

**Clinical trial results:****A Multistage, Phase II Study Evaluating the Safety and Efficacy of Cobimetinib Plus Paclitaxel, Cobimetinib Plus Atezolizumab Plus Paclitaxel, or Cobimetinib Plus Atezolizumab Plus Nab-Paclitaxel as First-Line Treatment for Patients With Metastatic Triple-Negative Breast Cancer****Summary**

| | |
|--------------------------|-------------------------|
| EudraCT number | 2014-002230-32 |
| Trial protocol | ES GB CZ BE FR LT LV IT |
| Global end of trial date | 17 September 2021 |

Results information

| | |
|--------------------------------|---|
| Result version number | v4 |
| This version publication date | 26 January 2023 |
| First version publication date | 08 September 2022 |
| Version creation reason | <ul style="list-style-type: none">• Correction of full data set Updates based on comments received from the NIH |

Trial information**Trial identification**

| | |
|-----------------------|---------|
| Sponsor protocol code | WO29479 |
|-----------------------|---------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT02322814 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|--|
| Sponsor organisation name | F. Hoffmann-La Roche AG |
| Sponsor organisation address | Grenzacherstrasse 124, Basel, Switzerland, CH-4070 |
| Public contact | F. Hoffmann-La Roche AG, F. Hoffmann-La Roche AG, 41 616878333, global.trial_information@roche.com |
| Scientific contact | F. Hoffmann-La Roche AG, F. Hoffmann-La Roche AG, 41 616878333, global.trial_information@roche.com |

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

| | |
|--|-------------------|
| Analysis stage | Final |
| Date of interim/final analysis | 17 September 2021 |
| Is this the analysis of the primary completion data? | No |
| Global end of trial reached? | Yes |
| Global end of trial date | 17 September 2021 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

The objective of this trial was to evaluate the safety and tolerability and estimate the efficacy of cobimetinib plus paclitaxel versus placebo plus paclitaxel in Cohort I, of cobimetinib plus atezolizumab plus paclitaxel in Cohort II, and of cobimetinib plus atezolizumab plus nab-paclitaxel in Cohort III in participants with metastatic or locally advanced, triple-negative adenocarcinoma of the breast who have not received prior systemic therapy for metastatic breast cancer (MBC).

Protection of trial subjects:

All study subjects were required to read and sign and Informed Consent Form.

Background therapy: -

Evidence for comparator: -

| | |
|---|---------------|
| Actual start date of recruitment | 12 March 2015 |
| Long term follow-up planned | Yes |
| Long term follow-up rationale | Efficacy |
| Long term follow-up duration | 3 Months |
| Independent data monitoring committee (IDMC) involvement? | No |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|------------------------|
| Country: Number of subjects enrolled | France: 10 |
| Country: Number of subjects enrolled | Latvia: 18 |
| Country: Number of subjects enrolled | Australia: 14 |
| Country: Number of subjects enrolled | Israel: 2 |
| Country: Number of subjects enrolled | Korea, Republic of: 20 |
| Country: Number of subjects enrolled | Taiwan: 8 |
| Country: Number of subjects enrolled | United States: 22 |
| Country: Number of subjects enrolled | Czechia: 2 |
| Country: Number of subjects enrolled | Italy: 12 |
| Country: Number of subjects enrolled | Romania: 10 |
| Country: Number of subjects enrolled | Spain: 24 |
| Country: Number of subjects enrolled | Belgium: 21 |
| Country: Number of subjects enrolled | United Kingdom: 6 |
| Worldwide total number of subjects | 169 |
| EEA total number of subjects | 97 |

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) | 137 |
| From 65 to 84 years | 32 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

The study recruited participants with metastatic or locally advanced, triple-negative adenocarcinoma of the breast who had not received prior systemic therapy for metastatic breast cancer. Locally advanced disease must not have been amenable to resection with curative intent.

Pre-assignment

Screening details:

One participant from Cohort III never started any treatment.

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 |

Blinding implementation details:

The run-in stage of Cohort I and all of Cohorts II and III were open label. The expansion (randomized) stage of Cohort I was double-blind.

Arms

| | |
|------------------------------|-------------------------|
| Are arms mutually exclusive? | Yes |
| Arm title | Cohort I: Safety Run-In |

Arm description:

Participants received cobimetinib plus paclitaxel until 12 participants completed one cycle of study treatment (28 days).

| | |
|--|-----------------|
| Arm type | Experimental |
| Investigational medicinal product name | Paclitaxel |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

Paclitaxel was administered at a dose of 80 milligrams per square meter (mg/m²) by intravenous (IV) infusion on Day 1, Day 8, and Day 15 of each 28-day cycle according to prescribing information.

| | |
|--|--------------------|
| Investigational medicinal product name | Cobimetinib |
| Investigational medicinal product code | |
| Other name | Cotellic |
| Pharmaceutical forms | Film-coated tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Cobimetinib was administered orally at a dose of 60 milligrams (mg) per day, once a day, on Day 3 through Day 23 of each 28-day treatment cycle.

| | |
|------------------|-----------------------------------|
| Arm title | Cohort I: Cobimetinib, Paclitaxel |
|------------------|-----------------------------------|

Arm description:

Participants received a combination of cobimetinib plus paclitaxel in 28-day cycles until disease progression, unacceptable toxicity, investigator decision, death, withdrawal of consent, or completion of study.

| | |
|----------|--------------|
| Arm type | Experimental |
|----------|--------------|

| | |
|--|--------------------|
| Investigational medicinal product name | Cobimetinib |
| Investigational medicinal product code | |
| Other name | Cotellic |
| Pharmaceutical forms | Film-coated tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Cobimetinib was administered orally at a dose of 60 milligrams (mg) per day, once a day, on Day 3 through Day 23 of each 28-day treatment cycle.

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

Dosage and administration details:

Paclitaxel was administered at a dose of 80 milligrams per square meter (mg/m²) by intravenous (IV) infusion on Day 1, Day 8, and Day 15 of each 28-day cycle according to prescribing information.

| | |
|------------------|-------------------------------|
| Arm title | Cohort I: Placebo, Paclitaxel |
|------------------|-------------------------------|

Arm description:

Participants received a combination of cobimetinib placebo plus paclitaxel in 28-day cycles until disease progression, unacceptable toxicity, investigator decision, death, withdrawal of consent, or completion of study.

| | |
|--|-----------------|
| Arm type | Placebo |
| Investigational medicinal product name | Paclitaxel |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

Paclitaxel was administered at a dose of 80 milligrams per square meter (mg/m²) by intravenous (IV) infusion on Day 1, Day 8, and Day 15 of each 28-day cycle according to prescribing information.

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

Dosage and administration details:

Placebo matching to cobimetinib was administered orally, once a day, on Day 3 through Day 23 of each 28 day treatment cycle.

| | |
|------------------|--|
| Arm title | Cohort II: Cobimetinib, Paclitaxel, Atezolizumab |
|------------------|--|

Arm description:

Participants received cobimetinib plus paclitaxel plus atezolizumab in 28-day cycles until disease progression, unacceptable toxicity, investigator decision, death, withdrawal of consent, or completion of study.

| | |
|--|-----------------|
| Arm type | Experimental |
| Investigational medicinal product name | Atezolizumab |
| Investigational medicinal product code | |
| Other name | Tecentriq |
| Pharmaceutical forms | Infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

Atezolizumab was administered to Cohorts II and III at a dose of 840 mg IV every 2 weeks on Days 1 and 15 of each 28-day treatment cycle.

| | |
|--|--------------------|
| Investigational medicinal product name | Cobimetinib |
| Investigational medicinal product code | |
| Other name | Cotellic |
| Pharmaceutical forms | Film-coated tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Cobimetinib was administered orally at a dose of 60 milligrams (mg) per day, once a day, on Day 3 through Day 23 of each 28-day treatment cycle.

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

Dosage and administration details:

Paclitaxel was administered at a dose of 80 milligrams per square meter (mg/m²) by intravenous (IV) infusion on Day 1, Day 8, and Day 15 of each 28-day cycle according to prescribing information.

| | |
|------------------|---|
| Arm title | Cohort III: Cobimetinib, Nab-Paclitaxel, Atezolizumab |
|------------------|---|

Arm description:

Participants received cobimetinib plus nab-paclitaxel plus atezolizumab until disease progression, unacceptable toxicity, investigator decision, death, withdrawal of consent, or completion of study.

| | |
|--|-----------------|
| Arm type | Experimental |
| Investigational medicinal product name | Nab-Paclitaxel |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

Nab-Paclitaxel was administered to Cohort III according to the local prescribing information at a starting dose of 100 mg/m² by IV infusion on Days 1, 8, and 15 of each 28 day cycle.

| | |
|--|-----------------|
| Investigational medicinal product name | Atezolizumab |
| Investigational medicinal product code | |
| Other name | Tecentriq |
| Pharmaceutical forms | Infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

Atezolizumab was administered to Cohorts II and III at a dose of 840 mg IV every 2 weeks on Days 1 and 15 of each 28-day treatment cycle.

| | |
|--|--------------------|
| Investigational medicinal product name | Cobimetinib |
| Investigational medicinal product code | |
| Other name | Cotellic |
| Pharmaceutical forms | Film-coated tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Cobimetinib was administered orally at a dose of 60 milligrams (mg) per day, once a day, on Day 3 through Day 23 of each 28-day treatment cycle.

| Number of subjects in period 1 | Cohort I: Safety Run-In | Cohort I: Cobimetinib, Paclitaxel | Cohort I: Placebo, Paclitaxel |
|--------------------------------|-------------------------|-----------------------------------|-------------------------------|
| | | | |
| Started | 16 | 47 | 43 |
| Completed | 0 | 0 | 0 |
| Not completed | 16 | 47 | 43 |
| Death | 7 | 32 | 29 |
| Progressive Disease | - | - | - |
| Withdrawal by Subject | 5 | 2 | 4 |
| Study Terminated by Sponsor | - | 9 | 7 |
| Lost to follow-up | 1 | 3 | 3 |
| Various Reasons | 2 | 1 | - |
| Protocol deviation | 1 | - | - |

| Number of subjects in period 1 | Cohort II: Cobimetinib, Paclitaxel, Atezolizumab | Cohort III: Cobimetinib, Nab-Paclitaxel, Atezolizumab |
|--------------------------------|--|---|
| | | |
| Started | 32 | 31 |
| Completed | 0 | 0 |
| Not completed | 32 | 31 |
| Death | 23 | 14 |
| Progressive Disease | 1 | 1 |
| Withdrawal by Subject | 1 | 3 |
| Study Terminated by Sponsor | 5 | 13 |
| Lost to follow-up | 1 | - |
| Various Reasons | 1 | - |
| Protocol deviation | - | - |

Baseline characteristics

Reporting groups

| | |
|--|---|
| Reporting group title | Cohort I: Safety Run-In |
| Reporting group description: Participants received cobimetinib plus paclitaxel until 12 participants completed one cycle of study treatment (28 days). | |
| Reporting group title | Cohort I: Cobimetinib, Paclitaxel |
| Reporting group description: Participants received a combination of cobimetinib plus paclitaxel in 28-day cycles until disease progression, unacceptable toxicity, investigator decision, death, withdrawal of consent, or completion of study. | |
| Reporting group title | Cohort I: Placebo, Paclitaxel |
| Reporting group description: Participants received a combination of cobimetinib placebo plus paclitaxel in 28-day cycles until disease progression, unacceptable toxicity, investigator decision, death, withdrawal of consent, or completion of study. | |
| Reporting group title | Cohort II: Cobimetinib, Paclitaxel, Atezolizumab |
| Reporting group description: Participants received cobimetinib plus paclitaxel plus atezolizumab in 28-day cycles until disease progression, unacceptable toxicity, investigator decision, death, withdrawal of consent, or completion of study. | |
| Reporting group title | Cohort III: Cobimetinib, Nab-Paclitaxel, Atezolizumab |
| Reporting group description: Participants received cobimetinib plus nab-paclitaxel plus atezolizumab until disease progression, unacceptable toxicity, investigator decision, death, withdrawal of consent, or completion of study. | |

| Reporting group values | Cohort I: Safety Run-In | Cohort I: Cobimetinib, Paclitaxel | Cohort I: Placebo, Paclitaxel |
|--|-------------------------|-----------------------------------|-------------------------------|
| Number of subjects | 16 | 47 | 43 |
| Age Categorical Units: Subjects | | | |
| In utero | 0 | 0 | 0 |
| Preterm newborn infants (gestational age < 37 wks) | 0 | 0 | 0 |
| Newborns (0-27 days) | 0 | 0 | 0 |
| Infants and toddlers (28 days-23 months) | 0 | 0 | 0 |
| Children (2-11 years) | 0 | 0 | 0 |
| Adolescents (12-17 years) | 0 | 0 | 0 |
| Adults (18-64 years) | 13 | 40 | 34 |
| From 65-84 years | 3 | 7 | 9 |
| 85 years and over | 0 | 0 | 0 |
| Age Continuous Units: years | | | |
| arithmetic mean | 53.6 | 54.2 | 52.9 |
| standard deviation | ± 12.7 | ± 10.3 | ± 13.7 |
| Gender Categorical Units: Subjects | | | |
| Female | 16 | 47 | 43 |
| Male | 0 | 0 | 0 |

| | | | |
|---------------------------|----|----|----|
| Race (NIH/OMB) | | | |
| Units: Subjects | | | |
| Asian | 3 | 11 | 9 |
| Black or African American | 2 | 2 | 0 |
| White | 10 | 32 | 34 |
| Other | 1 | 0 | 0 |
| Unknown | 0 | 2 | 0 |
| Ethnicity (NIH/OMB) | | | |
| Units: Subjects | | | |
| Hispanic or Latino | 1 | 3 | 7 |
| Not Hispanic or Latino | 13 | 41 | 35 |
| Not Stated | 2 | 2 | 1 |
| Unknown | 0 | 1 | 0 |

| Reporting group values | Cohort II: Cobimetinib, Paclitaxel, Atezolizumab | Cohort III: Cobimetinib, Nab-Paclitaxel, Atezolizumab | Total |
|--|--|---|-------|
| Number of subjects | 32 | 31 | 169 |
| Age Categorical | | | |
| Units: Subjects | | | |
| In utero | 0 | 0 | 0 |
| Preterm newborn infants (gestational age < 37 wks) | 0 | 0 | 0 |
| Newborns (0-27 days) | 0 | 0 | 0 |
| Infants and toddlers (28 days-23 months) | 0 | 0 | 0 |
| Children (2-11 years) | 0 | 0 | 0 |
| Adolescents (12-17 years) | 0 | 0 | 0 |
| Adults (18-64 years) | 24 | 26 | 137 |
| From 65-84 years | 8 | 5 | 32 |
| 85 years and over | 0 | 0 | 0 |
| Age Continuous | | | |
| Units: years | | | |
| arithmetic mean | 53.7 | 52.2 | |
| standard deviation | ± 13.1 | ± 11.8 | - |
| Gender Categorical | | | |
| Units: Subjects | | | |
| Female | 32 | 31 | 169 |
| Male | 0 | 0 | 0 |
| Race (NIH/OMB) | | | |
| Units: Subjects | | | |
| Asian | 2 | 5 | 30 |
| Black or African American | 1 | 0 | 5 |
| White | 28 | 25 | 129 |
| Other | 1 | 1 | 3 |
| Unknown | 0 | 0 | 2 |
| Ethnicity (NIH/OMB) | | | |
| Units: Subjects | | | |
| Hispanic or Latino | 2 | 3 | 16 |
| Not Hispanic or Latino | 30 | 28 | 147 |
| Not Stated | 0 | 0 | 5 |
| Unknown | 0 | 0 | 1 |

End points

End points reporting groups

| | |
|--|---|
| Reporting group title | Cohort I: Safety Run-In |
| Reporting group description: Participants received cobimetinib plus paclitaxel until 12 participants completed one cycle of study treatment (28 days). | |
| Reporting group title | Cohort I: Cobimetinib, Paclitaxel |
| Reporting group description: Participants received a combination of cobimetinib plus paclitaxel in 28-day cycles until disease progression, unacceptable toxicity, investigator decision, death, withdrawal of consent, or completion of study. | |
| Reporting group title | Cohort I: Placebo, Paclitaxel |
| Reporting group description: Participants received a combination of cobimetinib placebo plus paclitaxel in 28-day cycles until disease progression, unacceptable toxicity, investigator decision, death, withdrawal of consent, or completion of study. | |
| Reporting group title | Cohort II: Cobimetinib, Paclitaxel, Atezolizumab |
| Reporting group description: Participants received cobimetinib plus paclitaxel plus atezolizumab in 28-day cycles until disease progression, unacceptable toxicity, investigator decision, death, withdrawal of consent, or completion of study. | |
| Reporting group title | Cohort III: Cobimetinib, Nab-Paclitaxel, Atezolizumab |
| Reporting group description: Participants received cobimetinib plus nab-paclitaxel plus atezolizumab until disease progression, unacceptable toxicity, investigator decision, death, withdrawal of consent, or completion of study. | |

Primary: Cohort I: Progression-Free Survival, as Determined by Investigator Using Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST v1.1)

| | |
|---|--|
| End point title | Cohort I: Progression-Free Survival, as Determined by Investigator Using Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST v1.1) ^[1] |
| End point description: PFS was defined as the time from randomization to the first occurrence of disease progression or relapse, as determined by the investigator, using RECIST v1.1. As per RECIST v1.1, progressive disease (PD) is defined as at least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (nadir), including baseline. In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 millimeters (mm). The appearance of one or more new lesions is also considered progression. Data were only collected from participants in the Cohort I Expansion Stage (Cohort I: Cobimetinib, Paclitaxel, Cohort I: Placebo, Paclitaxel) for this outcome measure. ITT population was defined as all enrolled participants, whether or not the assigned study treatment was received. | |
| End point type | Primary |
| End point timeframe: Randomization up to disease progression or relapse, whichever occurs first (up to approximately 2 years) | |
| Notes: [1] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: The primary objective was to estimate the clinical benefit of cobimetinib plus paclitaxel relative to placebo plus paclitaxel, as measured by investigator-assessed PFS, so only these two arms have data related to primary endpoint. | |

| End point values | Cohort I: Cobimetinib, Paclitaxel | Cohort I: Placebo, Paclitaxel | | |
|----------------------------------|---|-------------------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 47 | 43 | | |
| Units: Weeks | | | | |
| median (confidence interval 95%) | 23.71 (18.14 to 32.14) | 16.43 (8.14 to 31.14) | | |

Statistical analyses

| Statistical analysis title | Cobimetinib vs. Placebo |
|---|---|
| Comparison groups | Cohort I: Cobimetinib, Paclitaxel v Cohort I: Placebo, Paclitaxel |
| Number of subjects included in analysis | 90 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.247 |
| Method | Logrank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.73 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.43 |
| upper limit | 1.24 |

Primary: Cohort II, III: Percentage of Participants With Confirmed Overall Response (OR) (Partial Response [PR] or Complete Response [CR]), as Determined by the Investigator Using RECIST v1.1

| | |
|-----------------|--|
| End point title | Cohort II, III: Percentage of Participants With Confirmed Overall Response (OR) (Partial Response [PR] or Complete Response [CR]), as Determined by the Investigator Using RECIST v1.1 ^{[2][3]} |
|-----------------|--|

End point description:

OR was defined as the rate of a PR or CR occurring after randomization and confirmed ≥ 28 days later as determined by the investigator using RECIST v1.1. As per RECIST v1.1, CR is defined as the disappearance of all target lesions. Any pathological lymph nodes (whether target or nontarget) must have reduction in short axis to < 10 mm. PR is defined as at least a 30% decrease in the sum of diameters of all target and new measurable lesions. ITT population was defined as all enrolled participants, whether or not the assigned study treatment was received.

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

End point timeframe:

Randomization up to disease progression or relapse, whichever occurs first (up to approximately 5.25 years)

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: No statistical analyses for this end point.

[3] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: This analysis was only performed on Cohorts II and III and hence why not all arms are presented.

| End point values | Cohort II: Cobimetinib, Paclitaxel, Atezolizumab | Cohort III: Cobimetinib, Nab-Paclitaxel, Atezolizumab | | |
|-----------------------------------|--|---|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 32 | 31 | | |
| Units: Percentage of participants | | | | |
| number (not applicable) | | | | |
| Responders | 37.5 | 32.3 | | |
| Non-Responders | 62.5 | 67.7 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Cohort I, II, III: Overall Survival (OS)

| | |
|-----------------|---|
| End point title | Cohort I, II, III: Overall Survival (OS) ^[4] |
|-----------------|---|

End point description:

OS was defined as the time from randomization to death from any cause. Data were only collected from participants in the Cohort I Expansion Stage (Cohort I: Cobimetinib, Paclitaxel, Cohort I: Placebo, Paclitaxel) along with the Cohort II and III for this outcome measure. ITT population was defined as all enrolled participants, whether or not the assigned study treatment was received. 9999999 = The upper limit of 95% CI was not evaluable due to insufficient events observed.

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

End point timeframe:

Randomization up to death from any cause (up to approximately 6.5 years)

Notes:

[4] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: The analysis excludes the Safety Run-In cohort.

| End point values | Cohort I: Cobimetinib, Paclitaxel | Cohort I: Placebo, Paclitaxel | Cohort II: Cobimetinib, Paclitaxel, Atezolizumab | Cohort III: Cobimetinib, Nab-Paclitaxel, Atezolizumab |
|----------------------------------|-----------------------------------|-------------------------------|--|---|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 47 | 43 | 32 | 31 |
| Units: Months | | | | |
| median (confidence interval 95%) | 16.72 (13.50 to 20.24) | 19.58 (14.75 to 29.37) | 11.04 (9.53 to 22.51) | 15.57 (14.26 to 9999999) |

Statistical analyses

| | |
|----------------------------|---|
| Statistical analysis title | Cohort I: Cobimetinib vs. Placebo |
| Comparison groups | Cohort I: Cobimetinib, Paclitaxel v Cohort I: Placebo, Paclitaxel |

| | |
|---|-------------------|
| Number of subjects included in analysis | 90 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.5912 |
| Method | Logrank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 1.18 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.65 |
| upper limit | 2.13 |

Secondary: Cohort I: Percentage of Participants With Confirmed OR (PR or CR), as Determined by the Investigator Using RECIST v1.1

| | |
|-----------------|---|
| End point title | Cohort I: Percentage of Participants With Confirmed OR (PR or CR), as Determined by the Investigator Using RECIST v1.1 ^[5] |
|-----------------|---|

End point description:

OR was defined as the rate of a PR or CR occurring after randomization and confirmed ≥ 28 days later as determined by the investigator using RECIST v1.1. As per RECIST v1.1, CR is defined as the disappearance of all target lesions. Any pathological lymph nodes (whether target or nontarget) must have reduction in short axis to < 10 mm. PR is defined as at least a 30% decrease in the sum of diameters of all target and new measurable lesions. Data were only collected from participants in the Cohort I Expansion Stage (Cohort I: Cobimetinib, Paclitaxel, Cohort I: Placebo, Paclitaxel) for this outcome measure. ITT population was defined as all enrolled participants, whether or not the assigned study treatment was received.

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

End point timeframe:

Randomization up to disease progression or relapse, whichever occurs first (up to approximately 2 years)

Notes:

[5] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: This analysis was only performed on Cohort I and hence why not all arms are presented.

| End point values | Cohort I: Cobimetinib, Paclitaxel | Cohort I: Placebo, Paclitaxel | | |
|-----------------------------------|---|-------------------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 47 | 43 | | |
| Units: Percentage of participants | | | | |
| number (not applicable) | | | | |
| Responders | 38.3 | 20.9 | | |
| Non-Responders | 61.7 | 79.1 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Cohort I, II, III: Duration of Response (DOR), as Determined by the

Investigator Using RECIST v1.1

| | |
|-----------------|--|
| End point title | Cohort I, II, III: Duration of Response (DOR), as Determined by the Investigator Using RECIST v1.1 |
|-----------------|--|

End point description:

DOR was defined as the time from the first occurrence of a documented objective response to the time of relapse, as determined by the investigator using RECIST v1.1 or death from any cause during the study, whichever occurred first. ITT population was defined as all enrolled participants, whether or not the assigned study treatment was received. 9999999 = The upper limit of 95% CI was not evaluable due to insufficient events observed.

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

End point timeframe:

Time from the first occurrence of documented objective response to time of relapse or death, whichever occurs first (up to approximately 6.5 years)

| End point values | Cohort I: Safety Run-In | Cohort I: Cobimetinib, Paclitaxel | Cohort I: Placebo, Paclitaxel | Cohort II: Cobimetinib, Paclitaxel, Atez- olizumab |
|----------------------------------|----------------------------|---|-------------------------------------|---|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 16 | 47 | 43 | 32 |
| Units: Months | | | | |
| median (confidence interval 95%) | 39.29 (23.14 to 56.29) | 23.14 (16.14 to 26.57) | 24.14 (17.14 to 9999999) | 5.78 (4.44 to 16.33) |

| End point values | Cohort III: Cobimetinib, Nab-Paclitaxel, Atezolizumab | | | |
|----------------------------------|--|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 31 | | | |
| Units: Months | | | | |
| median (confidence interval 95%) | 11.42 (5.78 to 17.94) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Cohort I, II, III: Percentage of Participants With Unconfirmed Overall Response (OR_uc) (Unconfirmed PR or CR), as Determined by the Investigator Using RECIST v1.1

| | |
|-----------------|--|
| End point title | Cohort I, II, III: Percentage of Participants With Unconfirmed Overall Response (OR_uc) (Unconfirmed PR or CR), as Determined by the Investigator Using RECIST v1.1 ^[6] |
|-----------------|--|

End point description:

ORR_uc (ORR confirmation not required) was defined as the rate of a PR or CR occurring after randomization as determined by the investigator using RECIST v1.1, confirmation not required. As per RECIST v1.1, CR is defined as the disappearance of all target lesions. Any pathological lymph nodes (whether target or nontarget) must have reduction in short axis to <10 mm. PR is defined as at least a 30% decrease in the sum of diameters of all target and new measurable lesions. Data were only

collected from participants in the Cohort I Expansion Stage (Cohort I: Cobimetinib, Paclitaxel, Cohort I: Placebo, Paclitaxel) along with the Cohort II and III for this outcome measure. ITT population was defined as all enrolled participants, whether or not the assigned study treatment was received.

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

End point timeframe:

Randomization up to disease progression or relapse, whichever occurs first (up to approximately 6.5 years)

Notes:

[6] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: The analysis excludes the Safety Run-In cohort.

| End point values | Cohort I: Cobimetinib, Paclitaxel | Cohort I: Placebo, Paclitaxel | Cohort II: Cobimetinib, Paclitaxel, Atez- olizumab | Cohort III: Cobimetinib, Nab-Paclitaxel, Atezolizumab |
|-----------------------------------|---|-------------------------------------|---|--|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 47 | 43 | 32 | 31 |
| Units: Percentage of participants | | | | |
| number (not applicable) | | | | |
| Responders | 42.6 | 25.6 | 46.9 | 45.2 |
| Non-Responders | 57.4 | 74.4 | 53.1 | 54.8 |

Statistical analyses

No statistical analyses for this end point

Secondary: Cohort II, III: Progression-Free Survival, as Determined by Investigator Using RECIST v1.1

| | |
|-----------------|---|
| End point title | Cohort II, III: Progression-Free Survival, as Determined by Investigator Using RECIST v1.1 ^[7] |
|-----------------|---|

End point description:

PFS was defined as the time from randomization to the first occurrence of disease progression or relapse, as determined by the investigator, using RECIST v1.1. As per RECIST v1.1, PD is defined as at least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (nadir), including baseline. In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. The appearance of one or more new lesions is also considered progression. ITT population was defined as all enrolled participants, whether or not the assigned study treatment was received.

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

End point timeframe:

Randomization up to disease progression or relapse, whichever occurs first (up to approximately 6.5 years)

Notes:

[7] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: This analysis was only performed on Cohorts II and III and hence why not all arms are presented.

| End point values | Cohort II: Cobimetinib, Paclitaxel, Atezolizumab | Cohort III: Cobimetinib, Nab-Paclitaxel, Atezolizumab | | |
|----------------------------------|--|---|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 32 | 31 | | |
| Units: Months | | | | |
| median (confidence interval 95%) | 3.75 (3.02 to 7.29) | 7.66 (3.65 to 11.04) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Cohort I, II, III: Percentage of Participants With Adverse Events (AEs)

| | |
|--|---|
| End point title | Cohort I, II, III: Percentage of Participants With Adverse Events (AEs) |
| End point description: The safety-evaluable population was defined as participants who received any amount of any study drug. | |
| End point type | Secondary |
| End point timeframe: Randomization up to end of study (up to approximately 6.5 years) | |

| End point values | Cohort I: Safety Run-In | Cohort I: Cobimetinib, Paclitaxel | Cohort I: Placebo, Paclitaxel | Cohort II: Cobimetinib, Paclitaxel, Atezolizumab |
|-----------------------------------|-------------------------|-----------------------------------|-------------------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 16 | 47 | 43 | 32 |
| Units: Percentage of participants | | | | |
| number (not applicable) | 93.8 | 97.9 | 100.0 | 100.0 |

| End point values | Cohort III: Cobimetinib, Nab-Paclitaxel, Atezolizumab | | | |
|-----------------------------------|---|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 31 | | | |
| Units: Percentage of participants | | | | |
| number (not applicable) | 100.0 | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Cohort I, II, III: Maximum Plasma Concentration (Cmax) of Cobimetinib

| | |
|-----------------|--|
| End point title | Cohort I, II, III: Maximum Plasma Concentration (Cmax) of Cobimetinib ^[8] |
|-----------------|--|

End point description:

The pharmacokinetic (PK) population included all participants with evaluable PK data who received at least one dose of study drug.

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

End point timeframe:

Safety Run-In: Predose (Hour [Hr] 0) on Cycle (Cy) 1 Day (D) 8; predose (Hr 0), 0.5, 1, 2, 4, 6 Hr postdose (2, 4 Hr postdose for Cohorts II, III) on Cy1 D15; Expansion: predose (Hr 0), 1-4 Hr postdose on Cy1 D15; predose (Hr 0) on Cy2 D15 (Cy=28 days)

Notes:

[8] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: This analysis was only performed on the arms with Cobimetinib and hence why not all arms are presented.

| End point values | Cohort I: Safety Run-In | Cohort I: Cobimetinib, Paclitaxel | Cohort II: Cobimetinib, Paclitaxel, Atez- olizumab | Cohort III: Cobimetinib, Nab-Paclitaxel, Atezolizumab |
|---|----------------------------|---|---|--|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 11 | 8 | 17 | 15 |
| Units: Nanograms per millilitre (ng/mL) | | | | |
| geometric mean (geometric coefficient of variation) | 285 (± 62.2) | 266 (± 82.0) | 213 (± 68.0) | 407 (± 90.7) |

Statistical analyses

No statistical analyses for this end point

Secondary: Cohort I, II, III: Minimum Plasma Concentration (Cmin) of Cobimetinib

| | |
|-----------------|--|
| End point title | Cohort I, II, III: Minimum Plasma Concentration (Cmin) of Cobimetinib ^[9] |
|-----------------|--|

End point description:

The PK population included all participants with evaluable PK data who received at least one dose of study drug.

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

End point timeframe:

Safety Run-In: Predose (Hr 0) on Cy 1 D8; predose (Hr 0), 0.5, 1, 2, 4, 6 Hr postdose (2, 4 Hr postdose for Cohorts II, III) on Cy1 D15; Expansion: predose (Hr 0), 1-4 Hr postdose on Cy1 D15; predose (Hr 0) on Cy2 D15 (Cy=28 days)

Notes:

[9] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: This analysis was only performed on the arms with Cobimetinib and hence why not all arms are presented.

| End point values | Cohort I: Safety Run-In | Cohort I: Cobimetinib, Paclitaxel | Cohort II: Cobimetinib, Paclitaxel, Atez- olizumab | Cohort III: Cobimetinib, Nab-Paclitaxel, Atezolizumab |
|---|----------------------------|---|---|--|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 13 | 38 | 14 | 13 |
| Units: ng/mL | | | | |
| geometric mean (geometric coefficient of variation) | 65.6 (\pm 1279.5) | 130 (\pm 190.7) | 138 (\pm 79.0) | 136 (\pm 67.2) |

Statistical analyses

No statistical analyses for this end point

Secondary: Secondary: Cohort I: Area Under the Concentration-Time Curve From Time Zero to Dosing Interval (AUC0-tau; Total Exposure) of Cobimetinib

| | |
|-----------------|--|
| End point title | Secondary: Cohort I: Area Under the Concentration-Time Curve From Time Zero to Dosing Interval (AUC0-tau; Total Exposure) of Cobimetinib ^[10] |
|-----------------|--|

End point description:

The PK population included all participants with evaluable PK data who received at least one dose of study drug. Data were only collected from participants in the Cohort I: Safety Run-In stage for this outcome measure.

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

End point timeframe:

Safety Run-In: Predose (Hr 0) on Cy 1 D8; predose (Hr 0), 0.5, 1, 2, 4, 6 Hr postdose on Cy1 D15; Expansion: predose (Hr 0), 1-4 Hr postdose on Cy1 D15 (Cy=28 days)

Notes:

[10] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: This analysis was only performed on the arms with Cobimetinib and hence why not all arms are presented.

| End point values | Cohort I: Safety Run-In | | | |
|---|----------------------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 11 | | | |
| Units: Nanograms/milliliter/hour (hr*ng/mL) | | | | |
| geometric mean (geometric coefficient of variation) | 1620 (\pm 80.0) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Cohort I, II: Cmax of Paclitaxel

| | |
|-----------------|--|
| End point title | Cohort I, II: Cmax of Paclitaxel ^[11] |
|-----------------|--|

End point description:

The PK population included all participants with evaluable PK data who received at least one dose of study drug. Data were only collected from Cohort I: Safety Run-In and Cohort II participants for this

outcome measure.

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

End point timeframe:

Safety Run-In: Predose (Hr 0) on Cy1 D8; predose (Hr 0), 0.5, 1, 2, 4, and 6 Hr postdose (2, 4 Hr postdose for Cohort II) (infusion duration: 1 Hr) on Cy1 D15 (Cy=28 days)

Notes:

[11] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: This analysis was only performed on the arms with Paclitaxel and hence why not all arms are presented.

| End point values | Cohort I: Safety Run-In | Cohort II:Cobimetinib, Paclitaxel,Atez olizumab | | |
|---|----------------------------|---|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 11 | 14 | | |
| Units: ng/mL | | | | |
| geometric mean (geometric coefficient of variation) | 1770 (\pm 553.4) | 283 (\pm 490.9) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Cohort I, II: Cmin of Paclitaxel

| | |
|-----------------|--|
| End point title | Cohort I, II: Cmin of Paclitaxel ^[12] |
|-----------------|--|

End point description:

The PK population included all participants with evaluable PK data who received at least one dose of study drug. Data were only collected from Cohort I: Safety Run-In and Cohort II participants for this outcome measure.

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

End point timeframe:

Safety Run-In: Predose (Hr 0) on Cy1 D8; predose (Hr 0), 0.5, 1, 2, 4, and 6 Hr postdose (2, 4 Hr postdose for Cohort II) (infusion duration: 1 Hr) on Cy1 D15 (Cy=28 days)

Notes:

[12] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: This analysis was only performed on the arms with Paclitaxel and hence why not all arms are presented.

| End point values | Cohort I: Safety Run-In | Cohort II:Cobimetinib, Paclitaxel,Atez olizumab | | |
|---|----------------------------|---|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 13 | 15 | | |
| Units: ng/mL | | | | |
| geometric mean (geometric coefficient of variation) | 1.40 (\pm 89.9) | 1.26 (\pm 53.3) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Cohort I: AUC0-tau of Paclitaxel

| | |
|-----------------|--|
| End point title | Cohort I: AUC0-tau of Paclitaxel ^[13] |
|-----------------|--|

End point description:

The PK population included all participants with evaluable PK data who received at least one dose of study drug. Data were only collected from participants in the Cohort I: Safety Run-In stage for this outcome measure.

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

End point timeframe:

Safety Run-In: Predose (Hr 0) on Cy1 D8; predose (Hr 0), 0.5, 1, 2, 4, and 6 Hr postdose (infusion duration: 1 Hr) on Cy1 D15 (Cy=28 days)

Notes:

[13] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: This analysis was only performed on the arms with Paclitaxel and hence why not all arms are presented.

| End point values | Cohort I: Safety Run-In | | | |
|---|----------------------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 10 | | | |
| Units: hr*ng/mL | | | | |
| geometric mean (geometric coefficient of variation) | 4220 (\pm 310.4) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Cohort III: Cmax of Nab-Paclitaxel

| | |
|-----------------|--|
| End point title | Cohort III: Cmax of Nab-Paclitaxel ^[14] |
|-----------------|--|

End point description:

The PK population included all participants with evaluable PK data who received at least one dose of study drug.

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

End point timeframe:

Safety Run-In: Predose (Hr 0) on Cy1 D8; predose (Hr 0), 2, 4 Hr postdose (infusion duration: 30 minutes) on Cy1 D15 (Cy=28 days)

Notes:

[14] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: This analysis was only performed on the arms with Nab-Paclitaxel and hence why not all

arms are presented.

| | | | | |
|---|--|--|--|--|
| End point values | Cohort III: Cobimetinib, Nab-Paclitaxel, Atezolizumab | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 13 | | | |
| Units: ng/mL | | | | |
| geometric mean (geometric coefficient of variation) | 277 (\pm 658.5) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Cohort III: Cmin of Nab-Paclitaxel

| | |
|------------------------|---|
| End point title | Cohort III: Cmin of Nab-Paclitaxel ^[15] |
| End point description: | The PK population included all participants with evaluable PK data who received at least one dose of study drug. |
| End point type | Secondary |
| End point timeframe: | Safety Run-In: Predose (Hr 0) on Cy1 D8; predose (Hr 0), 2, 4 Hr postdose (infusion duration: 30 minutes) on Cy1 D15 (Cy=28 days) |

Notes:

[15] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: This analysis was only performed on the arms with Nab-Paclitaxel and hence why not all arms are presented.

| | | | | |
|---|--|--|--|--|
| End point values | Cohort III: Cobimetinib, Nab-Paclitaxel, Atezolizumab | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 12 | | | |
| Units: ng/mL | | | | |
| geometric mean (geometric coefficient of variation) | 2.05 (\pm 173.9) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Cohort III: AUC0-tau of Nab-Paclitaxel

| | |
|-----------------|--|
| End point title | Cohort III: AUC0-tau of Nab-Paclitaxel ^[16] |
|-----------------|--|

End point description:

The PK population included all participants with evaluable PK data who received at least one dose of study drug. This outcome measure could not be estimated because only sparse PK samples were collected.

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

End point timeframe:

Safety Run-In: Predose (Hr 0) on Cy1 D8; predose (Hr 0), 2, 4 Hr postdose (infusion duration: 30 minutes) on Cy1 D15 (Cy=28 days)

Notes:

[16] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: This analysis was only performed on the arms with Nab-Paclitaxel and hence why not all arms are presented.

| | | | | |
|---|--|--|--|--|
| End point values | Cohort III: Cobimetinib, Nab-Paclitaxel, Atezolizumab | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 0 ^[17] | | | |
| Units: hr*ng/mL | | | | |
| geometric mean (geometric coefficient of variation) | () | | | |

Notes:

[17] - This outcome measure could not be estimated because only sparse PK samples were collected.

Statistical analyses

No statistical analyses for this end point

Secondary: Cohort II, III: Cmax (in Serum) of Atezolizumab

| | |
|-----------------|---|
| End point title | Cohort II, III: Cmax (in Serum) of Atezolizumab ^[18] |
|-----------------|---|

End point description:

The PK population included all participants with evaluable PK data who received at least one dose of study drug

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

End point timeframe:

Safety Run-In, Expansion: Predose (Hr0), 0.5Hr postdose (infusion duration:1Hr) on D1 of Cy1, 3; predose (Hr0) on D1 of Cy2, 4, 8, every 8 Cy up to end of treatment (EOT); 120 days after EOT (approximately 5.25 years) (Cy=28 days)

Notes:

[18] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: This analysis was only performed on the arms with Atezolizumab and hence why not all arms are presented.

| | | | | |
|---|--|---|--|--|
| End point values | Cohort II: Cobimetinib, Paclitaxel, Atezolizumab | Cohort III: Cobimetinib, Nab-Paclitaxel, Atezolizumab | | |
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 10 | 10 | | |
| Units: ng/mL | | | | |
| geometric mean (geometric coefficient of variation) | 346 (± 48.3) | 374 (± 38.8) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Cohort II, III: Cmin (in Serum) of Atezolizumab

| | |
|-----------------|---|
| End point title | Cohort II, III: Cmin (in Serum) of Atezolizumab ^[19] |
|-----------------|---|

End point description:

The PK population included all participants with evaluable PK data who received at least one dose of study drug

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

End point timeframe:

Safety Run-In, Expansion: Predose (Hr 0), 0.5 Hr postdose (infusion duration: 1 Hr) on D1 of Cy1, 3; predose (Hr 0) on D1 of Cy2, 4, 8, every 8 Cy up to EOT; 120 days after EOT (approximately 5.5 years) (Cy=28 days)

Notes:

[19] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: This analysis was only performed on the arms with Atezolizumab and hence why not all arms are presented.

| End point values | Cohort II: Cobimetinib, Paclitaxel, Atezolizumab | Cohort III: Cobimetinib, Nab-Paclitaxel, Atezolizumab | | |
|---|--|---|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 10 | 10 | | |
| Units: ng/mL | | | | |
| geometric mean (geometric coefficient of variation) | 144 (± 34.6) | 109 (± 89.9) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Cohort II, III: AUC0-tau (in Serum) of Atezolizumab

| | |
|-----------------|---|
| End point title | Cohort II, III: AUC0-tau (in Serum) of Atezolizumab ^[20] |
|-----------------|---|

End point description:

The PK population included all participants with evaluable PK data who received at least one dose of study drug. This outcome measure could not be estimated because only sparse PK samples were collected.

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

End point timeframe:

Safety Run-In, Expansion: Predose (Hr 0), 0.5 Hr postdose (infusion duration: 1 Hr) on D1 of Cy1, 3; predose (Hr 0) on D1 of Cy2, 4, 8, every 8 Cy up to EOT (approximately 5.5 years); 120 days after EOT (approximately 5.5 years) (Cy=28 days)

Notes:

[20] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: This analysis was only performed on the arms with Atezolizumab and hence why not all arms are presented.

| End point values | Cohort II: Cobimetinib, Paclitaxel, Atezolizumab | Cohort III: Cobimetinib, Nab-Paclitaxel, Atezolizumab | | |
|---|--|---|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 0 ^[21] | 0 ^[22] | | |
| Units: hr*ng/mL | | | | |
| geometric mean (geometric coefficient of variation) | () | () | | |

Notes:

[21] - This outcome measure could not be estimated because only sparse PK samples were collected.

[22] - This outcome measure could not be estimated because only sparse PK samples were collected.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From randomization up until 6.5 years

Adverse event reporting additional description:

The number of deaths displays information from the ITT population. One participant in Cohort III didn't receive treatment and is not counted in the AE tables. The safety population was defined as participants who received any amount of any study drug. The serious and non-serious AEs are reported with data from this population.

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

Dictionary used

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

| | |
|--------------------|------|
| Dictionary version | 24.0 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|-------------------------|
| Reporting group title | Cohort I: Safety Run-In |
|-----------------------|-------------------------|

Reporting group description:

Participants received cobimetinib plus paclitaxel until 12 participants completed one cycle of study treatment (28 days).

| | |
|-----------------------|-------------------------------|
| Reporting group title | Cohort I: Placebo, Paclitaxel |
|-----------------------|-------------------------------|

Reporting group description:

Participants received a combination of cobimetinib placebo plus paclitaxel in 28-day cycles until disease progression, unacceptable toxicity, investigator decision, death, withdrawal of consent, or completion of study.

| | |
|-----------------------|-----------------------------------|
| Reporting group title | Cohort I: Cobimetinib, Paclitaxel |
|-----------------------|-----------------------------------|

Reporting group description:

Participants received a combination of cobimetinib plus paclitaxel in 28-day cycles until disease progression, unacceptable toxicity, investigator decision, death, withdrawal of consent, or completion of study.

| | |
|-----------------------|--|
| Reporting group title | Cohort II: Cobimetinib, Paclitaxel, Atezolizumab |
|-----------------------|--|

Reporting group description:

Participants received cobimetinib plus paclitaxel plus atezolizumab in 28-day cycles until disease progression, unacceptable toxicity, investigator decision, death, withdrawal of consent, or completion of study.

| | |
|-----------------------|---|
| Reporting group title | Cohort III: Cobimetinib, Nab-Paclitaxel, Atezolizumab |
|-----------------------|---|

Reporting group description:

Participants received cobimetinib plus nab-paclitaxel plus atezolizumab until disease progression, unacceptable toxicity, investigator decision, death, withdrawal of consent, or completion of study.

| Serious adverse events | Cohort I: Safety Run-In | Cohort I: Placebo, Paclitaxel | Cohort I: Cobimetinib, Paclitaxel |
|---|-------------------------|-------------------------------|-----------------------------------|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 6 / 16 (37.50%) | 8 / 43 (18.60%) | 17 / 47 (36.17%) |
| number of deaths (all causes) | 7 | 29 | 32 |
| number of deaths resulting from adverse events | 0 | 0 | 0 |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) TUMOUR HAEMORRHAGE | | | |

| | | | |
|--|-----------------|----------------|-----------------|
| subjects affected / exposed ^[1] | 0 / 16 (0.00%) | 0 / 43 (0.00%) | 1 / 47 (2.13%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vascular disorders | | | |
| ORTHOSTATIC HYPOTENSION | | | |
| subjects affected / exposed ^[2] | 1 / 16 (6.25%) | 0 / 43 (0.00%) | 0 / 47 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| EMBOLISM | | | |
| subjects affected / exposed ^[3] | 0 / 16 (0.00%) | 0 / 43 (0.00%) | 0 / 47 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| EMBOLISM VENOUS | | | |
| subjects affected / exposed ^[4] | 0 / 16 (0.00%) | 1 / 43 (2.33%) | 0 / 47 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| General disorders and administration site conditions | | | |
| FATIGUE | | | |
| subjects affected / exposed ^[5] | 0 / 16 (0.00%) | 1 / 43 (2.33%) | 0 / 47 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| PYREXIA | | | |
| subjects affected / exposed ^[6] | 2 / 16 (12.50%) | 0 / 43 (0.00%) | 6 / 47 (12.77%) |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 0 | 2 / 6 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| ASTHENIA | | | |
| subjects affected / exposed ^[7] | 1 / 16 (6.25%) | 1 / 43 (2.33%) | 0 / 47 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| MUCOSAL INFLAMMATION | | | |
| subjects affected / exposed ^[8] | 0 / 16 (0.00%) | 0 / 43 (0.00%) | 0 / 47 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|----------------|----------------|----------------|
| Respiratory, thoracic and mediastinal disorders | | | |
| LUNG INFILTRATION | | | |
| subjects affected / exposed ^[9] | 0 / 16 (0.00%) | 0 / 43 (0.00%) | 0 / 47 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| DYSPNOEA | | | |
| subjects affected / exposed ^[10] | 0 / 16 (0.00%) | 1 / 43 (2.33%) | 2 / 47 (4.26%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 3 / 3 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| EPISTAXIS | | | |
| subjects affected / exposed ^[11] | 0 / 16 (0.00%) | 0 / 43 (0.00%) | 0 / 47 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| PNEUMONITIS | | | |
| subjects affected / exposed ^[12] | 0 / 16 (0.00%) | 0 / 43 (0.00%) | 1 / 47 (2.13%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| PLEURITIC PAIN | | | |
| subjects affected / exposed ^[13] | 0 / 16 (0.00%) | 0 / 43 (0.00%) | 1 / 47 (2.13%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| RESPIRATORY FAILURE | | | |
| subjects affected / exposed ^[14] | 0 / 16 (0.00%) | 0 / 43 (0.00%) | 1 / 47 (2.13%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| PULMONARY EMBOLISM | | | |
| subjects affected / exposed ^[15] | 0 / 16 (0.00%) | 0 / 43 (0.00%) | 0 / 47 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Investigations | | | |
| BLOOD CREATININE INCREASED | | | |
| subjects affected / exposed ^[16] | 0 / 16 (0.00%) | 0 / 43 (0.00%) | 0 / 47 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|----------------|----------------|----------------|
| Cardiac disorders | | | |
| CARDIAC ARREST | | | |
| subjects affected / exposed ^[17] | 0 / 16 (0.00%) | 0 / 43 (0.00%) | 1 / 47 (2.13%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| MITRAL VALVE INCOMPETENCE | | | |
| subjects affected / exposed ^[18] | 1 / 16 (6.25%) | 0 / 43 (0.00%) | 0 / 47 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| CARDIAC FAILURE | | | |
| subjects affected / exposed ^[19] | 0 / 16 (0.00%) | 1 / 43 (2.33%) | 0 / 47 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Nervous system disorders | | | |
| BRAIN OEDEMA | | | |
| subjects affected / exposed ^[20] | 1 / 16 (6.25%) | 0 / 43 (0.00%) | 0 / 47 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| ENCEPHALOPATHY | | | |
| subjects affected / exposed ^[21] | 0 / 16 (0.00%) | 0 / 43 (0.00%) | 0 / 47 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| SYNCOPE | | | |
| subjects affected / exposed ^[22] | 0 / 16 (0.00%) | 0 / 43 (0.00%) | 1 / 47 (2.13%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| PRESYNCOPE | | | |
| subjects affected / exposed ^[23] | 1 / 16 (6.25%) | 0 / 43 (0.00%) | 0 / 47 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| OPTIC NEURITIS | | | |
| subjects affected / exposed ^[24] | 0 / 16 (0.00%) | 0 / 43 (0.00%) | 0 / 47 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|----------------|----------------|----------------|
| PARTIAL SEIZURES | | | |
| subjects affected / exposed ^[25] | 0 / 16 (0.00%) | 0 / 43 (0.00%) | 0 / 47 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Blood and lymphatic system disorders | | | |
| NEUTROPENIA | | | |
| subjects affected / exposed ^[26] | 0 / 16 (0.00%) | 0 / 43 (0.00%) | 1 / 47 (2.13%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| FEBRILE NEUTROPENIA | | | |
| subjects affected / exposed ^[27] | 0 / 16 (0.00%) | 1 / 43 (2.33%) | 1 / 47 (2.13%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Eye disorders | | | |
| PAPILLOEDEMA | | | |
| subjects affected / exposed ^[28] | 0 / 16 (0.00%) | 0 / 43 (0.00%) | 0 / 47 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrointestinal disorders | | | |
| DIARRHOEA | | | |
| subjects affected / exposed ^[29] | 0 / 16 (0.00%) | 0 / 43 (0.00%) | 1 / 47 (2.13%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| VOMITING | | | |
| subjects affected / exposed ^[30] | 0 / 16 (0.00%) | 0 / 43 (0.00%) | 0 / 47 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| INTESTINAL OBSTRUCTION | | | |
| subjects affected / exposed ^[31] | 0 / 16 (0.00%) | 0 / 43 (0.00%) | 0 / 47 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| NAUSEA | | | |

| | | | |
|--|----------------|----------------|----------------|
| subjects affected / exposed ^[32] | 0 / 16 (0.00%) | 0 / 43 (0.00%) | 0 / 47 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| ABDOMINAL PAIN | | | |
| subjects affected / exposed ^[33] | 0 / 16 (0.00%) | 0 / 43 (0.00%) | 0 / 47 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| GASTRIC PERFORATION | | | |
| subjects affected / exposed ^[34] | 0 / 16 (0.00%) | 0 / 43 (0.00%) | 0 / 47 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Skin and subcutaneous tissue disorders | | | |
| RASH | | | |
| subjects affected / exposed ^[35] | 0 / 16 (0.00%) | 0 / 43 (0.00%) | 0 / 47 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| RASH ERYTHEMATOUS | | | |
| subjects affected / exposed ^[36] | 0 / 16 (0.00%) | 0 / 43 (0.00%) | 0 / 47 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Musculoskeletal and connective tissue disorders | | | |
| BACK PAIN | | | |
| subjects affected / exposed ^[37] | 0 / 16 (0.00%) | 1 / 43 (2.33%) | 0 / 47 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infections and infestations | | | |
| PERIORBITAL CELLULITIS | | | |
| subjects affected / exposed ^[38] | 0 / 16 (0.00%) | 0 / 43 (0.00%) | 0 / 47 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| HERPES ZOSTER | | | |
| subjects affected / exposed ^[39] | 0 / 16 (0.00%) | 0 / 43 (0.00%) | 1 / 47 (2.13%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|----------------|----------------|----------------|
| SEPSIS | | | |
| subjects affected / exposed ^[40] | 0 / 16 (0.00%) | 0 / 43 (0.00%) | 1 / 47 (2.13%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| PNEUMONIA | | | |
| subjects affected / exposed ^[41] | 0 / 16 (0.00%) | 0 / 43 (0.00%) | 2 / 47 (4.26%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 2 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| UPPER RESPIRATORY TRACT INFECTION | | | |
| subjects affected / exposed ^[42] | 0 / 16 (0.00%) | 0 / 43 (0.00%) | 0 / 47 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| PNEUMOCYSTIS JIROVECI PNEUMONIA | | | |
| subjects affected / exposed ^[43] | 0 / 16 (0.00%) | 0 / 43 (0.00%) | 0 / 47 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| PYELONEPHRITIS ACUTE | | | |
| subjects affected / exposed ^[44] | 0 / 16 (0.00%) | 0 / 43 (0.00%) | 1 / 47 (2.13%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| KIDNEY INFECTION | | | |
| subjects affected / exposed ^[45] | 0 / 16 (0.00%) | 0 / 43 (0.00%) | 0 / 47 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| CELLULITIS | | | |
| subjects affected / exposed ^[46] | 0 / 16 (0.00%) | 0 / 43 (0.00%) | 4 / 47 (8.51%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 6 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| MASTITIS | | | |
| subjects affected / exposed ^[47] | 0 / 16 (0.00%) | 0 / 43 (0.00%) | 0 / 47 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| ERYSIPELAS | | | |

| | | | |
|---|----------------|----------------|----------------|
| subjects affected / exposed ^[48] | 1 / 16 (6.25%) | 0 / 43 (0.00%) | 1 / 47 (2.13%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| URINARY TRACT INFECTION | | | |
| subjects affected / exposed ^[49] | 0 / 16 (0.00%) | 1 / 43 (2.33%) | 3 / 47 (6.38%) |
| occurrences causally related to treatment / all | 0 / 0 | 2 / 2 | 1 / 5 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| STREPTOCOCCAL SEPSIS | | | |
| subjects affected / exposed ^[50] | 0 / 16 (0.00%) | 0 / 43 (0.00%) | 1 / 47 (2.13%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Metabolism and nutrition disorders | | | |
| HYPOKALAEMIA | | | |
| subjects affected / exposed ^[51] | 0 / 16 (0.00%) | 1 / 43 (2.33%) | 0 / 47 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| DECREASED APPETITE | | | |
| subjects affected / exposed ^[52] | 0 / 16 (0.00%) | 0 / 43 (0.00%) | 0 / 47 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| Serious adverse events | Cohort II: Cobimetinib,Paclitaxel,Atezolizumab | Cohort III: Cobimetinib, Nab-Paclitaxel, Atezolizumab | |
|---|---|--|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 16 / 32 (50.00%) | 15 / 31 (48.39%) | |
| number of deaths (all causes) | 23 | 14 | |
| number of deaths resulting from adverse events | 0 | 0 | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| TUMOUR HAEMORRHAGE | | | |
| subjects affected / exposed ^[1] | 0 / 32 (0.00%) | 0 / 30 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vascular disorders | | | |
| ORTHOSTATIC HYPOTENSION | | | |

| | | | |
|--|-----------------|----------------|--|
| subjects affected / exposed ^[2] | 0 / 32 (0.00%) | 0 / 30 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| EMBOLISM | | | |
| subjects affected / exposed ^[3] | 1 / 32 (3.13%) | 0 / 30 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| EMBOLISM VENOUS | | | |
| subjects affected / exposed ^[4] | 0 / 32 (0.00%) | 0 / 30 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| General disorders and administration site conditions | | | |
| FATIGUE | | | |
| subjects affected / exposed ^[5] | 0 / 32 (0.00%) | 0 / 30 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| PYREXIA | | | |
| subjects affected / exposed ^[6] | 4 / 32 (12.50%) | 2 / 30 (6.67%) | |
| occurrences causally related to treatment / all | 2 / 4 | 1 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| ASTHENIA | | | |
| subjects affected / exposed ^[7] | 0 / 32 (0.00%) | 0 / 30 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| MUCOSAL INFLAMMATION | | | |
| subjects affected / exposed ^[8] | 2 / 32 (6.25%) | 0 / 30 (0.00%) | |
| occurrences causally related to treatment / all | 2 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| LUNG INFILTRATION | | | |
| subjects affected / exposed ^[9] | 1 / 32 (3.13%) | 0 / 30 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |

| | | | |
|---|----------------|----------------|--|
| DYSпноEA | | | |
| subjects affected / exposed ^[10] | 1 / 32 (3.13%) | 0 / 30 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| EPISTAXIS | | | |
| subjects affected / exposed ^[11] | 0 / 32 (0.00%) | 1 / 30 (3.33%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| PNEUMONITIS | | | |
| subjects affected / exposed ^[12] | 0 / 32 (0.00%) | 0 / 30 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| PLEURITIC PAIN | | | |
| subjects affected / exposed ^[13] | 0 / 32 (0.00%) | 0 / 30 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| RESPIRATORY FAILURE | | | |
| subjects affected / exposed ^[14] | 1 / 32 (3.13%) | 0 / 30 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| PULMONARY EMBOLISM | | | |
| subjects affected / exposed ^[15] | 1 / 32 (3.13%) | 0 / 30 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Investigations | | | |
| BLOOD CREATININE INCREASED | | | |
| subjects affected / exposed ^[16] | 1 / 32 (3.13%) | 0 / 30 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac disorders | | | |
| CARDIAC ARREST | | | |
| subjects affected / exposed ^[17] | 0 / 32 (0.00%) | 0 / 30 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|----------------|----------------|--|
| MITRAL VALVE INCOMPETENCE | | | |
| subjects affected / exposed ^[18] | 0 / 32 (0.00%) | 0 / 30 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| CARDIAC FAILURE | | | |
| subjects affected / exposed ^[19] | 0 / 32 (0.00%) | 0 / 30 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nervous system disorders | | | |
| BRAIN OEDEMA | | | |
| subjects affected / exposed ^[20] | 0 / 32 (0.00%) | 0 / 30 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| ENCEPHALOPATHY | | | |
| subjects affected / exposed ^[21] | 0 / 32 (0.00%) | 1 / 30 (3.33%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| SYNCOPE | | | |
| subjects affected / exposed ^[22] | 0 / 32 (0.00%) | 0 / 30 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| PRESYNCOPE | | | |
| subjects affected / exposed ^[23] | 0 / 32 (0.00%) | 0 / 30 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| OPTIC NEURITIS | | | |
| subjects affected / exposed ^[24] | 1 / 32 (3.13%) | 0 / 30 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| PARTIAL SEIZURES | | | |
| subjects affected / exposed ^[25] | 0 / 32 (0.00%) | 1 / 30 (3.33%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Blood and lymphatic system disorders | | | |

| | | | |
|---|----------------|----------------|--|
| NEUTROPENIA | | | |
| subjects affected / exposed ^[26] | 0 / 32 (0.00%) | 0 / 30 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| FEBRILE NEUTROPENIA | | | |
| subjects affected / exposed ^[27] | 1 / 32 (3.13%) | 1 / 30 (3.33%) | |
| occurrences causally related to treatment / all | 1 / 1 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Eye disorders | | | |
| PAPILLOEDEMA | | | |
| subjects affected / exposed ^[28] | 1 / 32 (3.13%) | 0 / 30 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal disorders | | | |
| DIARRHOEA | | | |
| subjects affected / exposed ^[29] | 2 / 32 (6.25%) | 2 / 30 (6.67%) | |
| occurrences causally related to treatment / all | 2 / 2 | 2 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| VOMITING | | | |
| subjects affected / exposed ^[30] | 1 / 32 (3.13%) | 0 / 30 (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 ^[31] | 0 / 32 (0.00%) | 1 / 30 (3.33%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| NAUSEA | | | |
| subjects affected / exposed ^[32] | 1 / 32 (3.13%) | 0 / 30 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| ABDOMINAL PAIN | | | |
| subjects affected / exposed ^[33] | 1 / 32 (3.13%) | 0 / 30 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|--|----------------------------------|----------------------------------|--|
| GASTRIC PERFORATION subjects affected / exposed ^[34] occurrences causally related to treatment / all deaths causally related to treatment / all | 0 / 32 (0.00%) 0 / 0 0 / 0 | 1 / 30 (3.33%) 1 / 1 0 / 0 | |
| Skin and subcutaneous tissue disorders RASH subjects affected / exposed ^[35] occurrences causally related to treatment / all deaths causally related to treatment / all | 0 / 32 (0.00%) 0 / 0 0 / 0 | 1 / 30 (3.33%) 1 / 1 0 / 0 | |
| RASH ERYTHEMATOUS subjects affected / exposed ^[36] occurrences causally related to treatment / all deaths causally related to treatment / all | 0 / 32 (0.00%) 0 / 0 0 / 0 | 1 / 30 (3.33%) 1 / 1 0 / 0 | |
| Musculoskeletal and connective tissue disorders BACK PAIN subjects affected / exposed ^[37] occurrences causally related to treatment / all deaths causally related to treatment / all | 0 / 32 (0.00%) 0 / 0 0 / 0 | 0 / 30 (0.00%) 0 / 0 0 / 0 | |
| Infections and infestations PERIORBITAL CELLULITIS subjects affected / exposed ^[38] occurrences causally related to treatment / all deaths causally related to treatment / all | 1 / 32 (3.13%) 1 / 1 0 / 0 | 0 / 30 (0.00%) 0 / 0 0 / 0 | |
| HERPES ZOSTER subjects affected / exposed ^[39] occurrences causally related to treatment / all deaths causally related to treatment / all | 0 / 32 (0.00%) 0 / 0 0 / 0 | 0 / 30 (0.00%) 0 / 0 0 / 0 | |
| SEPSIS subjects affected / exposed ^[40] occurrences causally related to treatment / all deaths causally related to treatment / all | 0 / 32 (0.00%) 0 / 0 0 / 0 | 1 / 30 (3.33%) 1 / 1 0 / 0 | |
| PNEUMONIA | | | |

| | | | |
|---|----------------|----------------|--|
| subjects affected / exposed ^[41] | 1 / 32 (3.13%) | 0 / 30 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| UPPER RESPIRATORY TRACT INFECTION | | | |
| subjects affected / exposed ^[42] | 0 / 32 (0.00%) | 1 / 30 (3.33%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| PNEUMOCYSTIS JIROVECI PNEUMONIA | | | |
| subjects affected / exposed ^[43] | 0 / 32 (0.00%) | 1 / 30 (3.33%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| PYELONEPHRITIS ACUTE | | | |
| subjects affected / exposed ^[44] | 0 / 32 (0.00%) | 0 / 30 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| KIDNEY INFECTION | | | |
| subjects affected / exposed ^[45] | 0 / 32 (0.00%) | 1 / 30 (3.33%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| CELLULITIS | | | |
| subjects affected / exposed ^[46] | 1 / 32 (3.13%) | 0 / 30 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| MASTITIS | | | |
| subjects affected / exposed ^[47] | 1 / 32 (3.13%) | 2 / 30 (6.67%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| ERYSIPELAS | | | |
| subjects affected / exposed ^[48] | 0 / 32 (0.00%) | 0 / 30 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| URINARY TRACT INFECTION | | | |

| | | | |
|---|----------------|----------------|--|
| subjects affected / exposed ^[49] | 0 / 32 (0.00%) | 2 / 30 (6.67%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| STREPTOCOCCAL SEPSIS | | | |
| subjects affected / exposed ^[50] | 0 / 32 (0.00%) | 0 / 30 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Metabolism and nutrition disorders | | | |
| HYPOKALAEMIA | | | |
| subjects affected / exposed ^[51] | 0 / 32 (0.00%) | 1 / 30 (3.33%) | |
| occurrences causally related to treatment / all | 0 / 0 | 2 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| DECREASED APPETITE | | | |
| subjects affected / exposed ^[52] | 1 / 32 (3.13%) | 0 / 30 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

Notes:

[1] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.

Justification: The number of deaths displays information from the ITT population. One participant in Cohort III didn't receive treatment and is not counted in the AE tables. The safety population was defined as participants who received any amount of any study drug. The serious and non-serious AEs are reported with data from this population.

[2] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.

Justification: The number of deaths displays information from the ITT population. One participant in Cohort III didn't receive treatment and is not counted in the AE tables. The safety population was defined as participants who received any amount of any study drug. The serious and non-serious AEs are reported with data from this population.

[3] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.

Justification: The number of deaths displays information from the ITT population. One participant in Cohort III didn't receive treatment and is not counted in the AE tables. The safety population was defined as participants who received any amount of any study drug. The serious and non-serious AEs are reported with data from this population.

[4] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.

Justification: The number of deaths displays information from the ITT population. One participant in Cohort III didn't receive treatment and is not counted in the AE tables. The safety population was defined as participants who received any amount of any study drug. The serious and non-serious AEs are reported with data from this population.

[5] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.

Justification: The number of deaths displays information from the ITT population. One participant in Cohort III didn't receive treatment and is not counted in the AE tables. The safety population was defined as participants who received any amount of any study drug. The serious and non-serious AEs are reported with data from this population.

[6] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.

Justification: The number of deaths displays information from the ITT population. One participant in

Justification: The number of deaths displays information from the ITT population. One participant in Cohort III didn't receive treatment and is not counted in the AE tables. The safety population was defined as participants who received any amount of any study drug. The serious and non-serious AEs are reported with data from this population.

Cohort III didn't receive treatment and is not counted in the AE tables. The safety population was defined as participants who received any amount of any study drug. The serious and non-serious AEs are reported with data from this population.

[52] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.

Justification: The number of deaths displays information from the ITT population. One participant in Cohort III didn't receive treatment and is not counted in the AE tables. The safety population was defined as participants who received any amount of any study drug. The serious and non-serious AEs are reported with data from this population.

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

| Non-serious adverse events | Cohort I: Safety Run-In | Cohort I: Placebo, Paclitaxel | Cohort I: Cobimetinib, Paclitaxel |
|---|-------------------------|-------------------------------|-----------------------------------|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 15 / 16 (93.75%) | 43 / 43 (100.00%) | 46 / 47 (97.87%) |
| Vascular disorders | | | |
| HOT FLUSH | | | |
| subjects affected / exposed ^[53] | 0 / 16 (0.00%) | 2 / 43 (4.65%) | 1 / 47 (2.13%) |
| occurrences (all) | 0 | 2 | 1 |
| FLUSHING | | | |
| subjects affected / exposed ^[54] | 1 / 16 (6.25%) | 2 / 43 (4.65%) | 1 / 47 (2.13%) |
| occurrences (all) | 1 | 2 | 1 |
| HYPOTENSION | | | |
| subjects affected / exposed ^[55] | 1 / 16 (6.25%) | 1 / 43 (2.33%) | 0 / 47 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| HYPERTENSION | | | |
| subjects affected / exposed ^[56] | 0 / 16 (0.00%) | 3 / 43 (6.98%) | 4 / 47 (8.51%) |
| occurrences (all) | 0 | 5 | 7 |
| LYMPHOEDEMA | | | |
| subjects affected / exposed ^[57] | 0 / 16 (0.00%) | 1 / 43 (2.33%) | 4 / 47 (8.51%) |
| occurrences (all) | 0 | 3 | 4 |
| General disorders and administration site conditions | | | |
| PYREXIA | | | |
| subjects affected / exposed ^[58] | 4 / 16 (25.00%) | 8 / 43 (18.60%) | 9 / 47 (19.15%) |
| occurrences (all) | 7 | 13 | 15 |
| CHILLS | | | |
| subjects affected / exposed ^[59] | 1 / 16 (6.25%) | 0 / 43 (0.00%) | 3 / 47 (6.38%) |
| occurrences (all) | 1 | 0 | 3 |
| FATIGUE | | | |
| subjects affected / exposed ^[60] | 3 / 16 (18.75%) | 15 / 43 (34.88%) | 13 / 47 (27.66%) |
| occurrences (all) | 3 | 19 | 15 |
| MUCOSAL INFLAMMATION | | | |

| | | | |
|---|-----------------|------------------|------------------|
| subjects affected / exposed ^[61] | 1 / 16 (6.25%) | 2 / 43 (4.65%) | 4 / 47 (8.51%) |
| occurrences (all) | 3 | 3 | 9 |
| GAIT DISTURBANCE | | | |
| subjects affected / exposed ^[62] | 1 / 16 (6.25%) | 0 / 43 (0.00%) | 0 / 47 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| OEDEMA | | | |
| subjects affected / exposed ^[63] | 1 / 16 (6.25%) | 2 / 43 (4.65%) | 5 / 47 (10.64%) |
| occurrences (all) | 1 | 2 | 7 |
| GENERALISED OEDEMA | | | |
| subjects affected / exposed ^[64] | 0 / 16 (0.00%) | 0 / 43 (0.00%) | 1 / 47 (2.13%) |
| occurrences (all) | 0 | 0 | 1 |
| PAIN | | | |
| subjects affected / exposed ^[65] | 1 / 16 (6.25%) | 3 / 43 (6.98%) | 3 / 47 (6.38%) |
| occurrences (all) | 1 | 3 | 3 |
| INFLUENZA LIKE ILLNESS | | | |
| subjects affected / exposed ^[66] | 0 / 16 (0.00%) | 0 / 43 (0.00%) | 3 / 47 (6.38%) |
| occurrences (all) | 0 | 0 | 3 |
| ASTHENIA | | | |
| subjects affected / exposed ^[67] | 3 / 16 (18.75%) | 11 / 43 (25.58%) | 13 / 47 (27.66%) |
| occurrences (all) | 3 | 18 | 15 |
| CHEST PAIN | | | |
| subjects affected / exposed ^[68] | 0 / 16 (0.00%) | 7 / 43 (16.28%) | 5 / 47 (10.64%) |
| occurrences (all) | 0 | 9 | 5 |
| OEDEMA PERIPHERAL | | | |
| subjects affected / exposed ^[69] | 4 / 16 (25.00%) | 9 / 43 (20.93%) | 9 / 47 (19.15%) |
| occurrences (all) | 4 | 9 | 12 |
| PERIPHERAL SWELLING | | | |
| subjects affected / exposed ^[70] | 1 / 16 (6.25%) | 0 / 43 (0.00%) | 1 / 47 (2.13%) |
| occurrences (all) | 1 | 0 | 1 |
| Reproductive system and breast disorders | | | |
| CYSTOCELE | | | |
| subjects affected / exposed ^[71] | 1 / 16 (6.25%) | 0 / 43 (0.00%) | 0 / 47 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| BREAST PAIN | | | |

| | | | |
|---|-----------------|------------------|-----------------|
| subjects affected / exposed ^[72] | 0 / 16 (0.00%) | 3 / 43 (6.98%) | 1 / 47 (2.13%) |
| occurrences (all) | 0 | 5 | 1 |
| Respiratory, thoracic and mediastinal disorders | | | |
| PRODUCTIVE COUGH | | | |
| subjects affected / exposed ^[73] | 1 / 16 (6.25%) | 3 / 43 (6.98%) | 1 / 47 (2.13%) |
| occurrences (all) | 1 | 3 | 1 |
| NASAL DRYNESS | | | |
| subjects affected / exposed ^[74] | 2 / 16 (12.50%) | 0 / 43 (0.00%) | 2 / 47 (4.26%) |
| occurrences (all) | 2 | 0 | 2 |
| PLEURAL EFFUSION | | | |
| subjects affected / exposed ^[75] | 0 / 16 (0.00%) | 1 / 43 (2.33%) | 3 / 47 (6.38%) |
| occurrences (all) | 0 | 1 | 3 |
| DYSPHONIA | | | |
| subjects affected / exposed ^[76] | 2 / 16 (12.50%) | 3 / 43 (6.98%) | 2 / 47 (4.26%) |
| occurrences (all) | 2 | 3 | 3 |
| DYSPNOEA | | | |
| subjects affected / exposed ^[77] | 4 / 16 (25.00%) | 3 / 43 (6.98%) | 7 / 47 (14.89%) |
| occurrences (all) | 5 | 6 | 12 |
| OROPHARYNGEAL PAIN | | | |
| subjects affected / exposed ^[78] | 0 / 16 (0.00%) | 1 / 43 (2.33%) | 4 / 47 (8.51%) |
| occurrences (all) | 0 | 1 | 4 |
| EPISTAXIS | | | |
| subjects affected / exposed ^[79] | 2 / 16 (12.50%) | 4 / 43 (9.30%) | 4 / 47 (8.51%) |
| occurrences (all) | 2 | 5 | 5 |
| PNEUMONITIS | | | |
| subjects affected / exposed ^[80] | 0 / 16 (0.00%) | 1 / 43 (2.33%) | 0 / 47 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| PULMONARY EMBOLISM | | | |
| subjects affected / exposed ^[81] | 1 / 16 (6.25%) | 0 / 43 (0.00%) | 0 / 47 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| COUGH | | | |
| subjects affected / exposed ^[82] | 2 / 16 (12.50%) | 12 / 43 (27.91%) | 7 / 47 (14.89%) |
| occurrences (all) | 2 | 14 | 8 |
| Psychiatric disorders | | | |

| | | | |
|---|-----------------|-----------------|------------------|
| INSOMNIA | | | |
| subjects affected / exposed ^[83] | 2 / 16 (12.50%) | 7 / 43 (16.28%) | 3 / 47 (6.38%) |
| occurrences (all) | 2 | 8 | 3 |
| ANXIETY | | | |
| subjects affected / exposed ^[84] | 0 / 16 (0.00%) | 1 / 43 (2.33%) | 2 / 47 (4.26%) |
| occurrences (all) | 0 | 1 | 3 |
| Investigations | | | |
| NEUTROPHIL COUNT DECREASED | | | |
| subjects affected / exposed ^[85] | 0 / 16 (0.00%) | 1 / 43 (2.33%) | 2 / 47 (4.26%) |
| occurrences (all) | 0 | 1 | 2 |
| BLOOD POTASSIUM DECREASED | | | |
| subjects affected / exposed ^[86] | 0 / 16 (0.00%) | 0 / 43 (0.00%) | 0 / 47 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| TRANSFERRIN SATURATION DECREASED | | | |
| subjects affected / exposed ^[87] | 1 / 16 (6.25%) | 0 / 43 (0.00%) | 1 / 47 (2.13%) |
| occurrences (all) | 1 | 0 | 1 |
| ASPARTATE AMINOTRANSFERASE INCREASED | | | |
| subjects affected / exposed ^[88] | 3 / 16 (18.75%) | 2 / 43 (4.65%) | 3 / 47 (6.38%) |
| occurrences (all) | 5 | 2 | 5 |
| BLOOD CREATINE PHOSPHOKINASE INCREASED | | | |
| subjects affected / exposed ^[89] | 6 / 16 (37.50%) | 0 / 43 (0.00%) | 10 / 47 (21.28%) |
| occurrences (all) | 6 | 0 | 10 |
| CARBOHYDRATE ANTIGEN 15-3 INCREASED | | | |
| subjects affected / exposed ^[90] | 1 / 16 (6.25%) | 0 / 43 (0.00%) | 0 / 47 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| EJECTION FRACTION DECREASED | | | |
| subjects affected / exposed ^[91] | 0 / 16 (0.00%) | 0 / 43 (0.00%) | 3 / 47 (6.38%) |
| occurrences (all) | 0 | 0 | 3 |
| ALANINE AMINOTRANSFERASE INCREASED | | | |
| subjects affected / exposed ^[92] | 2 / 16 (12.50%) | 3 / 43 (6.98%) | 3 / 47 (6.38%) |
| occurrences (all) | 4 | 5 | 4 |
| WEIGHT DECREASED | | | |
| subjects affected / exposed ^[93] | 0 / 16 (0.00%) | 3 / 43 (6.98%) | 0 / 47 (0.00%) |
| occurrences (all) | 0 | 4 | 0 |

| | | | |
|--|-----------------|----------------|----------------|
| GAMMA-GLUTAMYLTRANSFERASE INCREASED | | | |
| subjects affected / exposed ^[94] | 1 / 16 (6.25%) | 2 / 43 (4.65%) | 1 / 47 (2.13%) |
| occurrences (all) | 1 | 5 | 1 |
| PLATELET COUNT DECREASED | | | |
| subjects affected / exposed ^[95] | 1 / 16 (6.25%) | 1 / 43 (2.33%) | 0 / 47 (0.00%) |
| occurrences (all) | 1 | 2 | 0 |
| HAEMOGLOBIN DECREASED | | | |
| subjects affected / exposed ^[96] | 1 / 16 (6.25%) | 2 / 43 (4.65%) | 1 / 47 (2.13%) |
| occurrences (all) | 1 | 2 | 1 |
| BLOOD ALKALINE PHOSPHATASE INCREASED | | | |
| subjects affected / exposed ^[97] | 0 / 16 (0.00%) | 1 / 43 (2.33%) | 3 / 47 (6.38%) |
| occurrences (all) | 0 | 2 | 3 |
| FIBRIN D DIMER INCREASED | | | |
| subjects affected / exposed ^[98] | 2 / 16 (12.50%) | 0 / 43 (0.00%) | 0 / 47 (0.00%) |
| occurrences (all) | 2 | 0 | 0 |
| SERUM FERRITIN INCREASED | | | |
| subjects affected / exposed ^[99] | 1 / 16 (6.25%) | 0 / 43 (0.00%) | 0 / 47 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| WHITE BLOOD CELL COUNT INCREASED | | | |
| subjects affected / exposed ^[100] | 1 / 16 (6.25%) | 0 / 43 (0.00%) | 0 / 47 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| MYOGLOBIN BLOOD INCREASED | | | |
| subjects affected / exposed ^[101] | 1 / 16 (6.25%) | 0 / 43 (0.00%) | 0 / 47 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| BLOOD THYROID STIMULATING HORMONE INCREASED | | | |
| subjects affected / exposed ^[102] | 1 / 16 (6.25%) | 0 / 43 (0.00%) | 0 / 47 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| NEUTROPHIL COUNT INCREASED | | | |
| subjects affected / exposed ^[103] | 1 / 16 (6.25%) | 0 / 43 (0.00%) | 0 / 47 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| WHITE BLOOD CELL COUNT DECREASED | | | |
| subjects affected / exposed ^[104] | 0 / 16 (0.00%) | 0 / 43 (0.00%) | 0 / 47 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| C-REACTIVE PROTEIN INCREASED | | | |

| | | | |
|---|----------------------|-----------------------|-----------------------|
| subjects affected / exposed ^[105] occurrences (all) | 1 / 16 (6.25%) 1 | 0 / 43 (0.00%) 0 | 0 / 47 (0.00%) 0 |
| BLOOD PRESSURE INCREASED subjects affected / exposed ^[106] occurrences (all) | 1 / 16 (6.25%) 1 | 0 / 43 (0.00%) 0 | 0 / 47 (0.00%) 0 |
| Injury, poisoning and procedural complications CHEST INJURY subjects affected / exposed ^[107] occurrences (all) | 1 / 16 (6.25%) 1 | 0 / 43 (0.00%) 0 | 0 / 47 (0.00%) 0 |
| INFUSION RELATED REACTION subjects affected / exposed ^[108] occurrences (all) | 2 / 16 (12.50%) 3 | 0 / 43 (0.00%) 0 | 0 / 47 (0.00%) 0 |
| Cardiac disorders TACHYCARDIA subjects affected / exposed ^[109] occurrences (all) | 0 / 16 (0.00%) 0 | 0 / 43 (0.00%) 0 | 1 / 47 (2.13%) 1 |
| PALPITATIONS subjects affected / exposed ^[110] occurrences (all) | 1 / 16 (6.25%) 1 | 1 / 43 (2.33%) 1 | 2 / 47 (4.26%) 2 |
| Nervous system disorders PERIPHERAL SENSORY NEUROPATHY subjects affected / exposed ^[111] occurrences (all) | 2 / 16 (12.50%) 2 | 9 / 43 (20.93%) 12 | 8 / 47 (17.02%) 12 |
| DYSGEUSIA subjects affected / exposed ^[112] occurrences (all) | 1 / 16 (6.25%) 1 | 4 / 43 (9.30%) 4 | 7 / 47 (14.89%) 7 |
| HEADACHE subjects affected / exposed ^[113] occurrences (all) | 3 / 16 (18.75%) 3 | 9 / 43 (20.93%) 14 | 7 / 47 (14.89%) 14 |
| DYSMETRIA subjects affected / exposed ^[114] occurrences (all) | 1 / 16 (6.25%) 1 | 0 / 43 (0.00%) 0 | 0 / 47 (0.00%) 0 |
| PARAESTHESIA subjects affected / exposed ^[115] occurrences (all) | 0 / 16 (0.00%) 0 | 5 / 43 (11.63%) 9 | 4 / 47 (8.51%) 5 |
| DYSTONIC TREMOR | | | |

| | | | |
|--|-----------------|------------------|------------------|
| subjects affected / exposed ^[116] | 1 / 16 (6.25%) | 0 / 43 (0.00%) | 0 / 47 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| DIZZINESS | | | |
| subjects affected / exposed ^[117] | 3 / 16 (18.75%) | 8 / 43 (18.60%) | 7 / 47 (14.89%) |
| occurrences (all) | 3 | 9 | 9 |
| HYPOAESTHESIA | | | |
| subjects affected / exposed ^[118] | 1 / 16 (6.25%) | 2 / 43 (4.65%) | 3 / 47 (6.38%) |
| occurrences (all) | 1 | 2 | 3 |
| HYPOGEUSIA | | | |
| subjects affected / exposed ^[119] | 2 / 16 (12.50%) | 0 / 43 (0.00%) | 0 / 47 (0.00%) |
| occurrences (all) | 2 | 0 | 0 |
| NEUROTOXICITY | | | |
| subjects affected / exposed ^[120] | 0 / 16 (0.00%) | 3 / 43 (6.98%) | 0 / 47 (0.00%) |
| occurrences (all) | 0 | 4 | 0 |
| NEUROPATHY PERIPHERAL | | | |
| subjects affected / exposed ^[121] | 1 / 16 (6.25%) | 7 / 43 (16.28%) | 4 / 47 (8.51%) |
| occurrences (all) | 1 | 10 | 4 |
| Blood and lymphatic system disorders | | | |
| NEUTROPENIA | | | |
| subjects affected / exposed ^[122] | 2 / 16 (12.50%) | 13 / 43 (30.23%) | 8 / 47 (17.02%) |
| occurrences (all) | 16 | 43 | 21 |
| ANAEMIA | | | |
| subjects affected / exposed ^[123] | 3 / 16 (18.75%) | 6 / 43 (13.95%) | 12 / 47 (25.53%) |
| occurrences (all) | 3 | 9 | 16 |
| EOSINOPHILIA | | | |
| subjects affected / exposed ^[124] | 1 / 16 (6.25%) | 0 / 43 (0.00%) | 0 / 47 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| LEUKOPENIA | | | |
| subjects affected / exposed ^[125] | 1 / 16 (6.25%) | 1 / 43 (2.33%) | 1 / 47 (2.13%) |
| occurrences (all) | 6 | 2 | 1 |
| Ear and labyrinth disorders | | | |
| TINNITUS | | | |
| subjects affected / exposed ^[126] | 0 / 16 (0.00%) | 0 / 43 (0.00%) | 0 / 47 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Eye disorders | | | |

| | | | |
|--|----------------|----------------|------------------|
| CHORIORETINOPATHY | | | |
| subjects affected / exposed ^[127] | 1 / 16 (6.25%) | 0 / 43 (0.00%) | 1 / 47 (2.13%) |
| occurrences (all) | 1 | 0 | 1 |
| CATARACT CORTICAL | | | |
| subjects affected / exposed ^[128] | 1 / 16 (6.25%) | 0 / 43 (0.00%) | 0 / 47 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| VISION BLURRED | | | |
| subjects affected / exposed ^[129] | 0 / 16 (0.00%) | 1 / 43 (2.33%) | 10 / 47 (21.28%) |
| occurrences (all) | 0 | 1 | 11 |
| VITREOUS FLOATERS | | | |
| subjects affected / exposed ^[130] | 1 / 16 (6.25%) | 0 / 43 (0.00%) | 0 / 47 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| EPISCLERITIS | | | |
| subjects affected / exposed ^[131] | 1 / 16 (6.25%) | 0 / 43 (0.00%) | 0 / 47 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| EYE PAIN | | | |
| subjects affected / exposed ^[132] | 1 / 16 (6.25%) | 0 / 43 (0.00%) | 2 / 47 (4.26%) |
| occurrences (all) | 1 | 0 | 2 |
| MACULAR FIBROSIS | | | |
| subjects affected / exposed ^[133] | 1 / 16 (6.25%) | 0 / 43 (0.00%) | 0 / 47 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| MACULAR OEDEMA | | | |
| subjects affected / exposed ^[134] | 0 / 16 (0.00%) | 0 / 43 (0.00%) | 1 / 47 (2.13%) |
| occurrences (all) | 0 | 0 | 1 |
| EYELID OEDEMA | | | |
| subjects affected / exposed ^[135] | 1 / 16 (6.25%) | 1 / 43 (2.33%) | 2 / 47 (4.26%) |
| occurrences (all) | 1 | 1 | 2 |
| CONJUNCTIVAL HAEMORRHAGE | | | |
| subjects affected / exposed ^[136] | 1 / 16 (6.25%) | 0 / 43 (0.00%) | 0 / 47 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| DRY EYE | | | |
| subjects affected / exposed ^[137] | 0 / 16 (0.00%) | 3 / 43 (6.98%) | 4 / 47 (8.51%) |
| occurrences (all) | 0 | 3 | 4 |
| RETINAL DRUSEN | | | |
| subjects affected / exposed ^[138] | 1 / 16 (6.25%) | 0 / 43 (0.00%) | 0 / 47 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |

| | | | |
|--|-----------------|-----------------|------------------|
| RETINAL DETACHMENT | | | |
| subjects affected / exposed ^[139] | 1 / 16 (6.25%) | 0 / 43 (0.00%) | 0 / 47 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| CATARACT | | | |
| subjects affected / exposed ^[140] | 1 / 16 (6.25%) | 0 / 43 (0.00%) | 0 / 47 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Gastrointestinal disorders | | | |
| DYSPHAGIA | | | |
| subjects affected / exposed ^[141] | 0 / 16 (0.00%) | 2 / 43 (4.65%) | 2 / 47 (4.26%) |
| occurrences (all) | 0 | 2 | 2 |
| GASTROESOPHAGEAL REFLUX DISEASE | | | |
| subjects affected / exposed ^[142] | 2 / 16 (12.50%) | 1 / 43 (2.33%) | 2 / 47 (4.26%) |
| occurrences (all) | 6 | 1 | 2 |
| CONSTIPATION | | | |
| subjects affected / exposed ^[143] | 4 / 16 (25.00%) | 9 / 43 (20.93%) | 8 / 47 (17.02%) |
| occurrences (all) | 4 | 11 | 11 |
| VOMITING | | | |
| subjects affected / exposed ^[144] | 5 / 16 (31.25%) | 7 / 43 (16.28%) | 8 / 47 (17.02%) |
| occurrences (all) | 6 | 8 | 13 |
| APHTHOUS ULCER | | | |
| subjects affected / exposed ^[145] | 1 / 16 (6.25%) | 0 / 43 (0.00%) | 0 / 47 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| DRY MOUTH | | | |
| subjects affected / exposed ^[146] | 2 / 16 (12.50%) | 1 / 43 (2.33%) | 6 / 47 (12.77%) |
| occurrences (all) | 2 | 1 | 6 |
| MOUTH ULCERATION | | | |
| subjects affected / exposed ^[147] | 0 / 16 (0.00%) | 0 / 43 (0.00%) | 2 / 47 (4.26%) |
| occurrences (all) | 0 | 0 | 3 |
| STOMATITIS | | | |
| subjects affected / exposed ^[148] | 5 / 16 (31.25%) | 5 / 43 (11.63%) | 13 / 47 (27.66%) |
| occurrences (all) | 8 | 5 | 18 |
| ABDOMINAL PAIN UPPER | | | |
| subjects affected / exposed ^[149] | 1 / 16 (6.25%) | 4 / 43 (9.30%) | 6 / 47 (12.77%) |
| occurrences (all) | 1 | 5 | 6 |
| HAEMORRHOIDS | | | |

| | | | |
|--|------------------|------------------|------------------|
| subjects affected / exposed ^[150] | 1 / 16 (6.25%) | 2 / 43 (4.65%) | 1 / 47 (2.13%) |
| occurrences (all) | 1 | 2 | 2 |
| DIARRHOEA | | | |
| subjects affected / exposed ^[151] | 10 / 16 (62.50%) | 13 / 43 (30.23%) | 36 / 47 (76.60%) |
| occurrences (all) | 29 | 19 | 66 |
| NAUSEA | | | |
| subjects affected / exposed ^[152] | 7 / 16 (43.75%) | 18 / 43 (41.86%) | 20 / 47 (42.55%) |
| occurrences (all) | 7 | 25 | 24 |
| ABDOMINAL PAIN | | | |
| subjects affected / exposed ^[153] | 3 / 16 (18.75%) | 3 / 43 (6.98%) | 5 / 47 (10.64%) |
| occurrences (all) | 3 | 3 | 6 |
| ABDOMINAL DISTENSION | | | |
| subjects affected / exposed ^[154] | 1 / 16 (6.25%) | 0 / 43 (0.00%) | 1 / 47 (2.13%) |
| occurrences (all) | 1 | 0 | 1 |
| DYSPEPSIA | | | |
| subjects affected / exposed ^[155] | 0 / 16 (0.00%) | 3 / 43 (6.98%) | 6 / 47 (12.77%) |
| occurrences (all) | 0 | 3 | 9 |
| Skin and subcutaneous tissue disorders | | | |
| PALMAR-PLANTAR ERYTHRODYSAESTHESIA SYNDROME | | | |
| subjects affected / exposed ^[156] | 1 / 16 (6.25%) | 1 / 43 (2.33%) | 0 / 47 (0.00%) |
| occurrences (all) | 4 | 1 | 0 |
| RASH | | | |
| subjects affected / exposed ^[157] | 8 / 16 (50.00%) | 5 / 43 (11.63%) | 22 / 47 (46.81%) |
| occurrences (all) | 18 | 6 | 34 |
| PRURITUS | | | |
| subjects affected / exposed ^[158] | 2 / 16 (12.50%) | 2 / 43 (4.65%) | 12 / 47 (25.53%) |
| occurrences (all) | 2 | 2 | 17 |
| SKIN LESION | | | |
| subjects affected / exposed ^[159] | 1 / 16 (6.25%) | 0 / 43 (0.00%) | 0 / 47 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| RASH MACULO-PAPULAR | | | |
| subjects affected / exposed ^[160] | 0 / 16 (0.00%) | 1 / 43 (2.33%) | 1 / 47 (2.13%) |
| occurrences (all) | 0 | 1 | 1 |
| DRY SKIN | | | |

| | | | |
|--|-----------------|------------------|------------------|
| subjects affected / exposed ^[161] | 1 / 16 (6.25%) | 0 / 43 (0.00%) | 6 / 47 (12.77%) |
| occurrences (all) | 1 | 0 | 7 |
| ERYTHEMA | | | |
| subjects affected / exposed ^[162] | 1 / 16 (6.25%) | 1 / 43 (2.33%) | 2 / 47 (4.26%) |
| occurrences (all) | 1 | 1 | 3 |
| DERMATITIS ACNEIFORM | | | |
| subjects affected / exposed ^[163] | 3 / 16 (18.75%) | 3 / 43 (6.98%) | 9 / 47 (19.15%) |
| occurrences (all) | 3 | 4 | 12 |
| INGROWING NAIL | | | |
| subjects affected / exposed ^[164] | 1 / 16 (6.25%) | 0 / 43 (0.00%) | 1 / 47 (2.13%) |
| occurrences (all) | 1 | 0 | 1 |
| NAIL DISCOLOURATION | | | |
| subjects affected / exposed ^[165] | 1 / 16 (6.25%) | 1 / 43 (2.33%) | 3 / 47 (6.38%) |
| occurrences (all) | 1 | 1 | 3 |
| SKIN FISSURES | | | |
| subjects affected / exposed ^[166] | 0 / 16 (0.00%) | 0 / 43 (0.00%) | 3 / 47 (6.38%) |
| occurrences (all) | 0 | 0 | 4 |
| RASH PAPULAR | | | |
| subjects affected / exposed ^[167] | 0 / 16 (0.00%) | 0 / 43 (0.00%) | 0 / 47 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| NAIL RIDGING | | | |
| subjects affected / exposed ^[168] | 0 / 16 (0.00%) | 0 / 43 (0.00%) | 0 / 47 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| ONYCHOMADESIS | | | |
| subjects affected / exposed ^[169] | 1 / 16 (6.25%) | 0 / 43 (0.00%) | 1 / 47 (2.13%) |
| occurrences (all) | 1 | 0 | 1 |
| ERYTHEMA NODOSUM | | | |
| subjects affected / exposed ^[170] | 1 / 16 (6.25%) | 0 / 43 (0.00%) | 0 / 47 (0.00%) |
| occurrences (all) | 2 | 0 | 0 |
| ALOPECIA | | | |
| subjects affected / exposed ^[171] | 5 / 16 (31.25%) | 19 / 43 (44.19%) | 21 / 47 (44.68%) |
| occurrences (all) | 5 | 20 | 22 |
| Renal and urinary disorders | | | |
| ACUTE KIDNEY INJURY | | | |
| subjects affected / exposed ^[172] | 0 / 16 (0.00%) | 0 / 43 (0.00%) | 0 / 47 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |

| | | | |
|---|-----------------|-----------------|-----------------|
| HAEMATURIA | | | |
| subjects affected / exposed ^[173] | 0 / 16 (0.00%) | 0 / 43 (0.00%) | 3 / 47 (6.38%) |
| occurrences (all) | 0 | 0 | 3 |
| DYSURIA | | | |
| subjects affected / exposed ^[174] | 1 / 16 (6.25%) | 1 / 43 (2.33%) | 4 / 47 (8.51%) |
| occurrences (all) | 1 | 1 | 5 |
| Endocrine disorders | | | |
| HYPOTHYROIDISM | | | |
| subjects affected / exposed ^[175] | 0 / 16 (0.00%) | 0 / 43 (0.00%) | 0 / 47 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Musculoskeletal and connective tissue disorders | | | |
| MUSCLE SPASMS | | | |
| subjects affected / exposed ^[176] | 1 / 16 (6.25%) | 2 / 43 (4.65%) | 1 / 47 (2.13%) |
| occurrences (all) | 1 | 2 | 1 |
| MUSCULAR WEAKNESS | | | |
| subjects affected / exposed ^[177] | 0 / 16 (0.00%) | 0 / 43 (0.00%) | 0 / 47 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| NECK PAIN | | | |
| subjects affected / exposed ^[178] | 0 / 16 (0.00%) | 1 / 43 (2.33%) | 2 / 47 (4.26%) |
| occurrences (all) | 0 | 1 | 2 |
| BACK PAIN | | | |
| subjects affected / exposed ^[179] | 2 / 16 (12.50%) | 2 / 43 (4.65%) | 6 / 47 (12.77%) |
| occurrences (all) | 2 | 2 | 6 |
| MUSCULOSKELETAL CHEST PAIN | | | |
| subjects affected / exposed ^[180] | 0 / 16 (0.00%) | 2 / 43 (4.65%) | 2 / 47 (4.26%) |
| occurrences (all) | 0 | 2 | 2 |
| BONE PAIN | | | |
| subjects affected / exposed ^[181] | 1 / 16 (6.25%) | 4 / 43 (9.30%) | 1 / 47 (2.13%) |
| occurrences (all) | 1 | 5 | 1 |
| ARTHRALGIA | | | |
| subjects affected / exposed ^[182] | 2 / 16 (12.50%) | 7 / 43 (16.28%) | 2 / 47 (4.26%) |
| occurrences (all) | 2 | 9 | 4 |
| JOINT SWELLING | | | |
| subjects affected / exposed ^[183] | 1 / 16 (6.25%) | 0 / 43 (0.00%) | 0 / 47 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| MYALGIA | | | |

| | | | |
|--|-----------------|-----------------|-----------------|
| subjects affected / exposed ^[184] | 2 / 16 (12.50%) | 6 / 43 (13.95%) | 6 / 47 (12.77%) |
| occurrences (all) | 2 | 8 | 8 |
| PAIN IN EXTREMITY | | | |
| subjects affected / exposed ^[185] | 1 / 16 (6.25%) | 5 / 43 (11.63%) | 2 / 47 (4.26%) |
| occurrences (all) | 1 | 5 | 2 |
| Infections and infestations | | | |
| RASH PUSTULAR | | | |
| subjects affected / exposed ^[186] | 0 / 16 (0.00%) | 1 / 43 (2.33%) | 1 / 47 (2.13%) |
| occurrences (all) | 0 | 1 | 1 |
| SINUSITIS | | | |
| subjects affected / exposed ^[187] | 0 / 16 (0.00%) | 0 / 43 (0.00%) | 0 / 47 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| FURUNCLE | | | |
| subjects affected / exposed ^[188] | 1 / 16 (6.25%) | 0 / 43 (0.00%) | 0 / 47 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| INFLUENZA | | | |
| subjects affected / exposed ^[189] | 1 / 16 (6.25%) | 1 / 43 (2.33%) | 0 / 47 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| NASOPHARYNGITIS | | | |
| subjects affected / exposed ^[190] | 1 / 16 (6.25%) | 1 / 43 (2.33%) | 2 / 47 (4.26%) |
| occurrences (all) | 1 | 1 | 4 |
| VAGINAL INFECTION | | | |
| subjects affected / exposed ^[191] | 1 / 16 (6.25%) | 0 / 43 (0.00%) | 0 / 47 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| PARONYCHIA | | | |
| subjects affected / exposed ^[192] | 1 / 16 (6.25%) | 2 / 43 (4.65%) | 4 / 47 (8.51%) |
| occurrences (all) | 1 | 4 | 5 |
| LOCALISED INFECTION | | | |
| subjects affected / exposed ^[193] | 1 / 16 (6.25%) | 0 / 43 (0.00%) | 0 / 47 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| UPPER RESPIRATORY TRACT INFECTION | | | |
| subjects affected / exposed ^[194] | 2 / 16 (12.50%) | 4 / 43 (9.30%) | 3 / 47 (6.38%) |
| occurrences (all) | 4 | 6 | 3 |
| PNEUMONIA | | | |

| | | | |
|--|-----------------|----------------|-----------------|
| subjects affected / exposed ^[195] | 0 / 16 (0.00%) | 1 / 43 (2.33%) | 3 / 47 (6.38%) |
| occurrences (all) | 0 | 1 | 3 |
| LYMPHANGITIS | | | |
| subjects affected / exposed ^[196] | 0 / 16 (0.00%) | 0 / 43 (0.00%) | 0 / 47 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| CYSTITIS | | | |
| subjects affected / exposed ^[197] | 0 / 16 (0.00%) | 1 / 43 (2.33%) | 3 / 47 (6.38%) |
| occurrences (all) | 0 | 1 | 4 |
| ORAL HERPES | | | |
| subjects affected / exposed ^[198] | 0 / 16 (0.00%) | 1 / 43 (2.33%) | 0 / 47 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| PHARYNGITIS | | | |
| subjects affected / exposed ^[199] | 0 / 16 (0.00%) | 0 / 43 (0.00%) | 3 / 47 (6.38%) |
| occurrences (all) | 0 | 0 | 3 |
| CELLULITIS | | | |
| subjects affected / exposed ^[200] | 0 / 16 (0.00%) | 1 / 43 (2.33%) | 0 / 47 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| NAIL INFECTION | | | |
| subjects affected / exposed ^[201] | 0 / 16 (0.00%) | 0 / 43 (0.00%) | 2 / 47 (4.26%) |
| occurrences (all) | 0 | 0 | 2 |
| LARYNGITIS | | | |
| subjects affected / exposed ^[202] | 1 / 16 (6.25%) | 0 / 43 (0.00%) | 2 / 47 (4.26%) |
| occurrences (all) | 1 | 0 | 2 |
| IMPETIGO | | | |
| subjects affected / exposed ^[203] | 1 / 16 (6.25%) | 0 / 43 (0.00%) | 0 / 47 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| URINARY TRACT INFECTION | | | |
| subjects affected / exposed ^[204] | 2 / 16 (12.50%) | 1 / 43 (2.33%) | 4 / 47 (8.51%) |
| occurrences (all) | 3 | 4 | 6 |
| Metabolism and nutrition disorders | | | |
| DEHYDRATION | | | |
| subjects affected / exposed ^[205] | 1 / 16 (6.25%) | 0 / 43 (0.00%) | 0 / 47 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| HYPOKALAEMIA | | | |
| subjects affected / exposed ^[206] | 0 / 16 (0.00%) | 1 / 43 (2.33%) | 5 / 47 (10.64%) |
| occurrences (all) | 0 | 1 | 8 |

| | | | |
|--|-----------------|------------------|-----------------|
| HYPOMAGNESAEMIA | | | |
| subjects affected / exposed ^[207] | 1 / 16 (6.25%) | 0 / 43 (0.00%) | 2 / 47 (4.26%) |
| occurrences (all) | 1 | 0 | 3 |
| DECREASED APPETITE | | | |
| subjects affected / exposed ^[208] | 3 / 16 (18.75%) | 10 / 43 (23.26%) | 9 / 47 (19.15%) |
| occurrences (all) | 3 | 14 | 11 |
| HYPOPHOSPHATAEMIA | | | |
| subjects affected / exposed ^[209] | 0 / 16 (0.00%) | 1 / 43 (2.33%) | 2 / 47 (4.26%) |
| occurrences (all) | 0 | 1 | 3 |
| DIABETES MELLITUS | | | |
| subjects affected / exposed ^[210] | 1 / 16 (6.25%) | 0 / 43 (0.00%) | 0 / 47 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |

| Non-serious adverse events | Cohort II: Cobimetinib, Paclitaxel, Atezolizumab | Cohort III: Cobimetinib, Nab-Paclitaxel, Atezolizumab | |
|---|---|--|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 32 / 32 (100.00%) | 29 / 31 (93.55%) | |
| Vascular disorders | | | |
| HOT FLUSH | | | |
| subjects affected / exposed ^[53] | 3 / 32 (9.38%) | 1 / 30 (3.33%) | |
| occurrences (all) | 3 | 1 | |
| FLUSHING | | | |
| subjects affected / exposed ^[54] | 1 / 32 (3.13%) | 0 / 30 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| HYPOTENSION | | | |
| subjects affected / exposed ^[55] | 2 / 32 (6.25%) | 1 / 30 (3.33%) | |
| occurrences (all) | 2 | 1 | |
| HYPERTENSION | | | |
| subjects affected / exposed ^[56] | 1 / 32 (3.13%) | 1 / 30 (3.33%) | |
| occurrences (all) | 1 | 1 | |
| LYMPHOEDEMA | | | |
| subjects affected / exposed ^[57] | 3 / 32 (9.38%) | 2 / 30 (6.67%) | |
| occurrences (all) | 5 | 2 | |
| General disorders and administration site conditions | | | |
| PYREXIA | | | |

| | | |
|---|------------------|------------------|
| subjects affected / exposed ^[58] | 1 / 32 (3.13%) | 9 / 30 (30.00%) |
| occurrences (all) | 1 | 12 |
| CHILLS | | |
| subjects affected / exposed ^[59] | 0 / 32 (0.00%) | 0 / 30 (0.00%) |
| occurrences (all) | 0 | 0 |
| FATIGUE | | |
| subjects affected / exposed ^[60] | 11 / 32 (34.38%) | 10 / 30 (33.33%) |
| occurrences (all) | 16 | 10 |
| MUCOSAL INFLAMMATION | | |
| subjects affected / exposed ^[61] | 5 / 32 (15.63%) | 5 / 30 (16.67%) |
| occurrences (all) | 6 | 9 |
| GAIT DISTURBANCE | | |
| subjects affected / exposed ^[62] | 0 / 32 (0.00%) | 0 / 30 (0.00%) |
| occurrences (all) | 0 | 0 |
| OEDEMA | | |
| subjects affected / exposed ^[63] | 0 / 32 (0.00%) | 3 / 30 (10.00%) |
| occurrences (all) | 0 | 4 |
| GENERALISED OEDEMA | | |
| subjects affected / exposed ^[64] | 0 / 32 (0.00%) | 2 / 30 (6.67%) |
| occurrences (all) | 0 | 2 |
| PAIN | | |
| subjects affected / exposed ^[65] | 0 / 32 (0.00%) | 1 / 30 (3.33%) |
| occurrences (all) | 0 | 1 |
| INFLUENZA LIKE ILLNESS | | |
| subjects affected / exposed ^[66] | 1 / 32 (3.13%) | 2 / 30 (6.67%) |
| occurrences (all) | 1 | 2 |
| ASTHENIA | | |
| subjects affected / exposed ^[67] | 6 / 32 (18.75%) | 6 / 30 (20.00%) |
| occurrences (all) | 11 | 8 |
| CHEST PAIN | | |
| subjects affected / exposed ^[68] | 2 / 32 (6.25%) | 1 / 30 (3.33%) |
| occurrences (all) | 4 | 1 |
| OEDEMA PERIPHERAL | | |
| subjects affected / exposed ^[69] | 7 / 32 (21.88%) | 5 / 30 (16.67%) |
| occurrences (all) | 12 | 6 |
| PERIPHERAL SWELLING | | |

| | | | |
|---|---|---|--|
| subjects affected / exposed ^[70] occurrences (all) | 0 / 32 (0.00%) 0 | 0 / 30 (0.00%) 0 | |
| Reproductive system and breast disorders CYSTOCELE subjects affected / exposed ^[71] occurrences (all) BREAST PAIN subjects affected / exposed ^[72] occurrences (all) | 0 / 32 (0.00%) 0 1 / 32 (3.13%) 1 | 0 / 30 (0.00%) 0 2 / 30 (6.67%) 3 | |
| Respiratory, thoracic and mediastinal disorders PRODUCTIVE COUGH subjects affected / exposed ^[73] occurrences (all) NASAL DRYNESS subjects affected / exposed ^[74] occurrences (all) PLEURAL EFFUSION subjects affected / exposed ^[75] occurrences (all) DYSPHONIA subjects affected / exposed ^[76] occurrences (all) DYSPNOEA subjects affected / exposed ^[77] occurrences (all) OROPHARYNGEAL PAIN subjects affected / exposed ^[78] occurrences (all) EPISTAXIS subjects affected / exposed ^[79] occurrences (all) PNEUMONITIS subjects affected / exposed ^[80] occurrences (all) PULMONARY EMBOLISM | 0 / 32 (0.00%) 0 0 / 32 (0.00%) 0 2 / 32 (6.25%) 2 1 / 32 (3.13%) 1 3 / 32 (9.38%) 3 1 / 32 (3.13%) 2 7 / 32 (21.88%) 8 2 / 32 (6.25%) 2 | 0 / 30 (0.00%) 0 0 / 30 (0.00%) 0 0 / 30 (0.00%) 0 2 / 30 (6.67%) 2 1 / 30 (3.33%) 1 2 / 30 (6.67%) 2 7 / 30 (23.33%) 8 1 / 30 (3.33%) 1 | |

| | | | |
|---|---|---|--|
| subjects affected / exposed ^[81] occurrences (all) COUGH subjects affected / exposed ^[82] occurrences (all) | 1 / 32 (3.13%) 1 6 / 32 (18.75%) 7 | 1 / 30 (3.33%) 1 5 / 30 (16.67%) 6 | |
| Psychiatric disorders INSOMNIA subjects affected / exposed ^[83] occurrences (all) ANXIETY subjects affected / exposed ^[84] occurrences (all) | 3 / 32 (9.38%) 3 1 / 32 (3.13%) 1 | 4 / 30 (13.33%) 5 3 / 30 (10.00%) 3 | |
| Investigations NEUTROPHIL COUNT DECREASED subjects affected / exposed ^[85] occurrences (all) BLOOD POTASSIUM DECREASED subjects affected / exposed ^[86] occurrences (all) TRANSFERRIN SATURATION DECREASED subjects affected / exposed ^[87] occurrences (all) ASPARTATE AMINOTRANSFERASE INCREASED subjects affected / exposed ^[88] occurrences (all) BLOOD CREATINE PHOSPHOKINASE INCREASED subjects affected / exposed ^[89] occurrences (all) CARBOHYDRATE ANTIGEN 15-3 INCREASED subjects affected / exposed ^[90] occurrences (all) EJECTION FRACTION DECREASED subjects affected / exposed ^[91] occurrences (all) | 4 / 32 (12.50%) 9 2 / 32 (6.25%) 2 1 / 32 (3.13%) 1 4 / 32 (12.50%) 6 5 / 32 (15.63%) 11 0 / 32 (0.00%) 0 1 / 32 (3.13%) 1 | 4 / 30 (13.33%) 7 0 / 30 (0.00%) 0 0 / 30 (0.00%) 0 5 / 30 (16.67%) 7 7 / 30 (23.33%) 13 0 / 30 (0.00%) 0 1 / 30 (3.33%) 1 | |

| | | |
|--|-----------------|-----------------|
| ALANINE AMINOTRANSFERASE INCREASED | | |
| subjects affected / exposed ^[92] | 4 / 32 (12.50%) | 6 / 30 (20.00%) |
| occurrences (all) | 7 | 7 |
| WEIGHT DECREASED | | |
| subjects affected / exposed ^[93] | 2 / 32 (6.25%) | 0 / 30 (0.00%) |
| occurrences (all) | 2 | 0 |
| GAMMA-GLUTAMYLTRANSFERASE INCREASED | | |
| subjects affected / exposed ^[94] | 0 / 32 (0.00%) | 0 / 30 (0.00%) |
| occurrences (all) | 0 | 0 |
| PLATELET COUNT DECREASED | | |
| subjects affected / exposed ^[95] | 1 / 32 (3.13%) | 0 / 30 (0.00%) |
| occurrences (all) | 1 | 0 |
| HAEMOGLOBIN DECREASED | | |
| subjects affected / exposed ^[96] | 0 / 32 (0.00%) | 0 / 30 (0.00%) |
| occurrences (all) | 0 | 0 |
| BLOOD ALKALINE PHOSPHATASE INCREASED | | |
| subjects affected / exposed ^[97] | 2 / 32 (6.25%) | 0 / 30 (0.00%) |
| occurrences (all) | 3 | 0 |
| FIBRIN D DIMER INCREASED | | |
| subjects affected / exposed ^[98] | 0 / 32 (0.00%) | 0 / 30 (0.00%) |
| occurrences (all) | 0 | 0 |
| SERUM FERRITIN INCREASED | | |
| subjects affected / exposed ^[99] | 0 / 32 (0.00%) | 0 / 30 (0.00%) |
| occurrences (all) | 0 | 0 |
| WHITE BLOOD CELL COUNT INCREASED | | |
| subjects affected / exposed ^[100] | 0 / 32 (0.00%) | 0 / 30 (0.00%) |
| occurrences (all) | 0 | 0 |
| MYOGLOBIN BLOOD INCREASED | | |
| subjects affected / exposed ^[101] | 0 / 32 (0.00%) | 0 / 30 (0.00%) |
| occurrences (all) | 0 | 0 |
| BLOOD THYROID STIMULATING HORMONE INCREASED | | |
| subjects affected / exposed ^[102] | 0 / 32 (0.00%) | 1 / 30 (3.33%) |
| occurrences (all) | 0 | 1 |
| NEUTROPHIL COUNT INCREASED | | |

| | | | |
|---|---|---|--|
| <p>subjects affected / exposed^[103]</p> <p>occurrences (all)</p> <p>WHITE BLOOD CELL COUNT DECREASED</p> <p>subjects affected / exposed^[104]</p> <p>occurrences (all)</p> <p>C-REACTIVE PROTEIN INCREASED</p> <p>subjects affected / exposed^[105]</p> <p>occurrences (all)</p> <p>BLOOD PRESSURE INCREASED</p> <p>subjects affected / exposed^[106]</p> <p>occurrences (all)</p> | <p>0 / 32 (0.00%)</p> <p>0</p> <p>3 / 32 (9.38%)</p> <p>9</p> <p>2 / 32 (6.25%)</p> <p>2</p> <p>0 / 32 (0.00%)</p> <p>0</p> | <p>0 / 30 (0.00%)</p> <p>0</p> <p>0 / 30 (0.00%)</p> <p>0</p> <p>0 / 30 (0.00%)</p> <p>0</p> <p>0 / 30 (0.00%)</p> <p>0</p> | |
| <p>Injury, poisoning and procedural complications</p> <p>CHEST INJURY</p> <p>subjects affected / exposed^[107]</p> <p>occurrences (all)</p> <p>INFUSION RELATED REACTION</p> <p>subjects affected / exposed^[108]</p> <p>occurrences (all)</p> | <p>0 / 32 (0.00%)</p> <p>0</p> <p>0 / 32 (0.00%)</p> <p>0</p> | <p>0 / 30 (0.00%)</p> <p>0</p> <p>0 / 30 (0.00%)</p> <p>0</p> | |
| <p>Cardiac disorders</p> <p>TACHYCARDIA</p> <p>subjects affected / exposed^[109]</p> <p>occurrences (all)</p> <p>PALPITATIONS</p> <p>subjects affected / exposed^[110]</p> <p>occurrences (all)</p> | <p>1 / 32 (3.13%)</p> <p>1</p> <p>0 / 32 (0.00%)</p> <p>0</p> | <p>2 / 30 (6.67%)</p> <p>2</p> <p>0 / 30 (0.00%)</p> <p>0</p> | |
| <p>Nervous system disorders</p> <p>PERIPHERAL SENSORY NEUROPATHY</p> <p>subjects affected / exposed^[111]</p> <p>occurrences (all)</p> <p>DYSGEUSIA</p> <p>subjects affected / exposed^[112]</p> <p>occurrences (all)</p> <p>HEADACHE</p> <p>subjects affected / exposed^[113]</p> <p>occurrences (all)</p> <p>DYSMETRIA</p> | <p>1 / 32 (3.13%)</p> <p>1</p> <p>1 / 32 (3.13%)</p> <p>1</p> <p>5 / 32 (15.63%)</p> <p>7</p> | <p>2 / 30 (6.67%)</p> <p>2</p> <p>2 / 30 (6.67%)</p> <p>3</p> <p>4 / 30 (13.33%)</p> <p>6</p> | |

| | | | |
|--|------------------|------------------|--|
| subjects affected / exposed ^[114] | 0 / 32 (0.00%) | 0 / 30 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| PARAESTHESIA | | | |
| subjects affected / exposed ^[115] | 4 / 32 (12.50%) | 0 / 30 (0.00%) | |
| occurrences (all) | 5 | 0 | |
| DYSTONIC TREMOR | | | |
| subjects affected / exposed ^[116] | 0 / 32 (0.00%) | 0 / 30 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| DIZZINESS | | | |
| subjects affected / exposed ^[117] | 4 / 32 (12.50%) | 3 / 30 (10.00%) | |
| occurrences (all) | 4 | 3 | |
| HYPOAESTHESIA | | | |
| subjects affected / exposed ^[118] | 0 / 32 (0.00%) | 0 / 30 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| HYPOGEUSIA | | | |
| subjects affected / exposed ^[119] | 0 / 32 (0.00%) | 0 / 30 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| NEUROTOXICITY | | | |
| subjects affected / exposed ^[120] | 0 / 32 (0.00%) | 0 / 30 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| NEUROPATHY PERIPHERAL | | | |
| subjects affected / exposed ^[121] | 8 / 32 (25.00%) | 7 / 30 (23.33%) | |
| occurrences (all) | 9 | 11 | |
| Blood and lymphatic system disorders | | | |
| NEUTROPENIA | | | |
| subjects affected / exposed ^[122] | 6 / 32 (18.75%) | 8 / 30 (26.67%) | |
| occurrences (all) | 6 | 18 | |
| ANAEMIA | | | |
| subjects affected / exposed ^[123] | 14 / 32 (43.75%) | 10 / 30 (33.33%) | |
| occurrences (all) | 19 | 24 | |
| EOSINOPHILIA | | | |
| subjects affected / exposed ^[124] | 0 / 32 (0.00%) | 0 / 30 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| LEUKOPENIA | | | |
| subjects affected / exposed ^[125] | 0 / 32 (0.00%) | 3 / 30 (10.00%) | |
| occurrences (all) | 0 | 9 | |

| | | | |
|--|-----------------|-----------------|--|
| Ear and labyrinth disorders | | | |
| TINNITUS | | | |
| subjects affected / exposed ^[126] | 3 / 32 (9.38%) | 0 / 30 (0.00%) | |
| occurrences (all) | 3 | 0 | |
| Eye disorders | | | |
| CHORIORETINOPATHY | | | |
| subjects affected / exposed ^[127] | 0 / 32 (0.00%) | 0 / 30 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| CATARACT CORTICAL | | | |
| subjects affected / exposed ^[128] | 0 / 32 (0.00%) | 0 / 30 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| VISION BLURRED | | | |
| subjects affected / exposed ^[129] | 4 / 32 (12.50%) | 4 / 30 (13.33%) | |
| occurrences (all) | 4 | 5 | |
| VITREOUS FLOATERS | | | |
| subjects affected / exposed ^[130] | 0 / 32 (0.00%) | 1 / 30 (3.33%) | |
| occurrences (all) | 0 | 1 | |
| EPISCLERITIS | | | |
| subjects affected / exposed ^[131] | 0 / 32 (0.00%) | 0 / 30 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| EYE PAIN | | | |
| subjects affected / exposed ^[132] | 0 / 32 (0.00%) | 1 / 30 (3.33%) | |
| occurrences (all) | 0 | 1 | |
| MACULAR FIBROSIS | | | |
| subjects affected / exposed ^[133] | 0 / 32 (0.00%) | 0 / 30 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| MACULAR OEDEMA | | | |
| subjects affected / exposed ^[134] | 0 / 32 (0.00%) | 2 / 30 (6.67%) | |
| occurrences (all) | 0 | 3 | |
| EYELID OEDEMA | | | |
| subjects affected / exposed ^[135] | 1 / 32 (3.13%) | 0 / 30 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| CONJUNCTIVAL HAEMORRHAGE | | | |
| subjects affected / exposed ^[136] | 1 / 32 (3.13%) | 0 / 30 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| DRY EYE | | | |

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|--|-----------------|------------------|--|
| subjects affected / exposed ^[137] | 0 / 32 (0.00%) | 3 / 30 (10.00%) | |
| occurrences (all) | 0 | 3 | |
| RETINAL DRUSEN | | | |
| subjects affected / exposed ^[138] | 0 / 32 (0.00%) | 0 / 30 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| RETINAL DETACHMENT | | | |
| subjects affected / exposed ^[139] | 0 / 32 (0.00%) | 0 / 30 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| CATARACT | | | |
| subjects affected / exposed ^[140] | 0 / 32 (0.00%) | 0 / 30 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Gastrointestinal disorders | | | |
| DYSPHAGIA | | | |
| subjects affected / exposed ^[141] | 2 / 32 (6.25%) | 0 / 30 (0.00%) | |
| occurrences (all) | 2 | 0 | |
| GASTROESOPHAGEAL REFLUX DISEASE | | | |
| subjects affected / exposed ^[142] | 2 / 32 (6.25%) | 0 / 30 (0.00%) | |
| occurrences (all) | 2 | 0 | |
| CONSTIPATION | | | |
| subjects affected / exposed ^[143] | 6 / 32 (18.75%) | 8 / 30 (26.67%) | |
| occurrences (all) | 7 | 13 | |
| VOMITING | | | |
| subjects affected / exposed ^[144] | 9 / 32 (28.13%) | 12 / 30 (40.00%) | |
| occurrences (all) | 16 | 16 | |
| APHTHOUS ULCER | | | |
| subjects affected / exposed ^[145] | 1 / 32 (3.13%) | 0 / 30 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| DRY MOUTH | | | |
| subjects affected / exposed ^[146] | 0 / 32 (0.00%) | 2 / 30 (6.67%) | |
| occurrences (all) | 0 | 2 | |
| MOUTH ULCERATION | | | |
| subjects affected / exposed ^[147] | 2 / 32 (6.25%) | 2 / 30 (6.67%) | |
| occurrences (all) | 2 | 3 | |
| STOMATITIS | | | |

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|--|------------------|------------------|--|
| subjects affected / exposed ^[148] | 5 / 32 (15.63%) | 5 / 30 (16.67%) | |
| occurrences (all) | 5 | 11 | |
| ABDOMINAL PAIN UPPER | | | |
| subjects affected / exposed ^[149] | 2 / 32 (6.25%) | 1 / 30 (3.33%) | |
| occurrences (all) | 2 | 1 | |
| HAEMORRHOIDS | | | |
| subjects affected / exposed ^[150] | 0 / 32 (0.00%) | 0 / 30 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| DIARRHOEA | | | |
| subjects affected / exposed ^[151] | 21 / 32 (65.63%) | 27 / 30 (90.00%) | |
| occurrences (all) | 48 | 55 | |
| NAUSEA | | | |
| subjects affected / exposed ^[152] | 13 / 32 (40.63%) | 15 / 30 (50.00%) | |
| occurrences (all) | 18 | 20 | |
| ABDOMINAL PAIN | | | |
| subjects affected / exposed ^[153] | 6 / 32 (18.75%) | 5 / 30 (16.67%) | |
| occurrences (all) | 8 | 6 | |
| ABDOMINAL DISTENSION | | | |
| subjects affected / exposed ^[154] | 0 / 32 (0.00%) | 2 / 30 (6.67%) | |
| occurrences (all) | 0 | 2 | |
| DYSPEPSIA | | | |
| subjects affected / exposed ^[155] | 1 / 32 (3.13%) | 5 / 30 (16.67%) | |
| occurrences (all) | 1 | 7 | |
| Skin and subcutaneous tissue disorders | | | |
| PALMAR-PLANTAR | | | |
| ERYTHRODYSAESTHESIA SYNDROME | | | |
| subjects affected / exposed ^[156] | 2 / 32 (6.25%) | 0 / 30 (0.00%) | |
| occurrences (all) | 2 | 0 | |
| RASH | | | |
| subjects affected / exposed ^[157] | 12 / 32 (37.50%) | 17 / 30 (56.67%) | |
| occurrences (all) | 22 | 22 | |
| PRURITUS | | | |
| subjects affected / exposed ^[158] | 4 / 32 (12.50%) | 4 / 30 (13.33%) | |
| occurrences (all) | 5 | 9 | |
| SKIN LESION | | | |

| | | |
|--|-----------------|-----------------|
| subjects affected / exposed ^[159] | 0 / 32 (0.00%) | 0 / 30 (0.00%) |
| occurrences (all) | 0 | 0 |
| RASH MACULO-PAPULAR | | |
| subjects affected / exposed ^[160] | 3 / 32 (9.38%) | 1 / 30 (3.33%) |
| occurrences (all) | 3 | 2 |
| DRY SKIN | | |
| subjects affected / exposed ^[161] | 4 / 32 (12.50%) | 5 / 30 (16.67%) |
| occurrences (all) | 5 | 7 |
| ERYTHEMA | | |
| subjects affected / exposed ^[162] | 1 / 32 (3.13%) | 3 / 30 (10.00%) |
| occurrences (all) | 1 | 4 |
| DERMATITIS ACNEIFORM | | |
| subjects affected / exposed ^[163] | 8 / 32 (25.00%) | 6 / 30 (20.00%) |
| occurrences (all) | 14 | 6 |
| INGROWING NAIL | | |
| subjects affected / exposed ^[164] | 0 / 32 (0.00%) | 0 / 30 (0.00%) |
| occurrences (all) | 0 | 0 |
| NAIL DISCOLOURATION | | |
| subjects affected / exposed ^[165] | 0 / 32 (0.00%) | 1 / 30 (3.33%) |
| occurrences (all) | 0 | 1 |
| SKIN FISSURES | | |
| subjects affected / exposed ^[166] | 1 / 32 (3.13%) | 1 / 30 (3.33%) |
| occurrences (all) | 1 | 1 |
| RASH PAPULAR | | |
| subjects affected / exposed ^[167] | 0 / 32 (0.00%) | 2 / 30 (6.67%) |
| occurrences (all) | 0 | 2 |
| NAIL RIDGING | | |
| subjects affected / exposed ^[168] | 2 / 32 (6.25%) | 0 / 30 (0.00%) |
| occurrences (all) | 2 | 0 |
| ONYCHOMADESIS | | |
| subjects affected / exposed ^[169] | 0 / 32 (0.00%) | 1 / 30 (3.33%) |
| occurrences (all) | 0 | 1 |
| ERYTHEMA NODOSUM | | |
| subjects affected / exposed ^[170] | 0 / 32 (0.00%) | 0 / 30 (0.00%) |
| occurrences (all) | 0 | 0 |
| ALOPECIA | | |

| | | | |
|---|----------------------|------------------------|--|
| subjects affected / exposed ^[171] occurrences (all) | 8 / 32 (25.00%) 8 | 10 / 30 (33.33%) 10 | |
| Renal and urinary disorders ACUTE KIDNEY INJURY subjects affected / exposed ^[172] occurrences (all) | 1 / 32 (3.13%) 3 | 2 / 30 (6.67%) 2 | |
| HAEMATURIA subjects affected / exposed ^[173] occurrences (all) | 0 / 32 (0.00%) 0 | 0 / 30 (0.00%) 0 | |
| DYSURIA subjects affected / exposed ^[174] occurrences (all) | 3 / 32 (9.38%) 3 | 1 / 30 (3.33%) 1 | |
| Endocrine disorders HYPOTHYROIDISM subjects affected / exposed ^[175] occurrences (all) | 5 / 32 (15.63%) 5 | 3 / 30 (10.00%) 3 | |
| Musculoskeletal and connective tissue disorders MUSCLE SPASMS subjects affected / exposed ^[176] occurrences (all) | 1 / 32 (3.13%) 1 | 2 / 30 (6.67%) 2 | |
| MUSCULAR WEAKNESS subjects affected / exposed ^[177] occurrences (all) | 2 / 32 (6.25%) 2 | 1 / 30 (3.33%) 1 | |
| NECK PAIN subjects affected / exposed ^[178] occurrences (all) | 2 / 32 (6.25%) 2 | 0 / 30 (0.00%) 0 | |
| BACK PAIN subjects affected / exposed ^[179] occurrences (all) | 4 / 32 (12.50%) 6 | 4 / 30 (13.33%) 5 | |
| MUSCULOSKELETAL CHEST PAIN subjects affected / exposed ^[180] occurrences (all) | 2 / 32 (6.25%) 2 | 0 / 30 (0.00%) 0 | |
| BONE PAIN subjects affected / exposed ^[181] occurrences (all) | 0 / 32 (0.00%) 0 | 1 / 30 (3.33%) 1 | |
| ARTHRALGIA | | | |

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|--|-----------------|-----------------|--|
| subjects affected / exposed ^[182] | 2 / 32 (6.25%) | 4 / 30 (13.33%) | |
| occurrences (all) | 2 | 4 | |
| JOINT SWELLING | | | |
| subjects affected / exposed ^[183] | 1 / 32 (3.13%) | 0 / 30 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| MYALGIA | | | |
| subjects affected / exposed ^[184] | 2 / 32 (6.25%) | 4 / 30 (13.33%) | |
| occurrences (all) | 4 | 4 | |
| PAIN IN EXTREMITY | | | |
| subjects affected / exposed ^[185] | 4 / 32 (12.50%) | 3 / 30 (10.00%) | |
| occurrences (all) | 5 | 5 | |
| Infections and infestations | | | |
| RASH PUSTULAR | | | |
| subjects affected / exposed ^[186] | 1 / 32 (3.13%) | 2 / 30 (6.67%) | |
| occurrences (all) | 2 | 2 | |
| SINUSITIS | | | |
| subjects affected / exposed ^[187] | 2 / 32 (6.25%) | 2 / 30 (6.67%) | |
| occurrences (all) | 2 | 2 | |
| FURUNCLE | | | |
| subjects affected / exposed ^[188] | 0 / 32 (0.00%) | 1 / 30 (3.33%) | |
| occurrences (all) | 0 | 1 | |
| INFLUENZA | | | |
| subjects affected / exposed ^[189] | 0 / 32 (0.00%) | 0 / 30 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| NASOPHARYNGITIS | | | |
| subjects affected / exposed ^[190] | 1 / 32 (3.13%) | 4 / 30 (13.33%) | |
| occurrences (all) | 2 | 8 | |
| VAGINAL INFECTION | | | |
| subjects affected / exposed ^[191] | 0 / 32 (0.00%) | 0 / 30 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| PARONYCHIA | | | |
| subjects affected / exposed ^[192] | 0 / 32 (0.00%) | 3 / 30 (10.00%) | |
| occurrences (all) | 0 | 3 | |
| LOCALISED INFECTION | | | |
| subjects affected / exposed ^[193] | 0 / 32 (0.00%) | 1 / 30 (3.33%) | |
| occurrences (all) | 0 | 1 | |

| | | | |
|--|-----------------|-----------------|--|
| UPPER RESPIRATORY TRACT INFECTION | | | |
| subjects affected / exposed ^[194] | 4 / 32 (12.50%) | 5 / 30 (16.67%) | |
| occurrences (all) | 5 | 5 | |
| PNEUMONIA | | | |
| subjects affected / exposed ^[195] | 0 / 32 (0.00%) | 1 / 30 (3.33%) | |
| occurrences (all) | 0 | 1 | |
| LYMPHANGITIS | | | |
| subjects affected / exposed ^[196] | 2 / 32 (6.25%) | 0 / 30 (0.00%) | |
| occurrences (all) | 2 | 0 | |
| CYSTITIS | | | |
| subjects affected / exposed ^[197] | 1 / 32 (3.13%) | 0 / 30 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| ORAL HERPES | | | |
| subjects affected / exposed ^[198] | 2 / 32 (6.25%) | 0 / 30 (0.00%) | |
| occurrences (all) | 3 | 0 | |
| PHARYNGITIS | | | |
| subjects affected / exposed ^[199] | 2 / 32 (6.25%) | 0 / 30 (0.00%) | |
| occurrences (all) | 2 | 0 | |
| CELLULITIS | | | |
| subjects affected / exposed ^[200] | 1 / 32 (3.13%) | 2 / 30 (6.67%) | |
| occurrences (all) | 1 | 3 | |
| NAIL INFECTION | | | |
| subjects affected / exposed ^[201] | 1 / 32 (3.13%) | 2 / 30 (6.67%) | |
| occurrences (all) | 1 | 2 | |
| LARYNGITIS | | | |
| subjects affected / exposed ^[202] | 0 / 32 (0.00%) | 1 / 30 (3.33%) | |
| occurrences (all) | 0 | 1 | |
| IMPETIGO | | | |
| subjects affected / exposed ^[203] | 0 / 32 (0.00%) | 0 / 30 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| URINARY TRACT INFECTION | | | |
| subjects affected / exposed ^[204] | 3 / 32 (9.38%) | 7 / 30 (23.33%) | |
| occurrences (all) | 4 | 9 | |
| Metabolism and nutrition disorders | | | |

| | | | |
|--|-----------------|-----------------|--|
| DEHYDRATION | | | |
| subjects affected / exposed ^[205] | 0 / 32 (0.00%) | 0 / 30 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| HYPOKALAEMIA | | | |
| subjects affected / exposed ^[206] | 5 / 32 (15.63%) | 3 / 30 (10.00%) | |
| occurrences (all) | 5 | 4 | |
| HYPOMAGNESAEMIA | | | |
| subjects affected / exposed ^[207] | 4 / 32 (12.50%) | 3 / 30 (10.00%) | |
| occurrences (all) | 5 | 3 | |
| DECREASED APPETITE | | | |
| subjects affected / exposed ^[208] | 4 / 32 (12.50%) | 3 / 30 (10.00%) | |
| occurrences (all) | 4 | 3 | |
| HYPOPHOSPHATAEMIA | | | |
| subjects affected / exposed ^[209] | 2 / 32 (6.25%) | 0 / 30 (0.00%) | |
| occurrences (all) | 2 | 0 | |
| DIABETES MELLITUS | | | |
| subjects affected / exposed ^[210] | 0 / 32 (0.00%) | 0 / 30 (0.00%) | |
| occurrences (all) | 0 | 0 | |

Notes:

[53] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.

Justification: The number of deaths displays information from the ITT population. One participant in Cohort III didn't receive treatment and is not counted in the AE tables. The safety population was defined as participants who received any amount of any study drug. The serious and non-serious AEs are reported with data from this population.

[54] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.

Justification: The number of deaths displays information from the ITT population. One participant in Cohort III didn't receive treatment and is not counted in the AE tables. The safety population was defined as participants who received any amount of any study drug. The serious and non-serious AEs are reported with data from this population.

[55] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.

Justification: The number of deaths displays information from the ITT population. One participant in Cohort III didn't receive treatment and is not counted in the AE tables. The safety population was defined as participants who received any amount of any study drug. The serious and non-serious AEs are reported with data from this population.

[56] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.

Justification: The number of deaths displays information from the ITT population. One participant in Cohort III didn't receive treatment and is not counted in the AE tables. The safety population was defined as participants who received any amount of any study drug. The serious and non-serious AEs are reported with data from this population.

[57] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.

Justification: The number of deaths displays information from the ITT population. One participant in Cohort III didn't receive treatment and is not counted in the AE tables. The safety population was defined as participants who received any amount of any study drug. The serious and non-serious AEs are reported with data from this population.

are reported with data from this population.

are reported with data from this population.

[137] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.

[138] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.

[139] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.

[140] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.

[141] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.

[142] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.

[143] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.

[144] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.

[145] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.

[146] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.

[147] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.

Justification: The number of deaths displays information from the ITT population. One participant in Cohort III didn't receive treatment and is not counted in the AE tables. The safety population was defined as participants who received any amount of any study drug. The serious and non-serious AEs are reported with data from this population.

exposed for the reporting group. These numbers are expected to be equal.

Justification: The number of deaths displays information from the ITT population. One participant in Cohort III didn't receive treatment and is not counted in the AE tables. The safety population was defined as participants who received any amount of any study drug. The serious and non-serious AEs are reported with data from this population.

[205] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.

Justification: The number of deaths displays information from the ITT population. One participant in Cohort III didn't receive treatment and is not counted in the AE tables. The safety population was defined as participants who received any amount of any study drug. The serious and non-serious AEs are reported with data from this population.

[206] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.

Justification: The number of deaths displays information from the ITT population. One participant in Cohort III didn't receive treatment and is not counted in the AE tables. The safety population was defined as participants who received any amount of any study drug. The serious and non-serious AEs are reported with data from this population.

[207] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.

Justification: The number of deaths displays information from the ITT population. One participant in Cohort III didn't receive treatment and is not counted in the AE tables. The safety population was defined as participants who received any amount of any study drug. The serious and non-serious AEs are reported with data from this population.

[208] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.

Justification: The number of deaths displays information from the ITT population. One participant in Cohort III didn't receive treatment and is not counted in the AE tables. The safety population was defined as participants who received any amount of any study drug. The serious and non-serious AEs are reported with data from this population.

[209] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.

Justification: The number of deaths displays information from the ITT population. One participant in Cohort III didn't receive treatment and is not counted in the AE tables. The safety population was defined as participants who received any amount of any study drug. The serious and non-serious AEs are reported with data from this population.

[210] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.

Justification: The number of deaths displays information from the ITT population. One participant in Cohort III didn't receive treatment and is not counted in the AE tables. The safety population was defined as participants who received any amount of any study drug. The serious and non-serious AEs are reported with data from this population.

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|------------------|--|
| 06 December 2017 | The following updates were made: [1] An exploratory patient-reported outcome (PRO) objective for Cohort I was corrected to align with the protocol version 4; [2] The risks associated with atezolizumab were updated; [3] Information and guidance for anticipated overlapping AEs for cobimetinib and atezolizumab along with atezolizumab treatment interruption were added; [4] Guidelines for managing participants who experience diarrhea was revised to clarify the management of diarrhea for all participants; [5] Management guidelines for AEs were revised; [6] Guidelines for managing participants who experienced atezolizumab-associated AEs was added. |
| 25 October 2018 | The following updates were made: [1] Subsequent reviews of the triplet treatment combinations for Cohorts II and III were updated to take place as needed; [2] The flexible wording that paclitaxel "may also be considered an IMP in this study, depending on local legislation" was removed; [3] Guidelines for managing participants who experienced atezolizumab-associated AEs was revised; [4] The reporting of the term "sudden death" was updated; [5] AE reporting for hospitalization was updated; [6] The reporting timeframe for SAEs and AESIs was updated for Cohorts II and III; [7] Language was updated for clarity in various sections of the protocol; [8] The process for reviewing and handling protocol deviations was updated; [9] Clarification was made regarding the predose atezolizumab serum sampling times. |
| 17 February 2021 | The following updates were made: [1] The list of approved indications for atezolizumab was updated; [2] "Immune-related" was changed to "immune-mediated" when describing events associated with atezolizumab; [3] Immunosuppressive medications were removed from the prohibited therapy section and added to the cautionary therapy; [4] List of atezolizumab was updated; [5] Guidelines for management of atezolizumab-associated dermatologic AEs was revised; [6] Language was added for clarity in various sections of the protocol; [7] Appendix 10 (Anaphylaxis Precautions) was modified to remove the requirement for use of a tourniquet; [8] Appendix 11 has been revised to indicate that caution should be used when considering atezolizumab for participants who previously experienced a severe or life-threatening skin adverse reaction while receiving another immunostimulatory anti-cancer agent. |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

The sponsor decided to terminate this study.

Notes: