted as nominal.

[20] - Cochran-Mantel-Haenszel (CMH) test stratified by tumor staging (locally advanced versus metastatic) and ECOG performance status (0 versus 1).

## Secondary: Objective Response Rate in All Participants - Primary Analysis

| End point title | Objective Response Rate in All Participants - Primary Analysis |
|---|---|

End point description:

Disease assessments were made using computed tomography (CT) scans of the full chest and abdomen and assessed by the investigator according to RECIST v1.1.
Objective response rate (ORR) is defined as the percentage of participants with a complete or partial response that was confirmed 4 weeks after the first documentation.
Complete Response (CR): The disappearance of all target and non-target lesions, and no new lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to < 10 mm.
Partial Response (PR): At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters, persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits, or any new lesions.

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

End point timeframe:

Tumor assessments were performed on Day 1 of Cycle 3 and Cycle 5, every 6 weeks until 1 year after starting treatment, and then every 12 weeks until radiographic progression, additional cancer treatment, or death; median time on follow-up was 20 months.

| **End point values** | Placebo + Carboplatin + Paclitaxel | Veliparib + Carboplatin + Paclitaxel | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 484[21] | 486[22] | | |
| Units: percentage of participants | | | | |
| number (confidence interval 95%) | 37.2 (32.9 to 41.7) | 37.0 (32.7 to 41.5) | | |

Notes:

[21] - Intent-to-treat population

[22] - Intent-to-treat population

### Statistical analyses

| **Statistical analysis title** | Analysis of ORR in All Participants |
|---|---|
| Comparison groups | Placebo + Carboplatin + Paclitaxel v Veliparib + Carboplatin + Paclitaxel |
| Number of subjects included in analysis | 970 |
| Analysis specification | Pre-specified |
| Analysis type | other[23] |
| P-value | = 0.963 [24] |
| Method | Cochran-Mantel-Haenszel |

Notes:

[23] - If the primary endpoint was not met, all analyses of secondary and other efficacy endpoints were to be performed in a descriptive manner and treated as exploratory, with P-values interpreted as nominal.

[24] - Stratified by tumor stage (locally advanced vs metastatic), smoking status (current smokers vs past smokers vs never smoked), and ECOG PS (0 vs 1).

## Secondary: Overall Survival in All Participants - Final Analysis

| End point title | Overall Survival in All Participants - Final Analysis |
|---|---|

End point description:

Overall survival was calculated as the time from the date that the participant was randomized to the date of death. All events of death were included, regardless of whether the event occurred while the participant was still taking study drug, or after the participant discontinued study drug. Participants who had not died prior to the analysis cut-off date were censored at the date they were last known to be alive. The distributions of OS on the two treatment arms were estimated using the Kaplan-Meier method.

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

End point timeframe:

From randomization to the end of study

| **End point values** | Placebo + Carboplatin + Paclitaxel | Veliparib + Carboplatin + Paclitaxel | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 484[25] | 486[26] | | |
| Units: months | | | | |
| median (confidence interval 95%) | 11.2 (10.1 to 12.6) | 12.2 (10.9 to 13.5) | | |

Notes:

[25] - Intent-to-treat population

[26] - Intent-to-treat population

### Statistical analyses

| **Statistical analysis title** | Final Analysis of OS in All Participants |
|---|---|
| Comparison groups | Placebo + Carboplatin + Paclitaxel v Veliparib + Carboplatin + Paclitaxel |
| Number of subjects included in analysis | 970 |
| Analysis specification | Pre-specified |
| Analysis type | other[27] |
| P-value | = 0.032 [28] |
| Method | Stratified Log-rank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.853 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.747 |
| upper limit | 0.974 |

Notes:

[27] - If the primary endpoint was not met, all analyses of secondary and other efficacy endpoints were to be performed in a descriptive manner and treated as exploratory, with P-values interpreted as nominal.

[28] - Stratified by tumor staging (locally advanced vs metastatic), smoking status (current smokers vs past vs never smokers), and ECOG PS (0 vs 1).

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Deaths are reported from randomization until the end of follow-up; median time on study was 49.8 and 47.1 months in the placebo and veliparib arms respectively.
AEs are reported from first dose of study drug until 30 days after last dose; max 181 days

Adverse event reporting additional description:

Adverse event data are reported for all participants who received at least 1 dose of study drug (veliparib/placebo).
One participant randomized to each arm who did not receive treatment and are not included in the safety analysis set died in addition to those in the table below.

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

### Dictionary used

| | |
|---|---|
| Dictionary name | MedDRA |
| Dictionary version | 21.0 |

### Reporting groups

| | |
|---|---|
| Reporting group title | Veliparib + Carboplatin + Paclitaxel |

Reporting group description:

Participants received veliparib 120 mg orally BID on Days -2 to 5 (7 consecutive days) of each 21-day cycle and carboplatin at an AUC 6 mg/mL/min and paclitaxel 200 mg/m² by IV infusion on Day 1 of each 21-day cycle for up to a maximum 6 cycles of treatment, until treatment toxicity which, in the Investigator's opinion, prohibited further therapy, or until radiographic progression.

| | |
|---|---|
| Reporting group title | Placebo + Carboplatin + Paclitaxel |

Reporting group description:

Participants received placebo orally BID on Days -2 to 5 (7 consecutive days) of each 21-day cycle and carboplatin at an AUC 6 mg/mL/min and paclitaxel 200 mg/m² by IV infusion on Day 1 of each 21-day cycle for up to a maximum 6 cycles of treatment, until treatment toxicity which, in the Investigator's opinion, prohibited further therapy, or until radiographic progression.

| **Serious adverse events** | Veliparib + Carboplatin + Paclitaxel | Placebo + Carboplatin + Paclitaxel | |
|---|---|---|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 155 / 485 (31.96%) | 164 / 482 (34.02%) | |
| number of deaths (all causes) | 435 | 443 | |
| number of deaths resulting from adverse events | 38 | 44 | |
| Vascular disorders | | | |
| AORTIC THROMBOSIS | | | |
| subjects affected / exposed | 1 / 485 (0.21%) | 0 / 482 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| EMBOLISM | | | |
| subjects affected / exposed | 1 / 485 (0.21%) | 0 / 482 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |

| | | | |
|---|---|---|---|
| HYPOTENSION | | | |
| subjects affected / exposed | 2 / 485 (0.41%) | 0 / 482 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| ORTHOSTATIC HYPOTENSION | | | |
| subjects affected / exposed | 1 / 485 (0.21%) | 0 / 482 (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 | 2 / 485 (0.41%) | 1 / 482 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| MALIGNANT NEOPLASM PROGRESSION | | | |
| subjects affected / exposed | 8 / 485 (1.65%) | 13 / 482 (2.70%) | |
| occurrences causally related to treatment / all | 1 / 8 | 0 / 13 | |
| deaths causally related to treatment / all | 0 / 6 | 0 / 9 | |
| METASTASES TO CENTRAL NERVOUS SYSTEM | | | |
| subjects affected / exposed | 0 / 485 (0.00%) | 2 / 482 (0.41%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| METASTASES TO HEART | | | |
| subjects affected / exposed | 0 / 485 (0.00%) | 1 / 482 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| METASTASES TO SPINE | | | |
| subjects affected / exposed | 1 / 485 (0.21%) | 0 / 482 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| NON-SMALL CELL LUNG CANCER | | | |
| subjects affected / exposed | 1 / 485 (0.21%) | 3 / 482 (0.62%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 3 | |

| | | | |
|---|---|---|---|
| deaths causally related to treatment / all | 0 / 1 | 0 / 3 | |
| TUMOUR COMPRESSION | | | |
| subjects affected / exposed | 0 / 485 (0.00%) | 1 / 482 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| TUMOUR PAIN | | | |
| subjects affected / exposed | 0 / 485 (0.00%) | 1 / 482 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Immune system disorders | | | |
| ANAPHYLACTIC REACTION | | | |
| subjects affected / exposed | 1 / 485 (0.21%) | 0 / 482 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| DRUG HYPERSENSITIVITY | | | |
| subjects affected / exposed | 3 / 485 (0.62%) | 7 / 482 (1.45%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 10 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| General disorders and administration site conditions | | | |
| ADVERSE DRUG REACTION | | | |
| subjects affected / exposed | 0 / 485 (0.00%) | 1 / 482 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| CHEST PAIN | | | |
| subjects affected / exposed | 4 / 485 (0.82%) | 1 / 482 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| DEATH | | | |
| subjects affected / exposed | 4 / 485 (0.82%) | 3 / 482 (0.62%) | |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 4 | 0 / 3 | |
| DISEASE PROGRESSION | | | |
| subjects affected / exposed | 1 / 485 (0.21%) | 1 / 482 (0.21%) | |
| occurrences causally related to | 1 / 1 | 0 / 1 | |

| | | | |
|---|---|---|---|
| treatment / all | | | |
| deaths causally related to treatment / all | 1 / 1 | 0 / 1 | |
| FATIGUE | | | |
| subjects affected / exposed | 1 / 485 (0.21%) | 3 / 482 (0.62%) | |
| occurrences causally related to treatment / all | 1 / 1 | 1 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| GENERAL PHYSICAL HEALTH DETERIORATION | | | |
| subjects affected / exposed | 1 / 485 (0.21%) | 3 / 482 (0.62%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| MULTIPLE ORGAN DYSFUNCTION SYNDROME | | | |
| subjects affected / exposed | 0 / 485 (0.00%) | 1 / 482 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 1 / 1 | |
| PAIN | | | |
| subjects affected / exposed | 0 / 485 (0.00%) | 2 / 482 (0.41%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| PERFORMANCE STATUS DECREASED | | | |
| subjects affected / exposed | 0 / 485 (0.00%) | 1 / 482 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| PYREXIA | | | |
| subjects affected / exposed | 2 / 485 (0.41%) | 3 / 482 (0.62%) | |
| occurrences causally related to treatment / all | 0 / 2 | 1 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Psychiatric disorders | | | |
| INSOMNIA | | | |
| subjects affected / exposed | 1 / 485 (0.21%) | 0 / 482 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Reproductive system and breast disorders | | | |

| | | | |
|---|---|---|---|
| OVARIAN MASS | | | |
| subjects affected / exposed | 0 / 485 (0.00%) | 1 / 482 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| PROSTATITIS | | | |
| subjects affected / exposed | 1 / 485 (0.21%) | 0 / 482 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| TESTICULAR CYST | | | |
| subjects affected / exposed | 0 / 485 (0.00%) | 1 / 482 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Injury, poisoning and procedural complications | | | |
| FALL | | | |
| subjects affected / exposed | 1 / 485 (0.21%) | 1 / 482 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| FEMORAL NECK FRACTURE | | | |
| subjects affected / exposed | 0 / 485 (0.00%) | 1 / 482 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| PROCEDURAL PAIN | | | |
| subjects affected / exposed | 0 / 485 (0.00%) | 1 / 482 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| SPINAL COMPRESSION FRACTURE | | | |
| subjects affected / exposed | 1 / 485 (0.21%) | 0 / 482 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| TOXICITY TO VARIOUS AGENTS | | | |
| subjects affected / exposed | 0 / 485 (0.00%) | 1 / 482 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|---|---|---|
| ULNA FRACTURE | | | |
| subjects affected / exposed | 1 / 485 (0.21%) | 0 / 482 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Investigations | | | |
| BLOOD CREATININE INCREASED | | | |
| subjects affected / exposed | 1 / 485 (0.21%) | 0 / 482 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 1 / 1 | 0 / 0 | |
| GENERAL PHYSICAL CONDITION ABNORMAL | | | |
| subjects affected / exposed | 0 / 485 (0.00%) | 1 / 482 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac disorders | | | |
| ACUTE CORONARY SYNDROME | | | |
| subjects affected / exposed | 0 / 485 (0.00%) | 2 / 482 (0.41%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| ACUTE MYOCARDIAL INFARCTION | | | |
| subjects affected / exposed | 3 / 485 (0.62%) | 1 / 482 (0.21%) | |
| occurrences causally related to treatment / all | 2 / 3 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| ANGINA PECTORIS | | | |
| subjects affected / exposed | 1 / 485 (0.21%) | 1 / 482 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| ARRHYTHMIA | | | |
| subjects affected / exposed | 1 / 485 (0.21%) | 0 / 482 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| ATRIAL FIBRILLATION | | | |
| subjects affected / exposed | 3 / 485 (0.62%) | 7 / 482 (1.45%) | |
| occurrences causally related to treatment / all | 0 / 3 | 3 / 7 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|---|---|---|
| ATRIAL FLUTTER | | | |
| subjects affected / exposed | 0 / 485 (0.00%) | 1 / 482 (0.21%) | |
| 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 | 2 / 485 (0.41%) | 2 / 482 (0.41%) | |
| occurrences causally related to treatment / all | 0 / 2 | 1 / 2 | |
| deaths causally related to treatment / all | 0 / 2 | 1 / 2 | |
| CARDIAC FAILURE | | | |
| subjects affected / exposed | 1 / 485 (0.21%) | 2 / 482 (0.41%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 2 | |
| CARDIAC FAILURE ACUTE | | | |
| subjects affected / exposed | 0 / 485 (0.00%) | 2 / 482 (0.41%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 2 | |
| CARDIAC FAILURE CONGESTIVE | | | |
| subjects affected / exposed | 1 / 485 (0.21%) | 0 / 482 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| CARDIOVASCULAR INSUFFICIENCY | | | |
| subjects affected / exposed | 1 / 485 (0.21%) | 1 / 482 (0.21%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 1 / 1 | 0 / 1 | |
| INTRACARDIAC MASS | | | |
| subjects affected / exposed | 1 / 485 (0.21%) | 0 / 482 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| MYOCARDIAL INFARCTION | | | |
| subjects affected / exposed | 1 / 485 (0.21%) | 1 / 482 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| PERICARDIAL EFFUSION | | | |
| subjects affected / exposed | 1 / 485 (0.21%) | 2 / 482 (0.41%) | |

| | | | |
|---|---|---|---|
| occurrences causally related to treatment / all | 0 / 1 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| SINUS TACHYCARDIA | | | |
| subjects affected / exposed | 1 / 485 (0.21%) | 0 / 482 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| TACHYCARDIA | | | |
| subjects affected / exposed | 0 / 485 (0.00%) | 1 / 482 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| ACUTE RESPIRATORY FAILURE | | | |
| subjects affected / exposed | 0 / 485 (0.00%) | 3 / 482 (0.62%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 3 | |
| ALVEOLITIS | | | |
| subjects affected / exposed | 0 / 485 (0.00%) | 1 / 482 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| ASPIRATION | | | |
| subjects affected / exposed | 1 / 485 (0.21%) | 0 / 482 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| ATELECTASIS | | | |
| subjects affected / exposed | 2 / 485 (0.41%) | 0 / 482 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| BRONCHIAL OBSTRUCTION | | | |
| subjects affected / exposed | 1 / 485 (0.21%) | 0 / 482 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| CHRONIC OBSTRUCTIVE PULMONARY DISEASE | | | |
| subjects affected / exposed | 1 / 485 (0.21%) | 2 / 482 (0.41%) | |

| | | | |
|---|---|---|---|
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| DYSPNOEA | | | |
| subjects affected / exposed | 4 / 485 (0.82%) | 6 / 482 (1.24%) | |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 6 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 1 | |
| HAEMOPTYSIS | | | |
| subjects affected / exposed | 7 / 485 (1.44%) | 3 / 482 (0.62%) | |
| occurrences causally related to treatment / all | 0 / 7 | 1 / 3 | |
| deaths causally related to treatment / all | 0 / 3 | 1 / 1 | |
| HYPOXIA | | | |
| subjects affected / exposed | 1 / 485 (0.21%) | 1 / 482 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| LUNG INFILTRATION | | | |
| subjects affected / exposed | 0 / 485 (0.00%) | 1 / 482 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| PLEURAL EFFUSION | | | |
| subjects affected / exposed | 8 / 485 (1.65%) | 4 / 482 (0.83%) | |
| occurrences causally related to treatment / all | 1 / 8 | 0 / 4 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| PNEUMONIA ASPIRATION | | | |
| subjects affected / exposed | 1 / 485 (0.21%) | 0 / 482 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| PNEUMONITIS | | | |
| subjects affected / exposed | 1 / 485 (0.21%) | 0 / 482 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| PNEUMOTHORAX | | | |
| subjects affected / exposed | 2 / 485 (0.41%) | 1 / 482 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | |

| | | | |
|---|---|---|---|
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| PNEUMOTHORAX SPONTANEOUS | | | |
| subjects affected / exposed | 1 / 485 (0.21%) | 0 / 482 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| PULMONARY EMBOLISM | | | |
| subjects affected / exposed | 5 / 485 (1.03%) | 6 / 482 (1.24%) | |
| occurrences causally related to treatment / all | 2 / 5 | 1 / 6 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 1 | |
| PULMONARY HAEMORRHAGE | | | |
| subjects affected / exposed | 2 / 485 (0.41%) | 3 / 482 (0.62%) | |
| occurrences causally related to treatment / all | 0 / 2 | 1 / 3 | |
| deaths causally related to treatment / all | 0 / 2 | 1 / 2 | |
| PULMONARY OEDEMA | | | |
| subjects affected / exposed | 0 / 485 (0.00%) | 1 / 482 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| RESPIRATORY DISORDER | | | |
| subjects affected / exposed | 0 / 485 (0.00%) | 1 / 482 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| RESPIRATORY DISTRESS | | | |
| subjects affected / exposed | 0 / 485 (0.00%) | 1 / 482 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| RESPIRATORY FAILURE | | | |
| subjects affected / exposed | 2 / 485 (0.41%) | 3 / 482 (0.62%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 2 | |
| Blood and lymphatic system disorders | | | |
| ANAEMIA | | | |
| subjects affected / exposed | 12 / 485 (2.47%) | 21 / 482 (4.36%) | |
| occurrences causally related to treatment / all | 5 / 18 | 7 / 24 | |

| | | | |
|---|---|---|---|
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| FEBRILE NEUTROPENIA | | | |
| subjects affected / exposed | 17 / 485 (3.51%) | 20 / 482 (4.15%) | |
| occurrences causally related to treatment / all | 10 / 18 | 12 / 21 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| LEUKOPENIA | | | |
| subjects affected / exposed | 2 / 485 (0.41%) | 0 / 482 (0.00%) | |
| occurrences causally related to treatment / all | 2 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| NEUTROPENIA | | | |
| subjects affected / exposed | 8 / 485 (1.65%) | 12 / 482 (2.49%) | |
| occurrences causally related to treatment / all | 2 / 8 | 3 / 12 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| PANCYTOPENIA | | | |
| subjects affected / exposed | 3 / 485 (0.62%) | 0 / 482 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 3 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| THROMBOCYTOPENIA | | | |
| subjects affected / exposed | 3 / 485 (0.62%) | 4 / 482 (0.83%) | |
| occurrences causally related to treatment / all | 3 / 5 | 2 / 5 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nervous system disorders | | | |
| CEREBRAL HAEMORRHAGE | | | |
| subjects affected / exposed | 0 / 485 (0.00%) | 1 / 482 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| CEREBROVASCULAR ACCIDENT | | | |
| subjects affected / exposed | 3 / 485 (0.62%) | 0 / 482 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| COGNITIVE DISORDER | | | |
| subjects affected / exposed | 0 / 485 (0.00%) | 1 / 482 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |

| | | | |
|---|---|---|---|
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| DIZZINESS | | | |
| subjects affected / exposed | 1 / 485 (0.21%) | 1 / 482 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| HEMIPARESIS | | | |
| subjects affected / exposed | 0 / 485 (0.00%) | 1 / 482 (0.21%) | |
| 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 | 1 / 485 (0.21%) | 0 / 482 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| PARTIAL SEIZURES | | | |
| subjects affected / exposed | 0 / 485 (0.00%) | 1 / 482 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| PERIPHERAL SENSORY NEUROPATHY | | | |
| subjects affected / exposed | 1 / 485 (0.21%) | 1 / 482 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| PRESYNCOPE | | | |
| subjects affected / exposed | 0 / 485 (0.00%) | 1 / 482 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| SEIZURE | | | |
| subjects affected / exposed | 1 / 485 (0.21%) | 0 / 482 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| SYNCOPE | | | |
| subjects affected / exposed | 2 / 485 (0.41%) | 0 / 482 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|---|---|---|
| TRANSIENT ISCHAEMIC ATTACK | | | |
| subjects affected / exposed | 2 / 485 (0.41%) | 1 / 482 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ear and labyrinth disorders | | | |
| VERTIGO | | | |
| subjects affected / exposed | 1 / 485 (0.21%) | 0 / 482 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal disorders | | | |
| ABDOMINAL PAIN | | | |
| subjects affected / exposed | 1 / 485 (0.21%) | 2 / 482 (0.41%) | |
| occurrences causally related to treatment / all | 1 / 1 | 1 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| ABDOMINAL PAIN UPPER | | | |
| subjects affected / exposed | 1 / 485 (0.21%) | 0 / 482 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| ASCITES | | | |
| subjects affected / exposed | 0 / 485 (0.00%) | 2 / 482 (0.41%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| CONSTIPATION | | | |
| subjects affected / exposed | 1 / 485 (0.21%) | 0 / 482 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| DIARRHOEA | | | |
| subjects affected / exposed | 2 / 485 (0.41%) | 5 / 482 (1.04%) | |
| occurrences causally related to treatment / all | 2 / 2 | 3 / 5 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| DIVERTICULAR PERFORATION | | | |
| subjects affected / exposed | 1 / 485 (0.21%) | 0 / 482 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|---|---|---|
| DUODENAL ULCER | | | |
| subjects affected / exposed | 0 / 485 (0.00%) | 1 / 482 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| DUODENAL ULCER PERFORATION | | | |
| subjects affected / exposed | 0 / 485 (0.00%) | 1 / 482 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| DYSPHAGIA | | | |
| subjects affected / exposed | 0 / 485 (0.00%) | 1 / 482 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| ENTERITIS | | | |
| subjects affected / exposed | 0 / 485 (0.00%) | 1 / 482 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| FAECES DISCOLOURED | | | |
| subjects affected / exposed | 0 / 485 (0.00%) | 1 / 482 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| GASTRIC HAEMORRHAGE | | | |
| subjects affected / exposed | 0 / 485 (0.00%) | 1 / 482 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| GASTRIC ULCER | | | |
| subjects affected / exposed | 0 / 485 (0.00%) | 1 / 482 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| GASTRITIS | | | |
| subjects affected / exposed | 0 / 485 (0.00%) | 1 / 482 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| GASTRITIS EROSIVE | | | |
| subjects affected / exposed | 1 / 485 (0.21%) | 0 / 482 (0.00%) | |

| | | | |
|---|---|---|---|
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| GASTROINTESTINAL HAEMORRHAGE | | | |
| subjects affected / exposed | 0 / 485 (0.00%) | 1 / 482 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| GASTROINTESTINAL PERFORATION | | | |
| subjects affected / exposed | 1 / 485 (0.21%) | 0 / 482 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| NAUSEA | | | |
| subjects affected / exposed | 0 / 485 (0.00%) | 4 / 482 (0.83%) | |
| occurrences causally related to treatment / all | 0 / 0 | 4 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| OESOPHAGEAL STENOSIS | | | |
| subjects affected / exposed | 0 / 485 (0.00%) | 1 / 482 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| SMALL INTESTINAL OBSTRUCTION | | | |
| subjects affected / exposed | 0 / 485 (0.00%) | 1 / 482 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| TONGUE OEDEMA | | | |
| subjects affected / exposed | 1 / 485 (0.21%) | 0 / 482 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| VOMITING | | | |
| subjects affected / exposed | 0 / 485 (0.00%) | 3 / 482 (0.62%) | |
| occurrences causally related to treatment / all | 0 / 0 | 3 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal and urinary disorders | | | |
| ACUTE KIDNEY INJURY | | | |
| subjects affected / exposed | 2 / 485 (0.41%) | 0 / 482 (0.00%) | |
| occurrences causally related to | 1 / 2 | 0 / 0 | |

| | | | |
|---|---|---|---|
| treatment / all | | | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| AZOTAEMIA | | | |
| subjects affected / exposed | 0 / 485 (0.00%) | 1 / 482 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| NEPHROLITHIASIS | | | |
| subjects affected / exposed | 0 / 485 (0.00%) | 1 / 482 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| RENAL COLIC | | | |
| subjects affected / exposed | 0 / 485 (0.00%) | 1 / 482 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| RENAL IMPAIRMENT | | | |
| subjects affected / exposed | 1 / 485 (0.21%) | 0 / 482 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| URINARY RETENTION | | | |
| subjects affected / exposed | 1 / 485 (0.21%) | 1 / 482 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hepatobiliary disorders | | | |
| HEPATITIS ACUTE | | | |
| subjects affected / exposed | 1 / 485 (0.21%) | 0 / 482 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| PORTAL VEIN THROMBOSIS | | | |
| subjects affected / exposed | 0 / 485 (0.00%) | 1 / 482 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Musculoskeletal and connective tissue disorders | | | |
| ARTHRALGIA | | | |
| subjects affected / exposed | 0 / 485 (0.00%) | 1 / 482 (0.21%) | |

| | | | |
|---|---|---|---|
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| BACK PAIN | | | |
| subjects affected / exposed | 2 / 485 (0.41%) | 3 / 482 (0.62%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| BONE PAIN | | | |
| subjects affected / exposed | 0 / 485 (0.00%) | 1 / 482 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| FLANK PAIN | | | |
| subjects affected / exposed | 0 / 485 (0.00%) | 1 / 482 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| INTERVERTEBRAL DISC PROTRUSION | | | |
| subjects affected / exposed | 1 / 485 (0.21%) | 0 / 482 (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 / 485 (0.00%) | 2 / 482 (0.41%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| MUSCULOSKELETAL CHEST PAIN | | | |
| subjects affected / exposed | 0 / 485 (0.00%) | 1 / 482 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| PAIN IN EXTREMITY | | | |
| subjects affected / exposed | 1 / 485 (0.21%) | 1 / 482 (0.21%) | |
| 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 | 0 / 485 (0.00%) | 1 / 482 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |

| | | | |
|---|---|---|---|
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Metabolism and nutrition disorders | | | |
| DECREASED APPETITE | | | |
| subjects affected / exposed | 1 / 485 (0.21%) | 1 / 482 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| DEHYDRATION | | | |
| subjects affected / exposed | 3 / 485 (0.62%) | 2 / 482 (0.41%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| ELECTROLYTE IMBALANCE | | | |
| subjects affected / exposed | 1 / 485 (0.21%) | 0 / 482 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| HYPERCALCAEMIA | | | |
| subjects affected / exposed | 1 / 485 (0.21%) | 3 / 482 (0.62%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| HYPERGLYCAEMIA | | | |
| subjects affected / exposed | 2 / 485 (0.41%) | 0 / 482 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| HYPERURICAEMIA | | | |
| subjects affected / exposed | 1 / 485 (0.21%) | 0 / 482 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| HYPOGLYCAEMIA | | | |
| subjects affected / exposed | 1 / 485 (0.21%) | 0 / 482 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| HYPOKALAEMIA | | | |
| subjects affected / exposed | 1 / 485 (0.21%) | 1 / 482 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |

| | | | |
|---|---|---|---|
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| HYPONATRAEMIA | | | |
| subjects affected / exposed | 1 / 485 (0.21%) | 1 / 482 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infections and infestations | | | |
| ANAL ABSCESS | | | |
| subjects affected / exposed | 1 / 485 (0.21%) | 0 / 482 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| BACTERAEMIA | | | |
| subjects affected / exposed | 1 / 485 (0.21%) | 0 / 482 (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 | 2 / 485 (0.41%) | 0 / 482 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| CLOSTRIDIUM DIFFICILE COLITIS | | | |
| subjects affected / exposed | 1 / 485 (0.21%) | 0 / 482 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| DIVERTICULITIS | | | |
| subjects affected / exposed | 1 / 485 (0.21%) | 0 / 482 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| EMPYEMA | | | |
| subjects affected / exposed | 0 / 485 (0.00%) | 1 / 482 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| ENTEROCOLITIS INFECTIOUS | | | |
| subjects affected / exposed | 0 / 485 (0.00%) | 1 / 482 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |

| | | | |
|---|---|---|---|
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| GASTROENTERITIS | | | |
| subjects affected / exposed | 2 / 485 (0.41%) | 1 / 482 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 2 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| INFECTION | | | |
| subjects affected / exposed | 0 / 485 (0.00%) | 2 / 482 (0.41%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| LOWER RESPIRATORY TRACT INFECTION | | | |
| subjects affected / exposed | 3 / 485 (0.62%) | 7 / 482 (1.45%) | |
| occurrences causally related to treatment / all | 1 / 3 | 1 / 7 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| LUNG ABSCESS | | | |
| subjects affected / exposed | 0 / 485 (0.00%) | 2 / 482 (0.41%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| LUNG INFECTION | | | |
| subjects affected / exposed | 3 / 485 (0.62%) | 0 / 482 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| MESENTERIC ABSCESS | | | |
| subjects affected / exposed | 1 / 485 (0.21%) | 0 / 482 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| NEUTROPENIC SEPSIS | | | |
| subjects affected / exposed | 0 / 485 (0.00%) | 2 / 482 (0.41%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| ORAL CANDIDIASIS | | | |
| subjects affected / exposed | 1 / 485 (0.21%) | 0 / 482 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|---|---|---|
| OSTEOMYELITIS | | | |
| subjects affected / exposed | 0 / 485 (0.00%) | 1 / 482 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| PNEUMONIA | | | |
| subjects affected / exposed | 23 / 485 (4.74%) | 19 / 482 (3.94%) | |
| occurrences causally related to treatment / all | 4 / 24 | 4 / 21 | |
| deaths causally related to treatment / all | 0 / 3 | 1 / 2 | |
| PNEUMONIA BACTERIAL | | | |
| subjects affected / exposed | 0 / 485 (0.00%) | 1 / 482 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| PNEUMONIA KLEBSIELLA | | | |
| subjects affected / exposed | 1 / 485 (0.21%) | 0 / 482 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| PNEUMONIA STAPHYLOCOCCAL | | | |
| subjects affected / exposed | 1 / 485 (0.21%) | 0 / 482 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| PULMONARY SEPSIS | | | |
| subjects affected / exposed | 1 / 485 (0.21%) | 1 / 482 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 1 | |
| PYELONEPHRITIS | | | |
| subjects affected / exposed | 1 / 485 (0.21%) | 0 / 482 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| RESPIRATORY TRACT INFECTION | | | |
| subjects affected / exposed | 4 / 485 (0.82%) | 5 / 482 (1.04%) | |
| occurrences causally related to treatment / all | 1 / 4 | 1 / 5 | |
| deaths causally related to treatment / all | 0 / 0 | 1 / 1 | |
| SEPSIS | | | |
| subjects affected / exposed | 4 / 485 (0.82%) | 2 / 482 (0.41%) | |

| | | | |
|---|---|---|---|
| occurrences causally related to treatment / all | 2 / 4 | 0 / 2 | |
| deaths causally related to treatment / all | 1 / 1 | 0 / 0 | |
| SEPTIC EMBOLUS | | | |
| subjects affected / exposed | 0 / 485 (0.00%) | 1 / 482 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| SEPTIC SHOCK | | | |
| subjects affected / exposed | 4 / 485 (0.82%) | 2 / 482 (0.41%) | |
| occurrences causally related to treatment / all | 0 / 4 | 1 / 2 | |
| deaths causally related to treatment / all | 0 / 2 | 1 / 1 | |
| SINUSITIS | | | |
| subjects affected / exposed | 0 / 485 (0.00%) | 1 / 482 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| SUBCUTANEOUS ABSCESS | | | |
| subjects affected / exposed | 0 / 485 (0.00%) | 1 / 482 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| UPPER RESPIRATORY TRACT INFECTION | | | |
| subjects affected / exposed | 0 / 485 (0.00%) | 1 / 482 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| URINARY TRACT INFECTION | | | |
| subjects affected / exposed | 1 / 485 (0.21%) | 1 / 482 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| URINARY TRACT INFECTION ENTEROCOCCAL | | | |
| subjects affected / exposed | 0 / 485 (0.00%) | 1 / 482 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

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

| **Non-serious adverse events** | Veliparib + Carboplatin + Paclitaxel | Placebo + Carboplatin + Paclitaxel | |
|---|---|---|---|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 441 / 485 (90.93%) | 438 / 482 (90.87%) | |
| Investigations | | | |
| WEIGHT DECREASED | | | |
| subjects affected / exposed | 26 / 485 (5.36%) | 36 / 482 (7.47%) | |
| occurrences (all) | 29 | 42 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| COUGH | | | |
| subjects affected / exposed | 62 / 485 (12.78%) | 69 / 482 (14.32%) | |
| occurrences (all) | 71 | 73 | |
| DYSPNOEA | | | |
| subjects affected / exposed | 70 / 485 (14.43%) | 55 / 482 (11.41%) | |
| occurrences (all) | 77 | 61 | |
| Blood and lymphatic system disorders | | | |
| ANAEMIA | | | |
| subjects affected / exposed | 157 / 485 (32.37%) | 146 / 482 (30.29%) | |
| occurrences (all) | 254 | 232 | |
| LEUKOPENIA | | | |
| subjects affected / exposed | 53 / 485 (10.93%) | 34 / 482 (7.05%) | |
| occurrences (all) | 86 | 46 | |
| LYMPHOPENIA | | | |
| subjects affected / exposed | 25 / 485 (5.15%) | 18 / 482 (3.73%) | |
| occurrences (all) | 37 | 22 | |
| NEUTROPENIA | | | |
| subjects affected / exposed | 152 / 485 (31.34%) | 133 / 482 (27.59%) | |
| occurrences (all) | 259 | 227 | |
| THROMBOCYTOPENIA | | | |
| subjects affected / exposed | 92 / 485 (18.97%) | 98 / 482 (20.33%) | |
| occurrences (all) | 173 | 185 | |
| Nervous system disorders | | | |
| DIZZINESS | | | |
| subjects affected / exposed | 26 / 485 (5.36%) | 24 / 482 (4.98%) | |
| occurrences (all) | 30 | 26 | |
| DYSGEUSIA | | | |
| subjects affected / exposed | 22 / 485 (4.54%) | 26 / 482 (5.39%) | |

| | | | |
|---|---|---|---|
| occurrences (all) | 22 | 29 | |
| NEUROPATHY PERIPHERAL | | | |
| subjects affected / exposed | 43 / 485 (8.87%) | 43 / 482 (8.92%) | |
| occurrences (all) | 57 | 58 | |
| PARAESTHESIA | | | |
| subjects affected / exposed | 27 / 485 (5.57%) | 43 / 482 (8.92%) | |
| occurrences (all) | 29 | 57 | |
| PERIPHERAL SENSORY NEUROPATHY | | | |
| subjects affected / exposed | 153 / 485 (31.55%) | 148 / 482 (30.71%) | |
| occurrences (all) | 217 | 220 | |
| General disorders and administration site conditions | | | |
| ASTHENIA | | | |
| subjects affected / exposed | 71 / 485 (14.64%) | 72 / 482 (14.94%) | |
| occurrences (all) | 114 | 118 | |
| FATIGUE | | | |
| subjects affected / exposed | 100 / 485 (20.62%) | 105 / 482 (21.78%) | |
| occurrences (all) | 134 | 143 | |
| OEDEMA PERIPHERAL | | | |
| subjects affected / exposed | 25 / 485 (5.15%) | 23 / 482 (4.77%) | |
| occurrences (all) | 30 | 24 | |
| PYREXIA | | | |
| subjects affected / exposed | 32 / 485 (6.60%) | 34 / 482 (7.05%) | |
| occurrences (all) | 37 | 44 | |
| Psychiatric disorders | | | |
| INSOMNIA | | | |
| subjects affected / exposed | 32 / 485 (6.60%) | 38 / 482 (7.88%) | |
| occurrences (all) | 36 | 40 | |
| Gastrointestinal disorders | | | |
| CONSTIPATION | | | |
| subjects affected / exposed | 74 / 485 (15.26%) | 84 / 482 (17.43%) | |
| occurrences (all) | 90 | 98 | |
| DIARRHOEA | | | |
| subjects affected / exposed | 83 / 485 (17.11%) | 76 / 482 (15.77%) | |
| occurrences (all) | 110 | 91 | |
| NAUSEA | | | |
| subjects affected / exposed | 116 / 485 (23.92%) | 112 / 482 (23.24%) | |

| | | | |
|---|---|---|---|
| occurrences (all) | 142 | 146 | |
| VOMITING | | | |
| subjects affected / exposed | 44 / 485 (9.07%) | 51 / 482 (10.58%) | |
| occurrences (all) | 61 | 65 | |
| Skin and subcutaneous tissue disorders | | | |
| ALOPECIA | | | |
| subjects affected / exposed | 232 / 485 (47.84%) | 220 / 482 (45.64%) | |
| occurrences (all) | 268 | 245 | |
| RASH | | | |
| subjects affected / exposed | 12 / 485 (2.47%) | 25 / 482 (5.19%) | |
| occurrences (all) | 13 | 32 | |
| Musculoskeletal and connective tissue disorders | | | |
| ARTHRALGIA | | | |
| subjects affected / exposed | 65 / 485 (13.40%) | 66 / 482 (13.69%) | |
| occurrences (all) | 77 | 97 | |
| MYALGIA | | | |
| subjects affected / exposed | 56 / 485 (11.55%) | 43 / 482 (8.92%) | |
| occurrences (all) | 83 | 59 | |
| PAIN IN EXTREMITY | | | |
| subjects affected / exposed | 46 / 485 (9.48%) | 40 / 482 (8.30%) | |
| occurrences (all) | 58 | 45 | |
| Metabolism and nutrition disorders | | | |
| DECREASED APPETITE | | | |
| subjects affected / exposed | 68 / 485 (14.02%) | 77 / 482 (15.98%) | |
| occurrences (all) | 84 | 88 | |
| HYPERGLYCAEMIA | | | |
| subjects affected / exposed | 33 / 485 (6.80%) | 36 / 482 (7.47%) | |
| occurrences (all) | 49 | 61 | |
| HYPOKALAEMIA | | | |
| subjects affected / exposed | 19 / 485 (3.92%) | 27 / 482 (5.60%) | |
| occurrences (all) | 21 | 34 | |
| HYPOMAGNESAEMIA | | | |
| subjects affected / exposed | 33 / 485 (6.80%) | 29 / 482 (6.02%) | |
| occurrences (all) | 48 | 35 | |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|---|---|
| 07 May 2014 | Updated inclusion/exclusion criteria and updated requirements for physical examination to include neurological evaluation and hearing assessment at Screening and C2D1 – C6D1, in agreement with regulatory feedback. |
| 10 July 2014 | Updated inclusion/exclusion criteria, moved duration of response (DOR) from a secondary endpoint to a tertiary endpoint, and clarified that confirmed response was required as part of ORR analysis in agreement with regulatory feedback. |
| 02 February 2016 | The primary endpoint was amended to OS in current smokers with OS of all subjects as a secondary endpoint (as Phase 2 data suggested that veliparib benefit may be most evident in smokers). Corresponding changes were also made to the sample size calculation and timing of efficacy and futility interim analysis to align with primary endpoint change. |

Notes:

### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported