



Clinical trial results:

A Double-Blind, Randomized, Two Arm Phase 2 Study of Nivolumab in Combination with Ipilimumab versus Nivolumab in Combination with Ipilimumab Placebo In Recurrent or Metastatic Squamous Cell Carcinoma of the Head and Neck (SCCHN) (CheckMate 714: CHECKpoint pathway and nivoluMAb clinical Trial Evaluation 714)

Summary

| | |
|--------------------------|-------------------------------|
| EudraCT number | 2016-001645-64 |
| Trial protocol | CZ ES IE BE NL SE NO GB FI IT |
| Global end of trial date | 11 March 2022 |

Results information

| | |
|--------------------------------|---------------|
| Result version number | v1 (current) |
| This version publication date | 28 March 2023 |
| First version publication date | 28 March 2023 |

Trial information

Trial identification

| | |
|-----------------------|-----------|
| Sponsor protocol code | CA209-714 |
|-----------------------|-----------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT02823574 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|---|
| Sponsor organisation name | Bristol-Myers Squibb |
| Sponsor organisation address | Chaussee de la Hulpe 185, Brussels, Belgium, 1170 |
| Public contact | EU Study Start-Up Unit, Bristol-Myers Squibb International Corporation, Clinical.Trials@bms.com |
| Scientific contact | Bristol-Myers Squibb Study Director, Bristol-Myers Squibb, Clinical.Trials@bms.gov |

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 | 22 April 2022 |
| Is this the analysis of the primary completion data? | No |

| | |
|----------------------------------|---------------|
| Global end of trial reached? | Yes |
| Global end of trial date | 11 March 2022 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

To compare the ORR and assess the DOR of the treatment of nivolumab in combination with ipilimumab vs nivolumab in combination with ipilimumab placebo, as determined by a blinded independent central review (BICR) using Response Evaluation Criteria In Solid Tumors (RECIST 1.1) criteria, for first-line treatment of recurrent or metastatic SCCHN in the platinum refractory setting.

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and in compliance with all International Conference on Harmonization Good Clinical Practice Guidelines. All the local regulatory requirements pertinent to safety of trial subjects were followed.

Background therapy: -

Evidence for comparator: -

| | |
|---|-------------------|
| Actual start date of recruitment | 22 September 2016 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | Yes |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|------------------------|
| Country: Number of subjects enrolled | Argentina: 1 |
| Country: Number of subjects enrolled | Belgium: 12 |
| Country: Number of subjects enrolled | Brazil: 45 |
| Country: Number of subjects enrolled | Canada: 46 |
| Country: Number of subjects enrolled | Chile: 1 |
| Country: Number of subjects enrolled | Finland: 2 |
| Country: Number of subjects enrolled | France: 79 |
| Country: Number of subjects enrolled | Ireland: 10 |
| Country: Number of subjects enrolled | Italy: 1 |
| Country: Number of subjects enrolled | Mexico: 13 |
| Country: Number of subjects enrolled | Netherlands: 13 |
| Country: Number of subjects enrolled | Norway: 20 |
| Country: Number of subjects enrolled | Romania: 37 |
| Country: Number of subjects enrolled | Russian Federation: 10 |
| Country: Number of subjects enrolled | South Africa: 1 |
| Country: Number of subjects enrolled | Spain: 22 |
| Country: Number of subjects enrolled | Sweden: 1 |
| Country: Number of subjects enrolled | Turkey: 3 |
| Country: Number of subjects enrolled | United Kingdom: 19 |

| | |
|--------------------------------------|-------------------|
| Country: Number of subjects enrolled | United States: 69 |
| Country: Number of subjects enrolled | Czechia: 20 |
| Worldwide total number of subjects | 425 |
| EEA total number of subjects | 217 |

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) | 301 |
| From 65 to 84 years | 122 |
| 85 years and over | 2 |

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

425 randomized and 423 participants treated.

Period 1

| | |
|------------------------------|-------------------------|
| Period 1 title | Randomization |
| Is this the baseline period? | Yes |
| Allocation method | Randomised - controlled |
| Blinding used | Double blind |
| Roles blinded | Subject, Investigator |

Arms

| | |
|------------------------------|-----|
| Are arms mutually exclusive? | Yes |
|------------------------------|-----|

| | |
|------------------|--|
| Arm title | Treatment A - Platinum Refractory Subgroup |
|------------------|--|

Arm description:

Participants with histologically confirmed Squamous Cell Carcinoma of the Head and Neck (SCCHN) that has recurred during or less than 6 months after completion of previous platinum-based chemotherapy. Treated with Nivolumab 3 mg/kg Q2W + Ipilimumab 1 mg/kg Q6W

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

Dosage and administration details:

100mg (10mg/mL)

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

Dosage and administration details:

200mg (5mg/mL)

| | |
|------------------|--|
| Arm title | Treatment B - Platinum Refractory Subgroup |
|------------------|--|

Arm description:

Participants with histologically confirmed Squamous Cell Carcinoma of the Head and Neck (SCCHN) that has recurred during or less than 6 months after completion of previous platinum-based chemotherapy. Treated with Nivolumab 3 mg/kg Q2W + Ipilimumab-Placebo Q6W

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

Dosage and administration details:

(0.9% sodium chloride injection or 5% dextrose injection

| | |
|---|--|
| Investigational medicinal product name | nivolumab |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for injection |
| Routes of administration | Intravenous use |
| Dosage and administration details: 100mg (10mg/mL) | |
| Arm title | Treatment A - Platinum Eligible Subgroup |

Arm description:

Participants with histologically confirmed Squamous Cell Carcinoma of the Head and Neck (SCCHN) who are platinum naive or have recurred 6 months or more after completion of previous platinum-based chemotherapy. Treated with Nivolumab 3 mg/kg Q2W + Ipilimumab 1 mg/kg Q6W

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

Dosage and administration details:

200mg (5mg/mL)

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

Dosage and administration details:

100mg (10mg/mL)

| | |
|------------------|--|
| Arm title | Treatment B - Platinum Eligible Subgroup |
|------------------|--|

Arm description:

Participants with histologically confirmed Squamous Cell Carcinoma of the Head and Neck (SCCHN) who are platinum naive or have recurred 6 months or more after completion of previous platinum-based chemotherapy. Treated with Nivolumab 3 mg/kg Q2W + Ipilimumab-Placebo Q6W

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

Dosage and administration details:

(0.9% sodium chloride injection or 5% dextrose injection)

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

Dosage and administration details:

100mg (10mg/mL)

| Number of subjects in period 1 | Treatment A - Platinum Refractory Subgroup | Treatment B - Platinum Refractory Subgroup | Treatment A - Platinum Eligible Subgroup |
|--------------------------------|--|--|--|
| Started | 159 | 82 | 123 |
| Completed | 158 | 82 | 122 |
| Not completed | 1 | 0 | 1 |
| AE unrelated to Study Drug | 1 | - | - |
| Disease Progression | - | - | 1 |

| Number of subjects in period 1 | Treatment B - Platinum Eligible Subgroup |
|--------------------------------|--|
| Started | 61 |
| Completed | 61 |
| Not completed | 0 |
| AE unrelated to Study Drug | - |
| Disease Progression | - |

Period 2

| | |
|------------------------------|-------------------------|
| Period 2 title | Treatment Period |
| Is this the baseline period? | No |
| Allocation method | Randomised - controlled |
| Blinding used | Double blind |
| Roles blinded | Subject, Investigator |

Arms

| | |
|------------------------------|--|
| Are arms mutually exclusive? | Yes |
| Arm title | Treatment A - Platinum Refractory Subgroup |

Arm description:

Participants with histologically confirmed Squamous Cell Carcinoma of the Head and Neck (SCCHN) that has recurred during or less than 6 months after completion of previous platinum-based chemotherapy. Treated with Nivolumab 3 mg/kg Q2W + Ipilimumab 1 mg/kg Q6W

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

Dosage and administration details:

200mg (5mg/mL)

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

Dosage and administration details:

100mg (10mg/mL)

| | |
|--|--|
| Arm title | Treatment B - Platinum Refractory Subgroup |
| Arm description: | |
| Participants with histologically confirmed Squamous Cell Carcinoma of the Head and Neck (SCCHN) that has recurred during or less than 6 months after completion of previous platinum-based chemotherapy. Treated with Nivolumab 3 mg/kg Q2W + Ipilimumab-Placebo Q6W | |
| Arm type | Experimental |
| Investigational medicinal product name | nivolumab |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for injection |
| Routes of administration | Intravenous use |
| Dosage and administration details: | |
| 100mg (10mg/mL) | |
| Investigational medicinal product name | placebo |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for injection |
| Routes of administration | Intravenous use |
| Dosage and administration details: | |
| 0.9% sodium chloride injection or 5% dextrose injection | |
| Arm title | Treatment A - Platinum Eligible Subgroup |

| | |
|--|--|
| Arm description: | |
| Participants with histologically confirmed Squamous Cell Carcinoma of the Head and Neck (SCCHN) who are platinum naïve or have recurred 6 months or more after completion of previous platinum-based chemotherapy. Treated with Nivolumab 3 mg/kg Q2W + Ipilimumab 1 mg/kg Q6W | |
| Arm type | Experimental |
| Investigational medicinal product name | ipilimumab |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for injection |
| Routes of administration | Intravenous use |
| Dosage and administration details: | |
| 200mg (5mg/mL) | |
| Investigational medicinal product name | nivolumab |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for injection |
| Routes of administration | Intravenous use |
| Dosage and administration details: | |
| 100mg (10mg/mL) | |
| Arm title | Treatment B - Platinum Eligible Subgroup |

| | |
|--|------------------------|
| Arm description: | |
| Participants with histologically confirmed Squamous Cell Carcinoma of the Head and Neck (SCCHN) who are platinum naïve or have recurred 6 months or more after completion of previous platinum-based chemotherapy. Treated with Nivolumab 3 mg/kg Q2W + Ipilimumab-Placebo Q6W | |
| Arm type | Experimental |
| Investigational medicinal product name | nivolumab |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for injection |
| Routes of administration | Intravenous use |

Dosage and administration details:

100mg (10mg/mL)

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

Dosage and administration details:

0.9% sodium chloride injection or 5% dextrose injection

| Number of subjects in period 2 | Treatment A - Platinum Refractory Subgroup | Treatment B - Platinum Refractory Subgroup | Treatment A - Platinum Eligible Subgroup |
|---|--|--|--|
| Started | 158 | 82 | 122 |
| Completed | 0 | 0 | 0 |
| Not completed | 158 | 82 | 122 |
| Adverse event, serious fatal | - | - | 3 |
| Participant withdrew consent | 4 | - | - |
| Poor/Non Compliance | 1 | - | - |
| Participant request to discontinue | 5 | - | 3 |
| Maximum Clinical Benefit | 8 | 4 | 7 |
| Adverse Event unrelated to to study Drug | 10 | 2 | 9 |
| Participant no longer meets study criteria | - | - | 1 |
| Other reasons | 5 | 9 | 3 |
| Study Drug Toxicity | 11 | 2 | 14 |
| Lost to follow-up | 1 | 1 | - |
| Disease Progression | 113 | 64 | 82 |

| Number of subjects in period 2 | Treatment B - Platinum Eligible Subgroup |
|---|--|
| Started | 61 |
| Completed | 0 |
| Not completed | 61 |
| Adverse event, serious fatal | 1 |
| Participant withdrew consent | 1 |
| Poor/Non Compliance | 1 |
| Participant request to discontinue | 2 |
| Maximum Clinical Benefit | 1 |
| Adverse Event unrelated to to study Drug | 2 |
| Participant no longer meets study criteria | - |
| Other reasons | 6 |

| | |
|---------------------|----|
| Study Drug Toxicity | 4 |
| Lost to follow-up | - |
| Disease Progression | 43 |

Baseline characteristics

Reporting groups

| | |
|-----------------------|--|
| Reporting group title | Treatment A - Platinum Refractory Subgroup |
|-----------------------|--|

Reporting group description:

Participants with histologically confirmed Squamous Cell Carcinoma of the Head and Neck (SCCHN) that has recurred during or less than 6 months after completion of previous platinum-based chemotherapy. Treated with Nivolumab 3 mg/kg Q2W + Ipilimumab 1 mg/kg Q6W

| | |
|-----------------------|--|
| Reporting group title | Treatment B - Platinum Refractory Subgroup |
|-----------------------|--|

Reporting group description:

Participants with histologically confirmed Squamous Cell Carcinoma of the Head and Neck (SCCHN) that has recurred during or less than 6 months after completion of previous platinum-based chemotherapy. Treated with Nivolumab 3 mg/kg Q2W + Ipilimumab-Placebo Q6W

| | |
|-----------------------|--|
| Reporting group title | Treatment A - Platinum Eligible Subgroup |
|-----------------------|--|

Reporting group description:

Participants with histologically confirmed Squamous Cell Carcinoma of the Head and Neck (SCCHN) who are platinum naive or have recurred 6 months or more after completion of previous platinum-based chemotherapy. Treated with Nivolumab 3 mg/kg Q2W + Ipilimumab 1 mg/kg Q6W

| | |
|-----------------------|--|
| Reporting group title | Treatment B - Platinum Eligible Subgroup |
|-----------------------|--|

Reporting group description:

Participants with histologically confirmed Squamous Cell Carcinoma of the Head and Neck (SCCHN) who are platinum naive or have recurred 6 months or more after completion of previous platinum-based chemotherapy. Treated with Nivolumab 3 mg/kg Q2W + Ipilimumab-Placebo Q6W

| Reporting group values | Treatment A - Platinum Refractory Subgroup | Treatment B - Platinum Refractory Subgroup | Treatment A - Platinum Eligible Subgroup |
|---|--|--|--|
| Number of subjects | 159 | 82 | 123 |
| Age Categorical Units: participants | | | |
| <=18 years | 0 | 0 | 0 |
| Between 18 and 65 years | 119 | 63 | 79 |
| >=65 years | 40 | 19 | 44 |
| Age continuous Units: years | | | |
| arithmetic mean | 58.2 | 57.9 | 61.8 |
| full range (min-max) | 24 to 82 | 36 to 77 | 37 to 88 |
| Sex: Female, Male Units: participants | | | |
| Female | 29 | 18 | 18 |
| Male | 130 | 64 | 105 |
| Race (NIH/OMB) Units: Subjects | | | |
| American Indian or Alaska Native | 0 | 0 | 0 |
| Asian | 3 | 1 | 0 |
| Native Hawaiian or Other Pacific Islander | 0 | 0 | 0 |
| Black or African American | 2 | 3 | 2 |
| White | 141 | 75 | 120 |
| More than one race | 0 | 0 | 0 |
| Unknown or Not Reported | 13 | 3 | 1 |
| Ethnicity (NIH/OMB) | | | |

| | | | |
|-------------------------|----|----|----|
| Units: Subjects | | | |
| Hispanic or Latino | 10 | 7 | 6 |
| Not Hispanic or Latino | 56 | 23 | 66 |
| Unknown or Not Reported | 93 | 52 | 51 |

| Reporting group values | Treatment B - Platinum Eligible Subgroup | Total | |
|--|--|-------|--|
| Number of subjects | 61 | 425 | |
| Age Categorical | | | |
| Units: participants | | | |
| <=18 years | 0 | 0 | |
| Between 18 and 65 years | 40 | 301 | |
| >=65 years | 21 | 124 | |
| Age continuous | | | |
| Units: years | | | |
| arithmetic mean | 60.8 | | |
| full range (min-max) | 33 to 79 | - | |
| Sex: Female, Male | | | |
| Units: participants | | | |
| Female | 14 | 79 | |
| Male | 47 | 346 | |
| Race (NIH/OMB) | | | |
| Units: Subjects | | | |
| American Indian or Alaska Native | 0 | 0 | |
| Asian | 1 | 5 | |
| Native Hawaiian or Other Pacific Islander | 0 | 0 | |
| Black or African American | 1 | 8 | |
| White | 58 | 394 | |
| More than one race | 0 | 0 | |
| Unknown or Not Reported | 1 | 18 | |
| Ethnicity (NIH/OMB) | | | |
| Units: Subjects | | | |
| Hispanic or Latino | 6 | 29 | |
| Not Hispanic or Latino | 25 | 170 | |
| Unknown or Not Reported | 30 | 226 | |

End points

End points reporting groups

| | |
|--|--|
| Reporting group title | Treatment A - Platinum Refractory Subgroup |
| Reporting group description: Participants with histologically confirmed Squamous Cell Carcinoma of the Head and Neck (SCCHN) that has recurred during or less than 6 months after completion of previous platinum-based chemotherapy. Treated with Nivolumab 3 mg/kg Q2W + Ipilimumab 1 mg/kg Q6W | |
| Reporting group title | Treatment B - Platinum Refractory Subgroup |
| Reporting group description: Participants with histologically confirmed Squamous Cell Carcinoma of the Head and Neck (SCCHN) that has recurred during or less than 6 months after completion of previous platinum-based chemotherapy. Treated with Nivolumab 3 mg/kg Q2W + Ipilimumab-Placebo Q6W | |
| Reporting group title | Treatment A - Platinum Eligible Subgroup |
| Reporting group description: Participants with histologically confirmed Squamous Cell Carcinoma of the Head and Neck (SCCHN) who are platinum naive or have recurred 6 months or more after completion of previous platinum-based chemotherapy. Treated with Nivolumab 3 mg/kg Q2W + Ipilimumab 1 mg/kg Q6W | |
| Reporting group title | Treatment B - Platinum Eligible Subgroup |
| Reporting group description: Participants with histologically confirmed Squamous Cell Carcinoma of the Head and Neck (SCCHN) who are platinum naive or have recurred 6 months or more after completion of previous platinum-based chemotherapy. Treated with Nivolumab 3 mg/kg Q2W + Ipilimumab-Placebo Q6W | |
| Reporting group title | Treatment A - Platinum Refractory Subgroup |
| Reporting group description: Participants with histologically confirmed Squamous Cell Carcinoma of the Head and Neck (SCCHN) that has recurred during or less than 6 months after completion of previous platinum-based chemotherapy. Treated with Nivolumab 3 mg/kg Q2W + Ipilimumab 1 mg/kg Q6W | |
| Reporting group title | Treatment B - Platinum Refractory Subgroup |
| Reporting group description: Participants with histologically confirmed Squamous Cell Carcinoma of the Head and Neck (SCCHN) that has recurred during or less than 6 months after completion of previous platinum-based chemotherapy. Treated with Nivolumab 3 mg/kg Q2W + Ipilimumab-Placebo Q6W | |
| Reporting group title | Treatment A - Platinum Eligible Subgroup |
| Reporting group description: Participants with histologically confirmed Squamous Cell Carcinoma of the Head and Neck (SCCHN) who are platinum naive or have recurred 6 months or more after completion of previous platinum-based chemotherapy. Treated with Nivolumab 3 mg/kg Q2W + Ipilimumab 1 mg/kg Q6W | |
| Reporting group title | Treatment B - Platinum Eligible Subgroup |
| Reporting group description: Participants with histologically confirmed Squamous Cell Carcinoma of the Head and Neck (SCCHN) who are platinum naive or have recurred 6 months or more after completion of previous platinum-based chemotherapy. Treated with Nivolumab 3 mg/kg Q2W + Ipilimumab-Placebo Q6W | |
| Subject analysis set title | Treatment A |
| Subject analysis set type | Intention-to-treat |
| Subject analysis set description: Participants in both Platinum Refractory Subgroup and Platinum Eligible Subgroup treated with Nivolumab 3 mg/kg Q2W + Ipilimumab 1 mg/kg Q6W | |
| Subject analysis set title | Treatment B |
| Subject analysis set type | Intention-to-treat |
| Subject analysis set description: Participants in both Platinum Refractory Subgroup and Platinum Eligible Subgroup treated with Nivolumab 3 mg/kg Q2W + Ipilimumab-Placebo Q6W | |

Primary: Objective Response Rate (ORR) as determined by Blinded Independent Central Review (BIRC) - Platinum refractory subgroup

| | |
|-----------------|--|
| End point title | Objective Response Rate (ORR) as determined by Blinded Independent Central Review (BIRC) - Platinum refractory subgroup ^[1] |
|-----------------|--|

End point description:

ORR is defined as best overall response (BOR) of a complete response (CR) or partial response (PR) divided by the number of randomized participants for each treatment group.

Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes(whether target or non-target) must have reduction in short axis to < 10 mm.

Partial Response (PR): At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.

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

End point timeframe:

Approximately up to 30 months (from FPFV to Data base lock)

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: Endpoints are specific for subgroups not baseline period

| End point values | Treatment A - Platinum Refractory Subgroup | Treatment B - Platinum Refractory Subgroup | | |
|-----------------------------------|--|--|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 159 | 82 | | |
| Units: percentage of participants | | | | |
| number (confidence interval 95%) | 13.2 (8.4 to 19.5) | 18.3 (10.6 to 28.4) | | |

Statistical analyses

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

Statistical analysis description:

Treatment A over Treatment B

| | |
|---|---|
| Comparison groups | Treatment A - Platinum Refractory Subgroup v Treatment B - Platinum Refractory Subgroup |
| Number of subjects included in analysis | 241 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.2897 |
| Method | Mantel-Haenszel |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 0.68 |
| Confidence interval | |
| level | 95.5 % |
| sides | 2-sided |
| lower limit | 0.33 |
| upper limit | 1.43 |

Primary: Duration of Response (DOR) as determined by Blinded Independent Central Review (BIRC) - Platinum refractory subgroup

| | |
|-----------------|--|
| End point title | Duration of Response (DOR) as determined by Blinded Independent Central Review (BIRC) - Platinum refractory subgroup ^{[2][3]} |
|-----------------|--|

End point description:

The time between the date of first confirmed response to the date of the first documented tumor progression, or death due to any cause, whichever occurs first.

Here "99999" signifies NA

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

End point timeframe:

Approximately up to 30 months (from FPFV to Data base lock)

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: Endpoints are specific for subgroups not baseline period

[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: Endpoints are specific for subgroups not baseline period

| End point values | Treatment A - Platinum Refractory Subgroup | Treatment B - Platinum Refractory Subgroup | | |
|----------------------------------|--|--|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 21 | 15 | | |
| Units: Months | | | | |
| median (confidence interval 95%) | 99999 (11.01 to 99999) | 11.07 (4.14 to 99999) | | |

Statistical analyses

No statistical analyses for this end point

Primary: Time to Response (TTR) as determined by Blinded Independent Central Review (BIRC) - Platinum refractory subgroup

| | |
|-----------------|--|
| End point title | Time to Response (TTR) as determined by Blinded Independent Central Review (BIRC) - Platinum refractory subgroup ^{[4][5]} |
|-----------------|--|

End point description:

Time to Response (TTR) for participants demonstrating a response (either CR or PR) was defined as the time from the date of randomization to the date of the first confirmed response.

Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes(whether target or non-target) must have reduction in short axis to < 10 mm.

Partial Response (PR): At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.

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

End point timeframe:

Approximately up to 30 months (from FPFV to Data base lock)

Notes:

[4] - 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: Endpoints are specific for subgroups not baseline period

[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: Endpoints are specific for subgroups not baseline period

| End point values | Treatment A - Platinum Refractory Subgroup | Treatment B - Platinum Refractory Subgroup | | |
|-------------------------------|---|---|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 21 | 15 | | |
| Units: Months | | | | |
| median (full range (min-max)) | 2.56 (1.1 to 6.6) | 1.51 (1.2 to 7.7) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Objective Response Rate (ORR) as determined by Blinded Independent Central Review (BIRC) - Platinum Eligible subgroup

| | |
|-----------------|--|
| End point title | Objective Response Rate (ORR) as determined by Blinded Independent Central Review (BIRC) - Platinum Eligible subgroup ^[6] |
|-----------------|--|

End point description:

ORR is defined as percentage of participants with a complete response (CR) or partial response (PR)

Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes(whether target or non-target) must have reduction in short axis to < 10 mm.

Partial Response (PR): At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.

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

End point timeframe:

From randomization to end of study. Approximately 63 Months

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: Endpoints are specific for subgroups not baseline period

| End point values | Treatment A - Platinum Eligible Subgroup | Treatment B - Platinum Eligible Subgroup | | |
|-----------------------------------|---|---|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 123 | 61 | | |
| Units: percentage of participants | | | | |
| number (confidence interval 95%) | 20.3 (13.6 to 28.5) | 29.5 (18.5 to 42.6) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Response (DOR) as determined by Blinded Independent Central Review (BIRC) - Platinum Eligible subgroup

| | |
|-----------------|---|
| End point title | Duration of Response (DOR) as determined by Blinded Independent Central Review (BIRC) - Platinum Eligible subgroup ^[7] |
|-----------------|---|

End point description:

The time between the date of first confirmed response to the date of the first documented tumor progression, or death due to any cause, whichever occurs first.

Here "99999" signifies NA

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

End point timeframe:

From randomization to disease progression or death. Approximately 63 Months

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: Endpoints are specific for subgroups not baseline period

| End point values | Treatment A - Platinum Eligible Subgroup | Treatment B - Platinum Eligible Subgroup | | |
|----------------------------------|--|--|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 25 | 18 | | |
| Units: Months | | | | |
| median (confidence interval 95%) | 27.04 (11.01 to 99999) | 24.61 (6.90 to 99999) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Progression Free Survival (PFS) as determined by Blinded Independent Central Review (BIRC) - Platinum Refractory subgroup

| | |
|-----------------|--|
| End point title | Progression Free Survival (PFS) as determined by Blinded Independent Central Review (BIRC) - Platinum Refractory subgroup ^[8] |
|-----------------|--|

End point description:

The time from randomization to the date of first documented disease progression, or death due to any cause, whichever occurs first.

Progressive Disease (PD): At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progression).

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

End point timeframe:

From randomization to disease progression or death. Approximately 63 Months

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: Endpoints are specific for subgroups not baseline period

| End point values | Treatment A - Platinum Refractory Subgroup | Treatment B - Platinum Refractory Subgroup | | |
|----------------------------------|--|--|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 159 | 82 | | |
| Units: Months | | | | |
| median (confidence interval 95%) | 2.50 (1.45 to 2.76) | 2.60 (1.54 to 3.38) | | |

Statistical analyses

| Statistical analysis title | Statistical Analysis |
|---|---|
| Comparison groups | Treatment A - Platinum Refractory Subgroup v Treatment B - Platinum Refractory Subgroup |
| Number of subjects included in analysis | 241 |
| Analysis specification | Pre-specified |
| Analysis type | |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 1.05 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.78 |
| upper limit | 1.41 |

Secondary: Progression Free Survival (PFS) as determined by Blinded Independent Central Review (BIRC) - Platinum Eligible subgroup

| | |
|-----------------|--|
| End point title | Progression Free Survival (PFS) as determined by Blinded Independent Central Review (BIRC) - Platinum Eligible subgroup ^[9] |
|-----------------|--|

End point description:

the time from randomization to the date of first documented disease progression, or death due to any cause, whichever occurs first.

Progressive Disease (PD): At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progression).

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

End point timeframe:

From randomization to disease progression or death. Approximately 63 Months

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: Endpoints are specific for subgroups not baseline period

| End point values | Treatment A - Platinum Eligible Subgroup | Treatment B - Platinum Eligible Subgroup | | |
|----------------------------------|--|--|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 123 | 61 | | |
| Units: Months | | | | |
| median (confidence interval 95%) | 2.76 (1.64 to 4.17) | 2.86 (1.51 to 5.65) | | |

Statistical analyses

| Statistical analysis title | Statistical Analysis |
|---|---|
| Comparison groups | Treatment A - Platinum Eligible Subgroup v Treatment B - Platinum Eligible Subgroup |
| Number of subjects included in analysis | 184 |
| Analysis specification | Pre-specified |
| Analysis type | |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 1.12 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.8 |
| upper limit | 1.59 |

Secondary: Overall Survival (OS)

| | |
|------------------------|---|
| End point title | Overall Survival (OS) |
| End point description: | Overall survival was defined as the time from randomization to the date of death from any cause. Participants were censored at the date they were last known to be alive and at the date of randomization if they were randomized but had no follow-up. |
| End point type | Secondary |
| End point timeframe: | From randomization to death. Approximately 63 Months |

| End point values | Treatment A | Treatment B | | |
|----------------------------------|----------------------|-----------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 282 | 143 | | |
| Units: Months | | | | |
| median (confidence interval 95%) | 9.76 (7.52 to 11.47) | 11.30 (8.48 to 14.00) | | |

Statistical analyses

| | |
|---|---------------------------|
| Statistical analysis title | Statistical Analysis |
| Comparison groups | Treatment A v Treatment B |
| Number of subjects included in analysis | 425 |
| Analysis specification | Pre-specified |
| Analysis type | |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 1.09 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.87 |
| upper limit | 1.36 |

Secondary: Overall Survival (OS) - Platinum Refractory Subgroup

| | |
|------------------------|---|
| End point title | Overall Survival (OS) - Platinum Refractory Subgroup ^[10] |
| End point description: | Overall survival was defined as the time from randomization to the date of death from any cause. Participants were censored at the date they were last known to be alive and at the date of randomization if they were randomized but had no follow-up. |
| End point type | Secondary |
| End point timeframe: | From randomization to death. Approximately 63 Months |

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: Endpoints are specific for subgroups not baseline period

| | | | | |
|----------------------------------|--|--|--|--|
| End point values | Treatment A - Platinum Refractory Subgroup | Treatment B - Platinum Refractory Subgroup | | |
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 159 | 82 | | |
| Units: Months | | | | |
| median (confidence interval 95%) | 9.76 (6.51 to 11.37) | 9.59 (7.13 to 14.26) | | |

Statistical analyses

| | |
|-----------------------------------|---|
| Statistical analysis title | Statistical Analysis |
| Comparison groups | Treatment A - Platinum Refractory Subgroup v Treatment B - Platinum Refractory Subgroup |

| | |
|---|-------------------|
| Number of subjects included in analysis | 241 |
| Analysis specification | Pre-specified |
| Analysis type | |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 1.08 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.81 |
| upper limit | 1.45 |

Secondary: Overall Survival (OS) - Platinum Eligible Subgroup

| | |
|---|--|
| End point title | Overall Survival (OS) - Platinum Eligible Subgroup ^[11] |
| End point description: | |
| Overall survival was defined as the time from randomization to the date of death from any cause. Participants were censored at the date they were last known to be alive and at the date of randomization if they were randomized but had no follow-up. | |
| End point type | Secondary |
| End point timeframe: | |
| From randomization to death. Approximately 63 Months | |
| 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: Endpoints are specific for subgroups not baseline period | |

| End point values | Treatment A - Platinum Eligible Subgroup | Treatment B - Platinum Eligible Subgroup | | |
|----------------------------------|--|--|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 123 | 61 | | |
| Units: Months | | | | |
| median (confidence interval 95%) | 9.71 (7.43 to 12.62) | 12.91 (9.33 to 22.01) | | |

Statistical analyses

| | |
|---|---|
| Statistical analysis title | Statistical Analysis |
| Comparison groups | Treatment A - Platinum Eligible Subgroup v Treatment B - Platinum Eligible Subgroup |
| Number of subjects included in analysis | 184 |
| Analysis specification | Pre-specified |
| Analysis type | |
| Parameter estimate | Cox proportional hazard |
| Point estimate | 1.14 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.81 |
| upper limit | 1.61 |

Secondary: ORR - Platinum Eligible Subgroup based on HPV p-16 status

| | |
|-----------------|---|
| End point title | ORR - Platinum Eligible Subgroup based on HPV p-16 status ^[12] |
|-----------------|---|

End point description:

ORR is defined as percentage of participants with a complete response (CR) or partial response (PR)

Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes(whether target or non-target) must have reduction in short axis to < 10 mm.

Partial Response (PR): At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.

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

End point timeframe:

From randomization to end of study. Approximately 63 Months

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: Endpoints are specific for subgroups not baseline period

| End point values | Treatment A - Platinum Eligible Subgroup | Treatment B - Platinum Eligible Subgroup | | |
|-----------------------------------|--|--|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 123 | 61 | | |
| Units: percentage of participants | | | | |
| number (confidence interval 95%) | | | | |
| Positive | 20.0 (8.4 to 36.9) | 41.2 (18.4 to 67.1) | | |
| Negative | 20.5 (12.6 to 30.4) | 25.0 (13.2 to 40.3) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: ORR - Platinum Eligible Subgroup based on Tumor Mutation Burden (TMB) Biomarker

| | |
|-----------------|---|
| End point title | ORR - Platinum Eligible Subgroup based on Tumor Mutation Burden (TMB) Biomarker ^[13] |
|-----------------|---|

End point description:

ORR is defined as percentage of participants with a complete response (CR) or partial response (PR)

Tumor Mutational Burden (TMB) refers to the number of nonsynonymous somatic mutations that exist within a tumor's genome as measured by the Foundation One CDx panel at Foundation Medicine. The analysis was done on subjects with baseline tumor mutation burden by a cutoff of 7

mutations/megabase (mut/Mb) and 10 mut/Mb

Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes(whether target or non-target) must have reduction in short axis to < 10 mm.

Partial Response (PR): At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.

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

End point timeframe:

From randomization to end of study. Approximately 63 Months

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: Endpoints are specific for subgroups not baseline period

| End point values | Treatment A - Platinum Eligible Subgroup | Treatment B - Platinum Eligible Subgroup | | |
|-----------------------------------|---|---|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 123 | 61 | | |
| Units: percentage of participants | | | | |
| number (confidence interval 95%) | | | | |
| TMB < 7 | 10.2 (3.8 to 20.8) | 30.8 (14.3 to 51.8) | | |
| TMB ≥ 7 | 34.2 (19.6 to 51.4) | 28.6 (11.3 to 52.2) | | |
| TMB < 10 | 17.3 (9.8 to 27.3) | 28.6 (14.6 to 46.3) | | |
| TMB ≥ 10 | 31.3 (11.0 to 58.7) | 33.3 (9.9 to 65.1) | | |
| TMB Not Reported | 23.1 (9.0 to 43.6) | 28.6 (8.4 to 58.1) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: ORR - Platinum Refractory Subgroup based on HPV p-16 Status

| | |
|-----------------|--|
| End point title | ORR - Platinum Refractory Subgroup based on HPV p-16 |
|-----------------|--|

End point description:

ORR is defined as percentage of participants with a complete response (CR) or partial response (PR)

Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes(whether target or non-target) must have reduction in short axis to < 10 mm.

Partial Response (PR): At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.

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

End point timeframe:

From randomization to end of study. Approximately 63 Months

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: Endpoints are specific for subgroups not baseline period

| End point values | Treatment A - Platinum Refractory Subgroup | Treatment B - Platinum Refractory Subgroup | | |
|---|---|---|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 159 | 82 | | |
| Units: percentage of participants | | | | |
| number (confidence interval 95%) | | | | |
| OROPHARYNGEAL HPV P-16 POSITIVE | 23.3 (9.9 to 42.3) | 37.5 (15.2 to 64.6) | | |
| OROPHARYNGEAL HPV P-16 NEGATIVE/ NON-OROPHARYNGEAL | 12.4 (7.3 to 19.4) | 16.7 (8.6 to 27.9) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: ORR - Platinum Refractory Subgroup based on Tumor Mutation Burden (TMB) Biomarker

| | |
|-----------------|---|
| End point title | ORR - Platinum Refractory Subgroup based on Tumor Mutation Burden (TMB) Biomarker ^[15] |
|-----------------|---|

End point description:

ORR is defined as percentage of participants with a complete response (CR) or partial response (PR)

Tumor Mutational Burden (TMB) refers to the number of nonsynonymous somatic mutations that exist within a tumor's genome as measured by the Foundation One CDx panel at Foundation Medicine. The analysis was done on subjects with baseline tumor mutation burden by a cutoff of 7 mutations/megabase (mut/Mb) and 10 mut/Mb

Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes(whether target or non-target) must have reduction in short axis to < 10 mm.

Partial Response (PR): At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.

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

End point timeframe:

From randomization to end of study. Approximately 63 Months

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: Endpoints are specific for subgroups not baseline period

| End point values | Treatment A - Platinum Refractory Subgroup | Treatment B - Platinum Refractory Subgroup | | |
|-----------------------------------|---|---|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 159 | 82 | | |
| Units: percentage of participants | | | | |

| number (confidence interval 95%) | | | | |
|----------------------------------|---------------------|---------------------|--|--|
| TMB < 7 | 9.0 (3.4 to 18.5) | 20.5 (9.3 to 36.5) | | |
| TMB ≥ 7 | 23.3 (11.8 to 38.6) | 19.0 (5.4 to 41.9) | | |
| TMB < 10 | 11.0 (5.4 to 19.3) | 22.4 (11.8 to 36.6) | | |
| TMB ≥ 10 | 31.6 (12.6 to 56.6) | 18.2 (2.3 to 51.8) | | |
| TMB Not Reported | 14.3 (5.9 to 27.2) | 18.2 (5.2 to 40.3) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Response (DOR) - Platinum Refractory subgroup based on HPV p-16 Status

| | |
|-----------------|--|
| End point title | Duration of Response (DOR) - Platinum Refractory subgroup based on HPV p-16 Status ^[16] |
|-----------------|--|

End point description:

The time between the date of first confirmed response to the date of the first documented tumor progression, or death due to any cause, whichever occurs first.

Here "99999" signifies NA

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

End point timeframe:

From randomization to disease progression or death. Approximately 63 Months

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: Endpoints are specific for subgroups not baseline period

| End point values | Treatment A - Platinum Refractory Subgroup | Treatment B - Platinum Refractory Subgroup | | |
|----------------------------------|--|--|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 21 | 15 | | |
| Units: Months | | | | |
| median (confidence interval 95%) | | | | |
| HPV p-16 Positive | 99999 (6.87 to 99999) | 11.10 (4.17 to 14.9) | | |
| HPV p-16 Negative | 39.43 (26.71 to 99999) | 8.34 (2.79 to 99999) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Response (DOR) - Platinum Refractory subgroup based on

Tumor Mutation Burden (TMB) Status

| | |
|-----------------|---|
| End point title | Duration of Response (DOR) - Platinum Refractory subgroup based on Tumor Mutation Burden (TMB) Status ^[17] |
|-----------------|---|

End point description:

The time between the date of first confirmed response to the date of the first documented tumor progression, or death due to any cause, whichever occurs first.

Here "99999" signifies NA

Tumor Mutational Burden (TMB) refers to the number of nonsynonymous somatic mutations that exist within a tumor's genome as measured by the Foundation One CDx panel at Foundation Medicine. The analysis was done on subjects with baseline tumor mutation burden by a cutoff of 7 mutations/megabase (mut/Mb) and 10 mut/Mb

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

End point timeframe:

From randomization to disease progression or death. Approximately 63 Months

Notes:

[17] - 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: Endpoints are specific for subgroups not baseline period

| End point values | Treatment A - Platinum Refractory Subgroup | Treatment B - Platinum Refractory Subgroup | | |
|----------------------------------|--|--|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 21 | 15 | | |
| Units: Months | | | | |
| median (confidence interval 95%) | | | | |
| TMB: <7 | 99999 (11.01 to 99999) | 11.14 (2.69 to 99999) | | |
| TMB ≥ 7 | 38.67 (3.06 to 39.43) | 8.59 (2.79 to 99999) | | |
| TMB: <10 | 99999 (3.06 to 99999) | 11.14 (4.17 to 99999) | | |
| TMB: ≥ 10 | 38.67 (6.87 to 38.67) | 7.54 (2.79 to 12.29) | | |
| TMB: Not Reported | 26.71 (6.93 to 26.71) | 8.21 (4.14 to 14.29) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Progression Free Survival (PFS) - Platinum Refractory subgroup based on HPV p-16 Status

| | |
|-----------------|---|
| End point title | Progression Free Survival (PFS) - Platinum Refractory subgroup based on HPV p-16 Status ^[18] |
|-----------------|---|

End point description:

the time from randomization to the date of first documented disease progression, or death due to any cause, whichever occurs first.

Progressive Disease (PD): At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progression).

| | |
|--|-----------|
| End point type | Secondary |
| End point timeframe: | |
| From randomization to disease progression or death. Approximately 63 Months | |
| 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: Endpoints are specific for subgroups not baseline period | |

| End point values | Treatment A - Platinum Refractory Subgroup | Treatment B - Platinum Refractory Subgroup | | |
|----------------------------------|--|--|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 159 | 82 | | |
| Units: Months | | | | |
| median (confidence interval 95%) | | | | |
| Postive | 4.11 (1.81 to 8.31) | 6.70 (1.28 to 13.67) | | |
| Negative | 1.84 (1.41 to 2.63) | 1.94 (1.41 to 3.02) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Progression Free Survival (PFS) - Platinum Refractory subgroup Based on Tumor Mutation Burden (TMB) Status

| | |
|-----------------|--|
| End point title | Progression Free Survival (PFS) - Platinum Refractory subgroup Based on Tumor Mutation Burden (TMB) Status ^[19] |
|-----------------|--|

End point description:

the time from randomization to the date of first documented disease progression, or death due to any cause, whichever occurs first.

Tumor Mutational Burden (TMB) refers to the number of nonsynonymous somatic mutations that exist within a tumor's genome as measured by the Foundation One CDx panel at Foundation Medicine. The analysis was done on subjects with baseline tumor mutation burden by a cutoff of 7 mutations/megabase (mut/Mb) and 10 mut/Mb

Progressive Disease (PD): At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progression).

| | |
|--|-----------|
| End point type | Secondary |
| End point timeframe: | |
| From randomization to disease progression or death. Approximately 63 Months | |
| 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: Endpoints are specific for subgroups not baseline period | |

| End point values | Treatment A - Platinum Refractory Subgroup | Treatment B - Platinum Refractory Subgroup | | |
|----------------------------------|--|--|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 159 | 82 | | |
| Units: Months | | | | |
| median (confidence interval 95%) | | | | |
| TMB: < 7 | 1.45 (1.38 to 2.60) | 2.50 (1.41 to 5.26) | | |
| TMB: ≥ 7 | 2.76 (1.45 to 4.11) | 1.54 (1.25 to 4.07) | | |
| TMB: < 10 | 1.68 (1.41 to 2.60) | 2.50 (1.41 to 4.24) | | |
| TMB: ≥ 10 | 2.81 (1.38 to 9.69) | 1.41 (1.25 to 4.07) | | |
| TMB: Not Reported | 2.66 (1.45 to 2.92) | 2.92 (1.28 to 7.00) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival (OS) - Platinum Refractory Subgroup based on HPV p-16 status

| | |
|-----------------|---|
| End point title | Overall Survival (OS) - Platinum Refractory Subgroup based on HPV p-16 status ^[20] |
|-----------------|---|

End point description:

Overall survival was defined as the time from randomization to the date of death from any cause. Participants were censored at the date they were last known to be alive and at the date of randomization if they were randomized but had no follow-up.

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

End point timeframe:

From randomization to death. Approximately 63 Months

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: Endpoints are specific for subgroups not baseline period

| End point values | Treatment A - Platinum Refractory Subgroup | Treatment B - Platinum Refractory Subgroup | | |
|----------------------------------|--|--|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 159 | 82 | | |
| Units: Months | | | | |
| median (confidence interval 95%) | | | | |
| Positive | 13.93 (5.98 to 33.81) | 14.32 (6.28 to 44.88) | | |
| Negative | 9.36 (5.98 to 10.87) | 9.59 (6.93 to 13.40) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival (OS) - Platinum Refractory Subgroup based on Tumor Mutation Burden (TMB) status

| | |
|-----------------|--|
| End point title | Overall Survival (OS) - Platinum Refractory Subgroup based on Tumor Mutation Burden (TMB) status ^[21] |
|-----------------|--|

End point description:

Overall survival was defined as the time from randomization to the date of death from any cause. Participants were censored at the date they were last known to be alive and at the date of randomization if they were randomized but had no follow-up.

Tumor Mutational Burden (TMB) refers to the number of nonsynonymous somatic mutations that exist within a tumor's genome as measured by the Foundation One CDx panel at Foundation Medicine. The analysis was done on subjects with baseline tumor mutation burden by a cutoff of 7 mutations/megabase (mut/Mb) and 10 mut/Mb

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

End point timeframe:

From randomization to death. Approximately 63 Months

Notes:

[21] - 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: Endpoints are specific for subgroups not baseline period

| End point values | Treatment A - Platinum Refractory Subgroup | Treatment B - Platinum Refractory Subgroup | | |
|----------------------------------|--|--|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 159 | 82 | | |
| Units: Months | | | | |
| median (confidence interval 95%) | | | | |
| TMB: <7 | 5.78 (3.45 to 9.76) | 8.77 (4.14 to 16.66) | | |
| TMB: ≥ 7 | 11.37 (6.41 to 16.95) | 7.16 (6.28 to 12.29) | | |
| TMB: < 10 | 7.52 (4.96 to 11.27) | 8.31 (4.90 to 13.04) | | |
| TMB: ≥10 | 6.51 (2.50 to 41.33) | 9.26 (1.35 to 17.51) | | |
| Not Reported | 13.86 (9.53 to 17318) | 20.01 (7.56 to 23.46) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival (OS) - Platinum Eligible Subgroup based on HPV p-16 status

| | |
|-----------------|---|
| End point title | Overall Survival (OS) - Platinum Eligible Subgroup based on HPV p-16 status ^[22] |
|-----------------|---|

End point description:

Overall survival was defined as the time from randomization to the date of death from any cause. Participants were censored at the date they were last known to be alive and at the date of randomization if they were randomized but had no follow-up.

Here "99999" signifies NA

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

End point timeframe:

From randomization to death. Approximately 63 Months

Notes:

[22] - 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: Endpoints are specific for subgroups not baseline period

| End point values | Treatment A - Platinum Eligible Subgroup | Treatment B - Platinum Eligible Subgroup | | |
|----------------------------------|--|--|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 123 | 61 | | |
| Units: Months | | | | |
| median (confidence interval 95%) | | | | |
| Positive | 16.66 (8.54 to 28.06) | 33.74 (12.91 to 99999) | | |
| Negative | 7.79 (5.06 to 12.39) | 9.46 (5.32 to 14.00) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival (OS) - Platinum Eligible Subgroup based on Tumor Mutation Burden (TMB) status

| | |
|-----------------|--|
| End point title | Overall Survival (OS) - Platinum Eligible Subgroup based on Tumor Mutation Burden (TMB) status ^[23] |
|-----------------|--|

End point description:

Overall survival was defined as the time from randomization to the date of death from any cause. Participants were censored at the date they were last known to be alive and at the date of randomization if they were randomized but had no follow-up.

Here "99999" signifies NA

Tumor Mutational Burden (TMB) refers to the number of nonsynonymous somatic mutations that exist within a tumor's genome as measured by the Foundation One CDx panel at Foundation Medicine. The analysis was done on subjects with baseline tumor mutation burden by a cutoff of 7 mutations/megabase (mut/Mb) and 10 mut/Mb

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

End point timeframe:

From randomization to death. Approximately 63 Months

Notes:

[23] - 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: Endpoints are specific for subgroups not baseline period

| End point values | Treatment A - Platinum Eligible Subgroup | Treatment B - Platinum Eligible Subgroup | | |
|----------------------------------|---|---|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 123 | 61 | | |
| Units: Months | | | | |
| median (confidence interval 95%) | | | | |
| TMB: <7 | 7.56 (4.83 to 12.25) | 18.27 (4.04 to 33.74) | | |
| TMB: ≥ 7 | 16.30 (9.43 to 36.30) | 13.08 (8.28 to 38.11) | | |
| TMB: < 10 | 9.99 (6.41 to 12.62) | 15.01 (7.62 to 27.47) | | |
| TMB: ≥10 | 16.72 (4.47 to 99999) | 14.77 (2.83 to 99999) | | |
| Not Reported | 8.00 (3.84 to 26.12) | 9.71 (2.56 to 18.79) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Progression Free Survival (PFS) - Platinum Eligible subgroup Based on Tumor Mutation Burden (TMB) Status

| | |
|-----------------|--|
| End point title | Progression Free Survival (PFS) - Platinum Eligible subgroup Based on Tumor Mutation Burden (TMB) Status ^[24] |
|-----------------|--|

End point description:

the time from randomization to the date of first documented disease progression, or death due to any cause, whichever occurs first.

Tumor Mutational Burden (TMB) refers to the number of nonsynonymous somatic mutations that exist within a tumor's genome as measured by the Foundation One CDx panel at Foundation Medicine. The analysis was done on subjects with baseline tumor mutation burden by a cutoff of 7 mutations/megabase (mut/Mb) and 10 mut/Mb

Progressive Disease (PD): At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progression).

Here "99999" signifies NA

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

End point timeframe:

From randomization to disease progression or death. Approximately 63 Months

Notes:

[24] - 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.

| End point values | Treatment A - Platinum Eligible Subgroup | Treatment B - Platinum Eligible Subgroup | | |
|----------------------------------|---|---|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 123 | 61 | | |
| Units: Months | | | | |
| median (confidence interval 95%) | | | | |
| TMB: < 7 | 2.63 (1.45 to 3.06) | 2.92 (1.38 to 9.59) | | |
| TMB: ≥ 7 | 5.82 (1.45 to 12.42) | 2.83 (1.41 to 13.01) | | |
| TMB: < 10 | 2.63 (1.45 to 3.06) | 2.99 (1.41 to 13.01) | | |
| TMB: ≥ 10 | 6.97 (1.41 to 99999) | 2.76 (0.72 to 27.60) | | |
| TMB: Not Reported | 2.71 (1.45 to 8.48) | 3.10 (1.38 to 9.82) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Progression Free Survival (PFS) - Platinum Eligible subgroup based on HPV p-16 Status

| | |
|-----------------|---|
| End point title | Progression Free Survival (PFS) - Platinum Eligible subgroup based on HPV p-16 Status ^[25] |
|-----------------|---|

End point description:

the time from randomization to the date of first documented disease progression, or death due to any cause, whichever occurs first.

Progressive Disease (PD): At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progression).

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

End point timeframe:

From randomization to disease progression or death. Approximately 63 Months

Notes:

[25] - 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: Endpoints are specific for subgroups not baseline period

| End point values | Treatment A - Platinum Eligible Subgroup | Treatment B - Platinum Eligible Subgroup | | |
|----------------------------------|---|---|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 123 | 61 | | |
| Units: Months | | | | |
| median (confidence interval 95%) | | | | |

| | | | | |
|----------|---------------------|----------------------|--|--|
| Postive | 2.92 (1.41 to 6.60) | 6.83 (1.38 to 49.84) | | |
| Negative | 2.66 (1.51 to 4.14) | 2.83 (1.51 to 4.24) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Response (DOR) - Platinum Eligible subgroup based on HPV p-16 Status

| | |
|-----------------|--|
| End point title | Duration of Response (DOR) - Platinum Eligible subgroup based on HPV p-16 Status ^[26] |
|-----------------|--|

End point description:

The time between the date of first confirmed response to the date of the first documented tumor progression, or death due to any cause, whichever occurs first.

Progressive Disease (PD): At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progression).

Here "99999" signifies NA

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

End point timeframe:

From randomization to disease progression or death. Approximately 63 Months

Notes:

[26] - 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: Endpoints are specific for subgroups not baseline period

| End point values | Treatment A - Platinum Eligible Subgroup | Treatment B - Platinum Eligible Subgroup | | |
|----------------------------------|--|--|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 25 | 18 | | |
| Units: Months | | | | |
| median (confidence interval 95%) | | | | |
| Positive | 33.84 (4.14 to 99999) | 48.49 (5.49 to 99999) | | |
| Negative | 27.04 (10.97 to 99999) | 19.32 (4.11 to 99999) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Response (DOR) - Platinum Eligible subgroup based on Tumor Mutation Burden (TMB) Status

| | |
|-----------------|---|
| End point title | Duration of Response (DOR) - Platinum Eligible subgroup based on Tumor Mutation Burden (TMB) Status ^[27] |
|-----------------|---|

End point description:

The time between the date of first confirmed response to the date of the first documented tumor progression, or death due to any cause, whichever occurs first.

Tumor Mutational Burden (TMB) refers to the number of nonsynonymous somatic mutations that exist within a tumor's genome as measured by the Foundation One CDx panel at Foundation Medicine. The analysis was done on subjects with baseline tumor mutation burden by a cutoff of 7 mutations/megabase (mut/Mb) and 10 mut/Mb.

Progressive Disease (PD): At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progression).

Here "99999" signifies NA

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

End point timeframe:

From randomization to disease progression or death. Approximately 63 Months

Notes:

[27] - 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: Endpoints are specific for subgroups not baseline period

| End point values | Treatment A - Platinum Eligible Subgroup | Treatment B - Platinum Eligible Subgroup | | |
|----------------------------------|---|---|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 25 | 18 | | |
| Units: Months | | | | |
| median (confidence interval 95%) | | | | |
| TMB: <7 | 10.97 (4.14 to 35.55) | 99999 (5.52 to 99999) | | |
| TMB ≥ 7 | 24.11 (10.97 to 99999) | 19.32 (5.49 to 24.61) | | |
| TMB: <10 | 13.67 (8.28 to 35.55) | 99999 (5.52 to 99999) | | |
| TMB: ≥ 10 | 99999 (5.78 to 99999) | 19.32 (5.49 to 24.61) | | |
| TMB: Not Reported | 99999 (27.04 to 99999) | 48.49 (4.11 to 99999) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Response (DOR) - Platinum Refractory subgroup based on PD-L1 Status

| | |
|-----------------|---|
| End point title | Duration of Response (DOR) - Platinum Refractory subgroup based on PD-L1 Status ^[28] |
|-----------------|---|

End point description:

The time between the date of first confirmed response to the date of the first documented tumor progression, or death due to any cause, whichever occurs first.

Tumor PD-L1 expression was defined as the percent of tumor cell membrane staining in a minimum of 100 evaluable tumor cells per validated Dako PD-L1 IHC assay.

Progressive Disease (PD): At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progression).

Here "99999 and -99999" signifies NA

Here "9999" signifies not calculated

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

End point timeframe:

From randomization to disease progression or death. Approximately 63 Months

Notes:

[28] - 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: Endpoints are specific for subgroups not baseline period

| End point values | Treatment A - Platinum Refractory Subgroup | Treatment B - Platinum Refractory Subgroup | | |
|----------------------------------|--|--|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 21 | 15 | | |
| Units: Months | | | | |
| median (confidence interval 95%) | | | | |
| PD-L1: $\geq 1\%$ | 39.43 (11.01 to 99999) | 8.34 (2.79 to 99999) | | |
| PD-L1: $< 25\%$ | 39.43 (6.87 to 99999) | 11.10 (4.17 to 38.51) | | |
| PD-L1: $\geq 25\%$ | 9999 (6.93 to 99999) | 8.34 (2.79 to 99999) | | |
| PD-L1: $< 50\%$ | 9999 (26.71 to 99999) | 11.14 (4.17 to 38.51) | | |
| PD-L1: $> 50\%$ | 9999 (6.93 to 99999) | 6.24 (4.14 to 8.34) | | |
| PD-L1: 1 - $< 25\%$ | 39.43 (3.06 to 39.43) | 9999 (4.17 to 99999) | | |
| PD-L1: Unquantifiable | 38.67 (-99999 to 99999) | 9999 (-99999 to 99999) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: ORR - Platinum Refractory Subgroup based on PD-L1 Expression

| | |
|-----------------|--|
| End point title | ORR - Platinum Refractory Subgroup based on PD-L1 Expression ^[29] |
|-----------------|--|

End point description:

ORR is defined as percentage of participants with a complete response (CR) or partial response (PR)

Tumor PD-L1 expression was defined as the percent of tumor cell membrane staining in a minimum of 100 evaluable tumor cells per validated Dako PD-L1 IHC assay

Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes(whether target or non-target) must have reduction in short axis to < 10 mm.

Partial Response (PR): At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.

Here "9999" signifies not calculated

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

End point timeframe:

From randomization to end of study. Approximately 63 Months

Notes:

[29] - 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: Endpoints are specific for subgroups not baseline period

| End point values | Treatment A - Platinum Refractory Subgroup | Treatment B - Platinum Refractory Subgroup | | |
|---|---|---|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 159 | 82 | | |
| Units: Percentage of Participants | | | | |
| number (confidence interval 95%) | | | | |
| <1% | 7.7 (2.1 to 18.5) | 25.8 (11.9 to 44.6) | | |
| PD-L1: ≥ 1% | 19.6 (12.0 to 29.1) | 19.6 (9.4 to 33.9) | | |
| PD-L1: < 25% | 11.1 (6.1 to 18.3) | 21.1 (11.4 to 33.9) | | |
| PD-L1: ≥ 25% | 33.3 (16.5 to 54.0) | 25.0 (8.7 to 49.1) | | |
| PD-L1: <50% | 13.2 (7.9 to 20.3) | 22.7 (13.3 to 34.7) | | |
| PD-L1: > 50% | 33.3 (11.8 to 61.6) | 18.2 (2.3 to 51.8) | | |
| PD-L1: 1 - < 25% | 13.8 (6.5 to 24.7) | 15.4 (4.4 to 34.9) | | |
| without quantifiable PD-L1 expression at baseline | 9999 (-9999 to 99999) | 9999 (-99999 to 99999) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival (OS) - Platinum Refractory Subgroup based on PD-L1 status

| | |
|-----------------|--|
| End point title | Overall Survival (OS) - Platinum Refractory Subgroup based on PD-L1 status ^[30] |
|-----------------|--|

End point description:

Overall survival was defined as the time from randomization to the date of death from any cause. Participants were censored at the date they were last known to be alive and at the date of randomization if they were randomized but had no follow-up.

Tumor PD-L1 expression was defined as the percent of tumor cell membrane staining in a minimum of 100 evaluable tumor cells per validated Dako PD-L1 IHC assay

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

End point timeframe:

From randomization to death. Approximately 63 Months

Notes:

[30] - 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: Endpoints are specific for subgroups not baseline period

| End point values | Treatment A - Platinum Refractory Subgroup | Treatment B - Platinum Refractory Subgroup | | |
|---|---|---|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 159 | 82 | | |
| Units: Months | | | | |
| median (confidence interval 95%) | | | | |
| <1% | 9.53 (6.31 to 12.62) | 12.29 (6.08 to 20.27) | | |
| PD-L1: ≥ 1% | 10.22 (5.95 to 14.52) | 9.02 (6.74 to 13.34) | | |
| PD-L1: < 25% | 9.95 (7.26 to 11.37) | 8.77 (6.28 to 14.78) | | |
| PD-L1: ≥ 25% | 5.78 (2.43 to 48.69) | 10.23 (7.03 to 16.66) | | |
| PD-L1: <50% | 9.76 (6.51 to 11.37) | 10.61 (6.74 to 14.26) | | |
| PD-L1: > 50% | 26.02 (2.43 to 48.69) | 7.33 (1.51 to 16.66) | | |
| PD-L1: 1 - < 25% | 10.32 (5.98 to 14.32) | 7.56 (4.86 to 17.51) | | |
| Without quantifiable PD-L1 expression at baseline | 6.93 (1.71 to 14.16) | 28.09 (7.56 to 44.88) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Progression Free Survival (PFS) - Platinum Refractory subgroup based on PD-L1 Status

| | |
|-----------------|--|
| End point title | Progression Free Survival (PFS) - Platinum Refractory subgroup based on PD-L1 Status ^[31] |
|-----------------|--|

End point description:

The time from randomization to the date of first documented disease progression, or death due to any cause, whichever occurs first.

Tumor PD-L1 expression was defined as the percent of tumor cell membrane staining in a minimum of 100 evaluable tumor cells per validated Dako PD-L1 IHC assay.

Progressive Disease (PD): At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progression).

Here "99999" signifies NA

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

End point timeframe:

From randomization to disease progression or death. Approximately 63 Months

Notes:

[31] - 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: Endpoints are specific for subgroups not baseline period

| End point values | Treatment A - Platinum Refractory Subgroup | Treatment B - Platinum Refractory Subgroup | | |
|---|---|---|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 159 | 82 | | |
| Units: Months | | | | |
| median (confidence interval 95%) | | | | |
| <1% | 2.60 (1.41 to 2.86) | 2.96 (1.38 to 5.32) | | |
| PD-L1: ≥ 1% | 2.60 (1.45 to 2.83) | 2.60 (1.41 to 4.11) | | |
| PD-L1: < 25% | 2.60 (1.45 to 2.83) | 2.79 (1.41 to 4.01) | | |
| PD-L1: ≥ 25% | 2.12 (1.38 to 13.77) | 1.54 (1.25 to 7.03) | | |
| PD-L1: <50% | 2.60 (1.45 to 2.79) | 2.79 (1.54 to 4.07) | | |
| PD-L1: > 50% | 2.79 (0.59 to 13.77) | 1.54 (0.66 to 7.03) | | |
| PD-L1: 1 - < 25% | 2.66 (1.45 to 2.83) | 2.60 (1.38 to 4.07) | | |
| Without Quantifiable PD-L1 expression at Baseline | 2.17 (1.08 to 2.66) | 1.71 (1.22 to 99999) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Response (DOR) - Platinum Eligible subgroup based on PD-L1 Status

| | |
|-----------------|---|
| End point title | Duration of Response (DOR) - Platinum Eligible subgroup based on PD-L1 Status ^[32] |
|-----------------|---|

End point description:

The time between the date of first confirmed response to the date of the first documented tumor progression, or death due to any cause, whichever occurs first.

Tumor PD-L1 expression was defined as the percent of tumor cell membrane staining in a minimum of 100 evaluable tumor cells per validated Dako PD-L1 IHC assay

Progressive Disease (PD): At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progression).

Here "99999" signifies NA

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

End point timeframe:

From randomization to disease progression or death. Approximately 63 Months

Notes:

[32] - 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: Endpoints are specific for subgroups not baseline period

| End point values | Treatment A - Platinum Eligible Subgroup | Treatment B - Platinum Eligible Subgroup | | |
|----------------------------------|---|---|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 25 | 18 | | |
| Units: Months | | | | |
| median (confidence interval 95%) | | | | |
| PD-L1: $\geq 1\%$ | 33.84 (8.28 to 99999) | 24.61 (4.11 to 99999) | | |
| PD-L1: $< 25\%$ | 13.17 (4.17 to 35.55) | 12.42 (4.11 to 99999) | | |
| PD-L1: $\geq 25\%$ | 99999 (8.28 to 99999) | 99999 (24.61 to 99999) | | |
| PD-L1: $< 50\%$ | 13.67 (5.78 to 35.55) | 15.87 (4.11 to 99999) | | |
| PD-L1: $> 50\%$ | 99999 (33.84 to 99999) | 99999 (24.61 to 99999) | | |
| PD-L1: 1 - $< 25\%$ | 13.13 (4.14 to 99999) | 6.21 (4.11 to 12.42) | | |
| PD-L1: Unquantifiable | 99999 (27.04 to 99999) | 28.99 (9.49 to 48.49) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: ORR - Platinum Eligible Subgroup based on PD-L1 Expression

| | |
|-----------------|---|
| End point title | ORR - Platinum Eligible Subgroup based on PD-L1 |
|-----------------|---|

End point description:

ORR is defined as percentage of participants with a complete response (CR) or partial response (PR)

Tumor PD-L1 expression was defined as the percent of tumor cell membrane staining in a minimum of 100 evaluable tumor cells per validated Dako PD-L1 IHC assay

Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes(whether target or non-target) must have reduction in short axis to < 10 mm.

Partial Response (PR): At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.

Here "99999" signifies NA

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

End point timeframe:

From randomization to end of study. Approximately 63 Months

Notes:

[33] - 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: Endpoints are specific for subgroups not baseline period

| End point values | Treatment A - Platinum Eligible Subgroup | Treatment B - Platinum Eligible Subgroup | | |
|---|---|---|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 123 | 61 | | |
| Units: percentage of participants | | | | |
| number (confidence interval 95%) | | | | |
| <1% | 15.7 (7.0 to 28.6) | 21.7 (7.5 to 43.7) | | |
| PD-L1: ≥ 1% | 21.5 (12.3 to 33.5) | 30.3 (15.6 to 48.7) | | |
| PD-L1: < 25% | 14.9 (8.2 to 24.2) | 24.3 (11.8 to 41.2) | | |
| PD-L1: ≥ 25% | 31.0 (15.3 to 50.8) | 31.6 (12.6 to 56.6) | | |
| PD-L1: <50% | 16.7 (9.8 to 25.6) | 24.4 (12.4 to 40.3) | | |
| PD-L1: > 50% | 30.0 (11.9 to 54.3) | 33.3 (11.8 to 61.6) | | |
| PD-L1: 1 - < 25% | 13.9 (4.7 to 29.5) | 28.6 (8.4 to 58.1) | | |
| Without quantifiable PD-L1 expression at baseline | 99999 (99999 to 99999) | 99999 (99999 to 99999) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival (OS) - Platinum Eligible Subgroup based on PD-L1 status

| | |
|-----------------|--|
| End point title | Overall Survival (OS) - Platinum Eligible Subgroup based on PD-L1 status ^[34] |
|-----------------|--|

End point description:

Overall survival was defined as the time from randomization to the date of death from any cause. Participants were censored at the date they were last known to be alive and at the date of randomization if they were randomized but had no follow-up.

Tumor PD-L1 expression was defined as the percent of tumor cell membrane staining in a minimum of 100 evaluable tumor cells per validated Dako PD-L1 IHC assay

Here "99999" signifies NA

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

End point timeframe:

From randomization to death. Approximately 63 Months

Notes:

[34] - 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: Endpoints are specific for subgroups not baseline period

| End point values | Treatment A - Platinum Eligible Subgroup | Treatment B - Platinum Eligible Subgroup | | |
|---|---|---|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 123 | 61 | | |
| Units: months | | | | |
| median (confidence interval 95%) | | | | |
| <1% | 12.52 (8.21 to 17.68) | 11.17 (3.42 to 21.52) | | |
| PD-L1: ≥ 1% | 7.56 (5.06 to 11.24) | 14.00 (7.62 to 23.66) | | |
| PD-L1: < 25% | 8.72 (5.91 to 12.25) | 11.17 (5.32 to 21.52) | | |
| PD-L1: ≥ 25% | 12.39 (5.06 to 36.30) | 14.00 (6.34 to 38.74) | | |
| PD-L1: <50% | 9.10 (6.57 to 12.62) | 9.92 (4.04 to 18.79) | | |
| PD-L1: > 50% | 9.40 (4.11 to 36.30) | 15.01 (7.62 to 99999) | | |
| PD-L1: 1 - < 25% | 6.16 (4.57 to 8.11) | 8.48 (2.83 to 22.41) | | |
| Without quantifiable PD-L1 expression at baseline | 26.12 (1.64 to 99999) | 33.74 (5.72 to 99999) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Progression Free Survival (PFS) - Platinum Eligible subgroup based on PD-L1 Status

| | |
|-----------------|--|
| End point title | Progression Free Survival (PFS) - Platinum Eligible subgroup based on PD-L1 Status ^[35] |
|-----------------|--|

End point description:

The time from randomization to the date of first documented disease progression, or death due to any cause, whichever occurs first.

Tumor PD-L1 expression was defined as the percent of tumor cell membrane staining in a minimum of 100 evaluable tumor cells per validated Dako PD-L1 IHC assay

Progressive Disease (PD): At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progression).

Here "99999" signifies NA

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

End point timeframe:

From randomization to disease progression or death. Approximately 63 Months

Notes:

[35] - 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: Endpoints are specific for subgroups not baseline period

| End point values | Treatment A - Platinum Eligible Subgroup | Treatment B - Platinum Eligible Subgroup | | |
|---|---|---|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 123 | 61 | | |
| Units: Months | | | | |
| median (confidence interval 95%) | | | | |
| <1% | 2.61 (1.38 to 5.78) | 2.73 (1.41 to 9.82) | | |
| PD-L1: ≥ 1% | 2.89 (1.51 to 4.21) | 2.99 (1.38 to 5.65) | | |
| PD-L1: < 25% | 2.37 (1.41 to 2.76) | 2.76 (1.41 to 5.65) | | |
| PD-L1: ≥ 25% | 5.75 (3.71 to 16.59) | 2.99 (1.38 to 99999) | | |
| PD-L1: <50% | 2.55 (1.45 to 2.89) | 2.76 (1.41 to 5.65) | | |
| PD-L1: > 50% | 4.21 (2.79 to 99999) | 2.99 (1.38 to 99999) | | |
| PD-L1: 1 - < 25% | 1.51 (1.41 to 2.86) | 3.10 (1.28 to 8.28) | | |
| Without quantifiable PD-L1 expression at baseline | 6.47 (1.51 to 99999) | 13.73 (1.28 to 49.84) | | |

Statistical analyses

No statistical analyses for this end point

Post-hoc: Objective Response Rate (ORR) as determined by Blinded Independent Central Review (BIRC) - Platinum refractory subgroup - Post Hoc Analysis

| | |
|-----------------|---|
| End point title | Objective Response Rate (ORR) as determined by Blinded Independent Central Review (BIRC) - Platinum refractory subgroup - Post Hoc Analysis ^[36] |
|-----------------|---|

End point description:

ORR is defined as percentage of participants with a complete response (CR) or partial response (PR)

Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes(whether target or non-target) must have reduction in short axis to < 10 mm.

Partial Response (PR): At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.

| | |
|----------------|----------|
| End point type | Post-hoc |
|----------------|----------|

End point timeframe:

From randomization to end of study. Approximately 63 Months

Notes:

[36] - 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: Endpoints are specific for subgroups not baseline period

| End point values | Treatment A - Platinum Refractory Subgroup | Treatment B - Platinum Refractory Subgroup | | |
|-----------------------------------|--|--|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 159 | 82 | | |
| Units: percentage of participants | | | | |
| number (confidence interval 95%) | 14.5 (9.4 to 20.9) | 20.7 (12.6 to 31.1) | | |

Statistical analyses

| Statistical analysis title | Statistical Analysis |
|---|---|
| Statistical analysis description: Treatment A over Treatment B | |
| Comparison groups | Treatment A - Platinum Refractory Subgroup v Treatment B - Platinum Refractory Subgroup |
| Number of subjects included in analysis | 241 |
| Analysis specification | Post-hoc |
| Analysis type | |
| Method | Mantel-Haenszel |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 0.64 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.32 |
| upper limit | 1.29 |

Post-hoc: Duration of Response (DOR) as determined by Blinded Independent Central Review (BIRC) - Platinum refractory subgroup - Post Hoc Analysis

| | |
|-----------------|--|
| End point title | Duration of Response (DOR) as determined by Blinded Independent Central Review (BIRC) - Platinum refractory subgroup - Post Hoc Analysis ^[37] |
|-----------------|--|

End point description:

The time between the date of first confirmed response to the date of the first documented tumor progression, or death due to any cause, whichever occurs first.

Progressive Disease (PD): At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progression).

Here "99999" signifies NA

| | |
|----------------|----------|
| End point type | Post-hoc |
|----------------|----------|

End point timeframe:

From randomization to disease progression or death. Approximately 63 Months

Notes:

[37] - 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: Endpoints are specific for subgroups not baseline period

| End point values | Treatment A - Platinum Refractory Subgroup | Treatment B - Platinum Refractory Subgroup | | |
|----------------------------------|---|---|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 23 | 17 | | |
| Units: Months | | | | |
| median (confidence interval 95%) | 39.43 (26.71 to 99999) | 11.07 (4.17 to 38.51) | | |

Statistical analyses

No statistical analyses for this end point

Post-hoc: Time to Response (TTR) as determined by Blinded Independent Central Review (BIRC) - Platinum refractory subgroup - Post Hoc Analysis

| | |
|-----------------|--|
| End point title | Time to Response (TTR) as determined by Blinded Independent Central Review (BIRC) - Platinum refractory subgroup - Post Hoc Analysis ^[38] |
|-----------------|--|

End point description:

Time to Response (TTR) for participants demonstrating a response (either CR or PR) was defined as the time from the date of randomization to the date of the first confirmed response.

Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes(whether target or non-target) must have reduction in short axis to < 10 mm.

Partial Response (PR): At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.

| | |
|----------------|----------|
| End point type | Post-hoc |
|----------------|----------|

End point timeframe:

From randomization to a confirmed response. Approximately 35 Months

Notes:

[38] - 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: Endpoints are specific for subgroups not baseline period

| End point values | Treatment A - Platinum Refractory Subgroup | Treatment B - Platinum Refractory Subgroup | | |
|-------------------------------|---|---|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 23 | 17 | | |
| Units: Months | | | | |
| median (full range (min-max)) | 2.63 (1.1 to 34.3) | 1.71 (1.2 to 7.7) | | |

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse Events and Serious Adverse Events: Approximately 32 months

All-Cause mortality: Approximately 65 months

Adverse event reporting additional description:

Adverse Event and Serious Adverse Events are measured from first dose to last dose + 100 days.

All-Cause mortality will be measured from the time of randomization to the end of study.

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

Dictionary used

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

| | |
|--------------------|------|
| Dictionary version | 24.1 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|--|
| Reporting group title | Treatment A - Platinum Refractory Subgroup |
|-----------------------|--|

Reporting group description:

Participants with histologically confirmed Squamous Cell Carcinoma of the Head and Neck (SCCHN) that has recurred during or less than 6 months after completion of previous platinum-based chemotherapy. Treated with Nivolumab 3 mg/kg Q2W + Ipilimumab 1 mg/kg Q6W

| | |
|-----------------------|--|
| Reporting group title | Treatment B - Platinum Eligible Subgroup |
|-----------------------|--|

Reporting group description:

Participants with histologically confirmed Squamous Cell Carcinoma of the Head and Neck (SCCHN) who are platinum naive or have recurred 6 months or more after completion of previous platinum-based chemotherapy. Treated with Nivolumab 3 mg/kg Q2W + Ipilimumab-Placebo Q6W

| | |
|-----------------------|--|
| Reporting group title | Treatment A - Platinum Eligible Subgroup |
|-----------------------|--|

Reporting group description:

Participants with histologically confirmed Squamous Cell Carcinoma of the Head and Neck (SCCHN) who are platinum naive or have recurred 6 months or more after completion of previous platinum-based chemotherapy. Treated with Nivolumab 3 mg/kg Q2W + Ipilimumab 1 mg/kg Q6W

| | |
|-----------------------|--|
| Reporting group title | Treatment B - Platinum Refractory Subgroup |
|-----------------------|--|

Reporting group description:

Participants with histologically confirmed Squamous Cell Carcinoma of the Head and Neck (SCCHN) that has recurred during or less than 6 months after completion of previous platinum-based chemotherapy. Treated with Nivolumab 3 mg/kg Q2W + Ipilimumab-Placebo Q6W

| Serious adverse events | Treatment A - Platinum Refractory Subgroup | Treatment B - Platinum Eligible Subgroup | Treatment A - Platinum Eligible Subgroup |
|--|--|--|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 103 / 159 (64.78%) | 35 / 61 (57.38%) | 89 / 123 (72.36%) |
| number of deaths (all causes) | 131 | 49 | 102 |
| number of deaths resulting from adverse events | | | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Cancer pain | | | |

| | | | |
|---|-------------------|------------------|-------------------|
| subjects affected / exposed ^[1] | 1 / 158 (0.63%) | 0 / 61 (0.00%) | 1 / 122 (0.82%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Basal cell carcinoma | | | |
| subjects affected / exposed ^[2] | 1 / 158 (0.63%) | 0 / 61 (0.00%) | 1 / 122 (0.82%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hepatocellular carcinoma | | | |
| subjects affected / exposed ^[3] | 0 / 158 (0.00%) | 0 / 61 (0.00%) | 1 / 122 (0.82%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Malignant neoplasm progression | | | |
| subjects affected / exposed ^[4] | 61 / 158 (38.61%) | 16 / 61 (26.23%) | 47 / 122 (38.52%) |
| occurrences causally related to treatment / all | 0 / 63 | 0 / 16 | 0 / 48 |
| deaths causally related to treatment / all | 0 / 58 | 0 / 16 | 0 / 45 |
| Malignant pleural effusion | | | |
| subjects affected / exposed ^[5] | 0 / 158 (0.00%) | 0 / 61 (0.00%) | 1 / 122 (0.82%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Metastases to bone | | | |
| subjects affected / exposed ^[6] | 1 / 158 (0.63%) | 0 / 61 (0.00%) | 0 / 122 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Second primary malignancy | | | |
| subjects affected / exposed ^[7] | 0 / 158 (0.00%) | 1 / 61 (1.64%) | 0 / 122 (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 |
| Tumour associated fever | | | |
| subjects affected / exposed ^[8] | 0 / 158 (0.00%) | 0 / 61 (0.00%) | 1 / 122 (0.82%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Tumour haemorrhage | | | |

| | | | |
|--|-----------------|----------------|-----------------|
| subjects affected / exposed ^[9] | 2 / 158 (1.27%) | 0 / 61 (0.00%) | 1 / 122 (0.82%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Tumour pain | | | |
| subjects affected / exposed ^[10] | 0 / 158 (0.00%) | 0 / 61 (0.00%) | 0 / 122 (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 |
| Vascular disorders | | | |
| Hypovolaemic shock | | | |
| subjects affected / exposed ^[11] | 0 / 158 (0.00%) | 0 / 61 (0.00%) | 0 / 122 (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 |
| Haemorrhage | | | |
| subjects affected / exposed ^[12] | 1 / 158 (0.63%) | 0 / 61 (0.00%) | 2 / 122 (1.64%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| Embolism | | | |
| subjects affected / exposed ^[13] | 0 / 158 (0.00%) | 0 / 61 (0.00%) | 0 / 122 (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 |
| Lymphoedema | | | |
| subjects affected / exposed ^[14] | 1 / 158 (0.63%) | 0 / 61 (0.00%) | 0 / 122 (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 |
| Peripheral venous disease | | | |
| subjects affected / exposed ^[15] | 0 / 158 (0.00%) | 0 / 61 (0.00%) | 2 / 122 (1.64%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Superior vena cava syndrome | | | |
| subjects affected / exposed ^[16] | 1 / 158 (0.63%) | 0 / 61 (0.00%) | 0 / 122 (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 |
| General disorders and administration site conditions | | | |

| | | | |
|---|-----------------|----------------|-----------------|
| Hyperthermia | | | |
| subjects affected / exposed ^[17] | 1 / 158 (0.63%) | 0 / 61 (0.00%) | 0 / 122 (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 |
| Generalised oedema | | | |
| subjects affected / exposed ^[18] | 1 / 158 (0.63%) | 0 / 61 (0.00%) | 0 / 122 (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 |
| General physical health deterioration | | | |
| subjects affected / exposed ^[19] | 0 / 158 (0.00%) | 0 / 61 (0.00%) | 3 / 122 (2.46%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 3 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Fatigue | | | |
| subjects affected / exposed ^[20] | 0 / 158 (0.00%) | 0 / 61 (0.00%) | 1 / 122 (0.82%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Face oedema | | | |
| subjects affected / exposed ^[21] | 1 / 158 (0.63%) | 0 / 61 (0.00%) | 0 / 122 (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 |
| Drug intolerance | | | |
| subjects affected / exposed ^[22] | 1 / 158 (0.63%) | 0 / 61 (0.00%) | 0 / 122 (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 |
| Death | | | |
| subjects affected / exposed ^[23] | 0 / 158 (0.00%) | 1 / 61 (1.64%) | 0 / 122 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| Chest pain | | | |
| subjects affected / exposed ^[24] | 0 / 158 (0.00%) | 0 / 61 (0.00%) | 0 / 122 (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 |
| Swelling | | | |

| | | | |
|---|-----------------|----------------|-----------------|
| subjects affected / exposed ^[25] | 1 / 158 (0.63%) | 0 / 61 (0.00%) | 0 / 122 (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 |
| Sudden death | | | |
| subjects affected / exposed ^[26] | 0 / 158 (0.00%) | 0 / 61 (0.00%) | 3 / 122 (2.46%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 3 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 3 |
| Pyrexia | | | |
| subjects affected / exposed ^[27] | 1 / 158 (0.63%) | 0 / 61 (0.00%) | 1 / 122 (0.82%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Impaired healing | | | |
| subjects affected / exposed ^[28] | 0 / 158 (0.00%) | 0 / 61 (0.00%) | 1 / 122 (0.82%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Mucosal inflammation | | | |
| subjects affected / exposed ^[29] | 1 / 158 (0.63%) | 0 / 61 (0.00%) | 2 / 122 (1.64%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Malaise | | | |
| subjects affected / exposed ^[30] | 0 / 158 (0.00%) | 1 / 61 (1.64%) | 1 / 122 (0.82%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Inflammation | | | |
| subjects affected / exposed ^[31] | 0 / 158 (0.00%) | 0 / 61 (0.00%) | 1 / 122 (0.82%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pain | | | |
| subjects affected / exposed ^[32] | 0 / 158 (0.00%) | 0 / 61 (0.00%) | 1 / 122 (0.82%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Immune system disorders | | | |
| Drug hypersensitivity | | | |

| | | | |
|---|-----------------|----------------|-----------------|
| subjects affected / exposed ^[33] | 0 / 158 (0.00%) | 0 / 61 (0.00%) | 1 / 122 (0.82%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Autoimmune lung disease | | | |
| subjects affected / exposed ^[34] | 1 / 158 (0.63%) | 0 / 61 (0.00%) | 0 / 122 (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 |
| Chronic obstructive pulmonary disease | | | |
| subjects affected / exposed ^[35] | 0 / 158 (0.00%) | 0 / 61 (0.00%) | 1 / 122 (0.82%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Dyspnoea | | | |
| subjects affected / exposed ^[36] | 4 / 158 (2.53%) | 1 / 61 (1.64%) | 4 / 122 (3.28%) |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 1 | 0 / 4 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Haemoptysis | | | |
| subjects affected / exposed ^[37] | 0 / 158 (0.00%) | 0 / 61 (0.00%) | 3 / 122 (2.46%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 3 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypoxia | | | |
| subjects affected / exposed ^[38] | 0 / 158 (0.00%) | 0 / 61 (0.00%) | 0 / 122 (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 |
| Laryngeal dyspnoea | | | |
| subjects affected / exposed ^[39] | 0 / 158 (0.00%) | 0 / 61 (0.00%) | 0 / 122 (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 |
| Lung disorder | | | |
| subjects affected / exposed ^[40] | 0 / 158 (0.00%) | 0 / 61 (0.00%) | 1 / 122 (0.82%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Laryngeal oedema | | | |

| | | | |
|---|-----------------|----------------|-----------------|
| subjects affected / exposed ^[41] | 0 / 158 (0.00%) | 0 / 61 (0.00%) | 1 / 122 (0.82%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Laryngeal obstruction | | | |
| subjects affected / exposed ^[42] | 1 / 158 (0.63%) | 0 / 61 (0.00%) | 0 / 122 (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 |
| Laryngeal haemorrhage | | | |
| subjects affected / exposed ^[43] | 0 / 158 (0.00%) | 1 / 61 (1.64%) | 1 / 122 (0.82%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Nasal obstruction | | | |
| subjects affected / exposed ^[44] | 0 / 158 (0.00%) | 1 / 61 (1.64%) | 0 / 122 (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 |
| Obstructive airways disorder | | | |
| subjects affected / exposed ^[45] | 0 / 158 (0.00%) | 0 / 61 (0.00%) | 1 / 122 (0.82%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pharyngeal oedema | | | |
| subjects affected / exposed ^[46] | 0 / 158 (0.00%) | 0 / 61 (0.00%) | 1 / 122 (0.82%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pleural effusion | | | |
| subjects affected / exposed ^[47] | 3 / 158 (1.90%) | 0 / 61 (0.00%) | 0 / 122 (0.00%) |
| occurrences causally related to treatment / all | 1 / 3 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumonitis | | | |
| subjects affected / exposed ^[48] | 1 / 158 (0.63%) | 1 / 61 (1.64%) | 2 / 122 (1.64%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 1 | 2 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumothorax | | | |

| | | | |
|---|-----------------|----------------|-----------------|
| subjects affected / exposed ^[49] | 0 / 158 (0.00%) | 0 / 61 (0.00%) | 2 / 122 (1.64%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pulmonary embolism | | | |
| subjects affected / exposed ^[50] | 1 / 158 (0.63%) | 1 / 61 (1.64%) | 0 / 122 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory distress | | | |
| subjects affected / exposed ^[51] | 1 / 158 (0.63%) | 0 / 61 (0.00%) | 0 / 122 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Respiratory failure | | | |
| subjects affected / exposed ^[52] | 3 / 158 (1.90%) | 1 / 61 (1.64%) | 2 / 122 (1.64%) |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 1 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Psychiatric disorders | | | |
| Insomnia | | | |
| subjects affected / exposed ^[53] | 0 / 158 (0.00%) | 0 / 61 (0.00%) | 1 / 122 (0.82%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Product issues | | | |
| Device leakage | | | |
| subjects affected / exposed ^[54] | 2 / 158 (1.27%) | 0 / 61 (0.00%) | 2 / 122 (1.64%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Device dislocation | | | |
| subjects affected / exposed ^[55] | 0 / 158 (0.00%) | 2 / 61 (3.28%) | 0 / 122 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Investigations | | | |
| Weight decreased | | | |
| subjects affected / exposed ^[56] | 1 / 158 (0.63%) | 0 / 61 (0.00%) | 0 / 122 (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 |

| | | | |
|---|-----------------|----------------|-----------------|
| Platelet count decreased subjects affected / exposed ^[57] | 0 / 158 (0.00%) | 0 / 61 (0.00%) | 0 / 122 (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 |
| Creatinine renal clearance decreased subjects affected / exposed ^[58] | 0 / 158 (0.00%) | 0 / 61 (0.00%) | 1 / 122 (0.82%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Injury, poisoning and procedural complications | | | |
| Head injury | | | |
| subjects affected / exposed ^[59] | 0 / 158 (0.00%) | 0 / 61 (0.00%) | 1 / 122 (0.82%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| Hand fracture | | | |
| subjects affected / exposed ^[60] | 0 / 158 (0.00%) | 0 / 61 (0.00%) | 0 / 122 (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 |
| Foot fracture | | | |
| subjects affected / exposed ^[61] | 0 / 158 (0.00%) | 0 / 61 (0.00%) | 0 / 122 (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 |
| Femur fracture | | | |
| subjects affected / exposed ^[62] | 0 / 158 (0.00%) | 0 / 61 (0.00%) | 1 / 122 (0.82%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Accidental overdose | | | |
| subjects affected / exposed ^[63] | 0 / 158 (0.00%) | 0 / 61 (0.00%) | 1 / 122 (0.82%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infusion related reaction | | | |
| subjects affected / exposed ^[64] | 0 / 158 (0.00%) | 0 / 61 (0.00%) | 1 / 122 (0.82%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|--|-----------------|----------------|-----------------|
| Spinal compression fracture subjects affected / exposed ^[65] | 1 / 158 (0.63%) | 0 / 61 (0.00%) | 0 / 122 (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 |
| Post procedural haemorrhage subjects affected / exposed ^[66] | 0 / 158 (0.00%) | 0 / 61 (0.00%) | 1 / 122 (0.82%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Overdose subjects affected / exposed ^[67] | 1 / 158 (0.63%) | 0 / 61 (0.00%) | 0 / 122 (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 |
| Toxicity to various agents subjects affected / exposed ^[68] | 1 / 158 (0.63%) | 0 / 61 (0.00%) | 0 / 122 (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 |
| Tracheal haemorrhage subjects affected / exposed ^[69] | 0 / 158 (0.00%) | 0 / 61 (0.00%) | 2 / 122 (1.64%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 3 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Upper limb fracture subjects affected / exposed ^[70] | 0 / 158 (0.00%) | 1 / 61 (1.64%) | 1 / 122 (0.82%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vasoplegia syndrome subjects affected / exposed ^[71] | 0 / 158 (0.00%) | 0 / 61 (0.00%) | 1 / 122 (0.82%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiac disorders Cardiac failure congestive subjects affected / exposed ^[72] | 0 / 158 (0.00%) | 0 / 61 (0.00%) | 1 / 122 (0.82%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Arrhythmia | | | |

| | | | |
|---|-----------------|----------------|-----------------|
| subjects affected / exposed ^[73] | 0 / 158 (0.00%) | 0 / 61 (0.00%) | 0 / 122 (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 arrest | | | |
| subjects affected / exposed ^[74] | 1 / 158 (0.63%) | 0 / 61 (0.00%) | 0 / 122 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Cardiac failure | | | |
| subjects affected / exposed ^[75] | 0 / 158 (0.00%) | 0 / 61 (0.00%) | 1 / 122 (0.82%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Acute myocardial infarction | | | |
| subjects affected / exposed ^[76] | 0 / 158 (0.00%) | 0 / 61 (0.00%) | 0 / 122 (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 |
| Pericardial effusion | | | |
| subjects affected / exposed ^[77] | 2 / 158 (1.27%) | 0 / 61 (0.00%) | 1 / 122 (0.82%) |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Myocardial infarction | | | |
| subjects affected / exposed ^[78] | 1 / 158 (0.63%) | 0 / 61 (0.00%) | 0 / 122 (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 |
| Nervous system disorders | | | |
| Carotid aneurysm rupture | | | |
| subjects affected / exposed ^[79] | 0 / 158 (0.00%) | 0 / 61 (0.00%) | 0 / 122 (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 |
| Ischaemic stroke | | | |
| subjects affected / exposed ^[80] | 0 / 158 (0.00%) | 0 / 61 (0.00%) | 0 / 122 (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 |
| Cerebrovascular accident | | | |

| | | | |
|---|-----------------|----------------|-----------------|
| subjects affected / exposed ^[81] | 0 / 158 (0.00%) | 0 / 61 (0.00%) | 1 / 122 (0.82%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cerebral ischaemia | | | |
| subjects affected / exposed ^[82] | 0 / 158 (0.00%) | 0 / 61 (0.00%) | 0 / 122 (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 |
| Nervous system disorder | | | |
| subjects affected / exposed ^[83] | 0 / 158 (0.00%) | 0 / 61 (0.00%) | 1 / 122 (0.82%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Syncope | | | |
| subjects affected / exposed ^[84] | 1 / 158 (0.63%) | 0 / 61 (0.00%) | 1 / 122 (0.82%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Neuropathy peripheral | | | |
| subjects affected / exposed ^[85] | 0 / 158 (0.00%) | 0 / 61 (0.00%) | 1 / 122 (0.82%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed ^[86] | 1 / 158 (0.63%) | 0 / 61 (0.00%) | 1 / 122 (0.82%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Lymph node pain | | | |
| subjects affected / exposed ^[87] | 1 / 158 (0.63%) | 0 / 61 (0.00%) | 0 / 122 (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 |
| Neutropenia | | | |
| subjects affected / exposed ^[88] | 0 / 158 (0.00%) | 0 / 61 (0.00%) | 1 / 122 (0.82%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Febrile bone marrow aplasia | | | |

| | | | |
|---|-----------------|----------------|-----------------|
| subjects affected / exposed ^[89] | 2 / 158 (1.27%) | 0 / 61 (0.00%) | 0 / 122 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Ear and labyrinth disorders | | | |
| Vestibular disorder | | | |
| subjects affected / exposed ^[90] | 1 / 158 (0.63%) | 0 / 61 (0.00%) | 0 / 122 (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 |
| Gastrointestinal disorders | | | |
| Ascites | | | |
| subjects affected / exposed ^[91] | 1 / 158 (0.63%) | 0 / 61 (0.00%) | 0 / 122 (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 |
| Abdominal distension | | | |
| subjects affected / exposed ^[92] | 0 / 158 (0.00%) | 0 / 61 (0.00%) | 1 / 122 (0.82%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Abdominal pain upper | | | |
| subjects affected / exposed ^[93] | 0 / 158 (0.00%) | 1 / 61 (1.64%) | 0 / 122 (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 |
| Diarrhoea | | | |
| subjects affected / exposed ^[94] | 3 / 158 (1.90%) | 0 / 61 (0.00%) | 4 / 122 (3.28%) |
| occurrences causally related to treatment / all | 3 / 3 | 0 / 0 | 2 / 4 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Constipation | | | |
| subjects affected / exposed ^[95] | 0 / 158 (0.00%) | 0 / 61 (0.00%) | 0 / 122 (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 |
| Colitis | | | |
| subjects affected / exposed ^[96] | 1 / 158 (0.63%) | 1 / 61 (1.64%) | 0 / 122 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Autoimmune colitis | | | |

| | | | |
|---|-----------------|----------------|-----------------|
| subjects affected / exposed ^[97] | 2 / 158 (1.27%) | 0 / 61 (0.00%) | 0 / 122 (0.00%) |
| occurrences causally related to treatment / all | 3 / 3 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Duodenitis | | | |
| subjects affected / exposed ^[98] | 0 / 158 (0.00%) | 0 / 61 (0.00%) | 1 / 122 (0.82%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Haematemesis | | | |
| subjects affected / exposed ^[99] | 0 / 158 (0.00%) | 0 / 61 (0.00%) | 1 / 122 (0.82%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrointestinal haemorrhage | | | |
| subjects affected / exposed ^[100] | 1 / 158 (0.63%) | 0 / 61 (0.00%) | 0 / 122 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Gastric ulcer | | | |
| subjects affected / exposed ^[101] | 1 / 158 (0.63%) | 0 / 61 (0.00%) | 0 / 122 (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 |
| Dysphagia | | | |
| subjects affected / exposed ^[102] | 3 / 158 (1.90%) | 0 / 61 (0.00%) | 5 / 122 (4.10%) |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 0 | 0 / 5 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hernial eventration | | | |
| subjects affected / exposed ^[103] | 0 / 158 (0.00%) | 0 / 61 (0.00%) | 0 / 122 (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 |
| Immune-mediated enterocolitis | | | |
| subjects affected / exposed ^[104] | 3 / 158 (1.90%) | 1 / 61 (1.64%) | 2 / 122 (1.64%) |
| occurrences causally related to treatment / all | 3 / 3 | 1 / 1 | 3 / 3 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Impaired gastric emptying | | | |

| | | | |
|---|-----------------|----------------|-----------------|
| subjects affected / exposed ^[105] | 0 / 158 (0.00%) | 0 / 61 (0.00%) | 0 / 122 (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 |
| Mouth haemorrhage | | | |
| subjects affected / exposed ^[106] | 2 / 158 (1.27%) | 1 / 61 (1.64%) | 1 / 122 (0.82%) |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Small intestinal perforation | | | |
| subjects affected / exposed ^[107] | 0 / 158 (0.00%) | 0 / 61 (0.00%) | 1 / 122 (0.82%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pancreatitis | | | |
| subjects affected / exposed ^[108] | 0 / 158 (0.00%) | 1 / 61 (1.64%) | 1 / 122 (0.82%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| Palatal disorder | | | |
| subjects affected / exposed ^[109] | 1 / 158 (0.63%) | 0 / 61 (0.00%) | 0 / 122 (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 |
| Oesophageal fistula | | | |
| subjects affected / exposed ^[110] | 0 / 158 (0.00%) | 0 / 61 (0.00%) | 0 / 122 (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 ^[111] | 0 / 158 (0.00%) | 0 / 61 (0.00%) | 0 / 122 (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 |
| Mouth ulceration | | | |
| subjects affected / exposed ^[112] | 0 / 158 (0.00%) | 0 / 61 (0.00%) | 0 / 122 (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 |
| Stomatitis | | | |

| | | | |
|---|-----------------|----------------|-----------------|
| subjects affected / exposed ^[113] | 0 / 158 (0.00%) | 0 / 61 (0.00%) | 0 / 122 (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 |
| Vomiting | | | |
| subjects affected / exposed ^[114] | 6 / 158 (3.80%) | 0 / 61 (0.00%) | 2 / 122 (1.64%) |
| occurrences causally related to treatment / all | 2 / 6 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hepatobiliary disorders | | | |
| Autoimmune hepatitis | | | |
| subjects affected / exposed ^[115] | 0 / 158 (0.00%) | 1 / 61 (1.64%) | 1 / 122 (0.82%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cholecystitis | | | |
| subjects affected / exposed ^[116] | 0 / 158 (0.00%) | 0 / 61 (0.00%) | 1 / 122 (0.82%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hepatitis | | | |
| subjects affected / exposed ^[117] | 0 / 158 (0.00%) | 1 / 61 (1.64%) | 0 / 122 (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 |
| Hepatotoxicity | | | |
| subjects affected / exposed ^[118] | 0 / 158 (0.00%) | 0 / 61 (0.00%) | 0 / 122 (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 |
| Immune-mediated hepatitis | | | |
| subjects affected / exposed ^[119] | 0 / 158 (0.00%) | 0 / 61 (0.00%) | 1 / 122 (0.82%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Skin and subcutaneous tissue disorders | | | |
| Pruritus | | | |
| subjects affected / exposed ^[120] | 1 / 158 (0.63%) | 0 / 61 (0.00%) | 0 / 122 (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 |
| Rash | | | |

| | | | |
|---|-----------------|----------------|-----------------|
| subjects affected / exposed ^[121] | 2 / 158 (1.27%) | 0 / 61 (0.00%) | 1 / 122 (0.82%) |
| occurrences causally related to treatment / all | 2 / 2 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| Rash maculo-papular | | | |
| subjects affected / exposed ^[122] | 1 / 158 (0.63%) | 0 / 61 (0.00%) | 0 / 122 (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 |
| Renal and urinary disorders | | | |
| Acute kidney injury | | | |
| subjects affected / exposed ^[123] | 2 / 158 (1.27%) | 1 / 61 (1.64%) | 0 / 122 (0.00%) |
| occurrences causally related to treatment / all | 1 / 2 | 2 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Renal failure | | | |
| subjects affected / exposed ^[124] | 1 / 158 (0.63%) | 0 / 61 (0.00%) | 2 / 122 (1.64%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Endocrine disorders | | | |
| Adrenal insufficiency | | | |
| subjects affected / exposed ^[125] | 0 / 158 (0.00%) | 0 / 61 (0.00%) | 2 / 122 (1.64%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 2 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypophysitis | | | |
| subjects affected / exposed ^[126] | 0 / 158 (0.00%) | 0 / 61 (0.00%) | 2 / 122 (1.64%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 2 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Adrenocortical insufficiency acute | | | |
| subjects affected / exposed ^[127] | 0 / 158 (0.00%) | 1 / 61 (1.64%) | 0 / 122 (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 |
| Musculoskeletal and connective tissue disorders | | | |
| Back pain | | | |
| subjects affected / exposed ^[128] | 1 / 158 (0.63%) | 0 / 61 (0.00%) | 0 / 122 (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 |

| | | | |
|---|-----------------|----------------|-----------------|
| Neck pain | | | |
| subjects affected / exposed ^[129] | 1 / 158 (0.63%) | 0 / 61 (0.00%) | 0 / 122 (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 |
| Spinal pain | | | |
| subjects affected / exposed ^[130] | 0 / 158 (0.00%) | 0 / 61 (0.00%) | 1 / 122 (0.82%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pathological fracture | | | |
| subjects affected / exposed ^[131] | 1 / 158 (0.63%) | 0 / 61 (0.00%) | 1 / 122 (0.82%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Osteonecrosis | | | |
| subjects affected / exposed ^[132] | 0 / 158 (0.00%) | 0 / 61 (0.00%) | 1 / 122 (0.82%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infections and infestations | | | |
| Abscess neck | | | |
| subjects affected / exposed ^[133] | 1 / 158 (0.63%) | 0 / 61 (0.00%) | 0 / 122 (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 |
| Bacteraemia | | | |
| subjects affected / exposed ^[134] | 1 / 158 (0.63%) | 0 / 61 (0.00%) | 0 / 122 (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 |
| Cellulitis | | | |
| subjects affected / exposed ^[135] | 2 / 158 (1.27%) | 0 / 61 (0.00%) | 0 / 122 (0.00%) |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Encephalitis | | | |
| subjects affected / exposed ^[136] | 0 / 158 (0.00%) | 0 / 61 (0.00%) | 0 / 122 (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 |
| Empyema | | | |

| | | | |
|---|-----------------|----------------|-----------------|
| subjects affected / exposed ^[137] | 0 / 158 (0.00%) | 1 / 61 (1.64%) | 0 / 122 (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 |
| Influenza | | | |
| subjects affected / exposed ^[138] | 0 / 158 (0.00%) | 0 / 61 (0.00%) | 1 / 122 (0.82%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Lower respiratory tract infection | | | |
| subjects affected / exposed ^[139] | 1 / 158 (0.63%) | 0 / 61 (0.00%) | 0 / 122 (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 |
| Ludwig angina | | | |
| subjects affected / exposed ^[140] | 0 / 158 (0.00%) | 0 / 61 (0.00%) | 1 / 122 (0.82%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Endocarditis | | | |
| subjects affected / exposed ^[141] | 0 / 158 (0.00%) | 0 / 61 (0.00%) | 0 / 122 (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 |
| Epiglottitis | | | |
| subjects affected / exposed ^[142] | 0 / 158 (0.00%) | 0 / 61 (0.00%) | 1 / 122 (0.82%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Focal peritonitis | | | |
| subjects affected / exposed ^[143] | 0 / 158 (0.00%) | 0 / 61 (0.00%) | 1 / 122 (0.82%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastroenteritis | | | |
| subjects affected / exposed ^[144] | 0 / 158 (0.00%) | 0 / 61 (0.00%) | 1 / 122 (0.82%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hepatic infection bacterial | | | |

| | | | |
|---|-----------------|----------------|-----------------|
| subjects affected / exposed ^[145] | 0 / 158 (0.00%) | 0 / 61 (0.00%) | 1 / 122 (0.82%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Herpes zoster | | | |
| subjects affected / exposed ^[146] | 1 / 158 (0.63%) | 0 / 61 (0.00%) | 0 / 122 (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 |
| Infective myositis | | | |
| subjects affected / exposed ^[147] | 0 / 158 (0.00%) | 1 / 61 (1.64%) | 0 / 122 (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 |
| Lymph node abscess | | | |
| subjects affected / exposed ^[148] | 0 / 158 (0.00%) | 1 / 61 (1.64%) | 0 / 122 (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 |
| Neutropenic sepsis | | | |
| subjects affected / exposed ^[149] | 0 / 158 (0.00%) | 0 / 61 (0.00%) | 0 / 122 (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 |
| Oral infection | | | |
| subjects affected / exposed ^[150] | 0 / 158 (0.00%) | 1 / 61 (1.64%) | 0 / 122 (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 |
| Pneumococcal sepsis | | | |
| subjects affected / exposed ^[151] | 0 / 158 (0.00%) | 0 / 61 (0.00%) | 0 / 122 (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 |
| Sepsis syndrome | | | |
| subjects affected / exposed ^[152] | 1 / 158 (0.63%) | 0 / 61 (0.00%) | 0 / 122 (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 |
| Pneumonia aspiration | | | |

| | | | |
|---|-------------------|----------------|------------------|
| subjects affected / exposed ^[153] | 2 / 158 (1.27%) | 1 / 61 (1.64%) | 3 / 122 (2.46%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | 0 / 3 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| Pneumonia pseudomonal | | | |
| subjects affected / exposed ^[154] | 0 / 158 (0.00%) | 0 / 61 (0.00%) | 1 / 122 (0.82%) |
| 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 ^[155] | 1 / 158 (0.63%) | 1 / 61 (1.64%) | 0 / 122 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumonia | | | |
| subjects affected / exposed ^[156] | 18 / 158 (11.39%) | 4 / 61 (6.56%) | 10 / 122 (8.20%) |
| occurrences causally related to treatment / all | 0 / 19 | 0 / 5 | 0 / 13 |
| deaths causally related to treatment / all | 0 / 6 | 0 / 1 | 0 / 0 |
| Septic shock | | | |
| subjects affected / exposed ^[157] | 0 / 158 (0.00%) | 1 / 61 (1.64%) | 0 / 122 (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 |
| Sinusitis | | | |
| subjects affected / exposed ^[158] | 0 / 158 (0.00%) | 0 / 61 (0.00%) | 0 / 122 (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 infection | | | |
| subjects affected / exposed ^[159] | 0 / 158 (0.00%) | 1 / 61 (1.64%) | 1 / 122 (0.82%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Staphylococcal bacteraemia | | | |
| subjects affected / exposed ^[160] | 0 / 158 (0.00%) | 0 / 61 (0.00%) | 0 / 122 (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 |
| Staphylococcal scalded skin syndrome | | | |

| | | | |
|---|-----------------|----------------|-----------------|
| subjects affected / exposed ^[161] | 0 / 158 (0.00%) | 0 / 61 (0.00%) | 1 / 122 (0.82%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Subcutaneous abscess | | | |
| subjects affected / exposed ^[162] | 0 / 158 (0.00%) | 0 / 61 (0.00%) | 0 / 122 (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 |
| Tracheitis | | | |
| subjects affected / exposed ^[163] | 2 / 158 (1.27%) | 0 / 61 (0.00%) | 0 / 122 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Tracheobronchitis | | | |
| subjects affected / exposed ^[164] | 1 / 158 (0.63%) | 0 / 61 (0.00%) | 0 / 122 (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 |
| Viral myocarditis | | | |
| subjects affected / exposed ^[165] | 0 / 158 (0.00%) | 0 / 61 (0.00%) | 0 / 122 (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 |
| Vascular access site infection | | | |
| subjects affected / exposed ^[166] | 1 / 158 (0.63%) | 0 / 61 (0.00%) | 0 / 122 (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 |
| Urinary tract infection | | | |
| subjects affected / exposed ^[167] | 1 / 158 (0.63%) | 1 / 61 (1.64%) | 2 / 122 (1.64%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| Tracheostomy infection | | | |
| subjects affected / exposed ^[168] | 0 / 158 (0.00%) | 1 / 61 (1.64%) | 1 / 122 (0.82%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Upper respiratory tract infection | | | |

| | | | |
|---|-----------------|----------------|-----------------|
| subjects affected / exposed ^[169] | 0 / 158 (0.00%) | 0 / 61 (0.00%) | 1 / 122 (0.82%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Viral upper respiratory tract infection | | | |
| subjects affected / exposed ^[170] | 1 / 158 (0.63%) | 0 / 61 (0.00%) | 0 / 122 (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 |
| Metabolism and nutrition disorders | | | |
| Diabetes mellitus | | | |
| subjects affected / exposed ^[171] | 0 / 158 (0.00%) | 0 / 61 (0.00%) | 2 / 122 (1.64%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 2 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Dehydration | | | |
| subjects affected / exposed ^[172] | 4 / 158 (2.53%) | 0 / 61 (0.00%) | 2 / 122 (1.64%) |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Failure to thrive | | | |
| subjects affected / exposed ^[173] | 0 / 158 (0.00%) | 0 / 61 (0.00%) | 1 / 122 (0.82%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Electrolyte imbalance | | | |
| subjects affected / exposed ^[174] | 0 / 158 (0.00%) | 0 / 61 (0.00%) | 1 / 122 (0.82%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Feeding disorder | | | |
| subjects affected / exposed ^[175] | 1 / 158 (0.63%) | 0 / 61 (0.00%) | 0 / 122 (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 |
| Hyperkalaemia | | | |
| subjects affected / exposed ^[176] | 0 / 158 (0.00%) | 0 / 61 (0.00%) | 0 / 122 (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 |
| Hyperglycaemia | | | |

| | | | |
|---|-----------------|----------------|-----------------|
| subjects affected / exposed ^[177] | 0 / 158 (0.00%) | 0 / 61 (0.00%) | 1 / 122 (0.82%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypercalcaemia | | | |
| subjects affected / exposed ^[178] | 6 / 158 (3.80%) | 1 / 61 (1.64%) | 1 / 122 (0.82%) |
| occurrences causally related to treatment / all | 0 / 6 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| Malnutrition | | | |
| subjects affected / exposed ^[179] | 1 / 158 (0.63%) | 0 / 61 (0.00%) | 0 / 122 (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 |
| Hyponatraemia | | | |
| subjects affected / exposed ^[180] | 2 / 158 (1.27%) | 1 / 61 (1.64%) | 0 / 122 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypokalaemia | | | |
| subjects affected / exposed ^[181] | 1 / 158 (0.63%) | 0 / 61 (0.00%) | 0 / 122 (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 |
| Hypernatraemia | | | |
| subjects affected / exposed ^[182] | 0 / 158 (0.00%) | 0 / 61 (0.00%) | 1 / 122 (0.82%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |

| Serious adverse events | Treatment B - Platinum Refractory Subgroup | | |
|---|--|--|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 52 / 82 (63.41%) | | |
| number of deaths (all causes) | 71 | | |
| number of deaths resulting from adverse events | | | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Cancer pain | | | |

| | | | | |
|---|------------------|--|--|--|
| subjects affected / exposed ^[1] | 0 / 82 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Basal cell carcinoma | | | | |
| subjects affected / exposed ^[2] | 0 / 82 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Hepatocellular carcinoma | | | | |
| subjects affected / exposed ^[3] | 0 / 82 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Malignant neoplasm progression | | | | |
| subjects affected / exposed ^[4] | 25 / 82 (30.49%) | | | |
| occurrences causally related to treatment / all | 0 / 25 | | | |
| deaths causally related to treatment / all | 0 / 25 | | | |
| Malignant pleural effusion | | | | |
| subjects affected / exposed ^[5] | 0 / 82 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Metastases to bone | | | | |
| subjects affected / exposed ^[6] | 0 / 82 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Second primary malignancy | | | | |
| subjects affected / exposed ^[7] | 0 / 82 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Tumour associated fever | | | | |
| subjects affected / exposed ^[8] | 0 / 82 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Tumour haemorrhage | | | | |

| | | | |
|--|----------------|--|--|
| subjects affected / exposed ^[9] | 1 / 82 (1.22%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Tumour pain | | | |
| subjects affected / exposed ^[10] | 1 / 82 (1.22%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Vascular disorders | | | |
| Hypovolaemic shock | | | |
| subjects affected / exposed ^[11] | 1 / 82 (1.22%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Haemorrhage | | | |
| subjects affected / exposed ^[12] | 1 / 82 (1.22%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Embolism | | | |
| subjects affected / exposed ^[13] | 1 / 82 (1.22%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Lymphoedema | | | |
| subjects affected / exposed ^[14] | 0 / 82 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Peripheral venous disease | | | |
| subjects affected / exposed ^[15] | 0 / 82 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Superior vena cava syndrome | | | |
| subjects affected / exposed ^[16] | 0 / 82 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| General disorders and administration site conditions | | | |

| | | | | |
|---|----------------|--|--|--|
| Hyperthermia | | | | |
| subjects affected / exposed ^[17] | 0 / 82 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Generalised oedema | | | | |
| subjects affected / exposed ^[18] | 0 / 82 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| General physical health deterioration | | | | |
| subjects affected / exposed ^[19] | 0 / 82 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Fatigue | | | | |
| subjects affected / exposed ^[20] | 0 / 82 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Face oedema | | | | |
| subjects affected / exposed ^[21] | 0 / 82 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Drug intolerance | | | | |
| subjects affected / exposed ^[22] | 0 / 82 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Death | | | | |
| subjects affected / exposed ^[23] | 0 / 82 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Chest pain | | | | |
| subjects affected / exposed ^[24] | 1 / 82 (1.22%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Swelling | | | | |

| | | | |
|---|----------------|--|--|
| subjects affected / exposed ^[25] | 0 / 82 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Sudden death | | | |
| subjects affected / exposed ^[26] | 0 / 82 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pyrexia | | | |
| subjects affected / exposed ^[27] | 1 / 82 (1.22%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Impaired healing | | | |
| subjects affected / exposed ^[28] | 0 / 82 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Mucosal inflammation | | | |
| subjects affected / exposed ^[29] | 0 / 82 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Malaise | | | |
| subjects affected / exposed ^[30] | 0 / 82 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Inflammation | | | |
| subjects affected / exposed ^[31] | 0 / 82 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pain | | | |
| subjects affected / exposed ^[32] | 0 / 82 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Immune system disorders | | | |
| Drug hypersensitivity | | | |

| | | | |
|---|----------------|--|--|
| subjects affected / exposed ^[33] | 0 / 82 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Autoimmune lung disease | | | |
| subjects affected / exposed ^[34] | 0 / 82 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Chronic obstructive pulmonary disease | | | |
| subjects affected / exposed ^[35] | 0 / 82 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Dyspnoea | | | |
| subjects affected / exposed ^[36] | 3 / 82 (3.66%) | | |
| occurrences causally related to treatment / all | 1 / 4 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Haemoptysis | | | |
| subjects affected / exposed ^[37] | 0 / 82 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hypoxia | | | |
| subjects affected / exposed ^[38] | 1 / 82 (1.22%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Laryngeal dyspnoea | | | |
| subjects affected / exposed ^[39] | 1 / 82 (1.22%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Lung disorder | | | |
| subjects affected / exposed ^[40] | 1 / 82 (1.22%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Laryngeal oedema | | | |

| | | | | |
|---|----------------|--|--|--|
| subjects affected / exposed ^[41] | 0 / 82 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Laryngeal obstruction | | | | |
| subjects affected / exposed ^[42] | 0 / 82 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Laryngeal haemorrhage | | | | |
| subjects affected / exposed ^[43] | 1 / 82 (1.22%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 1 | | | |
| Nasal obstruction | | | | |
| subjects affected / exposed ^[44] | 0 / 82 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Obstructive airways disorder | | | | |
| subjects affected / exposed ^[45] | 0 / 82 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Pharyngeal oedema | | | | |
| subjects affected / exposed ^[46] | 0 / 82 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Pleural effusion | | | | |
| subjects affected / exposed ^[47] | 1 / 82 (1.22%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Pneumonitis | | | | |
| subjects affected / exposed ^[48] | 2 / 82 (2.44%) | | | |
| occurrences causally related to treatment / all | 1 / 3 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Pneumothorax | | | | |

| | | | |
|---|----------------|--|--|
| subjects affected / exposed ^[49] | 1 / 82 (1.22%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pulmonary embolism | | | |
| subjects affected / exposed ^[50] | 0 / 82 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Respiratory distress | | | |
| subjects affected / exposed ^[51] | 0 / 82 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Respiratory failure | | | |
| subjects affected / exposed ^[52] | 0 / 82 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Psychiatric disorders | | | |
| Insomnia | | | |
| subjects affected / exposed ^[53] | 0 / 82 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Product issues | | | |
| Device leakage | | | |
| subjects affected / exposed ^[54] | 0 / 82 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Device dislocation | | | |
| subjects affected / exposed ^[55] | 0 / 82 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Investigations | | | |
| Weight decreased | | | |
| subjects affected / exposed ^[56] | 1 / 82 (1.22%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

| | | | |
|---|----------------|--|--|
| Platelet count decreased subjects affected / exposed ^[57] | 1 / 82 (1.22%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Creatinine renal clearance decreased subjects affected / exposed ^[58] | 0 / 82 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Injury, poisoning and procedural complications | | | |
| Head injury | | | |
| subjects affected / exposed ^[59] | 0 / 82 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hand fracture | | | |
| subjects affected / exposed ^[60] | 1 / 82 (1.22%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Foot fracture | | | |
| subjects affected / exposed ^[61] | 1 / 82 (1.22%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Femur fracture | | | |
| subjects affected / exposed ^[62] | 0 / 82 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Accidental overdose | | | |
| subjects affected / exposed ^[63] | 0 / 82 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Infusion related reaction | | | |
| subjects affected / exposed ^[64] | 0 / 82 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

| | | | |
|--|----------------|--|--|
| Spinal compression fracture subjects affected / exposed ^[65] | 0 / 82 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Post procedural haemorrhage subjects affected / exposed ^[66] | 1 / 82 (1.22%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Overdose subjects affected / exposed ^[67] | 0 / 82 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Toxicity to various agents subjects affected / exposed ^[68] | 0 / 82 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Tracheal haemorrhage subjects affected / exposed ^[69] | 0 / 82 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Upper limb fracture subjects affected / exposed ^[70] | 0 / 82 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Vasoplegia syndrome subjects affected / exposed ^[71] | 0 / 82 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cardiac disorders | | | |
| Cardiac failure congestive subjects affected / exposed ^[72] | 0 / 82 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Arrhythmia | | | |

| | | | |
|---|----------------|--|--|
| subjects affected / exposed ^[73] | 1 / 82 (1.22%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Cardiac arrest | | | |
| subjects affected / exposed ^[74] | 0 / 82 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cardiac failure | | | |
| subjects affected / exposed ^[75] | 0 / 82 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Acute myocardial infarction | | | |
| subjects affected / exposed ^[76] | 1 / 82 (1.22%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pericardial effusion | | | |
| subjects affected / exposed ^[77] | 0 / 82 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Myocardial infarction | | | |
| subjects affected / exposed ^[78] | 0 / 82 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Nervous system disorders | | | |
| Carotid aneurysm rupture | | | |
| subjects affected / exposed ^[79] | 1 / 82 (1.22%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Ischaemic stroke | | | |
| subjects affected / exposed ^[80] | 1 / 82 (1.22%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cerebrovascular accident | | | |

| | | | |
|---|----------------|--|--|
| subjects affected / exposed ^[81] | 0 / 82 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cerebral ischaemia | | | |
| subjects affected / exposed ^[82] | 1 / 82 (1.22%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Nervous system disorder | | | |
| subjects affected / exposed ^[83] | 0 / 82 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Syncope | | | |
| subjects affected / exposed ^[84] | 0 / 82 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Neuropathy peripheral | | | |
| subjects affected / exposed ^[85] | 0 / 82 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed ^[86] | 1 / 82 (1.22%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Lymph node pain | | | |
| subjects affected / exposed ^[87] | 0 / 82 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Neutropenia | | | |
| subjects affected / exposed ^[88] | 0 / 82 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Febrile bone marrow aplasia | | | |

| | | | |
|---|----------------|--|--|
| subjects affected / exposed ^[89] | 0 / 82 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Ear and labyrinth disorders | | | |
| Vestibular disorder | | | |
| subjects affected / exposed ^[90] | 0 / 82 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Gastrointestinal disorders | | | |
| Ascites | | | |
| subjects affected / exposed ^[91] | 0 / 82 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Abdominal distension | | | |
| subjects affected / exposed ^[92] | 0 / 82 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Abdominal pain upper | | | |
| subjects affected / exposed ^[93] | 0 / 82 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Diarrhoea | | | |
| subjects affected / exposed ^[94] | 1 / 82 (1.22%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Constipation | | | |
| subjects affected / exposed ^[95] | 1 / 82 (1.22%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Colitis | | | |
| subjects affected / exposed ^[96] | 0 / 82 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Autoimmune colitis | | | |

| | | | | |
|---|----------------|--|--|--|
| subjects affected / exposed ^[97] | 0 / 82 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Duodenitis | | | | |
| subjects affected / exposed ^[98] | 0 / 82 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Haematemesis | | | | |
| subjects affected / exposed ^[99] | 0 / 82 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Gastrointestinal haemorrhage | | | | |
| subjects affected / exposed ^[100] | 0 / 82 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Gastric ulcer | | | | |
| subjects affected / exposed ^[101] | 0 / 82 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Dysphagia | | | | |
| subjects affected / exposed ^[102] | 0 / 82 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Hernial eventration | | | | |
| subjects affected / exposed ^[103] | 1 / 82 (1.22%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Immune-mediated enterocolitis | | | | |
| subjects affected / exposed ^[104] | 1 / 82 (1.22%) | | | |
| occurrences causally related to treatment / all | 1 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Impaired gastric emptying | | | | |

| | | | | |
|---|----------------|--|--|--|
| subjects affected / exposed ^[105] | 1 / 82 (1.22%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 1 | | | |
| Mouth haemorrhage | | | | |
| subjects affected / exposed ^[106] | 0 / 82 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Small intestinal perforation | | | | |
| subjects affected / exposed ^[107] | 0 / 82 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Pancreatitis | | | | |
| subjects affected / exposed ^[108] | 0 / 82 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Palatal disorder | | | | |
| subjects affected / exposed ^[109] | 0 / 82 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Oesophageal fistula | | | | |
| subjects affected / exposed ^[110] | 1 / 82 (1.22%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Nausea | | | | |
| subjects affected / exposed ^[111] | 2 / 82 (2.44%) | | | |
| occurrences causally related to treatment / all | 1 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Mouth ulceration | | | | |
| subjects affected / exposed ^[112] | 1 / 82 (1.22%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Stomatitis | | | | |

| | | | |
|---|----------------|--|--|
| subjects affected / exposed ^[113] | 1 / 82 (1.22%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Vomiting | | | |
| subjects affected / exposed ^[114] | 3 / 82 (3.66%) | | |
| occurrences causally related to treatment / all | 2 / 3 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Hepatobiliary disorders | | | |
| Autoimmune hepatitis | | | |
| subjects affected / exposed ^[115] | 0 / 82 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cholecystitis | | | |
| subjects affected / exposed ^[116] | 0 / 82 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hepatitis | | | |
| subjects affected / exposed ^[117] | 0 / 82 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hepatotoxicity | | | |
| subjects affected / exposed ^[118] | 1 / 82 (1.22%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Immune-mediated hepatitis | | | |
| subjects affected / exposed ^[119] | 0 / 82 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Skin and subcutaneous tissue disorders | | | |
| Pruritus | | | |
| subjects affected / exposed ^[120] | 0 / 82 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Rash | | | |

| | | | |
|---|----------------|--|--|
| subjects affected / exposed ^[121] | 0 / 82 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Rash maculo-papular | | | |
| subjects affected / exposed ^[122] | 0 / 82 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Renal and urinary disorders | | | |
| Acute kidney injury | | | |
| subjects affected / exposed ^[123] | 0 / 82 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Renal failure | | | |
| subjects affected / exposed ^[124] | 0 / 82 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Endocrine disorders | | | |
| Adrenal insufficiency | | | |
| subjects affected / exposed ^[125] | 0 / 82 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hypophysitis | | | |
| subjects affected / exposed ^[126] | 0 / 82 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Adrenocortical insufficiency acute | | | |
| subjects affected / exposed ^[127] | 0 / 82 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Musculoskeletal and connective tissue disorders | | | |
| Back pain | | | |
| subjects affected / exposed ^[128] | 1 / 82 (1.22%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

| | | | |
|---|----------------|--|--|
| Neck pain | | | |
| subjects affected / exposed ^[129] | 0 / 82 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Spinal pain | | | |
| subjects affected / exposed ^[130] | 0 / 82 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pathological fracture | | | |
| subjects affected / exposed ^[131] | 0 / 82 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Osteonecrosis | | | |
| subjects affected / exposed ^[132] | 0 / 82 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Infections and infestations | | | |
| Abscess neck | | | |
| subjects affected / exposed ^[133] | 0 / 82 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Bacteraemia | | | |
| subjects affected / exposed ^[134] | 0 / 82 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cellulitis | | | |
| subjects affected / exposed ^[135] | 0 / 82 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Encephalitis | | | |
| subjects affected / exposed ^[136] | 1 / 82 (1.22%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Empyema | | | |

| | | | | |
|---|----------------|--|--|--|
| subjects affected / exposed ^[137] | 0 / 82 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Influenza | | | | |
| subjects affected / exposed ^[138] | 0 / 82 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Lower respiratory tract infection | | | | |
| subjects affected / exposed ^[139] | 1 / 82 (1.22%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Ludwig angina | | | | |
| subjects affected / exposed ^[140] | 0 / 82 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Endocarditis | | | | |
| subjects affected / exposed ^[141] | 1 / 82 (1.22%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Epiglottitis | | | | |
| subjects affected / exposed ^[142] | 0 / 82 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Focal peritonitis | | | | |
| subjects affected / exposed ^[143] | 0 / 82 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Gastroenteritis | | | | |
| subjects affected / exposed ^[144] | 0 / 82 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Hepatic infection bacterial | | | | |

| | | | | |
|---|----------------|--|--|--|
| subjects affected / exposed ^[145] | 0 / 82 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Herpes zoster | | | | |
| subjects affected / exposed ^[146] | 0 / 82 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Infective myositis | | | | |
| subjects affected / exposed ^[147] | 0 / 82 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Lymph node abscess | | | | |
| subjects affected / exposed ^[148] | 0 / 82 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Neutropenic sepsis | | | | |
| subjects affected / exposed ^[149] | 1 / 82 (1.22%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Oral infection | | | | |
| subjects affected / exposed ^[150] | 0 / 82 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Pneumococcal sepsis | | | | |
| subjects affected / exposed ^[151] | 1 / 82 (1.22%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Sepsis syndrome | | | | |
| subjects affected / exposed ^[152] | 0 / 82 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Pneumonia aspiration | | | | |

| | | | | |
|---|----------------|--|--|--|
| subjects affected / exposed ^[153] | 0 / 82 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Pneumonia pseudomonal | | | | |
| subjects affected / exposed ^[154] | 0 / 82 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Sepsis | | | | |
| subjects affected / exposed ^[155] | 0 / 82 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Pneumonia | | | | |
| subjects affected / exposed ^[156] | 5 / 82 (6.10%) | | | |
| occurrences causally related to treatment / all | 0 / 6 | | | |
| deaths causally related to treatment / all | 0 / 1 | | | |
| Septic shock | | | | |
| subjects affected / exposed ^[157] | 0 / 82 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Sinusitis | | | | |
| subjects affected / exposed ^[158] | 1 / 82 (1.22%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Skin infection | | | | |
| subjects affected / exposed ^[159] | 1 / 82 (1.22%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Staphylococcal bacteraemia | | | | |
| subjects affected / exposed ^[160] | 2 / 82 (2.44%) | | | |
| occurrences causally related to treatment / all | 0 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Staphylococcal scalded skin syndrome | | | | |

| | | | | |
|---|----------------|--|--|--|
| subjects affected / exposed ^[161] | 0 / 82 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Subcutaneous abscess | | | | |
| subjects affected / exposed ^[162] | 1 / 82 (1.22%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Tracheitis | | | | |
| subjects affected / exposed ^[163] | 0 / 82 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Tracheobronchitis | | | | |
| subjects affected / exposed ^[164] | 0 / 82 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Viral myocarditis | | | | |
| subjects affected / exposed ^[165] | 1 / 82 (1.22%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 1 | | | |
| Vascular access site infection | | | | |
| subjects affected / exposed ^[166] | 0 / 82 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Urinary tract infection | | | | |
| subjects affected / exposed ^[167] | 0 / 82 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Tracheostomy infection | | | | |
| subjects affected / exposed ^[168] | 0 / 82 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Upper respiratory tract infection | | | | |

| | | | |
|---|----------------|--|--|
| subjects affected / exposed ^[169] | 2 / 82 (2.44%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Viral upper respiratory tract infection | | | |
| subjects affected / exposed ^[170] | 0 / 82 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Metabolism and nutrition disorders | | | |
| Diabetes mellitus | | | |
| subjects affected / exposed ^[171] | 0 / 82 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Dehydration | | | |
| subjects affected / exposed ^[172] | 0 / 82 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Failure to thrive | | | |
| subjects affected / exposed ^[173] | 0 / 82 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Electrolyte imbalance | | | |
| subjects affected / exposed ^[174] | 0 / 82 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Feeding disorder | | | |
| subjects affected / exposed ^[175] | 0 / 82 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hyperkalaemia | | | |
| subjects affected / exposed ^[176] | 1 / 82 (1.22%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hyperglycaemia | | | |

| | | | |
|---|----------------|--|--|
| subjects affected / exposed ^[177] | 0 / 82 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hypercalcaemia | | | |
| subjects affected / exposed ^[178] | 2 / 82 (2.44%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Malnutrition | | | |
| subjects affected / exposed ^[179] | 0 / 82 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hyponatraemia | | | |
| subjects affected / exposed ^[180] | 2 / 82 (2.44%) | | |
| occurrences causally related to treatment / all | 2 / 3 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hypokalaemia | | | |
| subjects affected / exposed ^[181] | 0 / 82 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hypernatraemia | | | |
| subjects affected / exposed ^[182] | 0 / 82 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 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: Number exposed is reflecting all randomized participants

[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.

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[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.

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[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.

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[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.

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[166] - 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.

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

| Non-serious adverse events | Treatment A - Platinum Refractory Subgroup | Treatment B - Platinum Eligible Subgroup | Treatment A - Platinum Eligible Subgroup |
|--|--|--|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 139 / 159 (87.42%) | 54 / 61 (88.52%) | 118 / 123 (95.93%) |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |

| | | | |
|---|-------------------------|------------------------|-------------------------|
| Cancer pain subjects affected / exposed ^[183] occurrences (all) | 3 / 158 (1.90%) 3 | 4 / 61 (6.56%) 4 | 2 / 122 (1.64%) 2 |
| Vascular disorders | | | |
| Hypotension subjects affected / exposed ^[184] occurrences (all) | 6 / 158 (3.80%) 7 | 6 / 61 (9.84%) 6 | 5 / 122 (4.10%) 7 |
| Hypertension subjects affected / exposed ^[185] occurrences (all) | 2 / 158 (1.27%) 2 | 4 / 61 (6.56%) 4 | 5 / 122 (4.10%) 5 |
| General disorders and administration site conditions | | | |
| Asthenia subjects affected / exposed ^[186] occurrences (all) | 27 / 158 (17.09%) 42 | 7 / 61 (11.48%) 13 | 13 / 122 (10.66%) 18 |
| Chills subjects affected / exposed ^[187] occurrences (all) | 2 / 158 (1.27%) 3 | 0 / 61 (0.00%) 0 | 7 / 122 (5.74%) 7 |
| Face oedema subjects affected / exposed ^[188] occurrences (all) | 9 / 158 (5.70%) 9 | 2 / 61 (3.28%) 3 | 7 / 122 (5.74%) 7 |
| Fatigue subjects affected / exposed ^[189] occurrences (all) | 29 / 158 (18.35%) 31 | 22 / 61 (36.07%) 22 | 46 / 122 (37.70%) 55 |
| Mucosal inflammation subjects affected / exposed ^[190] occurrences (all) | 9 / 158 (5.70%) 9 | 2 / 61 (3.28%) 2 | 8 / 122 (6.56%) 9 |
| Pyrexia subjects affected / exposed ^[191] occurrences (all) | 15 / 158 (9.49%) 16 | 5 / 61 (8.20%) 8 | 15 / 122 (12.30%) 20 |
| Oedema peripheral subjects affected / exposed ^[192] occurrences (all) | 7 / 158 (4.43%) 7 | 1 / 61 (1.64%) 1 | 10 / 122 (8.20%) 10 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Productive cough subjects affected / exposed ^[193] occurrences (all) | 9 / 158 (5.70%) 12 | 7 / 61 (11.48%) 8 | 6 / 122 (4.92%) 6 |

| | | | |
|--|-------------------------|-----------------------|-------------------------|
| Dyspnoea subjects affected / exposed ^[194] occurrences (all) | 17 / 158 (10.76%) 17 | 9 / 61 (14.75%) 12 | 20 / 122 (16.39%) 22 |
| Cough subjects affected / exposed ^[195] occurrences (all) | 20 / 158 (12.66%) 22 | 9 / 61 (14.75%) 13 | 20 / 122 (16.39%) 21 |
| Psychiatric disorders | | | |
| Insomnia subjects affected / exposed ^[196] occurrences (all) | 13 / 158 (8.23%) 14 | 5 / 61 (8.20%) 5 | 5 / 122 (4.10%) 7 |
| Anxiety subjects affected / exposed ^[197] occurrences (all) | 9 / 158 (5.70%) 9 | 4 / 61 (6.56%) 4 | 2 / 122 (1.64%) 2 |
| Investigations | | | |
| Aspartate aminotransferase increased subjects affected / exposed ^[198] occurrences (all) | 9 / 158 (5.70%) 15 | 5 / 61 (8.20%) 8 | 11 / 122 (9.02%) 27 |
| Amylase increased subjects affected / exposed ^[199] occurrences (all) | 4 / 158 (2.53%) 7 | 3 / 61 (4.92%) 6 | 10 / 122 (8.20%) 19 |
| Alanine aminotransferase increased subjects affected / exposed ^[200] occurrences (all) | 8 / 158 (5.06%) 9 | 6 / 61 (9.84%) 9 | 7 / 122 (5.74%) 17 |
| Blood alkaline phosphatase increased subjects affected / exposed ^[201] occurrences (all) | 7 / 158 (4.43%) 17 | 3 / 61 (4.92%) 4 | 9 / 122 (7.38%) 16 |
| Weight decreased subjects affected / exposed ^[202] occurrences (all) | 20 / 158 (12.66%) 22 | 5 / 61 (8.20%) 5 | 25 / 122 (20.49%) 25 |
| Lipase increased subjects affected / exposed ^[203] occurrences (all) | 13 / 158 (8.23%) 18 | 5 / 61 (8.20%) 10 | 11 / 122 (9.02%) 17 |
| Blood thyroid stimulating hormone increased subjects affected / exposed ^[204] occurrences (all) | 4 / 158 (2.53%) 6 | 4 / 61 (6.56%) 6 | 5 / 122 (4.10%) 8 |
| Blood creatinine increased | | | |

| | | | |
|--|--|--|---|
| subjects affected / exposed ^[205] occurrences (all) | 11 / 158 (6.96%) 20 | 5 / 61 (8.20%) 6 | 7 / 122 (5.74%) 17 |
| Injury, poisoning and procedural complications Fall subjects affected / exposed ^[206] occurrences (all) | 1 / 158 (0.63%) 1 | 4 / 61 (6.56%) 5 | 2 / 122 (1.64%) 3 |
| Nervous system disorders Headache subjects affected / exposed ^[207] occurrences (all) Dizziness subjects affected / exposed ^[208] occurrences (all) | 14 / 158 (8.86%) 16 8 / 158 (5.06%) 8 | 6 / 61 (9.84%) 6 4 / 61 (6.56%) 4 | 11 / 122 (9.02%) 16 5 / 122 (4.10%) 6 |
| Blood and lymphatic system disorders Lymphopenia subjects affected / exposed ^[209] occurrences (all) Anaemia subjects affected / exposed ^[210] occurrences (all) | 12 / 158 (7.59%) 16 41 / 158 (25.95%) 50 | 2 / 61 (3.28%) 2 15 / 61 (24.59%) 18 | 0 / 122 (0.00%) 0 30 / 122 (24.59%) 39 |
| Gastrointestinal disorders Abdominal pain subjects affected / exposed ^[211] occurrences (all) Dysphagia subjects affected / exposed ^[212] occurrences (all) Nausea subjects affected / exposed ^[213] occurrences (all) Stomatitis subjects affected / exposed ^[214] occurrences (all) Vomiting subjects affected / exposed ^[215] occurrences (all) | 8 / 158 (5.06%) 14 16 / 158 (10.13%) 17 31 / 158 (19.62%) 41 2 / 158 (1.27%) 2 18 / 158 (11.39%) 23 | 4 / 61 (6.56%) 4 7 / 61 (11.48%) 7 13 / 61 (21.31%) 18 1 / 61 (1.64%) 1 5 / 61 (8.20%) 12 | 10 / 122 (8.20%) 15 18 / 122 (14.75%) 19 28 / 122 (22.95%) 38 6 / 122 (4.92%) 7 14 / 122 (11.48%) 25 |

| | | | |
|---|-------------------------|------------------------|-------------------------|
| Dyspepsia subjects affected / exposed ^[216] occurrences (all) | 6 / 158 (3.80%) 7 | 3 / 61 (4.92%) 4 | 7 / 122 (5.74%) 7 |
| Abdominal pain upper subjects affected / exposed ^[217] occurrences (all) | 7 / 158 (4.43%) 8 | 5 / 61 (8.20%) 6 | 4 / 122 (3.28%) 4 |
| Constipation subjects affected / exposed ^[218] occurrences (all) | 24 / 158 (15.19%) 32 | 9 / 61 (14.75%) 10 | 26 / 122 (21.31%) 28 |
| Dry mouth subjects affected / exposed ^[219] occurrences (all) | 11 / 158 (6.96%) 12 | 3 / 61 (4.92%) 3 | 9 / 122 (7.38%) 9 |
| Diarrhoea subjects affected / exposed ^[220] occurrences (all) | 33 / 158 (20.89%) 52 | 15 / 61 (24.59%) 20 | 27 / 122 (22.13%) 39 |
| Skin and subcutaneous tissue disorders | | | |
| Dry skin subjects affected / exposed ^[221] occurrences (all) | 10 / 158 (6.33%) 10 | 1 / 61 (1.64%) 1 | 6 / 122 (4.92%) 6 |
| Pruritus subjects affected / exposed ^[222] occurrences (all) | 33 / 158 (20.89%) 46 | 10 / 61 (16.39%) 13 | 24 / 122 (19.67%) 29 |
| Rash subjects affected / exposed ^[223] occurrences (all) | 32 / 158 (20.25%) 49 | 6 / 61 (9.84%) 7 | 19 / 122 (15.57%) 25 |
| Erythema subjects affected / exposed ^[224] occurrences (all) | 3 / 158 (1.90%) 3 | 1 / 61 (1.64%) 2 | 8 / 122 (6.56%) 9 |
| Endocrine disorders | | | |
| Hyperthyroidism subjects affected / exposed ^[225] occurrences (all) | 12 / 158 (7.59%) 13 | 1 / 61 (1.64%) 1 | 11 / 122 (9.02%) 11 |
| Hypothyroidism subjects affected / exposed ^[226] occurrences (all) | 28 / 158 (17.72%) 29 | 12 / 61 (19.67%) 15 | 23 / 122 (18.85%) 23 |
| Musculoskeletal and connective tissue disorders | | | |

| | | | |
|---|-------------------------|------------------------|-------------------------|
| Neck pain subjects affected / exposed ^[227] occurrences (all) | 18 / 158 (11.39%) 23 | 9 / 61 (14.75%) 12 | 7 / 122 (5.74%) 7 |
| Myalgia subjects affected / exposed ^[228] occurrences (all) | 5 / 158 (3.16%) 5 | 3 / 61 (4.92%) 4 | 8 / 122 (6.56%) 8 |
| Back pain subjects affected / exposed ^[229] occurrences (all) | 10 / 158 (6.33%) 10 | 5 / 61 (8.20%) 5 | 12 / 122 (9.84%) 13 |
| Arthralgia subjects affected / exposed ^[230] occurrences (all) | 20 / 158 (12.66%) 21 | 10 / 61 (16.39%) 10 | 18 / 122 (14.75%) 21 |
| Infections and infestations | | | |
| Pneumonia subjects affected / exposed ^[231] occurrences (all) | 10 / 158 (6.33%) 13 | 2 / 61 (3.28%) 3 | 8 / 122 (6.56%) 9 |
| Oral candidiasis subjects affected / exposed ^[232] occurrences (all) | 9 / 158 (5.70%) 9 | 2 / 61 (3.28%) 2 | 1 / 122 (0.82%) 1 |
| Nasopharyngitis subjects affected / exposed ^[233] occurrences (all) | 2 / 158 (1.27%) 2 | 4 / 61 (6.56%) 6 | 6 / 122 (4.92%) 8 |
| Metabolism and nutrition disorders | | | |
| Decreased appetite subjects affected / exposed ^[234] occurrences (all) | 21 / 158 (13.29%) 22 | 8 / 61 (13.11%) 8 | 25 / 122 (20.49%) 29 |
| Hypercalcaemia subjects affected / exposed ^[235] occurrences (all) | 18 / 158 (11.39%) 21 | 4 / 61 (6.56%) 5 | 11 / 122 (9.02%) 12 |
| Hyperglycaemia subjects affected / exposed ^[236] occurrences (all) | 5 / 158 (3.16%) 6 | 4 / 61 (6.56%) 5 | 5 / 122 (4.10%) 7 |
| Hyperkalaemia subjects affected / exposed ^[237] occurrences (all) | 7 / 158 (4.43%) 7 | 1 / 61 (1.64%) 2 | 0 / 122 (0.00%) 0 |
| Hypokalaemia | | | |

| | | | |
|--|------------------|----------------|-------------------|
| subjects affected / exposed ^[238] | 5 / 158 (3.16%) | 3 / 61 (4.92%) | 12 / 122 (9.84%) |
| occurrences (all) | 5 | 3 | 16 |
| Hypomagnesaemia | | | |
| subjects affected / exposed ^[239] | 8 / 158 (5.06%) | 6 / 61 (9.84%) | 9 / 122 (7.38%) |
| occurrences (all) | 8 | 10 | 13 |
| Hyponatraemia | | | |
| subjects affected / exposed ^[240] | 11 / 158 (6.96%) | 5 / 61 (8.20%) | 14 / 122 (11.48%) |
| occurrences (all) | 21 | 7 | 18 |

| Non-serious adverse events | Treatment B - Platinum Refractory Subgroup | | |
|---|--|--|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 76 / 82 (92.68%) | | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Cancer pain | | | |
| subjects affected / exposed ^[183] | 1 / 82 (1.22%) | | |
| occurrences (all) | 1 | | |
| Vascular disorders | | | |
| Hypotension | | | |
| subjects affected / exposed ^[184] | 2 / 82 (2.44%) | | |
| occurrences (all) | 2 | | |
| Hypertension | | | |
| subjects affected / exposed ^[185] | 3 / 82 (3.66%) | | |
| occurrences (all) | 4 | | |
| General disorders and administration site conditions | | | |
| Asthenia | | | |
| subjects affected / exposed ^[186] | 14 / 82 (17.07%) | | |
| occurrences (all) | 16 | | |
| Chills | | | |
| subjects affected / exposed ^[187] | 0 / 82 (0.00%) | | |
| occurrences (all) | 0 | | |
| Face oedema | | | |
| subjects affected / exposed ^[188] | 3 / 82 (3.66%) | | |
| occurrences (all) | 3 | | |
| Fatigue | | | |

| | | | |
|---|--|--|--|
| <p>subjects affected / exposed^[189]</p> <p>occurrences (all)</p> <p>Mucosal inflammation</p> <p>subjects affected / exposed^[190]</p> <p>occurrences (all)</p> <p>Pyrexia</p> <p>subjects affected / exposed^[191]</p> <p>occurrences (all)</p> <p>Oedema peripheral</p> <p>subjects affected / exposed^[192]</p> <p>occurrences (all)</p> | <p>21 / 82 (25.61%)</p> <p>22</p> <p>4 / 82 (4.88%)</p> <p>5</p> <p>9 / 82 (10.98%)</p> <p>12</p> <p>6 / 82 (7.32%)</p> <p>6</p> | | |
| <p>Respiratory, thoracic and mediastinal disorders</p> <p>Productive cough</p> <p>subjects affected / exposed^[193]</p> <p>occurrences (all)</p> <p>Dyspnoea</p> <p>subjects affected / exposed^[194]</p> <p>occurrences (all)</p> <p>Cough</p> <p>subjects affected / exposed^[195]</p> <p>occurrences (all)</p> | <p>2 / 82 (2.44%)</p> <p>2</p> <p>11 / 82 (13.41%)</p> <p>12</p> <p>8 / 82 (9.76%)</p> <p>13</p> | | |
| <p>Psychiatric disorders</p> <p>Insomnia</p> <p>subjects affected / exposed^[196]</p> <p>occurrences (all)</p> <p>Anxiety</p> <p>subjects affected / exposed^[197]</p> <p>occurrences (all)</p> | <p>7 / 82 (8.54%)</p> <p>9</p> <p>4 / 82 (4.88%)</p> <p>4</p> | | |
| <p>Investigations</p> <p>Aspartate aminotransferase increased</p> <p>subjects affected / exposed^[198]</p> <p>occurrences (all)</p> <p>Amylase increased</p> <p>subjects affected / exposed^[199]</p> <p>occurrences (all)</p> <p>Alanine aminotransferase increased</p> | <p>4 / 82 (4.88%)</p> <p>5</p> <p>5 / 82 (6.10%)</p> <p>13</p> | | |

| | | | |
|--|--|--|--|
| <p>subjects affected / exposed^[200]</p> <p>occurrences (all)</p> <p>Blood alkaline phosphatase increased</p> <p>subjects affected / exposed^[201]</p> <p>occurrences (all)</p> <p>Weight decreased</p> <p>subjects affected / exposed^[202]</p> <p>occurrences (all)</p> <p>Lipase increased</p> <p>subjects affected / exposed^[203]</p> <p>occurrences (all)</p> <p>Blood thyroid stimulating hormone increased</p> <p>subjects affected / exposed^[204]</p> <p>occurrences (all)</p> <p>Blood creatinine increased</p> <p>subjects affected / exposed^[205]</p> <p>occurrences (all)</p> | <p>4 / 82 (4.88%)</p> <p>5</p> <p>9 / 82 (10.98%)</p> <p>13</p> <p>9 / 82 (10.98%)</p> <p>10</p> <p>4 / 82 (4.88%)</p> <p>4</p> <p>1 / 82 (1.22%)</p> <p>2</p> <p>10 / 82 (12.20%)</p> <p>20</p> | | |
| <p>Injury, poisoning and procedural complications</p> <p>Fall</p> <p>subjects affected / exposed^[206]</p> <p>occurrences (all)</p> | <p>1 / 82 (1.22%)</p> <p>1</p> | | |
| <p>Nervous system disorders</p> <p>Headache</p> <p>subjects affected / exposed^[207]</p> <p>occurrences (all)</p> <p>Dizziness</p> <p>subjects affected / exposed^[208]</p> <p>occurrences (all)</p> | <p>5 / 82 (6.10%)</p> <p>7</p> <p>2 / 82 (2.44%)</p> <p>2</p> | | |
| <p>Blood and lymphatic system disorders</p> <p>Lymphopenia</p> <p>subjects affected / exposed^[209]</p> <p>occurrences (all)</p> <p>Anaemia</p> <p>subjects affected / exposed^[210]</p> <p>occurrences (all)</p> | <p>3 / 82 (3.66%)</p> <p>6</p> <p>33 / 82 (40.24%)</p> <p>45</p> | | |
| Gastrointestinal disorders | | | |

| | | | |
|--|------------------|--|--|
| Abdominal pain | | | |
| subjects affected / exposed ^[211] | 5 / 82 (6.10%) | | |
| occurrences (all) | 8 | | |
| Dysphagia | | | |
| subjects affected / exposed ^[212] | 10 / 82 (12.20%) | | |
| occurrences (all) | 16 | | |
| Nausea | | | |
| subjects affected / exposed ^[213] | 18 / 82 (21.95%) | | |
| occurrences (all) | 34 | | |
| Stomatitis | | | |
| subjects affected / exposed ^[214] | 5 / 82 (6.10%) | | |
| occurrences (all) | 5 | | |
| Vomiting | | | |
| subjects affected / exposed ^[215] | 9 / 82 (10.98%) | | |
| occurrences (all) | 18 | | |
| Dyspepsia | | | |
| subjects affected / exposed ^[216] | 0 / 82 (0.00%) | | |
| occurrences (all) | 0 | | |
| Abdominal pain upper | | | |
| subjects affected / exposed ^[217] | 0 / 82 (0.00%) | | |
| occurrences (all) | 0 | | |
| Constipation | | | |
| subjects affected / exposed ^[218] | 14 / 82 (17.07%) | | |
| occurrences (all) | 16 | | |
| Dry mouth | | | |
| subjects affected / exposed ^[219] | 4 / 82 (4.88%) | | |
| occurrences (all) | 5 | | |
| Diarrhoea | | | |
| subjects affected / exposed ^[220] | 17 / 82 (20.73%) | | |
| occurrences (all) | 30 | | |
| Skin and subcutaneous tissue disorders | | | |
| Dry skin | | | |
| subjects affected / exposed ^[221] | 5 / 82 (6.10%) | | |
| occurrences (all) | 11 | | |
| Pruritus | | | |

| | | | |
|---|---|--|--|
| <p>subjects affected / exposed^[222]</p> <p>occurrences (all)</p> <p>Rash</p> <p>subjects affected / exposed^[223]</p> <p>occurrences (all)</p> <p>Erythema</p> <p>subjects affected / exposed^[224]</p> <p>occurrences (all)</p> | <p>6 / 82 (7.32%)</p> <p>9</p> <p>9 / 82 (10.98%)</p> <p>14</p> <p>3 / 82 (3.66%)</p> <p>4</p> | | |
| <p>Endocrine disorders</p> <p>Hyperthyroidism</p> <p>subjects affected / exposed^[225]</p> <p>occurrences (all)</p> <p>Hypothyroidism</p> <p>subjects affected / exposed^[226]</p> <p>occurrences (all)</p> | <p>4 / 82 (4.88%)</p> <p>4</p> <p>10 / 82 (12.20%)</p> <p>11</p> | | |
| <p>Musculoskeletal and connective tissue disorders</p> <p>Neck pain</p> <p>subjects affected / exposed^[227]</p> <p>occurrences (all)</p> <p>Myalgia</p> <p>subjects affected / exposed^[228]</p> <p>occurrences (all)</p> <p>Back pain</p> <p>subjects affected / exposed^[229]</p> <p>occurrences (all)</p> <p>Arthralgia</p> <p>subjects affected / exposed^[230]</p> <p>occurrences (all)</p> | <p>11 / 82 (13.41%)</p> <p>12</p> <p>3 / 82 (3.66%)</p> <p>3</p> <p>11 / 82 (13.41%)</p> <p>12</p> <p>9 / 82 (10.98%)</p> <p>11</p> | | |
| <p>Infections and infestations</p> <p>Pneumonia</p> <p>subjects affected / exposed^[231]</p> <p>occurrences (all)</p> <p>Oral candidiasis</p> <p>subjects affected / exposed^[232]</p> <p>occurrences (all)</p> <p>Nasopharyngitis</p> | <p>5 / 82 (6.10%)</p> <p>6</p> <p>2 / 82 (2.44%)</p> <p>2</p> | | |

| | | | |
|--|------------------|--|--|
| subjects affected / exposed ^[233] | 1 / 82 (1.22%) | | |
| occurrences (all) | 3 | | |
| Metabolism and nutrition disorders | | | |
| Decreased appetite | | | |
| subjects affected / exposed ^[234] | 17 / 82 (20.73%) | | |
| occurrences (all) | 18 | | |
| Hypercalcaemia | | | |
| subjects affected / exposed ^[235] | 10 / 82 (12.20%) | | |
| occurrences (all) | 13 | | |
| Hyperglycaemia | | | |
| subjects affected / exposed ^[236] | 4 / 82 (4.88%) | | |
| occurrences (all) | 4 | | |
| Hyperkalaemia | | | |
| subjects affected / exposed ^[237] | 8 / 82 (9.76%) | | |
| occurrences (all) | 11 | | |
| Hypokalaemia | | | |
| subjects affected / exposed ^[238] | 2 / 82 (2.44%) | | |
| occurrences (all) | 2 | | |
| Hypomagnesaemia | | | |
| subjects affected / exposed ^[239] | 6 / 82 (7.32%) | | |
| occurrences (all) | 6 | | |
| Hyponatraemia | | | |
| subjects affected / exposed ^[240] | 11 / 82 (13.41%) | | |
| occurrences (all) | 14 | | |

Notes:

[183] - 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: Number exposed is reflecting all randomized participants

[184] - 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: Number exposed is reflecting all randomized participants

[185] - 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: Number exposed is reflecting all randomized participants

[186] - 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: Number exposed is reflecting all randomized participants

[187] - 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: Number exposed is reflecting all randomized participants

[188] - 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: Number exposed is reflecting all randomized participants

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Justification: Number exposed is reflecting all randomized participants

[229] - 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: Number exposed is reflecting all randomized participants

[230] - 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: Number exposed is reflecting all randomized participants

[231] - 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: Number exposed is reflecting all randomized participants

[232] - 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: Number exposed is reflecting all randomized participants

[233] - 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: Number exposed is reflecting all randomized participants

[234] - 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: Number exposed is reflecting all randomized participants

[235] - 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: Number exposed is reflecting all randomized participants

[236] - 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: Number exposed is reflecting all randomized participants

[237] - 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: Number exposed is reflecting all randomized participants

[238] - 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: Number exposed is reflecting all randomized participants

[239] - 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: Number exposed is reflecting all randomized participants

[240] - 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: Number exposed is reflecting all randomized participants

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|------------------|---|
| 19 July 2016 | PK and IMG Follow up visit samples no longer required to be collected; Updated Biomarker sample collection schedule; Updated Contraceptive language; Updated Algorithms for Renal, Hepatic, Pulmonary and Skin to match with updated Nivolumab IB v15 (includes Nivo IB 15 erratum update). Other minor edits, clarifications, corrections |
| 27 June 2017 | <ol style="list-style-type: none">1. Increase in the size of the platinum eligible population in order to provide greater statistical precision2. Alignment of protocol with responses to regulatory authorities3. Minor changes to eligibility criteria and study processes4. Clarification of outstanding issues and correction of typographical errors |
| 14 November 2017 | <p>To clarify additional detail about existing endpoints</p> <p>To provide clarity on the planned interim descriptive analyses for the platinum eligible cohort.</p> <p>Necessary window shortened in light of evolving data on radiotherapy plus immuno-oncology agents. Clarification of applicability to palliative and curative settings.</p> <p>To provide clarity, eliminate redundancy, and to align with the nivolumab program standards.</p> |

| | |
|-------------|---|
| 25 May 2018 | <p>Tumor mutational burden has been shown to be a predictive biomarker of efficacy for checkpoint inhibitors in several tumors. Therefore, it is important to elevate this endpoint</p> <p>To establish the methods which will be used to analyze the primary and secondary objective of the study.</p> <p>Provide clarification to sites regarding time permitted for treatment beyond progression, to align with recent evidence (CA209153) indicating limited activity of retreatment.</p> <p>Myocarditis is a potential serious adverse event for immunooncology agents. This guidance was included to reduce the risk of serious outcomes for subjects.</p> <p>To provide clarity that the sponsor will remain blinded to both cohorts until the time of the interim analysis.</p> |
|-------------|---|

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported