



Clinical trial results:

Adjuvant immunotherapy with anti-CTLA-4 monoclonal antibody (ipilimumab) versus placebo after complete resection of high-risk Stage III melanoma: A randomized, doubleblind Phase 3 trial of the EORTC Melanoma Group

Summary

| | |
|--------------------------|-------------------------------------|
| EudraCT number | 2007-001974-10 |
| Trial protocol | GB BE IT SE FI CZ DK DE ES FR AT NL |
| Global end of trial date | 26 November 2018 |

Results information

| | |
|--------------------------------|---------------|
| Result version number | v1 (current) |
| This version publication date | 21 March 2020 |
| First version publication date | 21 March 2020 |

Trial information

Trial identification

| | |
|-----------------------|-----------|
| Sponsor protocol code | CA184-029 |
|-----------------------|-----------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT00636168 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|---|
| Sponsor organisation name | Bristol-Myers Squibb |
| Sponsor organisation address | Chaussée 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.com |

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

| | |
|--|------------------|
| Analysis stage | Final |
| Date of interim/final analysis | 26 November 2018 |
| Is this the analysis of the primary completion data? | No |

| | |
|----------------------------------|------------------|
| Global end of trial reached? | Yes |
| Global end of trial date | 26 November 2018 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

The main objective of this trial was to determine whether post-operative adjuvant therapy with ipilimumab improves recurrence-free survival (RFS) as compared to placebo

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 | 24 June 2008 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | Yes |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|------------------------|
| Country: Number of subjects enrolled | Australia: 51 |
| Country: Number of subjects enrolled | Austria: 10 |
| Country: Number of subjects enrolled | Belgium: 16 |
| Country: Number of subjects enrolled | Canada: 34 |
| Country: Number of subjects enrolled | Czech Republic: 23 |
| Country: Number of subjects enrolled | Denmark: 70 |
| Country: Number of subjects enrolled | Finland: 13 |
| Country: Number of subjects enrolled | France: 178 |
| Country: Number of subjects enrolled | Germany: 101 |
| Country: Number of subjects enrolled | Italy: 168 |
| Country: Number of subjects enrolled | Norway: 17 |
| Country: Number of subjects enrolled | Poland: 15 |
| Country: Number of subjects enrolled | Russian Federation: 74 |
| Country: Number of subjects enrolled | Spain: 18 |
| Country: Number of subjects enrolled | Sweden: 13 |
| Country: Number of subjects enrolled | Switzerland: 51 |
| Country: Number of subjects enrolled | Netherlands: 28 |
| Country: Number of subjects enrolled | United Kingdom: 46 |
| Country: Number of subjects enrolled | United States: 285 |

| | |
|------------------------------------|------|
| Worldwide total number of subjects | 1211 |
| EEA total number of subjects | 716 |

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) | 968 |
| From 65 to 84 years | 243 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Protocol definition of Enrolled population: All 1211 participants who signed the Informed Consent Form; 951 were randomized to treatment and 945 were treated. Reasons for not being randomized: 193 were ineligible; 42 participants refused; 19 could not be randomized within 12 weeks after complete lymph node dissection; 6 due to other reasons.

Period 1

| | |
|------------------------------|--------------------------|
| Period 1 title | Randomized to Study Drug |
| 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 | Ipilimumab 10mg/kg |

Arm description:

Ipilimumab (10 mg/kg) as a single dose via a 90 minute intravenous (IV) infusion (not as bolus or IV push) during Days 1, 22, 43 and 64 (every 21 days in the Induction Phase) for a total of four separate doses, until disease recurrence, unacceptable toxicity or withdrawal of consent. During the maintenance phase, Ipilimumab was administered at a dose of 10 mg/kg, by IV infusion, every 12 weeks, beginning at Week 24, until disease recurrence, unacceptable toxicity or withdrawal of consent, for a maximum of 3 years (Week 156).

| | |
|--|--|
| Arm type | Experimental |
| Investigational medicinal product name | Ipilimumab |
| Investigational medicinal product code | BMS-73016, MDX-010 |
| Other name | human Anti-human CTL4(CD152) mAb |
| Pharmaceutical forms | Solution for infusion, Solution for injection, Solution for injection/infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

Ipilimumab (10 mg/kg) as a single dose via a 90 minute intravenous (IV) infusion (not as bolus or IV push) during Days 1, 22, 43 and 64 (every 21 days in the Induction Phase) for a total of four separate doses, until disease recurrence, unacceptable toxicity or withdrawal of consent. During the maintenance phase, Ipilimumab was administered at a dose of 10 mg/kg, by IV infusion, every 12 weeks, beginning at Week 24, until disease recurrence, unacceptable toxicity or withdrawal of consent, for a maximum of 3 years (Week 156).

| | |
|------------------|---------|
| Arm title | Placebo |
|------------------|---------|

Arm description:

Placebo as a single dose via a 90 minute intravenous (IV) infusion (not as bolus or IV push) during Days 1, 22, 43 and 64 (Induction Phase) for a total of four separate doses, until disease recurrence, unacceptable toxicity or withdrawal of consent. During the maintenance phase, placebo was administered by IV infusion every 12 weeks, beginning at Week 24, until disease recurrence, unacceptable toxicity or withdrawal of consent, for a maximum of 3 years (Week 156).

| | |
|--|---------------------------------|
| Arm type | Placebo |
| Investigational medicinal product name | Placebo |
| Investigational medicinal product code | |
| Other name | Saline Solution |
| Pharmaceutical forms | Solution for injection/infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

Placebo as a single dose via a 90 minute intravenous (IV) infusion (not as bolus or IV push) during Days 1, 22, 43 and 64 (Induction Phase) for a total of four separate doses, until disease recurrence, unacceptable toxicity or withdrawal of consent. During the maintenance phase, placebo was administered by IV infusion every 12 weeks, beginning at Week 24, until disease recurrence, unacceptable toxicity or withdrawal of consent, for a maximum of 3 years (Week 156).

| Number of subjects in period 1^[1] | Ipilimumab 10mg/kg | Placebo |
|---|---------------------------|----------------|
| Started | 475 | 476 |
| Completed | 471 | 474 |
| Not completed | 4 | 2 |
| Consent withdrawn by subject | 2 | 2 |
| Adverse event, non-fatal | 1 | - |
| No longer meets study criteria | 1 | - |

Notes:

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

Justification: 1211 participants were enrolled. Baseline characteristics were collected for the 951 randomized participants.

Period 2

| | |
|------------------------------|-------------------------|
| Period 2 title | Treated with Study Drug |
| 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 | Ipilimumab 10mg/kg |

Arm description:

Ipilimumab (10 mg/kg) as a single dose via a 90 minute intravenous (IV) infusion (not as bolus or IV push) during Days 1, 22, 43 and 64 (every 21 days in the Induction Phase) for a total of four separate doses, until disease recurrence, unacceptable toxicity or withdrawal of consent. During the maintenance phase, Ipilimumab was administered at a dose of 10 mg/kg, by IV infusion, every 12 weeks, beginning at Week 24, until disease recurrence, unacceptable toxicity or withdrawal of consent, for a maximum of 3 years (Week 156).

| | |
|--|--|
| Arm type | Experimental |
| Investigational medicinal product name | Ipilimumab |
| Investigational medicinal product code | BMS-73016, MDX-010 |
| Other name | human Anti-human CTL4(CD152) mAb |
| Pharmaceutical forms | Solution for infusion, Solution for injection, Solution for injection/infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

Ipilimumab (10 mg/kg) as a single dose via a 90 minute intravenous (IV) infusion (not as bolus or IV push) during Days 1, 22, 43 and 64 (every 21 days in the Induction Phase) for a total of four separate doses, until disease recurrence, unacceptable toxicity or withdrawal of consent. During the maintenance phase, Ipilimumab was administered at a dose of 10 mg/kg, by IV infusion, every 12 weeks, beginning

at Week 24, until disease recurrence, unacceptable toxicity or withdrawal of consent, for a maximum of 3 years (Week 156).

| | |
|--|---------------------------------|
| Arm title | Placebo |
| Arm description: | |
| Placebo as a single dose via a 90 minute intravenous (IV) infusion (not as bolus or IV push) during Days 1, 22, 43 and 64 (Induction Phase) for a total of four separate doses, until disease recurrence, unacceptable toxicity or withdrawal of consent. During the maintenance phase, placebo was administered by IV infusion every 12 weeks, beginning at Week 24, until disease recurrence, unacceptable toxicity or withdrawal of consent, for a maximum of 3 years (Week 156). | |
| Arm type | Placebo |
| Investigational medicinal product name | Placebo |
| Investigational medicinal product code | |
| Other name | Saline Solution |
| Pharmaceutical forms | Solution for injection/infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

Placebo as a single dose via a 90 minute intravenous (IV) infusion (not as bolus or IV push) during Days 1, 22, 43 and 64 (Induction Phase) for a total of four separate doses, until disease recurrence, unacceptable toxicity or withdrawal of consent. During the maintenance phase, placebo was administered by IV infusion every 12 weeks, beginning at Week 24, until disease recurrence, unacceptable toxicity or withdrawal of consent, for a maximum of 3 years (Week 156).

| Number of subjects in period 2 | Ipilimumab 10mg/kg | Placebo |
|---------------------------------------|--------------------|---------|
| Started | 471 | 474 |
| Completed | 63 | 143 |
| Not completed | 408 | 331 |
| Adverse event, serious fatal | 3 | - |
| Recurrence of disease | 135 | 282 |
| Participant withdrew consent | 16 | 21 |
| Adverse event, non-fatal | 250 | 22 |
| Pregnancy | 1 | - |
| Other reason | 1 | 3 |
| No longer meets study criteria | 1 | - |
| Poor/non-compliance | 1 | 3 |

Period 3

| | |
|------------------------------|-------------------------|
| Period 3 title | Long Term Follow-Up |
| 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 | Ipilimumab 10mg/kg |

Arm description:

Ipilimumab (10 mg/kg) as a single dose via a 90 minute intravenous (IV) infusion (not as bolus or IV push) during Days 1, 22, 43 and 64 (every 21 days in the Induction Phase) for a total of four separate doses, until disease recurrence, unacceptable toxicity or withdrawal of consent. During the maintenance phase, Ipilimumab was administered at a dose of 10 mg/kg, by IV infusion, every 12 weeks, beginning at Week 24, until disease recurrence, unacceptable toxicity or withdrawal of consent, for a maximum of 3 years (Week 156).

| | |
|--|--|
| Arm type | Experimental |
| Investigational medicinal product name | Ipilimumab |
| Investigational medicinal product code | BMS-73016, MDX-010 |
| Other name | human Anti-human CTL4(CD152) mAb |
| Pharmaceutical forms | Solution for infusion, Solution for injection, Solution for injection/infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

Ipilimumab (10 mg/kg) as a single dose via a 90 minute intravenous (IV) infusion (not as bolus or IV push) during Days 1, 22, 43 and 64 (every 21 days in the Induction Phase) for a total of four separate doses, until disease recurrence, unacceptable toxicity or withdrawal of consent. During the maintenance phase, Ipilimumab was administered at a dose of 10 mg/kg, by IV infusion, every 12 weeks, beginning at Week 24, until disease recurrence, unacceptable toxicity or withdrawal of consent, for a maximum of 3 years (Week 156).

| | |
|------------------|---------|
| Arm title | Placebo |
|------------------|---------|

Arm description:

Placebo as a single dose via a 90 minute intravenous (IV) infusion (not as bolus or IV push) during Days 1, 22, 43 and 64 (Induction Phase) for a total of four separate doses, until disease recurrence, unacceptable toxicity or withdrawal of consent. During the maintenance phase, placebo was administered by IV infusion every 12 weeks, beginning at Week 24, until disease recurrence, unacceptable toxicity or withdrawal of consent, for a maximum of 3 years (Week 156).

| | |
|--|---------------------------------|
| Arm type | Placebo |
| Investigational medicinal product name | Placebo |
| Investigational medicinal product code | |
| Other name | Saline Solution |
| Pharmaceutical forms | Solution for injection/infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

Placebo as a single dose via a 90 minute intravenous (IV) infusion (not as bolus or IV push) during Days 1, 22, 43 and 64 (Induction Phase) for a total of four separate doses, until disease recurrence, unacceptable toxicity or withdrawal of consent. During the maintenance phase, placebo was administered by IV infusion every 12 weeks, beginning at Week 24, until disease recurrence, unacceptable toxicity or withdrawal of consent, for a maximum of 3 years (Week 156).

| Number of subjects in period 3 | Ipilimumab 10mg/kg | Placebo |
|---------------------------------------|--------------------|---------|
| Started | 63 | 143 |
| Completed | 130 | 129 |
| Not completed | 11 | 14 |
| Adverse event, serious fatal | 8 | 9 |
| Participant withdrew consent | - | 2 |

| | | |
|--|----|---|
| Lost to follow-up | 3 | 3 |
| Joined | 78 | 0 |
| Randomized, consented to participate in LTFU | 78 | - |

Baseline characteristics

Reporting groups

| | |
|-----------------------|--------------------|
| Reporting group title | Ipilimumab 10mg/kg |
|-----------------------|--------------------|

Reporting group description:

Ipilimumab (10 mg/kg) as a single dose via a 90 minute intravenous (IV) infusion (not as bolus or IV push) during Days 1, 22, 43 and 64 (every 21 days in the Induction Phase) for a total of four separate doses, until disease recurrence, unacceptable toxicity or withdrawal of consent. During the maintenance phase, Ipilimumab was administered at a dose of 10 mg/kg, by IV infusion, every 12 weeks, beginning at Week 24, until disease recurrence, unacceptable toxicity or withdrawal of consent, for a maximum of 3 years (Week 156).

| | |
|-----------------------|---------|
| Reporting group title | Placebo |
|-----------------------|---------|

Reporting group description:

Placebo as a single dose via a 90 minute intravenous (IV) infusion (not as bolus or IV push) during Days 1, 22, 43 and 64 (Induction Phase) for a total of four separate doses, until disease recurrence, unacceptable toxicity or withdrawal of consent. During the maintenance phase, placebo was administered by IV infusion every 12 weeks, beginning at Week 24, until disease recurrence, unacceptable toxicity or withdrawal of consent, for a maximum of 3 years (Week 156).

| Reporting group values | Ipilimumab 10mg/kg | Placebo | Total |
|---|--------------------|---------|-------|
| Number of subjects | 475 | 476 | 951 |
| Age categorical Units: Subjects | | | |
| In utero | 0 | 0 | 0 |
| Preterm newborn infants (gestational age < 37 wks) | 0 | 0 | 0 |
| Newborns (0-27 days) | 0 | 0 | 0 |
| Infants and toddlers (28 days-23 months) | 0 | 0 | 0 |
| Children (2-11 years) | 0 | 0 | 0 |
| Adolescents (12-17 years) | 0 | 0 | 0 |
| Adults (18-64 years) | 395 | 389 | 784 |
| From 65-84 years | 80 | 87 | 167 |
| 85 years and over | 0 | 0 | 0 |
| Age Continuous Units: years | | | |
| arithmetic mean | 50.7 | 51.5 | |
| standard deviation | ± 12.9 | ± 12.82 | - |
| Sex: Female, Male Units: | | | |
| Female | 179 | 183 | 362 |
| Male | 296 | 293 | 589 |
| Race (NIH/OMB) Units: Subjects | | | |
| American Indian or Alaska Native | 0 | 0 | 0 |
| Asian | 1 | 0 | 1 |
| Native Hawaiian or Other Pacific Islander | 1 | 0 | 1 |
| Black or African American | 0 | 0 | 0 |
| White | 470 | 476 | 946 |
| More than one race | 0 | 0 | 0 |
| Unknown or Not Reported | 3 | 0 | 3 |

End points

End points reporting groups

| | |
|--|--------------------|
| Reporting group title | Ipilimumab 10mg/kg |
| Reporting group description: Ipilimumab (10 mg/kg) as a single dose via a 90 minute intravenous (IV) infusion (not as bolus or IV push) during Days 1, 22, 43 and 64 (every 21 days in the Induction Phase) for a total of four separate doses, until disease recurrence, unacceptable toxicity or withdrawal of consent. During the maintenance phase, Ipilimumab was administered at a dose of 10 mg/kg, by IV infusion, every 12 weeks, beginning at Week 24, until disease recurrence, unacceptable toxicity or withdrawal of consent, for a maximum of 3 years (Week 156). | |
| Reporting group title | Placebo |
| Reporting group description: Placebo as a single dose via a 90 minute intravenous (IV) infusion (not as bolus or IV push) during Days 1, 22, 43 and 64 (Induction Phase) for a total of four separate doses, until disease recurrence, unacceptable toxicity or withdrawal of consent. During the maintenance phase, placebo was administered by IV infusion every 12 weeks, beginning at Week 24, until disease recurrence, unacceptable toxicity or withdrawal of consent, for a maximum of 3 years (Week 156). | |
| Reporting group title | Ipilimumab 10mg/kg |
| Reporting group description: Ipilimumab (10 mg/kg) as a single dose via a 90 minute intravenous (IV) infusion (not as bolus or IV push) during Days 1, 22, 43 and 64 (every 21 days in the Induction Phase) for a total of four separate doses, until disease recurrence, unacceptable toxicity or withdrawal of consent. During the maintenance phase, Ipilimumab was administered at a dose of 10 mg/kg, by IV infusion, every 12 weeks, beginning at Week 24, until disease recurrence, unacceptable toxicity or withdrawal of consent, for a maximum of 3 years (Week 156). | |
| Reporting group title | Placebo |
| Reporting group description: Placebo as a single dose via a 90 minute intravenous (IV) infusion (not as bolus or IV push) during Days 1, 22, 43 and 64 (Induction Phase) for a total of four separate doses, until disease recurrence, unacceptable toxicity or withdrawal of consent. During the maintenance phase, placebo was administered by IV infusion every 12 weeks, beginning at Week 24, until disease recurrence, unacceptable toxicity or withdrawal of consent, for a maximum of 3 years (Week 156). | |
| Reporting group title | Ipilimumab 10mg/kg |
| Reporting group description: Ipilimumab (10 mg/kg) as a single dose via a 90 minute intravenous (IV) infusion (not as bolus or IV push) during Days 1, 22, 43 and 64 (every 21 days in the Induction Phase) for a total of four separate doses, until disease recurrence, unacceptable toxicity or withdrawal of consent. During the maintenance phase, Ipilimumab was administered at a dose of 10 mg/kg, by IV infusion, every 12 weeks, beginning at Week 24, until disease recurrence, unacceptable toxicity or withdrawal of consent, for a maximum of 3 years (Week 156). | |
| Reporting group title | Placebo |
| Reporting group description: Placebo as a single dose via a 90 minute intravenous (IV) infusion (not as bolus or IV push) during Days 1, 22, 43 and 64 (Induction Phase) for a total of four separate doses, until disease recurrence, unacceptable toxicity or withdrawal of consent. During the maintenance phase, placebo was administered by IV infusion every 12 weeks, beginning at Week 24, until disease recurrence, unacceptable toxicity or withdrawal of consent, for a maximum of 3 years (Week 156). | |

Primary: Recurrence free survival (RFS) per Independent Review Committee (IRC) in the Intent to Treat (ITT) Population

| | |
|-----------------|---|
| End point title | Recurrence free survival (RFS) per Independent Review Committee (IRC) in the Intent to Treat (ITT) Population |
|-----------------|---|

End point description:

Recurrence free survival (RFS) was programmatically determined based on the disease recurrence data provided by the IRC and was defined as the time between the date of randomization and the date of first recurrence or death (whatever the cause), whichever occurred first. A participant who died without

reported recurrence was considered to have recurrence on the date of death. For those participants who remained alive and recurrence-free, RFS was censored on the date of last evaluable post-randomization tumor assessment. For those who remained alive and had no recorded post-randomization tumor assessment, RFS was censored on the day of randomization. Participants with disease at baseline were considered to have an event on the day of randomization. The primary analysis was event-driven and planned when at least 512 RFS events assessed per IRC were collected. Intent-to-treat population: All randomized participants, analyzed in the arm to which they were allocated by randomization

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

End point timeframe:

Date of randomization to first date of recurrence or death or last available disease assessment with RFS data up to 5 years. Median follow-up was 2.7 years.

| End point values | Ipilimumab 10mg/kg | Placebo | | |
|----------------------------------|------------------------|------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 475 | 476 | | |
| Units: months | | | | |
| median (confidence interval 95%) | | | | |
| RFS per IRC in ITT | 26.09 (19.32 to 39.26) | 17.05 (13.40 to 21.62) | | |

Statistical analyses

| | |
|----------------------------|---|
| Statistical analysis title | Statistical Analysis for RFS per IRC in ITT |
|----------------------------|---|

Statistical analysis description:

Hazard ratio, and its 95 % confidence interval estimated using a Cox proportional hazards model, stratified by stage (IIIA vs. IIIB vs. IIIC with 1-3 positive lymph-nodes vs. IIIC with ≥ 4 positive lymph-nodes) as indicated at randomization, with treatment as the single covariate. 2-sided, 95% confidence intervals for median RFS computed by the Brookmeyer and Crowley method using log-log transformation. P-value was based on stratified 2-sided log-rank test.

| | |
|---|------------------------------|
| Comparison groups | Placebo v Ipilimumab 10mg/kg |
| Number of subjects included in analysis | 951 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.0013 |
| Method | Logrank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.75 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.64 |
| upper limit | 0.9 |

Primary: Number of participants with recurrence or death as per Independent Review Committee (IRC) in the Intent to Treat (ITT) Population

| | |
|-----------------|--|
| End point title | Number of participants with recurrence or death as per Independent Review Committee (IRC) in the Intent to Treat |
|-----------------|--|

End point description:

Recurrence was defined as appearance of one or more new melanoma lesions: local, regional or distant metastasis. Computerized tomography (CT) and magnetic resonance imaging (MRI) were mandatory to establish recurrence. A participant who died without reported recurrence was considered to have recurred on the date of death. Disease was assessed at randomization and every 12 weeks (± 2 weeks) for 3 years, then every 24 weeks until documented distant progression. Intent-to-treat population: All randomized participants, analyzed in the arm to which they were allocated by randomization

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

End point timeframe:

Date of randomization to first date of recurrence or death or last available disease assessment with RFS data upto 5 years. Median follow-up was 2.7 years.

Notes:

[1] - 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: Statistical analysis for this endpoint is the same as that for previous endpoint: Recurrence free survival (RFS) per Independent Review Committee (IRC) in the Intent to Treat (ITT) Population

| End point values | Ipilimumab 10mg/kg | Placebo | | |
|--|-----------------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 475 | 476 | | |
| Units: Participants | | | | |
| No. of participants with recurrence or death | 234 | 294 | | |

Statistical analyses

No statistical analyses for this end point

Primary: Recurrence-Free Survival (RFS) Rates per IRC at 1 year, 2 years, and 3 years in the ITT Population

| | |
|-----------------|---|
| End point title | Recurrence-Free Survival (RFS) Rates per IRC at 1 year, 2 years, and 3 years in the ITT Population ^[2] |
|-----------------|---|

End point description:

Yearly recurrence-free survival rates, eg. at 1 year, defined as the probability that a participant was recurrence-free at 1 year following randomization, were estimated for each treatment group using the Kaplan-Meier product-limit method, along with their corresponding log-log transformed 95% confidence intervals. RFS was defined as the time between the date of randomization and the date of first recurrence or death (whatever the cause), whichever occurred first. A participant who died without reported recurrence was considered to have recurrence on the date of death. For those who remained alive and had no recorded post-randomization tumor assessment, RFS was censored on the day of randomization. Participants with disease at baseline were considered to have an event on the day of randomization. Intent-to-treat population: All randomized participants, analyzed in the arm to which they were allocated by randomization

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

End point timeframe:

At years 1, 2, and 3

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: Only summary statistics were planned for this endpoint

| End point values | Ipilimumab 10mg/kg | Placebo | | |
|----------------------------------|---------------------------|---------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 475 | 476 | | |
| Units: Percentage | | | | |
| number (confidence interval 95%) | | | | |
| RFS Rate at 1 Year | 63.50 (58.89 to 67.74) | 56.13 (51.52 to 60.47) | | |
| RFS Rate at 2 Years | 51.45 (46.69 to 56.00) | 43.83 (39.27 to 48.28) | | |
| RFS Rate at 3 Years | 46.48 (41.46 to 51.34) | 34.79 (30.12 to 39.50) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Distant Metastasis-Free Survival (DMFS) per Independent Review Committee (IRC) in the Intent to Treat (ITT) Population

| | |
|-----------------|--|
| End point title | Distant Metastasis-Free Survival (DMFS) per Independent Review Committee (IRC) in the Intent to Treat (ITT) Population |
|-----------------|--|

End point description:

Distant Metastasis-Free Survival (DMFS) was programmatically determined based on the first date of distant metastasis provided by the IRC and was defined as the time between the date of randomization and the date of first distant metastasis or death (whatever the cause), whichever occurred first. A participant who died without reported disease distant metastasis was considered to have distant metastasis on the date of death. For those who remained alive and metastasis-free, DMFS was censored on the date of last evaluable post-randomization tumor assessment. Participants with disease at baseline were considered to have an event on the day of randomization. Disease was assessed at baseline (randomization) and every 12 weeks (± 2 weeks) for 3 years, then every 24 weeks until documented distant progression. Intent-to-treat population: All randomized participants, analyzed in the arm to which they were allocated by randomization

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

End point timeframe:

From June 2008 to January 2016 (approximately 90 months)

| End point values | Ipilimumab 10mg/kg | Placebo | | |
|----------------------------------|---------------------------|---------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 475 | 476 | | |
| Units: Months | | | | |
| median (confidence interval 95%) | | | | |
| DMFS per IRC in ITT | 48.30 (35.45 to 71.56) | 27.47 (21.91 to 34.79) | | |

Statistical analyses

| | |
|----------------------------|--|
| Statistical analysis title | Statistical Analysis for DMFS per IRC in ITT |
|----------------------------|--|

Statistical analysis description:

Medians and associated 2-sided 95% confidence intervals are calculated using the method of Brookmeyer and Crowley. Analysis was stratified for stage (IIIa vs. IIIb vs. IIIc with 1-3 positive lymph-nodes vs. IIIc with ≥ 4 positive lymph-nodes) as recorded at randomization. P-value was based on stratified 2-sided log-rank test. Hazard of 10 mg/kg Ipilimumab over hazard of Placebo, with 2-sided 95.8% confidence interval are based on a stratified Cox proportional hazards model

| | |
|---|------------------------------|
| Comparison groups | Ipilimumab 10mg/kg v Placebo |
| Number of subjects included in analysis | 951 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.0024 |
| Method | Logrank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.76 |
| Confidence interval | |
| level | 95.8 % |
| sides | 2-sided |
| lower limit | 0.64 |
| upper limit | 0.92 |

Secondary: Number of participants with Distant Metastasis-Free Survival (DMFS) per Independent Review Committee (IRC) in the Intent to Treat (ITT) Population

| | |
|-----------------|--|
| End point title | Number of participants with Distant Metastasis-Free Survival (DMFS) per Independent Review Committee (IRC) in the Intent to Treat (ITT) Population |
|-----------------|--|

End point description:

DMFS was programmatically determined based on the first date of distant metastasis provided by the IRC and was defined as the time between the date of randomization and the date of first distant metastasis or death (whatever the cause), whichever occurred first. A participant who died without reported disease distant metastasis was considered to have distant metastasis on the date of death. For those who remained alive and metastasis-free, DMFS was censored on the date of last evaluable post-randomization tumor assessment. For those who remained alive and had no recorded post-randomization tumor assessment, DMFS was censored on the day of randomization. Intent-to-treat population: All randomized participants, analyzed in the arm to which they were allocated by randomization

| | |
|----------------------|--|
| End point type | Secondary |
| End point timeframe: | From June 2008 to January 2016 (approximately 90 months) |

| End point values | Ipilimumab 10mg/kg | Placebo | | |
|---------------------------------------|--------------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 475 | 476 | | |
| Units: Participants | | | | |
| No. of participants with DMFS per IRC | 227 | 279 | | |

Statistical analyses

Secondary: Distant Metastasis-Free Survival (DMFS) Rates per IRC at 1 year, 2 years, 3 years, 4 years and 5 years in the ITT Population

| | |
|-----------------|--|
| End point title | Distant Metastasis-Free Survival (DMFS) Rates per IRC at 1 year, 2 years, 3 years, 4 years and 5 years in the ITT Population |
|-----------------|--|

End point description:

Yearly distant metastasis-free survival rates, e.g. at 1 year, defined as the probability that a participant was alive at 1 year following randomization, were estimated via the Kaplan-Meier method. Distant Metastasis-Free Survival (DMFS) was programmatically determined based on the first date of distant metastasis provided by the IRC and was defined as the time between the date of randomization and the date of first distant metastasis or death (whatever the cause), whichever occurred first. A participant who died without reported disease distant metastasis was considered to have distant metastasis on the date of death. For those who remained alive and metastasis-free, DMFS was censored on the date of last evaluable post-randomization tumor assessment. For those who remained alive and had no recorded post-randomization tumor assessment. Intent-to-treat population: All randomized participants, analyzed in the arm to which they were allocated by randomization

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

End point timeframe:

At years 1, 2, 3, 4 and 5

| End point values | Ipilimumab 10mg/kg | Placebo | | |
|----------------------------------|------------------------|------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 475 | 476 | | |
| Units: Percentage | | | | |
| number (confidence interval 95%) | | | | |
| DMFS Rate at 1 Year | 74.27 (69.98 to 78.04) | 65.77 (61.27 to 69.88) | | |
| DMFS Rate at 2 Years | 61.48 (56.75 to 65.85) | 53.26 (48.58 to 57.70) | | |
| DMFS Rate at 3 Years | 53.90 (49.04 to 58.50) | 45.17 (40.53 to 49.70) | | |
| DMFS Rate at 4 Years | 50.19 (45.30 to 54.87) | 41.48 (36.87 to 46.02) | | |
| DMFS Rate at 5 Years | 48.29 (43.36 to 53.04) | 38.90 (34.29 to 43.47) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival in the Intent to Treat (ITT) Population

| | |
|-----------------|--|
| End point title | Overall Survival in the Intent to Treat (ITT) Population |
|-----------------|--|

End point description:

OS was defined as the time from the date of randomization to the date of death. For those participants who had not died, OS was censored at the recorded last non-missing date of contact for which the participant was known to be alive. Here '99999' signifies data not available as the upper limit or median was not reached. Intent-to-treat population: All randomized participants, analyzed in the arm to which they were allocated by randomization

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

End point timeframe:

From June 2008 to January 2016 (approximately 90 months)

| End point values | Ipilimumab 10mg/kg | Placebo | | |
|----------------------------------|---------------------------|---------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 475 | 476 | | |
| Units: Months | | | | |
| median (confidence interval 95%) | | | | |
| OS in ITT | 86.60 (86.60 to 99999) | 99999 (59.30 to 99999) | | |

Statistical analyses

| Statistical analysis title | Statistical Analysis for OS in ITT |
|--|------------------------------------|
| Statistical analysis description: | |
| Medians and associated 2-sided 95% confidence intervals are calculated using the method of Brookmeyer and Crowley. Analysis was stratified for stage (IIa vs. IIb vs. IIc with 1-3 positive lymph-nodes vs. IIc with ≥ 4 positive lymph-nodes) as recorded at randomization. P-value was based on stratified 2-sided log-rank test. Hazard of 10 mg/kg Ipilimumab over hazard of Placebo, with 2-sided 95.1% confidence interval are based on a stratified Cox proportional hazards model | |
| Comparison groups | Ipilimumab 10mg/kg v Placebo |
| Number of subjects included in analysis | 951 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.0013 |
| Method | Logrank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.72 |
| Confidence interval | |
| level | 95.1 % |
| sides | 2-sided |
| lower limit | 0.58 |
| upper limit | 0.88 |

Secondary: Rate of Overall Survival (OS)

| | |
|---|-------------------------------|
| End point title | Rate of Overall Survival (OS) |
| End point description: | |
| OS was defined as the time from the date of randomization to the date of death. For those participants who had not died, OS was censored at the recorded last non-missing date of contact for which the participant was known to be alive. Yearly survival rates, e.g. at 3 years, defined as the probability that a participant was alive at 3 years following randomization, were estimated via the Kaplan-Meier method. Intent to Treat Population: All randomized participants, analyzed in the arm to which they were allocated by randomization | |
| End point type | Secondary |
| End point timeframe: | |
| From date of randomization to date of death, assessed up to 9 years | |

| End point values | Ipilimumab 10mg/kg | Placebo | | |
|-----------------------------------|------------------------|------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 475 | 476 | | |
| Units: Percentage of participants | | | | |
| number (confidence interval 95%) | | | | |
| OS Rate at 1 year | 93.53 (90.88 to 95.43) | 87.72 (84.40 to 90.37) | | |
| OS Rate at 2 years | 82.55 (78.76 to 85.73) | 75.27 (71.10 to 78.92) | | |
| OS Rate at 3 years | 74.20 (69.90 to 77.98) | 65.43 (60.91 to 69.56) | | |
| OS Rate at 4 years | 67.79 (63.24 to 71.90) | 60.34 (55.72 to 64.64) | | |
| OS Rate at 5 years | 65.42 (60.80 to 69.64) | 54.43 (49.71 to 58.89) | | |
| OS Rate at 7 years | 60.0 (55.0 to 64.7) | 51.3 (46.5 to 55.9) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants with On-Study Adverse Events (AEs) Leading to Discontinuation of Treatment, Serious AEs (SAEs), Drug-Related SAEs, Immune-related AEs (irAEs), Immune-mediated adverse reactions (imARs), Deaths in Treated Population

| | |
|-----------------|---|
| End point title | Number of Participants with On-Study Adverse Events (AEs) Leading to Discontinuation of Treatment, Serious AEs (SAEs), Drug-Related SAEs, Immune-related AEs (irAEs), Immune-mediated adverse reactions (imARs), Deaths in Treated Population |
|-----------------|---|

End point description:

AEs: Medical Dictionary for Regulatory Activities (MedDRA) version 22.0. irAEs=unknown etiology consistent with an immune phenomenon, considered as causally related to drug. imARs=based on investigator's assessment of immune-mediated etiology. AE=any new unfavorable symptom, sign, or disease or worsening of a preexisting condition that may not have a causal relationship with treatment. SAE=a medical event that at any dose results in death, persistent or significant disability/incapacity, or drug dependency/abuse; is life-threatening, an important medical event, or a congenital anomaly/birth defect; or requires or prolongs hospitalization. Drug-related (D-R)=having certain, probable, possible, or missing relationship to study drug. Grade (Gr) 1=Mild, Gr 2=Moderate, Gr 3=Severe, Gr 4= Potentially Life-threatening or disabling, Gr 5=Death. Safety population: All randomized participants who received at least 1 dose of study therapy

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

End point timeframe:

Day 1 up to 70 days after last dose; up to 5 years

| End point values | Ipilimumab 10mg/kg | Placebo | | |
|--|-----------------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 471 | 474 | | |
| Units: Participants | | | | |
| On-study AE leading to Discontinuation (Any Grade) | 247 | 43 | | |
| On-study SAE (At least 5%, Any Grade) | 257 | 128 | | |
| On-study D-R SAE (Any Grade) | 217 | 10 | | |
| On-study irAE (Any Grade) | 426 | 188 | | |
| On-study gastrointestinal irAE (Any Grade) | 217 | 85 | | |
| On-study endocrine irAE (Any Grade) | 178 | 38 | | |
| On-study liver irAE (Any Grade) | 115 | 20 | | |
| On-study skin irAE (Any Grade) | 298 | 99 | | |
| On-study neurological irAE (Any Grade) | 21 | 9 | | |
| On-study other irAE (Any Grade) | 111 | 23 | | |
| On-study imAR (Grade 3-4) | 194 | 16 | | |
| On-study imAR (Grade 5) | 1 | 0 | | |
| On-study enterocolitis imAR (Grade 5) | 1 | 0 | | |
| On-study enterocolitis imAR (Grade 3-4) | 76 | 4 | | |
| On-study endocrinopathy imAR (Grade 3-4) | 39 | 1 | | |
| On-study hepatitis imAR (Grade 3-4) | 51 | 1 | | |
| On-study dermatitis imAR (Grade 3-4) | 19 | 2 | | |
| On-study neuropathy imAR (Grade 3-4) | 10 | 0 | | |
| On-study other imAR (Grade 3-4) | 30 | 9 | | |
| Any Death | 162 | 214 | | |
| Death within 70 days of last dose study drug | 6 | 6 | | |
| Death within 30 days of last dose study drug | 1 | 0 | | |
| Drug-related Deaths | 4 | 0 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants with Serious Adverse Events (SAEs), Non-serious AEs (NSAEs) and number of Deaths: Overall study

| | |
|-----------------|--|
| End point title | Number of Participants with Serious Adverse Events (SAEs), Non-serious AEs (NSAEs) and number of Deaths: Overall study |
|-----------------|--|

End point description:

AEs: Medical Dictionary for Regulatory Activities (MedDRA) version 22.0. AE=any new unfavorable symptom, sign, or disease or worsening of a preexisting condition that may not have a causal relationship with treatment. SAE=a medical event that at any dose results in death, persistent or significant disability/incapacity, or drug dependency/abuse; is life-threatening, an important medical event, or a congenital anomaly/birth defect; or requires or prolongs hospitalization. Safety population: All randomized participants who received at least 1 dose of study therapy

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

End point timeframe:

SAEs and NSAEs: Day 1 up to 70 days after last dose(safety window). Deaths: All deaths regardless of 70 day safety window.Up to 10 years

| End point values | Ipilimumab 10mg/kg | Placebo | | |
|---|-----------------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 471 | 474 | | |
| Units: Participants | | | | |
| No. of deaths | 173 | 223 | | |
| No. of participants with SAEs | 257 | 128 | | |
| No of participants with NSAEs (freq. >= 5%) | 441 | 382 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Exposure Adjusted Incidence Rate of Adverse Events Including Multiple Occurrences of Unique Events

| | |
|-----------------|--|
| End point title | Exposure Adjusted Incidence Rate of Adverse Events Including Multiple Occurrences of Unique Events |
|-----------------|--|

End point description:

P-Y = person-years of exposure. Incidence rate per 100 person-years of exposure (IR/100 P-Y) was calculated as event count * 100 /person-years of exposure. MedDRA Version: 19. Duplicate AEs have been eliminated and overlapping and contiguous occurrences of the same event have been collapsed. All participants who received at least one dose of ipilimumab or placebo, adjusted for person-years (P-Y) of exposure; P-Y=467.4; P-Y=781.7 for ipilimumab and placebo, respectively.

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

End point timeframe:

Day 1 up to 70 days after last dose; up to 5 years

| End point values | Ipilimumab 10mg/kg | Placebo | | |
|--|-----------------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 471 | 474 | | |
| Units: Events per 100 person-years of exposure | | | | |
| number (not applicable) | | | | |
| Exp. adj. incidence rate of AEs | 1171.8 | 465.0 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Change from Baseline in Global Health Status Scores at Each Assessment Timepoint

| | |
|--|---|
| End point title | Mean Change from Baseline in Global Health Status Scores at Each Assessment Timepoint |
| End point description: | |
| Global health status was measured using European Organization for Research and Treatment of Cancer (EORTC) Quality Life Questionnaire (QLQ) C-30. This health related quality of life (HRQoL) questionnaire was comprised of 15 questions on functional scales, 13 questions on symptom scales and 2 on global health status scale. Global Health Status used a 7 point Likert-type scale of 1 (Very poor) to 7 (Excellent). All scales linearly transformed to 0-100 scales. Higher scores for Global Health Status indicate better HRQoL. An increase from baseline indicates improvement in HRQoL compared to baseline. All randomized participants (ITT) analyzed in the arm to which they were allocated by randomization were analyzed. At timepoint level, all randomized participants (ITT) with a measurement at the timepoint were analyzed. | |
| End point type | Secondary |
| End point timeframe: | |
| Baseline up to 2 years from randomization | |

| End point values | Ipilimumab 10mg/kg | Placebo | | |
|--------------------------------------|-----------------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 400 | 421 | | |
| Units: units on a scale | | | | |
| arithmetic mean (standard deviation) | | | | |
| Week 4 Day 22 | -2.29 (± 15.96) | 1.33 (± 14.02) | | |
| Week 7, Day 43 (360, 412) | -6.64 (± 20.44) | -0.10 (± 16.75) | | |
| Week 10 Day 64 (356, 405) | -9.06 (± 23.56) | -0.23 (± 16.18) | | |
| Week 24 Day 162 (300, 347) | -4.33 (± 21.55) | 1.37 (± 17.00) | | |
| Week 36 Day 246 (290, 307) | -5.09 (± 21.32) | 1.52 (± 18.52) | | |
| Week 48 Day 330 (275, 276) | -3.67 (± 20.17) | 1.54 (± 18.87) | | |
| Week 60 Day 414 (242, 255) | -5.30 (± 21.34) | 2.84 (± 17.05) | | |
| Week 72 day 498 (217, 248) | -4.07 (± 23.19) | 1.18 (± 17.46) | | |
| Week 84 Day 582 (205, 227) | -3.90 (± 22.06) | 1.84 (± 17.08) | | |
| Week 96 Day 666 (199, 214) | -4.48 (± 21.71) | 1.36 (± 18.67) | | |
| Week 108 Day 750 (162,177) | -4.27 (± 20.35) | 2.45 (± 16.72) | | |

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Time frame for AE reporting

Adverse event reporting additional description:

Adverse Events were collected for the safety population which included all 945 randomized subjects who received at least 1 dose of study therapy (471 in the ipilimumab group and 474 in the placebo group)

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

Dictionary used

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

| | |
|--------------------|------|
| Dictionary version | 22.0 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|---------|
| Reporting group title | PLACEBO |
|-----------------------|---------|

Reporting group description:

PLACEBO

| | |
|-----------------------|---------------------|
| Reporting group title | IPILIMUMAB 10 MG/KG |
|-----------------------|---------------------|

Reporting group description:

IPILIMUMAB 10 MG/KG

| Serious adverse events | PLACEBO | IPILIMUMAB 10 MG/KG | |
|---|--------------------|---------------------|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 128 / 474 (27.00%) | 257 / 471 (54.56%) | |
| number of deaths (all causes) | 223 | 173 | |
| number of deaths resulting from adverse events | | | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Malignant melanoma in situ | | | |
| subjects affected / exposed | 3 / 474 (0.63%) | 1 / 471 (0.21%) | |
| occurrences causally related to treatment / all | 1 / 3 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Squamous cell carcinoma of skin | | | |
| subjects affected / exposed | 4 / 474 (0.84%) | 0 / 471 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 4 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Metastases to adrenals | | | |
| subjects affected / exposed | 0 / 474 (0.00%) | 1 / 471 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Metastases to central nervous | | | |

| | | | |
|---|-----------------|-----------------|--|
| system | | | |
| subjects affected / exposed | 2 / 474 (0.42%) | 0 / 471 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Rectal cancer stage 0 | | | |
| subjects affected / exposed | 1 / 474 (0.21%) | 0 / 471 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Adrenal adenoma | | | |
| subjects affected / exposed | 1 / 474 (0.21%) | 0 / 471 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Metastases to skin | | | |
| subjects affected / exposed | 1 / 474 (0.21%) | 0 / 471 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Squamous cell carcinoma | | | |
| subjects affected / exposed | 6 / 474 (1.27%) | 0 / 471 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 9 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Adenocarcinoma | | | |
| subjects affected / exposed | 1 / 474 (0.21%) | 0 / 471 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Liposarcoma | | | |
| subjects affected / exposed | 0 / 474 (0.00%) | 1 / 471 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Malignant neoplasm progression | | | |
| subjects affected / exposed | 6 / 474 (1.27%) | 4 / 471 (0.85%) | |
| occurrences causally related to treatment / all | 0 / 9 | 2 / 5 | |
| deaths causally related to treatment / all | 0 / 6 | 2 / 4 | |
| Malignant pleural effusion | | | |

| | | | |
|---|------------------|-----------------|--|
| subjects affected / exposed | 1 / 474 (0.21%) | 0 / 471 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 3 | 0 / 0 | |
| Melanocytic naevus | | | |
| subjects affected / exposed | 1 / 474 (0.21%) | 0 / 471 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Metastases to bone | | | |
| subjects affected / exposed | 1 / 474 (0.21%) | 0 / 471 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 3 | 0 / 0 | |
| Metastases to lung | | | |
| subjects affected / exposed | 0 / 474 (0.00%) | 1 / 471 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Metastatic malignant melanoma | | | |
| subjects affected / exposed | 11 / 474 (2.32%) | 2 / 471 (0.42%) | |
| occurrences causally related to treatment / all | 0 / 12 | 1 / 2 | |
| deaths causally related to treatment / all | 0 / 8 | 1 / 2 | |
| Neoplasm progression | | | |
| subjects affected / exposed | 2 / 474 (0.42%) | 0 / 471 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Parathyroid tumour benign | | | |
| subjects affected / exposed | 1 / 474 (0.21%) | 0 / 471 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Melanoma recurrent | | | |
| subjects affected / exposed | 7 / 474 (1.48%) | 1 / 471 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 7 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 4 | 0 / 1 | |
| Metastases to lymph nodes | | | |

| | | | |
|---|------------------|-----------------|--|
| subjects affected / exposed | 2 / 474 (0.42%) | 1 / 471 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Metastasis | | | |
| subjects affected / exposed | 1 / 474 (0.21%) | 0 / 471 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Benign lung neoplasm | | | |
| subjects affected / exposed | 0 / 474 (0.00%) | 1 / 471 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Endobronchial lipoma | | | |
| subjects affected / exposed | 0 / 474 (0.00%) | 1 / 471 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Basal cell carcinoma | | | |
| subjects affected / exposed | 12 / 474 (2.53%) | 2 / 471 (0.42%) | |
| occurrences causally related to treatment / all | 2 / 13 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 2 | 0 / 0 | |
| Malignant melanoma | | | |
| subjects affected / exposed | 9 / 474 (1.90%) | 1 / 471 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 10 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 4 | 0 / 0 | |
| Prostate cancer | | | |
| subjects affected / exposed | 1 / 474 (0.21%) | 0 / 471 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Central nervous system melanoma | | | |
| subjects affected / exposed | 1 / 474 (0.21%) | 0 / 471 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 2 | 0 / 0 | |
| Oncocytoma | | | |

| | | | |
|--|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 474 (0.21%) | 0 / 471 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Papillary cystadenoma lymphomatosum | | | |
| subjects affected / exposed | 0 / 474 (0.00%) | 1 / 471 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Second primary malignancy | | | |
| subjects affected / exposed | 0 / 474 (0.00%) | 1 / 471 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vascular disorders | | | |
| Lymphoedema | | | |
| subjects affected / exposed | 1 / 474 (0.21%) | 1 / 471 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypotension | | | |
| subjects affected / exposed | 0 / 474 (0.00%) | 4 / 471 (0.85%) | |
| occurrences causally related to treatment / all | 0 / 0 | 4 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 3 / 3 | |
| Haematoma | | | |
| subjects affected / exposed | 2 / 474 (0.42%) | 0 / 471 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 1 / 1 | 0 / 0 | |
| Circulatory collapse | | | |
| subjects affected / exposed | 1 / 474 (0.21%) | 0 / 471 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Withdrawal hypertension | | | |
| subjects affected / exposed | 1 / 474 (0.21%) | 0 / 471 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| General disorders and administration site conditions | | | |

| | | | |
|---|-----------------|------------------|--|
| Disease progression | | | |
| subjects affected / exposed | 4 / 474 (0.84%) | 1 / 471 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 4 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 3 | 0 / 0 | |
| Influenza like illness | | | |
| subjects affected / exposed | 0 / 474 (0.00%) | 1 / 471 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pyrexia | | | |
| subjects affected / exposed | 1 / 474 (0.21%) | 18 / 471 (3.82%) | |
| occurrences causally related to treatment / all | 0 / 1 | 17 / 20 | |
| deaths causally related to treatment / all | 0 / 1 | 6 / 8 | |
| Asthenia | | | |
| subjects affected / exposed | 0 / 474 (0.00%) | 3 / 471 (0.64%) | |
| occurrences causally related to treatment / all | 0 / 0 | 3 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 1 / 1 | |
| Fatigue | | | |
| subjects affected / exposed | 1 / 474 (0.21%) | 5 / 471 (1.06%) | |
| occurrences causally related to treatment / all | 0 / 1 | 5 / 5 | |
| deaths causally related to treatment / all | 0 / 1 | 3 / 3 | |
| Disease recurrence | | | |
| subjects affected / exposed | 3 / 474 (0.63%) | 0 / 471 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Sudden death | | | |
| subjects affected / exposed | 0 / 474 (0.00%) | 1 / 471 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 1 / 1 | |
| Chest pain | | | |
| subjects affected / exposed | 2 / 474 (0.42%) | 3 / 471 (0.64%) | |
| occurrences causally related to treatment / all | 1 / 2 | 2 / 3 | |
| deaths causally related to treatment / all | 1 / 1 | 0 / 0 | |
| Multiple organ dysfunction syndrome | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 474 (0.00%) | 1 / 471 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 2 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 2 / 2 | |
| Retention cyst | | | |
| subjects affected / exposed | 1 / 474 (0.21%) | 0 / 471 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Immune system disorders | | | |
| Drug hypersensitivity | | | |
| subjects affected / exposed | 0 / 474 (0.00%) | 1 / 471 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 1 / 1 | |
| Autoimmune disorder | | | |
| subjects affected / exposed | 0 / 474 (0.00%) | 1 / 471 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Anaphylactoid reaction | | | |
| subjects affected / exposed | 0 / 474 (0.00%) | 1 / 471 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Sarcoidosis | | | |
| subjects affected / exposed | 1 / 474 (0.21%) | 3 / 471 (0.64%) | |
| occurrences causally related to treatment / all | 1 / 1 | 3 / 3 | |
| deaths causally related to treatment / all | 1 / 1 | 0 / 0 | |
| Hypersensitivity | | | |
| subjects affected / exposed | 0 / 474 (0.00%) | 3 / 471 (0.64%) | |
| occurrences causally related to treatment / all | 0 / 0 | 3 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Reproductive system and breast disorders | | | |
| Endometrial hyperplasia | | | |
| subjects affected / exposed | 1 / 474 (0.21%) | 0 / 471 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |

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| Ovarian cyst | | | |
| subjects affected / exposed | 1 / 474 (0.21%) | 0 / 471 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Interstitial lung disease | | | |
| subjects affected / exposed | 0 / 474 (0.00%) | 1 / 471 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pulmonary embolism | | | |
| subjects affected / exposed | 2 / 474 (0.42%) | 1 / 471 (0.21%) | |
| occurrences causally related to treatment / all | 2 / 2 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lung infiltration | | | |
| subjects affected / exposed | 0 / 474 (0.00%) | 1 / 471 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 1 / 1 | |
| Pulmonary sarcoidosis | | | |
| subjects affected / exposed | 0 / 474 (0.00%) | 2 / 471 (0.42%) | |
| occurrences causally related to treatment / all | 0 / 0 | 3 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 1 / 1 | |
| Pneumonitis | | | |
| subjects affected / exposed | 0 / 474 (0.00%) | 3 / 471 (0.64%) | |
| occurrences causally related to treatment / all | 0 / 0 | 4 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypoxia | | | |
| subjects affected / exposed | 0 / 474 (0.00%) | 1 / 471 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumothorax | | | |
| subjects affected / exposed | 1 / 474 (0.21%) | 0 / 471 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|-----------------|------------------|--|
| Eosinophilic pneumonia | | | |
| subjects affected / exposed | 0 / 474 (0.00%) | 1 / 471 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Oropharyngeal pain | | | |
| subjects affected / exposed | 0 / 474 (0.00%) | 1 / 471 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pulmonary granuloma | | | |
| subjects affected / exposed | 0 / 474 (0.00%) | 1 / 471 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Psychiatric disorders | | | |
| Depression | | | |
| subjects affected / exposed | 0 / 474 (0.00%) | 2 / 471 (0.42%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 1 / 1 | |
| Mental status changes | | | |
| subjects affected / exposed | 1 / 474 (0.21%) | 1 / 471 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 1 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Confusional state | | | |
| subjects affected / exposed | 0 / 474 (0.00%) | 1 / 471 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 1 / 1 | |
| Substance-Induced psychotic disorder | | | |
| subjects affected / exposed | 0 / 474 (0.00%) | 1 / 471 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Investigations | | | |
| Alanine aminotransferase increased | | | |
| subjects affected / exposed | 0 / 474 (0.00%) | 17 / 471 (3.61%) | |
| occurrences causally related to treatment / all | 0 / 0 | 30 / 31 | |
| deaths causally related to treatment / all | 0 / 0 | 15 / 16 | |

| | | | |
|--|-----------------|------------------|--|
| Thyroid function test abnormal subjects affected / exposed | 0 / 474 (0.00%) | 2 / 471 (0.42%) | |
| occurrences causally related to treatment / all | 0 / 0 | 2 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 2 / 2 | |
| Ejection fraction decreased subjects affected / exposed | 1 / 474 (0.21%) | 0 / 471 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Transaminases increased subjects affected / exposed | 0 / 474 (0.00%) | 3 / 471 (0.64%) | |
| occurrences causally related to treatment / all | 0 / 0 | 3 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 1 / 1 | |
| Lymph nodes scan abnormal subjects affected / exposed | 1 / 474 (0.21%) | 1 / 471 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Aspartate aminotransferase increased subjects affected / exposed | 0 / 474 (0.00%) | 15 / 471 (3.18%) | |
| occurrences causally related to treatment / all | 0 / 0 | 20 / 21 | |
| deaths causally related to treatment / all | 0 / 0 | 10 / 11 | |
| Lipase increased subjects affected / exposed | 0 / 474 (0.00%) | 1 / 471 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Weight decreased subjects affected / exposed | 0 / 474 (0.00%) | 1 / 471 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Blood corticotrophin decreased subjects affected / exposed | 1 / 474 (0.21%) | 0 / 471 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 1 / 1 | 0 / 0 | |
| Blood creatinine increased | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 474 (0.00%) | 1 / 471 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Liver function test increased | | | |
| subjects affected / exposed | 0 / 474 (0.00%) | 1 / 471 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gamma-Glutamyltransferase increased | | | |
| subjects affected / exposed | 0 / 474 (0.00%) | 1 / 471 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Influenza a virus test positive | | | |
| subjects affected / exposed | 1 / 474 (0.21%) | 0 / 471 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Injury, poisoning and procedural complications | | | |
| Femoral neck fracture | | | |
| subjects affected / exposed | 1 / 474 (0.21%) | 0 / 471 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Post procedural complication | | | |
| subjects affected / exposed | 0 / 474 (0.00%) | 1 / 471 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Seroma | | | |
| subjects affected / exposed | 1 / 474 (0.21%) | 0 / 471 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal stoma complication | | | |
| subjects affected / exposed | 0 / 474 (0.00%) | 1 / 471 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infusion related reaction | | | |

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|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 474 (0.00%) | 1 / 471 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Radius fracture | | | |
| subjects affected / exposed | 1 / 474 (0.21%) | 0 / 471 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Incisional hernia | | | |
| subjects affected / exposed | 1 / 474 (0.21%) | 0 / 471 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Fracture displacement | | | |
| subjects affected / exposed | 1 / 474 (0.21%) | 0 / 471 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory tract procedural complication | | | |
| subjects affected / exposed | 0 / 474 (0.00%) | 1 / 471 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac disorders | | | |
| Atrial flutter | | | |
| subjects affected / exposed | 1 / 474 (0.21%) | 0 / 471 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Atrial tachycardia | | | |
| subjects affected / exposed | 1 / 474 (0.21%) | 0 / 471 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Cardiopulmonary failure | | | |
| subjects affected / exposed | 0 / 474 (0.00%) | 1 / 471 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 2 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 2 / 2 | |
| Coronary artery disease | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 474 (0.21%) | 0 / 471 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Acute coronary syndrome | | | |
| subjects affected / exposed | 1 / 474 (0.21%) | 0 / 471 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Atrial fibrillation | | | |
| subjects affected / exposed | 1 / 474 (0.21%) | 3 / 471 (0.64%) | |
| occurrences causally related to treatment / all | 0 / 1 | 3 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 2 / 2 | |
| Bifascicular block | | | |
| subjects affected / exposed | 1 / 474 (0.21%) | 0 / 471 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Tachycardia | | | |
| subjects affected / exposed | 1 / 474 (0.21%) | 0 / 471 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Silent myocardial infarction | | | |
| subjects affected / exposed | 0 / 474 (0.00%) | 1 / 471 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Cardiac failure | | | |
| subjects affected / exposed | 0 / 474 (0.00%) | 1 / 471 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac arrest | | | |
| subjects affected / exposed | 0 / 474 (0.00%) | 1 / 471 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 1 / 1 | |
| Nervous system disorders | | | |
| Presyncope | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 474 (0.00%) | 1 / 471 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cranial nerve disorder | | | |
| subjects affected / exposed | 1 / 474 (0.21%) | 1 / 471 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 1 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Guillain-Barre syndrome | | | |
| subjects affected / exposed | 0 / 474 (0.00%) | 1 / 471 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 1 / 1 | |
| Haemorrhage intracranial | | | |
| subjects affected / exposed | 0 / 474 (0.00%) | 1 / 471 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Meningoradiculitis | | | |
| subjects affected / exposed | 0 / 474 (0.00%) | 1 / 471 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Syncope | | | |
| subjects affected / exposed | 0 / 474 (0.00%) | 2 / 471 (0.42%) | |
| occurrences causally related to treatment / all | 0 / 0 | 2 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 2 / 2 | |
| Ataxia | | | |
| subjects affected / exposed | 1 / 474 (0.21%) | 0 / 471 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Cerebral thrombosis | | | |
| subjects affected / exposed | 1 / 474 (0.21%) | 0 / 471 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Trigeminal nerve disorder | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 474 (0.00%) | 1 / 471 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 2 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Peripheral motor neuropathy | | | |
| subjects affected / exposed | 0 / 474 (0.00%) | 1 / 471 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Axonal neuropathy | | | |
| subjects affected / exposed | 0 / 474 (0.00%) | 1 / 471 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Neuropathy peripheral | | | |
| subjects affected / exposed | 0 / 474 (0.00%) | 1 / 471 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Polyneuropathy | | | |
| subjects affected / exposed | 0 / 474 (0.00%) | 1 / 471 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 2 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 2 / 2 | |
| Spinal cord compression | | | |
| subjects affected / exposed | 1 / 474 (0.21%) | 0 / 471 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Autoimmune neuropathy | | | |
| subjects affected / exposed | 0 / 474 (0.00%) | 1 / 471 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Peripheral sensory neuropathy | | | |
| subjects affected / exposed | 0 / 474 (0.00%) | 1 / 471 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 1 / 1 | |
| Carotid artery stenosis | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 474 (0.21%) | 0 / 471 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Headache | | | |
| subjects affected / exposed | 2 / 474 (0.42%) | 6 / 471 (1.27%) | |
| occurrences causally related to treatment / all | 1 / 2 | 6 / 6 | |
| deaths causally related to treatment / all | 1 / 2 | 2 / 2 | |
| Seizure | | | |
| subjects affected / exposed | 2 / 474 (0.42%) | 0 / 471 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 2 | 0 / 0 | |
| Blood and lymphatic system disorders | | | |
| Lymphadenopathy | | | |
| subjects affected / exposed | 3 / 474 (0.63%) | 5 / 471 (1.06%) | |
| occurrences causally related to treatment / all | 0 / 3 | 1 / 5 | |
| deaths causally related to treatment / all | 0 / 2 | 0 / 2 | |
| Lymphoid tissue hyperplasia | | | |
| subjects affected / exposed | 0 / 474 (0.00%) | 1 / 471 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Thrombocytopenia | | | |
| subjects affected / exposed | 1 / 474 (0.21%) | 1 / 471 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 1 | 3 / 3 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Ear and labyrinth disorders | | | |
| Hypoacusis | | | |
| subjects affected / exposed | 0 / 474 (0.00%) | 1 / 471 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Deafness unilateral | | | |
| subjects affected / exposed | 0 / 474 (0.00%) | 1 / 471 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Eye disorders | | | |

| | | | |
|---|-----------------|-----------------|--|
| Episcleritis | | | |
| subjects affected / exposed | 0 / 474 (0.00%) | 1 / 471 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Uveitis | | | |
| subjects affected / exposed | 0 / 474 (0.00%) | 1 / 471 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ulcerative keratitis | | | |
| subjects affected / exposed | 0 / 474 (0.00%) | 1 / 471 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Autoimmune uveitis | | | |
| subjects affected / exposed | 0 / 474 (0.00%) | 1 / 471 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal disorders | | | |
| Abdominal pain | | | |
| subjects affected / exposed | 1 / 474 (0.21%) | 3 / 471 (0.64%) | |
| occurrences causally related to treatment / all | 1 / 1 | 3 / 3 | |
| deaths causally related to treatment / all | 1 / 1 | 1 / 1 | |
| Colitis ulcerative | | | |
| subjects affected / exposed | 1 / 474 (0.21%) | 2 / 471 (0.42%) | |
| occurrences causally related to treatment / all | 1 / 1 | 4 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 4 / 4 | |
| Haemorrhoids | | | |
| subjects affected / exposed | 1 / 474 (0.21%) | 0 / 471 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nausea | | | |
| subjects affected / exposed | 1 / 474 (0.21%) | 4 / 471 (0.85%) | |
| occurrences causally related to treatment / all | 1 / 1 | 4 / 4 | |
| deaths causally related to treatment / all | 1 / 1 | 1 / 1 | |
| Pancreatitis | | | |

| | | | |
|---|-----------------|-------------------|--|
| subjects affected / exposed | 0 / 474 (0.00%) | 1 / 471 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 1 / 1 | |
| Pancreatitis acute | | | |
| subjects affected / exposed | 0 / 474 (0.00%) | 1 / 471 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Abdominal pain lower | | | |
| subjects affected / exposed | 0 / 474 (0.00%) | 1 / 471 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Diverticulum intestinal haemorrhagic | | | |
| subjects affected / exposed | 0 / 474 (0.00%) | 1 / 471 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal haemorrhage | | | |
| subjects affected / exposed | 0 / 474 (0.00%) | 1 / 471 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 1 / 1 | |
| Oesophageal haemorrhage | | | |
| subjects affected / exposed | 0 / 474 (0.00%) | 1 / 471 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Anal fissure | | | |
| subjects affected / exposed | 0 / 474 (0.00%) | 1 / 471 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Colitis | | | |
| subjects affected / exposed | 1 / 474 (0.21%) | 51 / 471 (10.83%) | |
| occurrences causally related to treatment / all | 1 / 1 | 62 / 63 | |
| deaths causally related to treatment / all | 1 / 1 | 25 / 26 | |
| Duodenal ulcer | | | |

| | | | |
|---|-----------------|------------------|--|
| subjects affected / exposed | 0 / 474 (0.00%) | 1 / 471 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 1 / 1 | |
| Vomiting | | | |
| subjects affected / exposed | 1 / 474 (0.21%) | 8 / 471 (1.70%) | |
| occurrences causally related to treatment / all | 1 / 1 | 7 / 8 | |
| deaths causally related to treatment / all | 0 / 0 | 4 / 4 | |
| Abdominal hernia | | | |
| subjects affected / exposed | 1 / 474 (0.21%) | 0 / 471 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Constipation | | | |
| subjects affected / exposed | 0 / 474 (0.00%) | 1 / 471 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Diarrhoea | | | |
| subjects affected / exposed | 6 / 474 (1.27%) | 36 / 471 (7.64%) | |
| occurrences causally related to treatment / all | 4 / 6 | 43 / 43 | |
| deaths causally related to treatment / all | 3 / 3 | 19 / 19 | |
| Intestinal perforation | | | |
| subjects affected / exposed | 0 / 474 (0.00%) | 2 / 471 (0.42%) | |
| occurrences causally related to treatment / all | 0 / 0 | 2 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 1 / 1 | |
| Gastritis | | | |
| subjects affected / exposed | 0 / 474 (0.00%) | 2 / 471 (0.42%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Rectal haemorrhage | | | |
| subjects affected / exposed | 0 / 474 (0.00%) | 1 / 471 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 1 / 1 | |
| Dysphagia | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 474 (0.00%) | 1 / 471 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Umbilical hernia | | | |
| subjects affected / exposed | 0 / 474 (0.00%) | 1 / 471 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Inguinal hernia | | | |
| subjects affected / exposed | 2 / 474 (0.42%) | 1 / 471 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Gastric haemorrhage | | | |
| subjects affected / exposed | 0 / 474 (0.00%) | 1 / 471 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Autoimmune colitis | | | |
| subjects affected / exposed | 0 / 474 (0.00%) | 4 / 471 (0.85%) | |
| occurrences causally related to treatment / all | 0 / 0 | 4 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Enteritis | | | |
| subjects affected / exposed | 0 / 474 (0.00%) | 2 / 471 (0.42%) | |
| occurrences causally related to treatment / all | 0 / 0 | 2 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 1 / 1 | |
| Enterocolitis haemorrhagic | | | |
| subjects affected / exposed | 0 / 474 (0.00%) | 1 / 471 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hepatobiliary disorders | | | |
| Hepatocellular injury | | | |
| subjects affected / exposed | 0 / 474 (0.00%) | 2 / 471 (0.42%) | |
| occurrences causally related to treatment / all | 0 / 0 | 3 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 1 / 1 | |
| Hepatotoxicity | | | |

| | | | |
|---|-----------------|------------------|--|
| subjects affected / exposed | 0 / 474 (0.00%) | 5 / 471 (1.06%) | |
| occurrences causally related to treatment / all | 0 / 0 | 8 / 8 | |
| deaths causally related to treatment / all | 0 / 0 | 6 / 6 | |
| Hepatitis | | | |
| subjects affected / exposed | 0 / 474 (0.00%) | 4 / 471 (0.85%) | |
| occurrences causally related to treatment / all | 0 / 0 | 4 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 2 / 2 | |
| Autoimmune hepatitis | | | |
| subjects affected / exposed | 1 / 474 (0.21%) | 12 / 471 (2.55%) | |
| occurrences causally related to treatment / all | 1 / 1 | 12 / 12 | |
| deaths causally related to treatment / all | 1 / 1 | 5 / 5 | |
| Hyperbilirubinaemia | | | |
| subjects affected / exposed | 0 / 474 (0.00%) | 1 / 471 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 3 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cholecystitis | | | |
| subjects affected / exposed | 1 / 474 (0.21%) | 0 / 471 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Skin and subcutaneous tissue disorders | | | |
| Rash | | | |
| subjects affected / exposed | 0 / 474 (0.00%) | 1 / 471 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 1 / 1 | |
| Pruritus | | | |
| subjects affected / exposed | 0 / 474 (0.00%) | 1 / 471 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 1 / 1 | |
| Angioedema | | | |
| subjects affected / exposed | 0 / 474 (0.00%) | 1 / 471 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Skin exfoliation | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 474 (0.21%) | 0 / 471 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Drug eruption | | | |
| subjects affected / exposed | 0 / 474 (0.00%) | 1 / 471 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 1 / 1 | |
| Exfoliative rash | | | |
| subjects affected / exposed | 1 / 474 (0.21%) | 0 / 471 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 1 / 1 | 0 / 0 | |
| Actinic keratosis | | | |
| subjects affected / exposed | 1 / 474 (0.21%) | 0 / 471 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Rash maculo-papular | | | |
| subjects affected / exposed | 0 / 474 (0.00%) | 1 / 471 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal and urinary disorders | | | |
| Cystitis haemorrhagic | | | |
| subjects affected / exposed | 0 / 474 (0.00%) | 1 / 471 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal failure | | | |
| subjects affected / exposed | 0 / 474 (0.00%) | 2 / 471 (0.42%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 1 / 2 | |
| Urinary tract obstruction | | | |
| subjects affected / exposed | 0 / 474 (0.00%) | 1 / 471 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 2 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hydronephrosis | | | |

| | | | |
|---|-----------------|------------------|--|
| subjects affected / exposed | 1 / 474 (0.21%) | 0 / 471 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Endocrine disorders | | | |
| Endocrine disorder | | | |
| subjects affected / exposed | 1 / 474 (0.21%) | 1 / 471 (0.21%) | |
| occurrences causally related to treatment / all | 1 / 1 | 1 / 1 | |
| deaths causally related to treatment / all | 1 / 1 | 1 / 1 | |
| Hyperadrenocorticism | | | |
| subjects affected / exposed | 1 / 474 (0.21%) | 0 / 471 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Hyperthyroidism | | | |
| subjects affected / exposed | 0 / 474 (0.00%) | 1 / 471 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 1 / 1 | |
| Hypophysitis | | | |
| subjects affected / exposed | 0 / 474 (0.00%) | 37 / 471 (7.86%) | |
| occurrences causally related to treatment / all | 0 / 0 | 38 / 38 | |
| deaths causally related to treatment / all | 0 / 0 | 15 / 15 | |
| Hypopituitarism | | | |
| subjects affected / exposed | 0 / 474 (0.00%) | 10 / 471 (2.12%) | |
| occurrences causally related to treatment / all | 0 / 0 | 10 / 10 | |
| deaths causally related to treatment / all | 0 / 0 | 4 / 4 | |
| Adrenal insufficiency | | | |
| subjects affected / exposed | 0 / 474 (0.00%) | 4 / 471 (0.85%) | |
| occurrences causally related to treatment / all | 0 / 0 | 5 / 5 | |
| deaths causally related to treatment / all | 0 / 0 | 2 / 2 | |
| Hypothyroidism | | | |
| subjects affected / exposed | 0 / 474 (0.00%) | 3 / 471 (0.64%) | |
| occurrences causally related to treatment / all | 0 / 0 | 3 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Thyroiditis | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 474 (0.00%) | 1 / 471 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Basedow's disease | | | |
| subjects affected / exposed | 0 / 474 (0.00%) | 1 / 471 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Autoimmune thyroiditis | | | |
| subjects affected / exposed | 0 / 474 (0.00%) | 1 / 471 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Adrenocorticotrophic hormone deficiency | | | |
| subjects affected / exposed | 0 / 474 (0.00%) | 1 / 471 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lymphocytic hypophysitis | | | |
| subjects affected / exposed | 0 / 474 (0.00%) | 5 / 471 (1.06%) | |
| occurrences causally related to treatment / all | 0 / 0 | 5 / 5 | |
| deaths causally related to treatment / all | 0 / 0 | 2 / 2 | |
| Musculoskeletal and connective tissue disorders | | | |
| Pain in extremity | | | |
| subjects affected / exposed | 1 / 474 (0.21%) | 0 / 471 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 1 / 1 | 0 / 0 | |
| Arthralgia | | | |
| subjects affected / exposed | 0 / 474 (0.00%) | 2 / 471 (0.42%) | |
| occurrences causally related to treatment / all | 0 / 0 | 2 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Neck mass | | | |
| subjects affected / exposed | 0 / 474 (0.00%) | 1 / 471 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Back pain | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 474 (0.21%) | 0 / 471 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Intervertebral disc protrusion | | | |
| subjects affected / exposed | 0 / 474 (0.00%) | 1 / 471 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Arthritis | | | |
| subjects affected / exposed | 2 / 474 (0.42%) | 1 / 471 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 2 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 1 / 1 | |
| Osteoarthritis | | | |
| subjects affected / exposed | 3 / 474 (0.63%) | 0 / 471 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Synovial cyst | | | |
| subjects affected / exposed | 1 / 474 (0.21%) | 0 / 471 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infections and infestations | | | |
| Bronchitis | | | |
| subjects affected / exposed | 0 / 474 (0.00%) | 1 / 471 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Cellulitis | | | |
| subjects affected / exposed | 4 / 474 (0.84%) | 1 / 471 (0.21%) | |
| occurrences causally related to treatment / all | 2 / 4 | 0 / 1 | |
| deaths causally related to treatment / all | 1 / 2 | 0 / 0 | |
| Endocarditis | | | |
| subjects affected / exposed | 0 / 474 (0.00%) | 1 / 471 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| External ear cellulitis | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 474 (0.21%) | 0 / 471 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Neuroborreliosis | | | |
| subjects affected / exposed | 0 / 474 (0.00%) | 1 / 471 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 1 / 1 | |
| Perirectal abscess | | | |
| subjects affected / exposed | 0 / 474 (0.00%) | 1 / 471 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Wound infection | | | |
| subjects affected / exposed | 1 / 474 (0.21%) | 0 / 471 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Cystitis | | | |
| subjects affected / exposed | 0 / 474 (0.00%) | 3 / 471 (0.64%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 2 | |
| Herpes zoster | | | |
| subjects affected / exposed | 0 / 474 (0.00%) | 1 / 471 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lung infection | | | |
| subjects affected / exposed | 0 / 474 (0.00%) | 1 / 471 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Meningitis bacterial | | | |
| subjects affected / exposed | 1 / 474 (0.21%) | 0 / 471 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Post procedural infection | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 474 (0.21%) | 0 / 471 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 1 / 1 | 0 / 0 | |
| Viral infection | | | |
| subjects affected / exposed | 1 / 474 (0.21%) | 0 / 471 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastroenteritis viral | | | |
| subjects affected / exposed | 1 / 474 (0.21%) | 0 / 471 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Sepsis | | | |
| subjects affected / exposed | 0 / 474 (0.00%) | 2 / 471 (0.42%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Septic embolus | | | |
| subjects affected / exposed | 0 / 474 (0.00%) | 1 / 471 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Tooth infection | | | |
| subjects affected / exposed | 0 / 474 (0.00%) | 1 / 471 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastroenteritis | | | |
| subjects affected / exposed | 1 / 474 (0.21%) | 1 / 471 (0.21%) | |
| occurrences causally related to treatment / all | 1 / 1 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 1 / 1 | |
| Infection | | | |
| subjects affected / exposed | 0 / 474 (0.00%) | 1 / 471 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 1 / 1 | |
| Meningitis aseptic | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 474 (0.00%) | 2 / 471 (0.42%) | |
| occurrences causally related to treatment / all | 0 / 0 | 2 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 1 / 1 | |
| Urinary tract infection | | | |
| subjects affected / exposed | 0 / 474 (0.00%) | 1 / 471 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 1 / 1 | |
| Erysipelas | | | |
| subjects affected / exposed | 7 / 474 (1.48%) | 2 / 471 (0.42%) | |
| occurrences causally related to treatment / all | 1 / 8 | 1 / 2 | |
| deaths causally related to treatment / all | 0 / 4 | 0 / 0 | |
| Localised infection | | | |
| subjects affected / exposed | 1 / 474 (0.21%) | 1 / 471 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 1 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Meningitis | | | |
| subjects affected / exposed | 0 / 474 (0.00%) | 2 / 471 (0.42%) | |
| occurrences causally related to treatment / all | 0 / 0 | 2 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 1 / 1 | |
| Staphylococcal infection | | | |
| subjects affected / exposed | 0 / 474 (0.00%) | 2 / 471 (0.42%) | |
| occurrences causally related to treatment / all | 0 / 0 | 2 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 1 / 1 | |
| Otitis externa | | | |
| subjects affected / exposed | 1 / 474 (0.21%) | 0 / 471 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Diarrhoea infectious | | | |
| subjects affected / exposed | 0 / 474 (0.00%) | 1 / 471 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal infection | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 474 (0.00%) | 1 / 471 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Laryngitis | | | |
| subjects affected / exposed | 0 / 474 (0.00%) | 1 / 471 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Osteomyelitis | | | |
| subjects affected / exposed | 0 / 474 (0.00%) | 1 / 471 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Skin infection | | | |
| subjects affected / exposed | 1 / 474 (0.21%) | 1 / 471 (0.21%) | |
| occurrences causally related to treatment / all | 1 / 1 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 1 / 1 | |
| Appendicitis | | | |
| subjects affected / exposed | 1 / 474 (0.21%) | 3 / 471 (0.64%) | |
| occurrences causally related to treatment / all | 0 / 1 | 1 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Appendicitis perforated | | | |
| subjects affected / exposed | 3 / 474 (0.63%) | 0 / 471 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 3 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Bacteraemia | | | |
| subjects affected / exposed | 0 / 474 (0.00%) | 1 / 471 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bacterial infection | | | |
| subjects affected / exposed | 1 / 474 (0.21%) | 1 / 471 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 1 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 1 | 1 / 1 | |
| Beta haemolytic streptococcal infection | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 474 (0.00%) | 1 / 471 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Groin infection | | | |
| subjects affected / exposed | 1 / 474 (0.21%) | 0 / 471 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Pneumonia | | | |
| subjects affected / exposed | 1 / 474 (0.21%) | 4 / 471 (0.85%) | |
| occurrences causally related to treatment / all | 1 / 1 | 2 / 4 | |
| deaths causally related to treatment / all | 1 / 1 | 0 / 1 | |
| Herpes ophthalmic | | | |
| subjects affected / exposed | 0 / 474 (0.00%) | 1 / 471 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| H1n1 influenza | | | |
| subjects affected / exposed | 0 / 474 (0.00%) | 1 / 471 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Metabolism and nutrition disorders | | | |
| Dehydration | | | |
| subjects affected / exposed | 0 / 474 (0.00%) | 4 / 471 (0.85%) | |
| occurrences causally related to treatment / all | 0 / 0 | 2 / 5 | |
| deaths causally related to treatment / all | 0 / 0 | 2 / 5 | |
| Hypoglycaemia | | | |
| subjects affected / exposed | 0 / 474 (0.00%) | 1 / 471 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypercalcaemia | | | |
| subjects affected / exposed | 1 / 474 (0.21%) | 0 / 471 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 1 / 1 | 0 / 0 | |
| Hyponatraemia | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 474 (0.21%) | 2 / 471 (0.42%) | |
| occurrences causally related to treatment / all | 0 / 1 | 3 / 4 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 1 | |
| Hyperglycaemia | | | |
| subjects affected / exposed | 0 / 474 (0.00%) | 1 / 471 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypokalaemia | | | |
| subjects affected / exposed | 0 / 474 (0.00%) | 1 / 471 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |

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

| Non-serious adverse events | PLACEBO | IPILIMUMAB 10 MG/KG | |
|---|--------------------|---------------------|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 382 / 474 (80.59%) | 441 / 471 (93.63%) | |
| Investigations | | | |
| Alanine aminotransferase increased | | | |
| subjects affected / exposed | 26 / 474 (5.49%) | 95 / 471 (20.17%) | |
| occurrences (all) | 41 | 115 | |
| Blood lactate dehydrogenase increased | | | |
| subjects affected / exposed | 12 / 474 (2.53%) | 33 / 471 (7.01%) | |
| occurrences (all) | 15 | 38 | |
| Blood testosterone decreased | | | |
| subjects affected / exposed | 8 / 474 (1.69%) | 29 / 471 (6.16%) | |
| occurrences (all) | 10 | 32 | |
| Aspartate aminotransferase increased | | | |
| subjects affected / exposed | 26 / 474 (5.49%) | 72 / 471 (15.29%) | |
| occurrences (all) | 36 | 85 | |
| Lipase increased | | | |
| subjects affected / exposed | 30 / 474 (6.33%) | 42 / 471 (8.92%) | |
| occurrences (all) | 41 | 53 | |
| Weight decreased | | | |

| | | | |
|--|--------------------|--------------------|--|
| subjects affected / exposed | 42 / 474 (8.86%) | 149 / 471 (31.63%) | |
| occurrences (all) | 54 | 167 | |
| Weight increased | | | |
| subjects affected / exposed | 114 / 474 (24.05%) | 71 / 471 (15.07%) | |
| occurrences (all) | 163 | 90 | |
| Nervous system disorders | | | |
| Dizziness | | | |
| subjects affected / exposed | 18 / 474 (3.80%) | 29 / 471 (6.16%) | |
| occurrences (all) | 26 | 34 | |
| Headache | | | |
| subjects affected / exposed | 85 / 474 (17.93%) | 150 / 471 (31.85%) | |
| occurrences (all) | 122 | 205 | |
| General disorders and administration site conditions | | | |
| Influenza like illness | | | |
| subjects affected / exposed | 30 / 474 (6.33%) | 35 / 471 (7.43%) | |
| occurrences (all) | 50 | 45 | |
| Oedema peripheral | | | |
| subjects affected / exposed | 27 / 474 (5.70%) | 21 / 471 (4.46%) | |
| occurrences (all) | 28 | 23 | |
| Pyrexia | | | |
| subjects affected / exposed | 22 / 474 (4.64%) | 73 / 471 (15.50%) | |
| occurrences (all) | 33 | 100 | |
| Asthenia | | | |
| subjects affected / exposed | 38 / 474 (8.02%) | 29 / 471 (6.16%) | |
| occurrences (all) | 49 | 43 | |
| Fatigue | | | |
| subjects affected / exposed | 143 / 474 (30.17%) | 188 / 471 (39.92%) | |
| occurrences (all) | 207 | 242 | |
| Gastrointestinal disorders | | | |
| Abdominal pain | | | |
| subjects affected / exposed | 44 / 474 (9.28%) | 64 / 471 (13.59%) | |
| occurrences (all) | 48 | 86 | |
| Nausea | | | |
| subjects affected / exposed | 82 / 474 (17.30%) | 117 / 471 (24.84%) | |
| occurrences (all) | 120 | 144 | |
| Colitis | | | |

| | | | |
|--|---------------------------|---------------------------|--|
| subjects affected / exposed occurrences (all) | 5 / 474 (1.05%) 6 | 43 / 471 (9.13%) 54 | |
| Vomiting subjects affected / exposed occurrences (all) | 27 / 474 (5.70%) 34 | 61 / 471 (12.95%) 65 | |
| Constipation subjects affected / exposed occurrences (all) | 30 / 474 (6.33%) 31 | 31 / 471 (6.58%) 33 | |
| Diarrhoea subjects affected / exposed occurrences (all) | 141 / 474 (29.75%) 245 | 229 / 471 (48.62%) 381 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Dyspnoea subjects affected / exposed occurrences (all) | 16 / 474 (3.38%) 17 | 31 / 471 (6.58%) 33 | |
| Cough subjects affected / exposed occurrences (all) | 48 / 474 (10.13%) 57 | 68 / 471 (14.44%) 78 | |
| Skin and subcutaneous tissue disorders | | | |
| Rash subjects affected / exposed occurrences (all) | 80 / 474 (16.88%) 116 | 186 / 471 (39.49%) 274 | |
| Pruritus subjects affected / exposed occurrences (all) | 70 / 474 (14.77%) 100 | 203 / 471 (43.10%) 290 | |
| Dermatitis acneiform subjects affected / exposed occurrences (all) | 6 / 474 (1.27%) 7 | 26 / 471 (5.52%) 29 | |
| Psychiatric disorders | | | |
| Anxiety subjects affected / exposed occurrences (all) | 25 / 474 (5.27%) 26 | 21 / 471 (4.46%) 23 | |
| Insomnia subjects affected / exposed occurrences (all) | 21 / 474 (4.43%) 21 | 45 / 471 (9.55%) 49 | |
| Endocrine disorders | | | |

| | | | |
|--|------------------------|-------------------------|--|
| Hypophysitis subjects affected / exposed occurrences (all) | 2 / 474 (0.42%) 2 | 56 / 471 (11.89%) 65 | |
| Hypothyroidism subjects affected / exposed occurrences (all) | 7 / 474 (1.48%) 9 | 47 / 471 (9.98%) 54 | |
| Musculoskeletal and connective tissue disorders | | | |
| Musculoskeletal pain subjects affected / exposed occurrences (all) | 26 / 474 (5.49%) 29 | 16 / 471 (3.40%) 19 | |
| Pain in extremity subjects affected / exposed occurrences (all) | 36 / 474 (7.59%) 43 | 21 / 471 (4.46%) 21 | |
| Arthralgia subjects affected / exposed occurrences (all) | 45 / 474 (9.49%) 50 | 34 / 471 (7.22%) 39 | |
| Back pain subjects affected / exposed occurrences (all) | 41 / 474 (8.65%) 49 | 29 / 471 (6.16%) 31 | |
| Myalgia subjects affected / exposed occurrences (all) | 24 / 474 (5.06%) 28 | 21 / 471 (4.46%) 25 | |
| Infections and infestations | | | |
| Nasopharyngitis subjects affected / exposed occurrences (all) | 31 / 474 (6.54%) 36 | 21 / 471 (4.46%) 23 | |
| Metabolism and nutrition disorders | | | |
| Decreased appetite subjects affected / exposed occurrences (all) | 16 / 474 (3.38%) 17 | 65 / 471 (13.80%) 75 | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|-----------------|---|
| 19 January 2009 | After careful review of a Serious Adverse Event (Grade 3 toxic epidermal necrolysis [TEN] with subsequent Grade 5 Sepsis) by the Data Monitoring Committee that has been established for the ipilimumab program, the dose skipping criteria for ipilimumab is being modified in order to make it more conservative. Because this is a safety amendment that is intended to avoid potentially life threatening events, all sites are asked to implement this amendment immediately (prior to IRB / IEC / HA review and approval). This revision applies to all subjects that are currently receiving ipilimumab therapy. |
| 29 April 2011 | In accordance with the FDA approved label, BMS now requires that all the patients participating in clinical studies with ipilimumab, regardless of the dose used, have their TSH level assessed at baseline and before each dose. Results do not have to be known at the time of dosing with ipilimumab as treatment modifications should be based on signs and symptoms related to endocrinopathies consistent with existing guidelines within the investigator brochure and protocol. If a subject has thyroid dysfunction and concomitant symptoms (i.e. fatigue), the subject should be monitored more frequently and be treated as per standard medical practice. TSH and free T4 levels should be obtained to determine if thyroid abnormalities are present. TSH, prolactin and a morning cortisol level will help to differentiate primary adrenal insufficiency from primary pituitary insufficiency. Appropriate hormone replacement therapy should be instituted if an endocrinopathy is documented. |
| 13 May 2015 | The main protocol is amended to follow the NCCN guidelines and Swiss guidelines, which describe that routine radiologic imaging to screen for asymptomatic recurrence/metastatic disease is not recommended after 5 years by NCCN and recommend to only perform a physical examination in recurrence-free patients after 5 years. [Ref. NCCN guidelines version 4, 2014, J Natl Compr Canc Netw. 2014 May;12(5):621-9); Updated Swiss guidelines for the treatment and follow-up of cutaneous melanoma. Swiss Med Wkly. 2011 Dec 15;141: w13320. doi: 10.4414/smw.2011.13320]. This amendment also includes updated background information as well as updated clinical safety data on the study medication and a new section of Adverse Event of Interest This amendment also includes update of contact details and some administrative updates and a change in nomenclature for HAA into ADA |
| 25 January 2016 | With the change in treatment landscape of melanoma subjects, OS might be affected due to treatment with subsequent therapy and hence the potential treatment effect might be attenuated. Therefore, the final OS analysis will be performed at the time of the final DMFS analysis, recognizing the drop in power for OS (75% power anticipated). The applicable statistical sections have been updated accordingly. In addition, the protocol is being amended to include a long term follow-up phase. The main protocol is also amended to describe the end of activities of the several CROs (responsible for the on-site monitoring, medical monitoring/SAE contacts and Independent Review Committee) involved in the study, which will occur at the time of the DMFS/OS analyses. After the database lock for the DMFS/OS final analyses, the SAE contacts will change from the current CRO to BMS. Lastly, this amendment also includes update of contact details and some administrative updates. |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported