# Clinical trial results:
# A Phase 1b/3, Multicenter, Trial of Talimogene Laherparepvec in Combination With Pembrolizumab (MK-3475) for Treatment of Unresectable Stage IIIB to IVM1c Melanoma (MASTERKEY-265)

## Summary

| | |
|---|---|
| EudraCT number | 2014-000185-22 |
| Trial protocol | SE ES BE DE AT GR IT FI CZ PT HU |
| Global end of trial date | 11 March 2021 |

### Results information

| | |
|---|---|
| Result version number | v1 (current) |
| This version publication date | 24 March 2022 |
| First version publication date | 24 March 2022 |

## Trial information

### Trial identification

| | |
|---|---|
| Sponsor protocol code | 20110265 |

### Additional study identifiers

| | |
|---|---|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT02263508 |
| WHO universal trial number (UTN) | - |

Notes:

### Sponsors

| | |
|---|---|
| Sponsor organisation name | Amgen Inc. |
| Sponsor organisation address | One Amgen Center Drive, Thousand Oaks, CA, United States, 91320 |
| Public contact | IHQ Medical Info-Clinical Trials, Amgen (EUROPE) GmbH, MedInfoInternational@amgen.com |
| Scientific contact | IHQ Medical Info-Clinical Trials, Amgen (EUROPE) GmbH, MedInfoInternational@amgen.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 March 2021 |
| Is this the analysis of the primary completion data? | No |

| | |
|---|---|
| Global end of trial reached? | Yes |
| Global end of trial date | 11 March 2021 |
| Was the trial ended prematurely? | Yes |

Notes:

## General information about the trial

Main objective of the trial:

Phase 1b: To evaluate the safety, as assessed by incidence of dose limiting toxicity (DLT), of talimogene laherparepvec (T-VEC) in combination with pembrolizumab in subjects with previously untreated, unresectable, stage IIIB to IVM1c melanoma.
Phase 3: To evaluate the efficacy of talimogene laherparepvec with pembrolizumab versus placebo with pembrolizumab, as assessed by progression-free survival (PFS) (response evaluation by blinded independent central review [BICR] using modified Response Evaluation Criteria in Solid Tumors [RECIST] 1.1) and overall survival (OS).

Protection of trial subjects:

This study was conducted in accordance with International Council for Harmonisation (ICH) Good Clinical Practice (GCP) regulations/guidelines.
The study protocol and all amendments, the informed consent form, and any accompanying materials provided to the subjects were reviewed and approved by an Institutional Review Board (IRB) or Independent Ethics Committee (IEC) at each study center.
The investigator or his/her designee informed the subject of all aspects pertaining to the subject's participation in the study before any screening procedures were performed.

Background therapy: -

Evidence for comparator: -

| | |
|---|---|
| Actual start date of recruitment | 08 December 2014 |
| Long term follow-up planned | Yes |
| Long term follow-up rationale | Efficacy, Safety |
| Long term follow-up duration | 60 Months |
| Independent data monitoring committee (IDMC) involvement? | Yes |

Notes:

## Population of trial subjects

### Subjects enrolled per country

| | |
|---|---|
| Country: Number of subjects enrolled | Australia: 76 |
| Country: Number of subjects enrolled | Austria: 18 |
| Country: Number of subjects enrolled | Belgium: 4 |
| Country: Number of subjects enrolled | Canada: 12 |
| Country: Number of subjects enrolled | Czechia: 43 |
| Country: Number of subjects enrolled | Finland: 4 |
| Country: Number of subjects enrolled | France: 24 |
| Country: Number of subjects enrolled | Germany: 74 |
| Country: Number of subjects enrolled | Greece: 43 |
| Country: Number of subjects enrolled | Hungary: 8 |
| Country: Number of subjects enrolled | Italy: 17 |
| Country: Number of subjects enrolled | Korea, Republic of: 11 |

| | |
|---|---|
| Country: Number of subjects enrolled | Netherlands: 13 |
| Country: Number of subjects enrolled | Poland: 53 |
| Country: Number of subjects enrolled | Portugal: 11 |
| Country: Number of subjects enrolled | Russian Federation: 39 |
| Country: Number of subjects enrolled | South Africa: 35 |
| Country: Number of subjects enrolled | Spain: 23 |
| Country: Number of subjects enrolled | Switzerland: 21 |
| Country: Number of subjects enrolled | United Kingdom: 18 |
| Country: Number of subjects enrolled | United States: 166 |
| Worldwide total number of subjects | 713 |
| EEA total number of subjects | 335 |

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) | 368 |
| From 65 to 84 years | 313 |
| 85 years and over | 32 |

## Subject disposition

### Recruitment

Recruitment details:

This study was conducted at 134 centers in Australia, Canada, Europe, South Africa, South Korea, and the United States.
Phase 1b was an open-label, single-arm study and Phase 3 was a randomized, double-blind, placebo-controlled study.

### Pre-assignment

Screening details:

In Phase 3 participants were randomized equally to 1 of 2 arms.
Randomization was stratified by stage of disease: less advanced stages (IIIB, IIIC, and IVM1a) versus more advanced stages (IVM1b and IVM1c) and by prior BRAF inhibitor therapy (no prior BRAF inhibitor vs BRAF inhibitor with or without MEK inhibitor).

### Period 1

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

### Arms

| | |
|---|---|
| Are arms mutually exclusive? | Yes |
| **Arm title** | Phase 1b: Talimogene Laherparepvec + Pembrolizumab |

Arm description:

Participants received talimogene laherparepvec at an initial dose of up to 4 mL 10 plaque-forming units (PFU)/mL by intralesional injection on day 1 of week 1. Subsequent doses of talimogene laherparepvec at up to 4 mL of $10^8$ PFU/mL began 3 weeks after the first dose and were administered every 2 weeks until disappearance of injectable lesions, complete response (CR), confirmed disease progression (PD) per modified Immune-related Response Criteria (irRC), intolerance of study treatment, 24 months from the date of the first dose of pembrolizumab, or end of study, whichever occurred first. Participants also received 200 mg pembrolizumab administered intravenously every 2 weeks starting at the time of the third dose of talimogene laherparepvec (week 6) until confirmed PD per modified irRC, treatment intolerance, 24 months from the first dose, or end of study, whichever occurred first.

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | Talimogene Laherparepvec |
| Investigational medicinal product code | AMG 678 |
| Other name | IMLYGIC®, OncoVEX^GM-CSF, T-VEC |
| Pharmaceutical forms | Solution for injection |
| Routes of administration | Intralesional use |

Dosage and administration details:

Talimogene laherparepvec administered by intratumoral injection at an initial dose of up to 4 mL 10 plaque-forming units (PFU)/mL followed by up to 4 mL of $10^8$ PFU/mL 3 weeks later and every 2 weeks thereafter.

| | |
|---|---|
| Investigational medicinal product name | Pembrolizumab |
| Investigational medicinal product code | MK-3475 |
| Other name | Keytruda® |
| Pharmaceutical forms | Solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

Administered at a dose of 200 mg as an intravenous infusion over approximately 30 minutes.

| | |
|---|---|
| **Arm title** | Phase 3: Placebo + Pembrolizumab |

Arm description:

Participants received up to 4 mL placebo to talimogene laherparepvec by intralesional injection on day 1

of week 0. Subsequent doses of placebo (up to 4 mL) began 3 weeks after the first dose and were administered every 2 weeks until the fifth injection (week 9), and then synchronously with pembrolizumab thereafter every 3 weeks until disappearance of injectable lesions, complete response per modified Immune-related Response Criteria simulating Response Evaluation Criteria in Solid Tumors (irRC-RECIST) (iCR), confirmed iPD per modified irRC-RECIST, intolerance of study treatment, 24 months from the date of the first dose of placebo, or end of study, whichever occurred first. Participants also received 200 mg pembrolizumab administered intravenously every 3 weeks starting on day 1 of week 0, until confirmed iPD per modified irRC-RECIST, treatment intolerance, 24 months from the first dose, or end of study, whichever occurred first.

| | |
|---|---|
| Arm type | Active comparator |
| Investigational medicinal product name | Pembrolizumab |
| Investigational medicinal product code | MK-3475 |
| Other name | Keytruda® |
| Pharmaceutical forms | Solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

Administered at a dose of 200 mg as an intravenous infusion over approximately 30 minutes.

| | |
|---|---|
| Investigational medicinal product name | Placebo for Talimogene Laherparepvec |
| Investigational medicinal product code | AMG 678 |
| Other name | |
| Pharmaceutical forms | Solution for injection |
| Routes of administration | Intralesional use |

Dosage and administration details:

Administered by intratumoral injection at an initial dose of up to 4 mL followed by up to 4 mL 3 weeks later and every 2 weeks thereafter.

| | |
|---|---|
| **Arm title** | Phase 3: Talimogene Laherparepvec + Pembrolizumab |

Arm description:

Participants received talimogene laherparepvec at an initial dose of up to 4 mL 10 PFU/mL by intralesional injection on day 1. Subsequent doses of talimogene laherparepvec at $10^8$ PFU/mL (up to 4 mL) began 3 weeks after the first dose and were administered every 2 weeks until the fifth injection of talimogene laherparepvec (week 9), and then synchronously with pembrolizumab thereafter every 3 weeks until disappearance of injectable lesions, iCR, confirmed iPD per modified irRC-RECIST, intolerance of study treatment, 24 months from the date of the first dose of talimogene laherparepvec, or end of study, whichever occurred first. Participants also received 200 mg pembrolizumab administered intravenously every 3 weeks starting on day 1 of week 0, until confirmed iPD per modified irRC-RECIST, treatment intolerance, 24 months from the first dose, or end of study, whichever occurred first.

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | Talimogene Laherparepvec |
| Investigational medicinal product code | AMG 678 |
| Other name | IMLYGIC®, OncoVEX^GM-CSF, T-VEC |
| Pharmaceutical forms | Solution for injection |
| Routes of administration | Intralesional use |

Dosage and administration details:

Talimogene laherparepvec administered by intratumoral injection at an initial dose of up to 4 mL 10 plaque-forming units (PFU)/mL followed by up to 4 mL of $10^8$ PFU/mL 3 weeks later and every 2 weeks thereafter.

| | |
|---|---|
| Investigational medicinal product name | Pembrolizumab |
| Investigational medicinal product code | MK-3475 |
| Other name | Keytruda® |
| Pharmaceutical forms | Solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

Administered at a dose of 200 mg as an intravenous infusion over approximately 30 minutes.

| **Number of subjects in period 1** | Phase 1b: Talimogene Laherparepvec + Pembrolizumab | Phase 3: Placebo + Pembrolizumab | Phase 3: Talimogene Laherparepvec + Pembrolizumab |
|---|---|---|---|
| Started | 21 | 346 | 346 |
| Received T-VEC/Placebo | 21 | 345 | 343 |
| Received Pembrolizumab | 21 | 345 | 343 |
| Completed | 0 | 0 | 0 |
| Not completed | 21 | 346 | 346 |
| Adverse event, serious fatal | 6 | 151 | 140 |
| Consent withdrawn by subject | 1 | 23 | 17 |
| Sponsor Decision | 12 | 165 | 182 |
| Lost to follow-up | 2 | 7 | 7 |

## Baseline characteristics

### Reporting groups

| Reporting group title | Phase 1b: Talimogene Laherparepvec + Pembrolizumab |
|---|---|

Reporting group description:

Participants received talimogene laherparepvec at an initial dose of up to 4 mL 10 plaque-forming units (PFU)/mL by intralesional injection on day 1 of week 1. Subsequent doses of talimogene laherparepvec at up to 4 mL of $10^8$ PFU/mL began 3 weeks after the first dose and were administered every 2 weeks until disappearance of injectable lesions, complete response (CR), confirmed disease progression (PD) per modified Immune-related Response Criteria (irRC), intolerance of study treatment, 24 months from the date of the first dose of pembrolizumab, or end of study, whichever occurred first. Participants also received 200 mg pembrolizumab administered intravenously every 2 weeks starting at the time of the third dose of talimogene laherparepvec (week 6) until confirmed PD per modified irRC, treatment intolerance, 24 months from the first dose, or end of study, whichever occurred first.

| Reporting group title | Phase 3: Placebo + Pembrolizumab |
|---|---|

Reporting group description:

Participants received up to 4 mL placebo to talimogene laherparepvec by intralesional injection on day 1 of week 0. Subsequent doses of placebo (up to 4 mL) began 3 weeks after the first dose and were administered every 2 weeks until the fifth injection (week 9), and then synchronously with pembrolizumab thereafter every 3 weeks until disappearance of injectable lesions, complete response per modified Immune-related Response Criteria simulating Response Evaluation Criteria in Solid Tumors (irRC-RECIST) (iCR), confirmed iPD per modified irRC-RECIST, intolerance of study treatment, 24 months from the date of the first dose of placebo, or end of study, whichever occurred first. Participants also received 200 mg pembrolizumab administered intravenously every 3 weeks starting on day 1 of week 0, until confirmed iPD per modified irRC-RECIST, treatment intolerance, 24 months from the first dose, or end of study, whichever occurred first.

| Reporting group title | Phase 3: Talimogene Laherparepvec + Pembrolizumab |
|---|---|

Reporting group description:

Participants received talimogene laherparepvec at an initial dose of up to 4 mL 10 PFU/mL by intralesional injection on day 1. Subsequent doses of talimogene laherparepvec at $10^8$ PFU/mL (up to 4 mL) began 3 weeks after the first dose and were administered every 2 weeks until the fifth injection of talimogene laherparepvec (week 9), and then synchronously with pembrolizumab thereafter every 3 weeks until disappearance of injectable lesions, iCR, confirmed iPD per modified irRC-RECIST, intolerance of study treatment, 24 months from the date of the first dose of talimogene laherparepvec, or end of study, whichever occurred first. Participants also received 200 mg pembrolizumab administered intravenously every 3 weeks starting on day 1 of week 0, until confirmed iPD per modified irRC-RECIST, treatment intolerance, 24 months from the first dose, or end of study, whichever occurred first.

| Reporting group values | Phase 1b: Talimogene Laherparepvec + Pembrolizumab | Phase 3: Placebo + Pembrolizumab | Phase 3: Talimogene Laherparepvec + Pembrolizumab |
|---|---|---|---|
| Number of subjects | 21 | 346 | 346 |
| Age categorical<br>Units: Subjects | | | |
| Adults (18-64 years) | 14 | 177 | 177 |
| From 65-84 years | 6 | 157 | 150 |
| 85 years and over | 1 | 12 | 19 |
| Age Continuous<br>Units: years | | | |
| arithmetic mean | 60.2 | 62.3 | 63.1 |
| standard deviation | ± 13.4 | ± 14.5 | ± 13.7 |
| Sex: Female, Male<br>Units: participants | | | |
| Female | 13 | 127 | 147 |
| Male | 8 | 219 | 199 |

| | | | |
|---|---|---|---|
| Ethnicity (NIH/OMB)<br>Units: Subjects | | | |
| Hispanic or Latino | 0 | 9 | 13 |
| Not Hispanic or Latino | 21 | 337 | 331 |
| Unknown or Not Reported | 0 | 0 | 2 |
| Race/Ethnicity, Customized<br>Units: Subjects | | | |
| American Indian or Alaska Native | 0 | 0 | 0 |
| Asian | 0 | 4 | 7 |
| Black (or African American) | 0 | 1 | 2 |
| Native Hawaiian or Other Pacific Islander | 0 | 0 | 0 |
| White | 21 | 335 | 327 |
| Other | 0 | 6 | 10 |
| Disease Stage per the American Joint Committee on Cancer (AJCC) 7th Edition | | | |
| Stage IIIB: Ulcerated lesion and 1 lymph node or 2-3 nodes with micrometastasis, or any-depth lesion with no ulceration, and 1 lymph node or 2-3 nodes with macrometastasis; Stage IIIC: Ulcerated lesion and 1 lymph node with macrometastasis; 2-3 nodes with macrometastasis or ≥4 metastatic lymph nodes, matted lymph nodes, or in-transit met(s)/satellite(s); Stage IV: M1a: Spread to skin, subcutaneous tissue, or lymph nodes; normal lactate dehydrogenase (LDH) level; M1b: Spread to lungs, normal LDH; M1c: Spread to all other visceral organs, normal LDH or any distant disease with elevated LDH. | | | |
| Units: Subjects | | | |
| Stage IIIB - IVM1a | 9 | 169 | 169 |
| Stage IVM1b/c | 12 | 177 | 177 |
| Prior Serine/Threonine Protein Kinase B-Raf (BRAF) Inhibitor Therapy<br>Units: Subjects | | | |
| Yes | 0 | 29 | 29 |
| No | 0 | 317 | 317 |
| Not collected | 21 | 0 | 0 |
| Programmed Cell Death-1 Ligand 1 (PD-L1) Status | | | |
| PD-L1 expression in tumor cells was assessed at a central laboratory using a clinical trial immunohistochemistry assay (22C3 antibody) and scored on a unique melanoma (MEL) scale of 0 to 5; a score ≥ 2 (membranous staining in ≥ 1% of cells within tumor nests, including neoplastic cells and intercalated and contiguous immune cells) was considered positive. | | | |
| Units: Subjects | | | |
| Positive | 17 | 218 | 231 |
| Not Positive | 4 | 128 | 115 |
| BRAF V600 Mutation Status | | | |
| Mutation status of v-raf murine sarcoma viral oncogene homolog B1 (BRAF) gene was based on a gene mutation that results in an amino acid substitution from valine (V) to glutamic acid (E) at codon 600 (V600E) and/or a substitution from valine to lysine (K) (V600K). | | | |
| Units: Subjects | | | |
| Mutation | 4 | 116 | 124 |
| Mutation not present | 17 | 215 | 211 |
| Missing/unknown | 0 | 15 | 11 |

| **Reporting group values** | Total | | |
|---|---|---|---|
| Number of subjects | 713 | | |
| Age categorical<br>Units: Subjects | | | |
| Adults (18-64 years) | 368 | | |
| From 65-84 years | 313 | | |

| | | | |
|---|---|---|---|
| 85 years and over | 32 | | |

| | | | |
|---|---|---|---|
| Age Continuous<br>Units: years<br>arithmetic mean<br>standard deviation | -<br>- | | |
| Sex: Female, Male<br>Units: participants | | | |
| Female | 287 | | |
| Male | 426 | | |
| Ethnicity (NIH/OMB)<br>Units: Subjects | | | |
| Hispanic or Latino | 22 | | |
| Not Hispanic or Latino | 689 | | |
| Unknown or Not Reported | 2 | | |
| Race/Ethnicity, Customized<br>Units: Subjects | | | |
| American Indian or Alaska Native | 0 | | |
| Asian | 11 | | |
| Black (or African American) | 3 | | |
| Native Hawaiian or Other Pacific Islander | 0 | | |
| White | 683 | | |
| Other | 16 | | |
| Disease Stage per the American Joint Committee on Cancer (AJCC) 7th Edition | | | |
| Stage IIIB: Ulcerated lesion and 1 lymph node or 2-3 nodes with micrometastasis, or any-depth lesion with no ulceration, and 1 lymph node or 2-3 nodes with macrometastasis; Stage IIIC: Ulcerated lesion and 1 lymph node with macrometastasis; 2-3 nodes with macrometastasis or ≥4 metastatic lymph nodes, matted lymph nodes, or in-transit met(s)/satellite(s); Stage IV: M1a: Spread to skin, subcutaneous tissue, or lymph nodes; normal lactate dehydrogenase (LDH) level; M1b: Spread to lungs, normal LDH; M1c: Spread to all other visceral organs, normal LDH or any distant disease with elevated LDH. | | | |
| Units: Subjects | | | |
| Stage IIIB - IVM1a | 347 | | |
| Stage IVM1b/c | 366 | | |
| Prior Serine/Threonine Protein Kinase B-Raf (BRAF) Inhibitor Therapy<br>Units: Subjects | | | |
| Yes | 58 | | |
| No | 634 | | |
| Not collected | 21 | | |
| Programmed Cell Death-1 Ligand 1 (PD-L1) Status | | | |
| PD-L1 expression in tumor cells was assessed at a central laboratory using a clinical trial immunohistochemistry assay (22C3 antibody) and scored on a unique melanoma (MEL) scale of 0 to 5; a score ≥ 2 (membranous staining in ≥ 1% of cells within tumor nests, including neoplastic cells and intercalated and contiguous immune cells) was considered positive. | | | |
| Units: Subjects | | | |
| Positive | 466 | | |
| Not Positive | 247 | | |
| BRAF V600 Mutation Status | | | |
| Mutation status of v-raf murine sarcoma viral oncogene homolog B1 (BRAF) gene was based on a gene mutation that results in an amino acid substitution from valine (V) to glutamic acid (E) at codon 600 | | | |

| (V600E) and/or a substitution from valine to lysine (K) (V600K). | | | |
|---|---|---|---|
| Units: Subjects | | | |
| Mutation | 244 | | |
| Mutation not present | 443 | | |
| Missing/unknown | 26 | | |

## End points

### End points reporting groups

| Reporting group title | Phase 1b: Talimogene Laherparepvec + Pembrolizumab |
|---|---|

Reporting group description:

Participants received talimogene laherparepvec at an initial dose of up to 4 mL 10 plaque-forming units (PFU)/mL by intralesional injection on day 1 of week 1. Subsequent doses of talimogene laherparepvec at up to 4 mL of $10^8$ PFU/mL began 3 weeks after the first dose and were administered every 2 weeks until disappearance of injectable lesions, complete response (CR), confirmed disease progression (PD) per modified Immune-related Response Criteria (irRC), intolerance of study treatment, 24 months from the date of the first dose of pembrolizumab, or end of study, whichever occurred first. Participants also received 200 mg pembrolizumab administered intravenously every 2 weeks starting at the time of the third dose of talimogene laherparepvec (week 6) until confirmed PD per modified irRC, treatment intolerance, 24 months from the first dose, or end of study, whichever occurred first.

| Reporting group title | Phase 3: Placebo + Pembrolizumab |
|---|---|

Reporting group description:

Participants received up to 4 mL placebo to talimogene laherparepvec by intralesional injection on day 1 of week 0. Subsequent doses of placebo (up to 4 mL) began 3 weeks after the first dose and were administered every 2 weeks until the fifth injection (week 9), and then synchronously with pembrolizumab thereafter every 3 weeks until disappearance of injectable lesions, complete response per modified Immune-related Response Criteria simulating Response Evaluation Criteria in Solid Tumors (irRC-RECIST) (iCR), confirmed iPD per modified irRC-RECIST, intolerance of study treatment, 24 months from the date of the first dose of placebo, or end of study, whichever occurred first. Participants also received 200 mg pembrolizumab administered intravenously every 3 weeks starting on day 1 of week 0, until confirmed iPD per modified irRC-RECIST, treatment intolerance, 24 months from the first dose, or end of study, whichever occurred first.

| Reporting group title | Phase 3: Talimogene Laherparepvec + Pembrolizumab |
|---|---|

Reporting group description:

Participants received talimogene laherparepvec at an initial dose of up to 4 mL 10 PFU/mL by intralesional injection on day 1. Subsequent doses of talimogene laherparepvec at $10^8$ PFU/mL (up to 4 mL) began 3 weeks after the first dose and were administered every 2 weeks until the fifth injection of talimogene laherparepvec (week 9), and then synchronously with pembrolizumab thereafter every 3 weeks until disappearance of injectable lesions, iCR, confirmed iPD per modified irRC-RECIST, intolerance of study treatment, 24 months from the date of the first dose of talimogene laherparepvec, or end of study, whichever occurred first. Participants also received 200 mg pembrolizumab administered intravenously every 3 weeks starting on day 1 of week 0, until confirmed iPD per modified irRC-RECIST, treatment intolerance, 24 months from the first dose, or end of study, whichever occurred first.

### Primary: Phase 1b: Number of Participants With Dose-limiting Toxicities (DLTs)

| End point title | Phase 1b: Number of Participants With Dose-limiting Toxicities (DLTs)[1][2] |
|---|---|

End point description:

A DLT was defined as any toxicity related to study drug which met any of the following criteria based on Common Terminology Criteria for Adverse Events (CTCAE) version 4.0:
-Grade 4 non-hematologic toxicity.
-Grade 3 or higher pneumonitis.
-Grade 3 non-hematologic toxicity lasting > 3 days despite optimal supportive care, excluding grade 3 fatigue.
-Any grade 3 or higher non-hematologic laboratory value if medical intervention was required, or the abnormality lead to hospitalization, or the abnormality persisted for > 1 week.
-Febrile neutropenia grade 3 or 4.
-Thrombocytopenia < 25 x 10^9/L if associated with a bleeding event which does not result in hemodynamic instability but required an elective platelet infusion, or a life-threatening bleeding event which resulted in urgent intervention and admission to intensive care unit.
-Grade 5 toxicity (ie, death).
-Any other intolerable toxicity leading to permanent discontinuation of talimogene laherparepvec or pembrolizumab.

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

End point timeframe:

The DLT evaluation period was 6 weeks from the initial administration of pembrolizumab (week 6 to 12).

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 analyses were not conducted in Phase 1b

[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint was pre-specified for Phase 1b participants only.

| **End point values** | Phase 1b: Talimogene Laherparepvec + Pembrolizumab | | | |
|---|---|---|---|---|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 21 | | | |
| Units: participants | 0 | | | |

## Statistical analyses

No statistical analyses for this end point

## Primary: Phase 3: Progression Free Survival (PFS) by Blinded Independent Central Review Assessed Using Modified RECIST 1.1

| End point title | Phase 3: Progression Free Survival (PFS) by Blinded Independent Central Review Assessed Using Modified RECIST 1.1[3] |
|---|---|

End point description:

PFS per modified Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 is defined as the interval from randomization to the earlier event of progressive disease (PD) per modified RECIST 1.1 or death from any cause.
PD: Increase in size of target lesions from nadir by ≥ 20% and ≥ 5 mm absolute increase above nadir, or the appearance of a new lesion.
Median PFS was calculated using the Kaplan-Meier method. Participants without an event were censored at their last evaluable tumor assessment if available; otherwise on their randomization date.
The primary analysis of PFS was specified to be conducted when 407 PFS events had occurred (data cut-off date 02 March 2020).

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

End point timeframe:

From randomization until the data-cut-off date of 02 March 2020; median (range) time on follow-up was 25.5 (0.6, 44.7) months in the Placebo + Pembrolizumab arm and 25.6 (0.3, 45.8) months in the Talimogene Laherparepvec + Pembrolizumab arm.

Notes:

[3] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint was pre-specified for Phase 3 participants only.

| **End point values** | Phase 3: Placebo + Pembrolizumab | Phase 3: Talimogene Laherparepvec + Pembrolizumab | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 346 | 346 | | |
| Units: months | | | | |

| | | | | |
|---|---|---|---|---|
| median (confidence interval 95%) | 8.5 (5.72 to 13.54) | 14.3 (10.25 to 22.11) | | |

### Statistical analyses

| Statistical analysis title | Analysis of PFS |
|---|---|
| Comparison groups | Phase 3: Placebo + Pembrolizumab v Phase 3: Talimogene Laherparepvec + Pembrolizumab |
| Number of subjects included in analysis | 692 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.13 [4] |
| Method | Stratified log-rank test |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.86 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.71 |
| upper limit | 1.04 |

Notes:

[4] - Log-rank test stratified by randomization factors (disease stage, prior BRAF inhibitor therapy) and baseline PD-L1 status.

### Primary: Phase 3: Overall Survival

| End point title | Phase 3: Overall Survival[5] |
|---|---|

End point description:

Overall survival (OS) is defined as the interval from randomization to death from any cause.
Median overall survival was calculated using the Kaplan-Meier method. Participants without an event were censored at their last known alive date. "99999" indicates values that could not be estimated due to the low number of events.

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

End point timeframe:

From randomization until the end of study; median (range) time on follow-up was 34.8 (0.6, 58.3) months in the Placebo + Pembrolizumab arm and 36.8 (0.3, 58.4) months in the Talimogene Laherparepvec + Pembrolizumab arm.

Notes:

[5] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint was pre-specified for Phase 3 participants only.

| End point values | Phase 3: Placebo + Pembrolizumab | Phase 3: Talimogene Laherparepvec + Pembrolizumab | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 346 | 346 | | |
| Units: months | | | | |
| median (confidence interval 95%) | 99999 (99999 to 99999) | 99999 (99999 to 99999) | | |

### Statistical analyses

| Statistical analysis title | Analysis of OS |
|---|---|
| Comparison groups | Phase 3: Placebo + Pembrolizumab v Phase 3: Talimogene Laherparepvec + Pembrolizumab |
| Number of subjects included in analysis | 692 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.77 [6] |
| Method | Stratified log-rank test |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.97 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.77 |
| upper limit | 1.21 |

Notes:

[6] - Log-rank test stratified by randomization factors (disease stage, prior BRAF inhibitor therapy) and baseline PD-L1 status.

### Secondary: Phase 1b: Objective Response Rate (ORR)

| End point title | Phase 1b: Objective Response Rate (ORR)[7] |
|---|---|

End point description:

ORR is defined as the percentage of participants with a best overall response of complete response (CR) or partial response (PR) using the modified Immune-related Response Criteria (irRC), by Investigator assessment.
CR was defined as the disappearance of all lesions; PR was defined as a decrease in tumor area ≥ 50% relative to baseline, response must have been confirmed by a second, consecutive assessment at least 4 weeks apart.
Radiographic imaging for assessment of lesions was performed using computed tomography (CT), positron emission tomography (PET), magnetic resonance imaging (MRI), or ultrasound. Clinical measurement of cutaneous, subcutaneous, and palpable nodal tumor lesions was conducted with calipers.

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

End point timeframe:

Tumor assessments were performed at week 6 (prior to initiation of pembrolizumab), week 18, and every 12 weeks thereafter until confirmed PD or start of new anticancer treatment; median (range) time on follow-up was 58.6 (1.4, 61.6) months.

Notes:

[7] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint was pre-specified for Phase 1b participants only.

| End point values | Phase 1b: Talimogene Laherparepvec + Pembrolizumab | | | |
|---|---|---|---|---|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 21 | | | |
| Units: percentage of participants | | | | |
| number (confidence interval 95%) | 61.9 (38.4 to 81.9) | | | |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Phase 1b: Best Overall Response (BOR)

| End point title | Phase 1b: Best Overall Response (BOR)[8] |
|---|---|

End point description:

Best overall response is defined as the best overall visit response in the following order: CR, PR, stable disease (SD), progressive disease (PD), or unevaluable (UE), based on investigator assessment using the modified irRC up to the start of any subsequent anti-cancer therapy.
CR was defined as the disappearance of all lesions; PR was defined as a decrease in tumor area ≥ 50% relative to baseline; PD was defined as an increase in tumor area ≥ 25% relative to nadir; and SD was defined as any outcome not meeting the criteria for response or PD with ≥ 77 days elapsed after enrollment. Responses and PD must have been confirmed by a second, consecutive assessment at least 4 weeks apart.

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

End point timeframe:

Tumor assessments were performed at week 6 (prior to initiation of pembrolizumab), week 18, and every 12 weeks thereafter until confirmed PD or start of new anticancer treatment; median (range) time on follow-up was 58.6 (1.4, 61.6) months.

Notes:

[8] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint was pre-specified for Phase 1b participants only.

| End point values | Phase 1b: Talimogene Laherparepvec + Pembrolizumab | | | |
|---|---|---|---|---|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 21 | | | |
| Units: participants | | | | |
| Complete Response (CR) | 9 | | | |
| Partial Response (PR) | 4 | | | |
| Stable Disease (SD) | 1 | | | |
| Progressive Disease (PD) | 6 | | | |
| Unable to Evaluate (UE) | 1 | | | |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Phase 1b: Durable Response Rate (DRR)

| End point title | Phase 1b: Durable Response Rate (DRR)[9] |
|---|---|

End point description:

DRR is defined as the percentage of participants with a best overall response of CR or PR using the modified irRC per Investigator assessment with a duration of response of at least 6 months.
CR was defined as the disappearance of all lesions; PR was defined as a decrease in tumor area ≥ 50% relative to baseline, response must have been confirmed by a second, consecutive assessment at least 4 weeks apart.

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

End point timeframe:

Tumor assessments were performed at week 6 (prior to initiation of pembrolizumab), week 18, and every 12 weeks thereafter until confirmed PD or start of new anticancer treatment; median (range) time on follow-up was 58.6 (1.4, 61.6) months.

Notes:

[9] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint was pre-specified for Phase 1b participants only.

| **End point values** | Phase 1b: Talimogene Laherparepvec + Pembrolizumab | | | |
|---|---|---|---|---|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 21 | | | |
| Units: percentage of participants | | | | |
| number (confidence interval 95%) | 57.1 (34.0 to 78.2) | | | |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Phase 1b: Duration of Response (DOR)

| End point title | Phase 1b: Duration of Response (DOR)[10] |
|---|---|

End point description:

Duration of response (DOR) is defined as the time from the date of an initial response (CR or PR) that is subsequently confirmed to the earlier of confirmed PD or death. Participants who had not ended their response at the time of analysis were censored at their last evaluable tumor assessment before start of the first subsequent anticancer therapy. "99999" indicates values that could not be estimated due to the low number of events.

CR was defined as the disappearance of all lesions; PR was defined as a decrease in tumor area ≥ 50% relative to baseline; PD was defined as an increase in tumor area ≥ 25% relative to nadir. Response and PD must have been confirmed by a second, consecutive assessment at least 4 weeks apart.

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

End point timeframe:

Tumor assessments were performed at week 6 (prior to initiation of pembrolizumab), week 18, and every 12 weeks thereafter until confirmed PD or start of new anticancer treatment; median (range) time on follow-up was 58.6 (1.4, 61.6) months.

Notes:

[10] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint was pre-specified for Phase 1b participants only.

| **End point values** | Phase 1b: Talimogene Laherparepvec + Pembrolizumab | | | |
|---|---|---|---|---|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 13[11] | | | |
| Units: months | | | | |
| median (confidence interval 95%) | 99999 (99999 to 99999) | | | |

Notes:

[11] - Participants enrolled in Phase 1b who received ≥ 1 dose of study drug with a CR or PR.

### Statistical analyses

No statistical analyses for this end point

## Secondary: Phase 1b: Disease Control Rate (DCR)

| End point title | Phase 1b: Disease Control Rate (DCR)[12] |
|---|---|

End point description:

DCR is defined as the percentage of participants with a best overall response of CR, PR, or SD using the modified irRC per Investigator assessment.
CR was defined as the disappearance of all lesions; PR was defined as a decrease in tumor area ≥ 50% relative to baseline, response must have been confirmed by a second, consecutive assessment at least 4 weeks apart; and SD was defined as any outcome not meeting the criteria for response or PD with ≥ 84 days elapsed after enrollment.

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

End point timeframe:

Tumor assessments were performed at week 6 (prior to initiation of pembrolizumab), week 18, and every 12 weeks thereafter until confirmed PD or start of new anticancer treatment; median (range) time on follow-up was 58.6 (1.4, 61.6) months.

Notes:

[12] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint was pre-specified for Phase 1b participants only.

| **End point values** | Phase 1b: Talimogene Laherparepvec + Pembrolizumab | | | |
|---|---|---|---|---|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 21 | | | |
| Units: percentage of participants | | | | |
| number (confidence interval 95%) | 66.7 (43.0 to 85.4) | | | |

### Statistical analyses

No statistical analyses for this end point

## Secondary: Phase 1b: Overall Survival (OS)

| End point title | Phase 1b: Overall Survival (OS)[13] |
|---|---|

End point description:

Overall survival is defined as the interval from first dose to death from any cause.
OS was estimated using the Kaplan-Meier method. Participants without an event were censored at their last known alive date. "99999" indicates values that could not be estimated due to the low number of events.

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

End point timeframe:

From first dose until the end of study; median (range) time on follow-up was 70.6 (1.4, 74.5) months.

Notes:

[13] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint was pre-specified for Phase 1b participants only.

| **End point values** | Phase 1b: Talimogene Laherparepvec + Pembrolizumab | | | |
|---|---|---|---|---|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 21 | | | |
| Units: months | | | | |
| median (confidence interval 95%) | 99999 (99999 to 99999) | | | |

### Statistical analyses

No statistical analyses for this end point

## Secondary: Phase 1b: Progression-free Survival (PFS)

| End point title | Phase 1b: Progression-free Survival (PFS)[14] |
|---|---|

End point description:

Progression-free survival is defined as the time from first dose to the earlier event of confirmed PD per modified irRC or death from any cause. PFS was estimated using the Kaplan-Meier method. Participants without an event were censored at their last evaluable tumor assessment. "99999" indicates values that could not be estimated due to the low number of events.

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

End point timeframe:

From first dose until the end of study; median (range) time on follow-up was 70.6 (1.4, 74.5) months.

Notes:

[14] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint was pre-specified for Phase 1b participants only.

| End point values | Phase 1b: Talimogene Laherparepvec + Pembrolizumab | | | |
|---|---|---|---|---|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 21 | | | |
| Units: months | | | | |
| median (confidence interval 95%) | 99999 (99999 to 99999) | | | |

### Statistical analyses

No statistical analyses for this end point

## Secondary: Phase 3: Complete Response Rate Assessed Using Modified irRC-RECIST (iCRR)

| End point title | Phase 3: Complete Response Rate Assessed Using Modified irRC-RECIST (iCRR)[15] |
|---|---|

End point description:

Complete response rate per modified Immune-related Response Criteria (irRC) simulating RECIST 1.1 (irRC-RECIST) is defined as the percentage of participants with a best overall response of complete response assessed using the modified irRC-RECIST (iCR) evaluated by blinded independent central review.

iCR: Disappearance of all lesions (whether measurable or not and whether baseline or new) and confirmation by a repeat, consecutive assessment at least 4 weeks after the criteria were first met. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.

Modifications to the irRC-RECIST 1.1 included an increase in the total number of target lesions and new measurable lesions to 10 with a maximum of 5 target lesions per organ, and target lesions must have been measurable by CT or MRI only.

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

End point timeframe:

Tumor assessments were performed every 12 weeks after initiation of treatment until confirmed PD or start of new anticancer treatment; median (range) time on follow-up was 30.6 (0.6, 53.0) months and 31.4 (0.3, 52.5) months in each group, respectively.

Notes:

[15] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint was pre-specified for Phase 3 participants only.

| End point values | Phase 3: Placebo + Pembrolizumab | Phase 3: Talimogene Laherparepvec + Pembrolizumab | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 346 | 346 | | |
| Units: percentage of participants | | | | |
| number (confidence interval 95%) | 8.1 (5.22 to 10.97) | 14.5 (10.75 to 18.16) | | |

### Statistical analyses

| Statistical analysis title | Analysis of iCRR |
|---|---|
| Comparison groups | Phase 3: Placebo + Pembrolizumab v Phase 3: Talimogene Laherparepvec + Pembrolizumab |
| Number of subjects included in analysis | 692 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.012 [16] |
| Method | Regression, Logistic |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 1.88 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 1.15 |
| upper limit | 3.07 |

Notes:

[16] - Logistic regression stratified by randomization stratification factors (disease stage and prior BRAF inhibitor therapy) and the baseline PD-L1 status.

## Secondary: Phase 3: Progression Free Survival Assessed Using Modified irRC-RECIST (iPFS)

| End point title | Phase 3: Progression Free Survival Assessed Using Modified irRC-RECIST (iPFS)[17] |
|---|---|

End point description:

PFS per modified irRC-RECIST is defined as the interval from randomization to the earlier event of progressive disease assessed by modified irRC-RECIST (iPD) evaluated by blinded independent central review, or death from any cause.
iPD: Increase in tumor burden ≥ 20% and at least 5 mm absolute increase relative to nadir (minimum recorded tumor burden) confirmed by a repeat, consecutive assessment at least 4 weeks after the initial detection.
Median iPFS was calculated using the Kaplan-Meier method. Participants without an event were censored at their last evaluable tumor assessment if available; otherwise on their randomization date. "99999" indicates values that could not be estimated due to the low number of events.
The primary analysis of iPFS was specified to be conducted when 256 iPFS events had occurred (data cut-off date 29 September 2020).

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

End point timeframe:

From randomization until the data cut-off date of 29 September 2020; median time on follow-up was 30.6 (0.6, 53.0) months in the Placebo + Pembrolizumab arm and 31.4 (0.3, 52.5) months in the Talimogene Laherparepvec + Pembrolizumab arm.

Notes:

[17] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint was pre-specified for Phase 3 participants only.

| End point values | Phase 3: Placebo + Pembrolizumab | Phase 3: Talimogene Laherparepvec + Pembrolizumab | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 346 | 346 | | |
| Units: months | | | | |
| median (confidence interval 95%) | 25.3 (17.68 to 99999) | 99999 (99999 to 99999) | | |

### Statistical analyses

| Statistical analysis title | Analysis of iPFS |
|---|---|
| Comparison groups | Phase 3: Talimogene Laherparepvec + Pembrolizumab v Phase 3: Placebo + Pembrolizumab |
| Number of subjects included in analysis | 692 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.14 [18] |
| Method | Stratified log-rank test |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 1.05 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.82 |
| upper limit | 1.34 |

Notes:

[18] - Log-rank test stratified by randomization factors (disease stage, prior BRAF inhibitor therapy) and baseline PD-L1 status.

### Secondary: Phase 3: Overall Survival Excluding Stage IVM1c Participants

| End point title | Phase 3: Overall Survival Excluding Stage IVM1c Participants[19] |
|---|---|

End point description:

Overall survival is defined as the interval from randomization to death from any cause.
Median OS was calculated using the Kaplan-Meier method. Participants without an event were censored at the last known alive date. "99999" indicates values that could not be estimated due to the low number of events.

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

End point timeframe:

From randomization until the end of study; median (range) time on follow-up was 34.8 (0.6, 58.3) months in the Placebo + Pembrolizumab arm and 36.8 (0.3, 58.4) months in the Talimogene Laherparepvec + Pembrolizumab arm.

Notes:

[19] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint was pre-specified for Phase 3 participants only.

| End point values | Phase 3: Placebo + Pembrolizumab | Phase 3: Talimogene Laherparepvec + Pembrolizumab | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 203[20] | 201[21] | | |
| Units: months | | | | |
| median (confidence interval 95%) | 99999 (99999 to 99999) | 99999 (99999 to 99999) | | |

Notes:

[20] - Participants randomized in Phase 3 with stage IIIB to IVM1a/b.

[21] - Participants randomized in Phase 3 with stage IIIB to IVM1a/b.

## Statistical analyses

| **Statistical analysis title** | Analysis of OS Excluding Stage IVM1c Participants |
|---|---|
| Comparison groups | Phase 3: Placebo + Pembrolizumab v Phase 3: Talimogene Laherparepvec + Pembrolizumab |
| Number of subjects included in analysis | 404 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.47 [22] |
| Method | Stratified log-rank test |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.88 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.63 |
| upper limit | 1.24 |

Notes:

[22] - Log-rank test stratified by randomization factors (disease stage, prior BRAF inhibitor therapy) and baseline PD-L1 status.

## Secondary: Phase 3: Objective Response Rate Assessed Using Modified RECIST 1.1

| End point title | Phase 3: Objective Response Rate Assessed Using Modified RECIST 1.1[23] |
|---|---|

End point description:

ORR is defined as the percentage of participants with a best overall response of complete response (CR) or partial response (PR) assessed using modified RECIST version 1.1, evaluated by blinded independent central review.
CR was defined as the disappearance of all lesions except lymph node short axis < 10 mm; PR was defined as a ≥ 30% reduction in sum of diameters in target lesions. Confirmation of CR or PR was not required.

Modifications to conventional RECIST 1.1 included the following: target lesions were measurable on CT or MRI; otherwise, they were considered as nontarget lesions. A maximum of 10 target lesions was allowed with up to 5 per organ.

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

End point timeframe:

Tumor assessments were performed every 12 weeks after initiation of treatment until confirmed PD or start of new anticancer treatment; median (range) time on follow-up was 30.6 (0.6, 53.0) months and 31.4 (0.3, 52.5) months in each group, respectively.

Notes:

[23] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint was pre-specified for Phase 3 participants only.

| End point values | Phase 3: Placebo + Pembrolizumab | Phase 3: Talimogene Laherparepvec + Pembrolizumab | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 346 | 346 | | |
| Units: percentage of participants | | | | |
| number (confidence interval 95%) | 41.3 (36.14 to 46.52) | 48.6 (43.29 to 53.82) | | |

### Statistical analyses

| Statistical analysis title | Analysis of ORR |
|---|---|
| Comparison groups | Phase 3: Placebo + Pembrolizumab v Phase 3: Talimogene Laherparepvec + Pembrolizumab |
| Number of subjects included in analysis | 692 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.081 [24] |
| Method | Regression, Logistic |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 1.32 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.97 |
| upper limit | 1.79 |

Notes:

[24] - Logistic regression stratified by randomization stratification factors (disease stage and prior BRAF inhibitor therapy) and the baseline PD-L1 status.

### Secondary: Phase 3: Best Overall Response Assessed Using Modified RECIST 1.1

| End point title | Phase 3: Best Overall Response Assessed Using Modified RECIST 1.1[25] |
|---|---|

End point description:

Best overall response is defined as the best overall visit response up to and including the first overall visit response of PD in the following order: CR, PR, SD, non-CR/Non-PD (NN), PD or UE assessed using modified RECIST version 1.1, evaluated by blinded independent central review.
CR was defined as the disappearance of all lesions except lymph node short axis < 10 mm; PR was defined as a ≥ 30% reduction in sum of diameters in target lesions. Confirmation of CR or PR was not required. NN was defined as persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits. SD was defined as neither sufficient shrinkage of target lesions to qualify for CR or PR nor sufficient increase to qualify for PD with ≥ 84 days elapsed after randomization. PD was defined as an increase from nadir by ≥ 20% or ≥ 5 mm absolute increase above nadir of target lesions or appearance of any new lesion.

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

End point timeframe:

Tumor assessments were performed every 12 weeks after initiation of treatment until confirmed PD or start of new anticancer treatment; median (range) time on follow-up was 30.6 (0.6, 53.0) months and 31.4 (0.3, 52.5) months in each group, respectively.

Notes:

[25] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint was pre-specified for Phase 3 participants only.

| End point values | Phase 3: Placebo + Pembrolizumab | Phase 3: Talimogene Laherparepvec + Pembrolizumab | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 346 | 346 | | |
| Units: participants | | | | |
| Complete response (CR) | 40 | 62 | | |
| Partial response (PR) | 103 | 106 | | |
| Stable disease (SD) | 30 | 28 | | |
| Non-CR/Non-PD (NN) | 16 | 11 | | |
| Progressive disease (PD) | 120 | 106 | | |
| Unevaluable (UE) | 11 | 3 | | |
| Not done | 26 | 30 | | |

### Statistical analyses

No statistical analyses for this end point

## Secondary: Phase 3: Durable Response Rate (DRR) Assessed Using Modified RECIST 1.1

| End point title | Phase 3: Durable Response Rate (DRR) Assessed Using Modified RECIST 1.1[26] |
|---|---|

End point description:

DRR is defined as the percentage of participants with a CR or PR per modified RECIST 1.1 and evaluated by blinded independent central review with a duration of response for ≥ 6 months.

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

End point timeframe:

Tumor assessments were performed every 12 weeks after initiation of treatment until confirmed PD or start of new anticancer treatment; median (range) time on follow-up was 30.6 (0.6, 53.0) months and 31.4 (0.3, 52.5) months in each group, respectively.

Notes:

[26] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint was pre-specified for Phase 3 participants only.

| End point values | Phase 3: Placebo + Pembrolizumab | Phase 3: Talimogene Laherparepvec + Pembrolizumab | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 346 | 346 | | |
| Units: percentage of participants | | | | |
| number (confidence interval 95%) | 34.1 (29.11 to 39.10) | 42.2 (36.99 to 47.40) | | |

### Statistical analyses

| Statistical analysis title | Analysis of DRR |
|---|---|
| Comparison groups | Phase 3: Placebo + Pembrolizumab v Phase 3: Talimogene Laherparepvec + Pembrolizumab |
| Number of subjects included in analysis | 692 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.039 [27] |
| Method | Regression, Logistic |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 1.39 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 1.02 |
| upper limit | 1.9 |

Notes:

[27] - Logistic regression stratified by randomization stratification factors (disease stage and prior BRAF inhibitor therapy) and the baseline PD-L1 status.

## Secondary: Phase 3: Duration of Response (DOR) Assessed Using Modified RECIST 1.1

| End point title | Phase 3: Duration of Response (DOR) Assessed Using Modified RECIST 1.1[28] |
|---|---|

End point description:

Duration of response (DOR) is defined as the time from the date of an initial response of CR or PR to the earlier of PD per modified RECIST 1.1, or death. Participants who had not ended their response at the time of analysis were censored at their last evaluable tumor assessment date before start of the first subsequent anticancer therapy. "99999" indicates values that could not be estimated due to the low number of events.

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

End point timeframe:

From randomization until the data cut-off date of 29 September 2020; median time on follow-up was 30.6 (0.6, 53.0) months in the Placebo + Pembrolizumab arm and 31.4 (0.3, 52.5) months in the Talimogene Laherparepvec + Pembrolizumab arm.

Notes:

[28] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint was pre-specified for Phase 3 participants only.

| End point values | Phase 3: Placebo + Pembrolizumab | Phase 3: Talimogene Laherparepvec + Pembrolizumab | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 143 | 168 | | |
| Units: months | | | | |
| median (confidence interval 95%) | 99999 (99999 to 99999) | 43.7 (-99999 to 99999) | | |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Phase 3: Disease Control Rate (DCR) Assessed Using RECIST 1.1

| End point title | Phase 3: Disease Control Rate (DCR) Assessed Using RECIST 1.1[29] |
|---|---|

End point description:

Disease control rate (DCR) per modified RECIST 1.1 is defined as the percentage of participants with a best overall response of CR, PR or SD evaluated by blinded independent central review.
CR was defined as the disappearance of all lesions except lymph node short axis < 10 mm; PR was defined as a ≥ 30% reduction in sum of diameters in target lesions. Confirmation of CR or PR was not required. SD was defined as neither sufficient shrinkage of target lesions to qualify for CR or PR nor sufficient increase to qualify for PD with ≥ 84 days elapsed after randomization.

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

End point timeframe:

Tumor assessments were performed every 12 weeks after initiation of treatment until confirmed PD or start of new anticancer treatment; median (range) time on follow-up was 30.6 (0.6, 53.0) months and 31.4 (0.3, 52.5) months in each group, respectively.

Notes:

[29] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint was pre-specified for Phase 3 participants only.

| **End point values** | Phase 3: Placebo + Pembrolizumab | Phase 3: Talimogene Laherparepvec + Pembrolizumab | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 346 | 346 | | |
| Units: percentage of participants | | | | |
| number (confidence interval 95%) | 50.0 (44.73 to 55.27) | 56.6 (51.43 to 61.87) | | |

### Statistical analyses

| **Statistical analysis title** | Analysis of DCR |
|---|---|
| Comparison groups | Phase 3: Placebo + Pembrolizumab v Phase 3: Talimogene Laherparepvec + Pembrolizumab |
| Number of subjects included in analysis | 692 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.11 [30] |
| Method | Regression, Logistic |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 1.28 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.94 |
| upper limit | 1.75 |

Notes:

[30] - Logistic regression stratified by randomization stratification factors (disease stage and prior BRAF inhibitor therapy) and the baseline PD-L1 status.

## Secondary: Phase 3: Objective Response Rate Assessed Using Modified irRC-RECIST (iORR)

| End point title | Phase 3: Objective Response Rate Assessed Using Modified irRC-RECIST (iORR)[31] |
|---|---|

End point description:

Objective response rate per modified irRC-RECIST is defined as the percentage of participants with a best overall response of iCR or partial response assessed using modified irRC-RECIST (iPR) evaluated by blinded independent central review.

iCR: Disappearance of all lesions (whether measurable or not and whether baseline or new) and confirmation by a repeat, consecutive assessment at least 4 weeks from the date first documented. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.
iPR: Decrease in tumor burden ≥ 30% relative to baseline confirmed by a consecutive assessment at least 4 weeks after first documentation.

Modifications to the irRC-RECIST 1.1 included an increase in the total number of target lesions and new measurable lesions to 10 with a maximum of 5 target lesions per organ, and target lesions must be measurable by CT or MRI only.

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

End point timeframe:

Tumor assessments were performed every 12 weeks after initiation of treatment until confirmed PD or start of new anticancer treatment; median (range) time on follow-up was 30.6 (0.6, 53.0) months and 31.4 (0.3, 52.5) months in each group, respectively.

Notes:

[31] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint was pre-specified for Phase 3 participants only.

| **End point values** | Phase 3: Placebo + Pembrolizumab | Phase 3: Talimogene Laherparepvec + Pembrolizumab | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 346 | 346 | | |
| Units: percentage of participants | | | | |
| number (confidence interval 95%) | 39.9 (34.72 to 45.04) | 49.1 (43.87 to 54.40) | | |

## Statistical analyses

| **Statistical analysis title** | Analysis of iORR |
|---|---|
| Comparison groups | Phase 3: Placebo + Pembrolizumab v Phase 3: Talimogene Laherparepvec + Pembrolizumab |
| Number of subjects included in analysis | 692 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.02 [32] |
| Method | Regression, Logistic |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 1.44 |

| Confidence interval | |
|---|---|
| level | 95 % |
| sides | 2-sided |
| lower limit | 1.06 |
| upper limit | 1.96 |

Notes:

[32] - Logistic regression stratified by randomization stratification factors (disease stage and prior BRAF inhibitor therapy) and the baseline PD-L1 status.

## Secondary: Phase 3: Best Overall Response Assessed Using Modified irRC-RECIST

| End point title | Phase 3: Best Overall Response Assessed Using Modified irRC-RECIST[33] |
|---|---|

End point description:

Best overall response is defined as the best overall visit response in the following order: iCR, iPR, stable disease per modified irRC-RECIST (iSD), iPD, or UE per modified irRC-RECIST (iUE), evaluated by blinded independent central review.
iCR: Disappearance of all lesions and confirmation by a repeat, consecutive assessment at least 4 weeks from the date first documented. Any pathological lymph nodes must have reduction in short axis to <10 mm.
iPR: Decrease in tumor burden ≥ 30% relative to baseline confirmed by a consecutive assessment at least 4 weeks after first documentation.
iPD: Increase in tumor burden ≥ 20 % and at least 5 mm absolute increase relative to nadir confirmed by a repeat, consecutive assessment at least 4 weeks from the initial detection.
iSD: Neither sufficient shrinkage to qualify for iCR or iPR nor sufficient increase to qualify for iPD with ≥ 84 days elapsed after randomization.

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

End point timeframe:

Tumor assessments were performed every 12 weeks after initiation of treatment until confirmed PD or start of new anticancer treatment; median (range) time on follow-up was 30.6 (0.6, 53.0) months and 31.4 (0.3, 52.5) months in each group, respectively.

Notes:

[33] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint was pre-specified for Phase 3 participants only.

| **End point values** | Phase 3: Placebo + Pembrolizumab | Phase 3: Talimogene Laherparepvec + Pembrolizumab | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 346 | 346 | | |
| Units: participants | | | | |
| Complete response (iCR) | 28 | 50 | | |
| Partial response (iPR) | 110 | 120 | | |
| Stable disease (iSD) | 57 | 51 | | |
| Progressive disease (iPD) | 56 | 65 | | |
| Unevaluable (iUE) | 69 | 30 | | |
| Not done | 26 | 30 | | |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Phase 3: Durable Response Rate Assessed Using Modified irRC-RECIST (iDRR)

| End point title | Phase 3: Durable Response Rate Assessed Using Modified irRC-RECIST (iDRR)[34] |
|---|---|

End point description:

Durable response rate per modified irRC-RECIST is defined as the percentage of participants with a best overall response of iCR or iPR per modified irRC-RECIST evaluated by blinded independent central review with a duration of response ≥ 6 months.
iCR: Disappearance of all lesions (whether measurable or not and whether baseline or new) and confirmation by a repeat, consecutive assessment at least 4 weeks from the date first documented. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.
iPR: Decrease in tumor burden ≥ 30% relative to baseline confirmed by a consecutive assessment at least 4 weeks after first documentation.

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

End point timeframe:

Tumor assessments were performed every 12 weeks after initiation of treatment until confirmed PD or start of new anticancer treatment; median (range) time on follow-up was 30.6 (0.6, 53.0) months and 31.4 (0.3, 52.5) months in each group, respectively.

Notes:

[34] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint was pre-specified for Phase 3 participants only.

| **End point values** | Phase 3: Placebo + Pembrolizumab | Phase 3: Talimogene Laherparepvec + Pembrolizumab | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 346 | 346 | | |
| Units: percentage of participants | | | | |
| number (confidence interval 95%) | 34.4 (29.39 to 39.40) | 45.7 (40.42 to 50.91) | | |

### Statistical analyses

| **Statistical analysis title** | Analysis of iDRR |
|---|---|
| Comparison groups | Phase 3: Placebo + Pembrolizumab v Phase 3: Talimogene Laherparepvec + Pembrolizumab |
| Number of subjects included in analysis | 692 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.004 [35] |
| Method | Regression, Logistic |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 1.59 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 1.16 |
| upper limit | 2.17 |

Notes:

[35] - Logistic regression stratified by randomization stratification factors (disease stage and prior BRAF inhibitor therapy) and the baseline PD-L1 status.

## Secondary: Phase 3: Duration of Response Assessed Using Modified irRC-RECIST (iDOR)

| End point title | Phase 3: Duration of Response Assessed Using Modified irRC-RECIST (iDOR)[36] |
|---|---|

End point description:

Duration of response per modified irRC-RECIST is defined as the time from the date of an initial response of iCR or iPR that was subsequently confirmed to the earlier of iPD per modified irRC-RECIST evaluated by blinded independent central review, or death. Participants who had not ended their response at the time of analysis were censored at their last evaluable tumor assessment date before the start of the first subsequent anticancer therapy. "99999" indicates values that could not be estimated due to the low number of events.

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

End point timeframe:

From randomization until the data cut-off date of 29 September 2020; median time on follow-up was 30.6 (0.6, 53.0) months in the Placebo + Pembrolizumab arm and 31.4 (0.3, 52.5) months in the Talimogene Laherparepvec + Pembrolizumab arm.

Notes:

[36] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint was pre-specified for Phase 3 participants only.

| **End point values** | Phase 3: Placebo + Pembrolizumab | Phase 3: Talimogene Laherparepvec + Pembrolizumab | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 138 | 170 | | |
| Units: months | | | | |
| median (confidence interval 95%) | 99999 (99999 to 99999) | 43.7 (34.53 to 43.73) | | |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Phase 3: Disease Control Rate Assessed Using Modified irRC-RECIST (iDCR)

| End point title | Phase 3: Disease Control Rate Assessed Using Modified irRC-RECIST (iDCR)[37] |
|---|---|

End point description:

Disease control rate per modified irRC-RECIST is defined as the percentage of participants with a best overall response of iCR, iCR, or iSD assessed using modified irRC-RECIST evaluated by blinded independent central review.

iCR: Disappearance of all lesions (whether measurable or not and whether baseline or new) and confirmation by a repeat, consecutive assessment at least 4 weeks from the date first documented. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.
iPR: Decrease in tumor burden ≥ 30% relative to baseline confirmed by a consecutive assessment at least 4 weeks after first documentation.
iSD: Neither sufficient shrinkage to qualify for iCR or iPR nor sufficient increase to qualify for iPD with ≥ 84 days elapsed after randomization.

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

End point timeframe:

Tumor assessments were performed every 12 weeks after initiation of treatment until confirmed PD or start of new anticancer treatment; median (range) time on follow-up was 30.6 (0.6, 53.0) months and 31.4 (0.3, 52.5) months in each group, respectively.

Notes:

[37] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint was pre-specified for Phase 3 participants only.

| **End point values** | Phase 3: Placebo + Pembrolizumab | Phase 3: Talimogene Laherparepvec + Pembrolizumab | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 346 | 346 | | |
| Units: percentage of participants | | | | |
| number (confidence interval 95%) | 56.4 (51.13 to 61.58) | 63.9 (58.81 to 68.93) | | |

## Statistical analyses

| **Statistical analysis title** | Analysis of iDCR |
|---|---|
| Comparison groups | Phase 3: Placebo + Pembrolizumab v Phase 3: Talimogene Laherparepvec + Pembrolizumab |
| Number of subjects included in analysis | 692 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.058 [38] |
| Method | Regression, Logistic |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 1.35 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.99 |
| upper limit | 1.85 |

Notes:

[38] - Logistic regression stratified by randomization stratification factors (disease stage and prior BRAF inhibitor therapy) and the baseline PD-L1 status.

## Secondary: Phase 3: Change From Baseline in European Organisation for Research and Treatment of Cancer Quality of Life Core Module (EORTC QLQ-C30) Global Health Status (GHS)/Quality of Life (QOL) Score

| End point title | Phase 3: Change From Baseline in European Organisation for Research and Treatment of Cancer Quality of Life Core Module (EORTC QLQ-C30) Global Health Status (GHS)/Quality of Life (QOL) Score[39] |
|---|---|

End point description:

The European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-C30 (EORTC QLQ-C30) is a 30-question tool used to assess the overall quality of life in cancer patients. It consists of 15 domains: 1 global health status/quality of life scale, 5 functional scales, and 9 symptom scales/items.

The global health/QoL scale consists of 2 questions that ask participants to rate their overall health and overall quality of life during the past week on a scale from 1 (very poor) to 7 (excellent). The GHS/QoL subscale score was derived as the mean of each score then transformed to a scale from 0 to 100 where higher scores represent a better health status and a positive change from baseline indicates improvement.
The overall change from baseline (calculated from all on-treatment visits) was calculated using a restricted maximum likelihood-based mixed model for repeated measures (MMRM) (see model details in statistical analysis section).

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

End point timeframe:

Baseline and day 1 of weeks 3, 6, 9, 12, then every 6 weeks until end of study treatment; median (range) duration of treatment was 39.0 (0.1, 107.3) weeks in Placebo + Pembrolizumab and 54.1 (0.1, 109.6) weeks in Talimogene Laherparepvec + Pembrolizumab.

Notes:

[39] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint was pre-specified for Phase 3 participants only.

| **End point values** | Phase 3: Placebo + Pembrolizumab | Phase 3: Talimogene Laherparepvec + Pembrolizumab | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 329[40] | 328[41] | | |
| Units: score on a scale | | | | |
| least squares mean (standard error) | -0.20 (± 1.02) | -0.02 (± 1.02) | | |

Notes:

[40] - Participants who received at least 1 dose of study drug with baseline and ≥ 1 on-treatment value.

[41] - Participants who received at least 1 dose of study drug with baseline and ≥ 1 on-treatment value.

## Statistical analyses

| **Statistical analysis title** | Analysis of EORTC QLQ-C30 GHS/QOL |
|---|---|

Statistical analysis description:

Mixed Model for Repeated Measures include the fixed and categorical effects of treatment, visit and treatment-by-visit interaction, the fixed and continuous covariates of baseline HRQL score, randomization stratification factors (stage of disease and prior BRAF inhibitor therapy per IVRS) and baseline PD-L1 status (positive and not positive). Random subject effect was modeled using within subject-error correlation structure.

| Comparison groups | Phase 3: Placebo + Pembrolizumab v Phase 3: Talimogene Laherparepvec + Pembrolizumab |
|---|---|
| Number of subjects included in analysis | 657 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.84 |
| Method | Mixed Model for Repeated Measures |
| Parameter estimate | Difference |
| Point estimate | 0.19 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.67 |
| upper limit | 2.05 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.95 |

## Secondary: Number of Participants with Treatment-emergent Adverse Events (TEAEs)

| End point title | Number of Participants with Treatment-emergent Adverse Events (TEAEs) |
|---|---|

End point description:

An adverse event (AE) is any untoward medical occurrence in a clinical trial subject, including worsening of a pre-existing medical condition. The event does not necessarily have a causal relationship with study treatment. TEAEs include AEs from the first dose of study drug to 30 days after the last dose.
A serious adverse event (SAE) is an AE that met at least 1 of the following criteria:
-fatal;
-life threatening;
-required in-patient hospitalization or prolongation of existing hospitalization;
-resulted in persistent or significant disability/incapacity;
-congenital anomaly/birth defect;
-other medically important serious event.
Treatment-emergent SAEs are any SAE occurring from first dose of study drug through 90 days after the last dose or 30 days after the last dose if new anticancer therapy was started, whichever was earlier.
AEs were graded for severity using CTCAE V4.0, where Grade 1 = Mild; Grade 2 = Moderate; Grade 3 = Severe; Grade 4 = Life-threatening; Grade 5.

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

End point timeframe:

From first dose to 30 days after last dose (90 days for SAEs); median (range) duration was 48 (5.1, 110.1) weeks in Phase 1b, 39 (0.1, 107.3) weeks in Placebo + Pembrolizumab and 56 (0.1, 109.6) weeks in Phase 3 Talimogene Laherparepvec + Pembrolizumab.

| **End point values** | Phase 1b: Talimogene Laherparepvec + Pembrolizumab | Phase 3: Placebo + Pembrolizumab | Phase 3: Talimogene Laherparepvec + Pembrolizumab | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 21 | 344 | 344 | |
| Units: participants | | | | |
| Any treatment-emergent adverse events | 21 | 331 | 338 | |
| Grade ≥ 2 | 20 | 279 | 306 | |
| Grade ≥ 3 | 13 | 151 | 161 | |
| Grade ≥ 4 | 2 | 29 | 33 | |
| Serious adverse events | 8 | 141 | 154 | |
| Leading to discontinuation of T-VEC/Placebo | 0 | 24 | 26 | |
| Leading to discontinuation of pembrolizumab | 2 | 41 | 43 | |
| Fatal adverse events | 1 | 42 | 45 | |

## Statistical analyses

No statistical analyses for this end point

## Adverse events information

Timeframe for reporting adverse events:

From first dose of study drug to 30 days after last dose (90 days for SAEs); median (range) duration was 48 (5.1, 110) weeks in Phase 1b, 39 (0.1, 107) weeks in Placebo arm and 56 (0.1, 110) weeks in T-VEC arm. Deaths are reported up to the end of study.

Adverse event reporting additional description:

Adverse events are reported for all subjects who received at least 1 dose of T-VEC or pembrolizumab. One subject who was randomized in Phase 3 to receive placebo received T-VEC; thus the Safety Analysis Set consisted of 344 subjects in the talimogene laherparepvec + pembrolizumab group and 344 subjects in the placebo + pembrolizumab arm.

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

## Dictionary used

| | |
|---|---|
| Dictionary name | MedDRA |
| Dictionary version | 23.1 |

## Reporting groups

| | |
|---|---|
| Reporting group title | Phase 1b: Talimogene Laherparepvec + Pembrolizumab |

Reporting group description:

Participants received talimogene laherparepvec at an initial dose of up to 4 mL 10 plaque-forming units (PFU)/mL by intralesional injection. Subsequent doses of talimogene laherparepvec at up to 4 mL of $10^8$ PFU/mL began 3 weeks after the first dose and were administered every 2 weeks until disappearance of injectable lesions, complete response (CR), confirmed disease progression (PD) per modified Immune-related Response Criteria (irRC), intolerance of study treatment, 24 months from the date of the first dose of pembrolizumab, or end of study, whichever occurred first. Participants also received 200 mg pembrolizumab administered intravenously every 2 weeks starting at the time of the third dose of talimogene laherparepvec (week 6) until confirmed PD per modified irRC, treatment intolerance, 24 months from the first dose, or end of study, whichever occurred first.

| | |
|---|---|
| Reporting group title | Phase 3: Placebo + Pembrolizumab |

Reporting group description:

Participants received up to 4 mL placebo to talimogene laherparepvec by intralesional injection on day 1 of week 0. Subsequent doses of placebo (up to 4 mL) began 3 weeks after the first dose and were administered every 2 weeks until the fifth injection (week 9), and then synchronously with pembrolizumab thereafter every 3 weeks until disappearance of injectable lesions, complete response per modified Immune-related Response Criteria simulating Response Evaluation Criteria in Solid Tumors (irRC-RECIST) (iCR), confirmed iPD per modified irRC-RECIST, intolerance of study treatment, 24 months from the date of the first dose of placebo, or end of study, whichever occurred first. Participants also received 200 mg pembrolizumab administered intravenously every 3 weeks starting on day 1 of week 0, until confirmed iPD per modified irRC-RECIST, treatment intolerance, 24 months from the first dose, or end of study, whichever occurred first.

| | |
|---|---|
| Reporting group title | Phase 3: Talimogene Laherparepvec + Pembrolizumab |

Reporting group description:

Participants received talimogene laherparepvec at an initial dose of up to 4 mL 10 PFU/mL by intralesional injection on day 1. Subsequent doses of talimogene laherparepvec at $10^8$ PFU/mL (up to 4 mL) began 3 weeks after the first dose and were administered every 2 weeks until the fifth injection of talimogene laherparepvec (week 9), and then synchronously with pembrolizumab thereafter every 3 weeks until disappearance of injectable lesions, iCR, confirmed iPD per modified irRC-RECIST, intolerance of study treatment, 24 months from the date of the first dose of talimogene laherparepvec, or end of study, whichever occurred first. Participants also received 200 mg pembrolizumab administered intravenously every 3 weeks starting on day 1 of week 0, until confirmed iPD per modified irRC-RECIST, treatment intolerance, 24 months from the first dose, or end of study, whichever occurred first.

| **Serious adverse events** | Phase 1b: Talimogene Laherparepvec + Pembrolizumab | Phase 3: Placebo + Pembrolizumab | Phase 3: Talimogene Laherparepvec + Pembrolizumab |
|---|---|---|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 8 / 21 (38.10%) | 141 / 344 (40.99%) | 154 / 344 (44.77%) |
| number of deaths (all causes) | 6 | 155 | 145 |
| number of deaths resulting from adverse events | | | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Adenocarcinoma gastric | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 0 / 344 (0.00%) | 1 / 344 (0.29%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Adenocarcinoma of colon | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 1 / 344 (0.29%) | 0 / 344 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Basal cell carcinoma | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 1 / 344 (0.29%) | 1 / 344 (0.29%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Bladder adenocarcinoma stage unspecified | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 0 / 344 (0.00%) | 1 / 344 (0.29%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Breast cancer | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 1 / 344 (0.29%) | 0 / 344 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Endometrial cancer | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 1 / 344 (0.29%) | 0 / 344 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Intraductal proliferative breast lesion | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 21 (4.76%) | 0 / 344 (0.00%) | 0 / 344 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Malignant melanoma | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 26 / 344 (7.56%) | 27 / 344 (7.85%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 26 | 1 / 29 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 19 | 0 / 20 |
| Malignant neoplasm progression | | | |
| subjects affected / exposed | 1 / 21 (4.76%) | 0 / 344 (0.00%) | 1 / 344 (0.29%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| Melanoma recurrent | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 1 / 344 (0.29%) | 0 / 344 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Metastases to bone | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 0 / 344 (0.00%) | 1 / 344 (0.29%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Metastases to central nervous system | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 1 / 344 (0.29%) | 3 / 344 (0.87%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 4 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| Metastases to lung | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 1 / 344 (0.29%) | 1 / 344 (0.29%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Metastases to nervous system | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 1 / 344 (0.29%) | 0 / 344 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Metastatic malignant melanoma | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 21 (0.00%) | 10 / 344 (2.91%) | 7 / 344 (2.03%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 11 | 0 / 8 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 8 | 0 / 5 |
| Squamous cell carcinoma of skin | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 0 / 344 (0.00%) | 2 / 344 (0.58%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Transitional cell carcinoma | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 1 / 344 (0.29%) | 0 / 344 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Tumour associated fever | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 0 / 344 (0.00%) | 1 / 344 (0.29%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Tumour haemorrhage | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 0 / 344 (0.00%) | 2 / 344 (0.58%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 3 / 4 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vascular disorders | | | |
| Arteritis | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 0 / 344 (0.00%) | 1 / 344 (0.29%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Deep vein thrombosis | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 0 / 344 (0.00%) | 1 / 344 (0.29%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Haemorrhage | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 1 / 344 (0.29%) | 1 / 344 (0.29%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypertensive crisis | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 21 (0.00%) | 0 / 344 (0.00%) | 1 / 344 (0.29%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypotension | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 1 / 344 (0.29%) | 0 / 344 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Labile blood pressure | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 1 / 344 (0.29%) | 0 / 344 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Peripheral artery occlusion | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 2 / 344 (0.58%) | 0 / 344 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Subclavian vein thrombosis | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 0 / 344 (0.00%) | 1 / 344 (0.29%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Thrombophlebitis | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 1 / 344 (0.29%) | 0 / 344 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vena cava thrombosis | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 0 / 344 (0.00%) | 1 / 344 (0.29%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Surgical and medical procedures | | | |
| Axillary lymphadenectomy | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 1 / 344 (0.29%) | 0 / 344 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| General disorders and administration site conditions | | | |

| | | | |
|---|---|---|---|
| Asthenia | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 2 / 344 (0.58%) | 1 / 344 (0.29%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Chest pain | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 0 / 344 (0.00%) | 1 / 344 (0.29%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Chills | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 0 / 344 (0.00%) | 1 / 344 (0.29%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Condition aggravated | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 0 / 344 (0.00%) | 1 / 344 (0.29%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| Death | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 0 / 344 (0.00%) | 2 / 344 (0.58%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| Disease progression | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 1 / 344 (0.29%) | 0 / 344 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| Fatigue | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 1 / 344 (0.29%) | 3 / 344 (0.87%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 3 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| General physical health deterioration | | | |
| subjects affected / exposed | 1 / 21 (4.76%) | 2 / 344 (0.58%) | 1 / 344 (0.29%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 3 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| Generalised oedema | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 21 (0.00%) | 1 / 344 (0.29%) | 1 / 344 (0.29%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 2 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Inflammation | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 0 / 344 (0.00%) | 2 / 344 (0.58%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Influenza like illness | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 0 / 344 (0.00%) | 1 / 344 (0.29%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Multiple organ dysfunction syndrome | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 2 / 344 (0.58%) | 1 / 344 (0.29%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 4 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 1 |
| Pain | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 1 / 344 (0.29%) | 0 / 344 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Performance status decreased | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 0 / 344 (0.00%) | 1 / 344 (0.29%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pyrexia | | | |
| subjects affected / exposed | 2 / 21 (9.52%) | 4 / 344 (1.16%) | 7 / 344 (2.03%) |
| occurrences causally related to treatment / all | 0 / 2 | 2 / 4 | 6 / 8 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Sudden death | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 1 / 344 (0.29%) | 1 / 344 (0.29%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| Swelling | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 21 (0.00%) | 1 / 344 (0.29%) | 0 / 344 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Immune system disorders | | | |
| Anaphylactic shock | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 1 / 344 (0.29%) | 0 / 344 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cytokine release syndrome | | | |
| subjects affected / exposed | 1 / 21 (4.76%) | 0 / 344 (0.00%) | 0 / 344 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Reproductive system and breast disorders | | | |
| Benign prostatic hyperplasia | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 1 / 344 (0.29%) | 1 / 344 (0.29%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gynaecomastia | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 0 / 344 (0.00%) | 1 / 344 (0.29%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Chronic obstructive pulmonary disease | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 0 / 344 (0.00%) | 2 / 344 (0.58%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Dyspnoea | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 3 / 344 (0.87%) | 5 / 344 (1.45%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 3 | 1 / 5 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| Immune-mediated pneumonitis | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 21 (0.00%) | 1 / 344 (0.29%) | 0 / 344 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Interstitial lung disease | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 1 / 344 (0.29%) | 0 / 344 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Lung infiltration | | | |
| subjects affected / exposed | 1 / 21 (4.76%) | 0 / 344 (0.00%) | 0 / 344 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pleural effusion | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 2 / 344 (0.58%) | 1 / 344 (0.29%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 3 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| Pneumonitis | | | |
| subjects affected / exposed | 1 / 21 (4.76%) | 4 / 344 (1.16%) | 5 / 344 (1.45%) |
| occurrences causally related to treatment / all | 1 / 1 | 4 / 4 | 6 / 6 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumothorax spontaneous | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 0 / 344 (0.00%) | 1 / 344 (0.29%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pulmonary embolism | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 1 / 344 (0.29%) | 2 / 344 (0.58%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| Pulmonary oedema | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 1 / 344 (0.29%) | 0 / 344 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| Pulmonary sarcoidosis | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 21 (0.00%) | 0 / 344 (0.00%) | 1 / 344 (0.29%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory failure | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 2 / 344 (0.58%) | 3 / 344 (0.87%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 2 | 1 / 3 |
| deaths causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 1 |
| Sleep apnoea syndrome | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 1 / 344 (0.29%) | 0 / 344 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Psychiatric disorders | | | |
| Completed suicide | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 1 / 344 (0.29%) | 1 / 344 (0.29%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| Confusional state | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 1 / 344 (0.29%) | 0 / 344 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Delirium | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 0 / 344 (0.00%) | 1 / 344 (0.29%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 2 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| Mental status changes | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 0 / 344 (0.00%) | 1 / 344 (0.29%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Obsessive-compulsive disorder | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 1 / 344 (0.29%) | 0 / 344 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Somatic symptom disorder | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 21 (0.00%) | 0 / 344 (0.00%) | 1 / 344 (0.29%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Investigations | | | |
| Alanine aminotransferase increased | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 0 / 344 (0.00%) | 1 / 344 (0.29%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Aspartate aminotransferase increased | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 0 / 344 (0.00%) | 1 / 344 (0.29%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| General physical condition abnormal | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 1 / 344 (0.29%) | 0 / 344 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Injury, poisoning and procedural complications | | | |
| Bone contusion | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 1 / 344 (0.29%) | 0 / 344 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Contusion | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 1 / 344 (0.29%) | 0 / 344 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Fall | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 0 / 344 (0.00%) | 2 / 344 (0.58%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Femur fracture | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 0 / 344 (0.00%) | 3 / 344 (0.87%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 3 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|---|---|---|
| Hip fracture | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 1 / 344 (0.29%) | 0 / 344 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Humerus fracture | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 1 / 344 (0.29%) | 1 / 344 (0.29%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infusion related reaction | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 0 / 344 (0.00%) | 1 / 344 (0.29%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Lumbar vertebral fracture | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 1 / 344 (0.29%) | 1 / 344 (0.29%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Multiple fractures | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 1 / 344 (0.29%) | 0 / 344 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Overdose | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 1 / 344 (0.29%) | 0 / 344 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pseudomeningocele | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 0 / 344 (0.00%) | 1 / 344 (0.29%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Radius fracture | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 1 / 344 (0.29%) | 0 / 344 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Skin laceration | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 21 (0.00%) | 1 / 344 (0.29%) | 0 / 344 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Spinal compression fracture | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 1 / 344 (0.29%) | 2 / 344 (0.58%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Synovial rupture | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 1 / 344 (0.29%) | 0 / 344 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Toxicity to various agents | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 0 / 344 (0.00%) | 1 / 344 (0.29%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| Traumatic arthritis | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 1 / 344 (0.29%) | 0 / 344 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Upper limb fracture | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 1 / 344 (0.29%) | 1 / 344 (0.29%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| **Cardiac disorders** | | | |
| Acute myocardial infarction | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 2 / 344 (0.58%) | 1 / 344 (0.29%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 3 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Acute coronary syndrome | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 1 / 344 (0.29%) | 0 / 344 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Angina pectoris | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 21 (0.00%) | 0 / 344 (0.00%) | 1 / 344 (0.29%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Atrial flutter | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 1 / 344 (0.29%) | 1 / 344 (0.29%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Atrial fibrillation | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 2 / 344 (0.58%) | 1 / 344 (0.29%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 3 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Atrioventricular block second degree | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 0 / 344 (0.00%) | 1 / 344 (0.29%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiac arrest | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 0 / 344 (0.00%) | 1 / 344 (0.29%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| Cardiac failure | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 2 / 344 (0.58%) | 1 / 344 (0.29%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| Cardiac failure acute | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 0 / 344 (0.00%) | 1 / 344 (0.29%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiac failure congestive | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 0 / 344 (0.00%) | 1 / 344 (0.29%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiogenic shock | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 21 (0.00%) | 1 / 344 (0.29%) | 0 / 344 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| Left ventricular failure | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 1 / 344 (0.29%) | 0 / 344 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Mitral valve prolapse | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 0 / 344 (0.00%) | 1 / 344 (0.29%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Myocardial infarction | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 3 / 344 (0.87%) | 4 / 344 (1.16%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 3 | 0 / 4 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| Myocarditis | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 1 / 344 (0.29%) | 0 / 344 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Supraventricular tachycardia | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 0 / 344 (0.00%) | 1 / 344 (0.29%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Nervous system disorders | | | |
| Altered state of consciousness | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 1 / 344 (0.29%) | 0 / 344 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Basal ganglia infarction | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 1 / 344 (0.29%) | 0 / 344 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Carotid artery stenosis | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 21 (0.00%) | 0 / 344 (0.00%) | 1 / 344 (0.29%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Central nervous system necrosis | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 0 / 344 (0.00%) | 1 / 344 (0.29%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cerebral haemorrhage | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 1 / 344 (0.29%) | 0 / 344 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| Dementia | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 1 / 344 (0.29%) | 0 / 344 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Dizziness | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 0 / 344 (0.00%) | 2 / 344 (0.58%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Embolic stroke | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 0 / 344 (0.00%) | 1 / 344 (0.29%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Epilepsy | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 1 / 344 (0.29%) | 1 / 344 (0.29%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Facial paralysis | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 1 / 344 (0.29%) | 0 / 344 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Headache | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 21 (0.00%) | 1 / 344 (0.29%) | 1 / 344 (0.29%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hemiparesis | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 1 / 344 (0.29%) | 0 / 344 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hydrocephalus | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 0 / 344 (0.00%) | 1 / 344 (0.29%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Ischaemic cerebral infarction | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 0 / 344 (0.00%) | 1 / 344 (0.29%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| Ischaemic stroke | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 1 / 344 (0.29%) | 0 / 344 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Migraine | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 1 / 344 (0.29%) | 0 / 344 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Nervous system disorder | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 0 / 344 (0.00%) | 1 / 344 (0.29%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Neurological symptom | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 1 / 344 (0.29%) | 0 / 344 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Paraesthesia | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 21 (0.00%) | 1 / 344 (0.29%) | 0 / 344 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Paraparesis | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 1 / 344 (0.29%) | 0 / 344 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Paraplegia | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 1 / 344 (0.29%) | 0 / 344 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Seizure | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 0 / 344 (0.00%) | 1 / 344 (0.29%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Speech disorder | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 1 / 344 (0.29%) | 0 / 344 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Spinal cord compression | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 1 / 344 (0.29%) | 0 / 344 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Syncope | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 2 / 344 (0.58%) | 1 / 344 (0.29%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Transient ischaemic attack | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 0 / 344 (0.00%) | 1 / 344 (0.29%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| **Blood and lymphatic system disorders** | | | |
| Anaemia | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 21 (0.00%) | 8 / 344 (2.33%) | 9 / 344 (2.62%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 17 | 1 / 9 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Anaemia of malignant disease | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 0 / 344 (0.00%) | 1 / 344 (0.29%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Febrile neutropenia | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 1 / 344 (0.29%) | 0 / 344 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Lymph node pain | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 1 / 344 (0.29%) | 0 / 344 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Granulomatous lymphadenitis | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 1 / 344 (0.29%) | 0 / 344 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Lymphadenopathy | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 0 / 344 (0.00%) | 2 / 344 (0.58%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Thrombocytopenia | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 2 / 344 (0.58%) | 0 / 344 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Ear and labyrinth disorders | | | |
| Vertigo | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 0 / 344 (0.00%) | 2 / 344 (0.58%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Eye disorders | | | |

| | | | |
|---|---|---|---|
| Papilloedema | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 0 / 344 (0.00%) | 1 / 344 (0.29%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Retinal oedema | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 0 / 344 (0.00%) | 1 / 344 (0.29%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Uveitis | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 1 / 344 (0.29%) | 0 / 344 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrointestinal disorders | | | |
| Abdominal pain | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 1 / 344 (0.29%) | 2 / 344 (0.58%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Abdominal pain upper | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 1 / 344 (0.29%) | 1 / 344 (0.29%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Ascites | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 2 / 344 (0.58%) | 1 / 344 (0.29%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Autoimmune colitis | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 1 / 344 (0.29%) | 0 / 344 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Colitis | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 0 / 344 (0.00%) | 5 / 344 (1.45%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 5 / 5 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Constipation | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 21 (0.00%) | 0 / 344 (0.00%) | 2 / 344 (0.58%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Diarrhoea | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 0 / 344 (0.00%) | 4 / 344 (1.16%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 4 / 4 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastritis | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 1 / 344 (0.29%) | 1 / 344 (0.29%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrointestinal haemorrhage | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 1 / 344 (0.29%) | 1 / 344 (0.29%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Haematochezia | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 1 / 344 (0.29%) | 1 / 344 (0.29%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Haemoperitoneum | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 0 / 344 (0.00%) | 1 / 344 (0.29%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Ileus | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 1 / 344 (0.29%) | 0 / 344 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Large intestine polyp | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 0 / 344 (0.00%) | 1 / 344 (0.29%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Mechanical ileus | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 21 (0.00%) | 1 / 344 (0.29%) | 0 / 344 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Nausea | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 0 / 344 (0.00%) | 2 / 344 (0.58%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Oesophageal motility disorder | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 0 / 344 (0.00%) | 1 / 344 (0.29%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pancreatitis | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 0 / 344 (0.00%) | 1 / 344 (0.29%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Rectal haemorrhage | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 0 / 344 (0.00%) | 1 / 344 (0.29%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vomiting | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 1 / 344 (0.29%) | 1 / 344 (0.29%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hepatobiliary disorders | | | |
| Autoimmune hepatitis | | | |
| subjects affected / exposed | 1 / 21 (4.76%) | 1 / 344 (0.29%) | 1 / 344 (0.29%) |
| occurrences causally related to treatment / all | 1 / 1 | 1 / 1 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cholecystitis | | | |
| subjects affected / exposed | 1 / 21 (4.76%) | 1 / 344 (0.29%) | 1 / 344 (0.29%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| Cholecystitis acute | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 21 (0.00%) | 1 / 344 (0.29%) | 0 / 344 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cholelithiasis | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 1 / 344 (0.29%) | 0 / 344 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hepatic failure | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 0 / 344 (0.00%) | 1 / 344 (0.29%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| Hepatitis | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 0 / 344 (0.00%) | 1 / 344 (0.29%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Jaundice | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 0 / 344 (0.00%) | 1 / 344 (0.29%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Skin and subcutaneous tissue disorders | | | |
| Dermatitis | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 0 / 344 (0.00%) | 2 / 344 (0.58%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 2 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Dermatitis bullous | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 1 / 344 (0.29%) | 0 / 344 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Drug eruption | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 1 / 344 (0.29%) | 0 / 344 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Eczema | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 21 (0.00%) | 1 / 344 (0.29%) | 0 / 344 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Rash | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 1 / 344 (0.29%) | 0 / 344 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Skin hypopigmentation | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 0 / 344 (0.00%) | 1 / 344 (0.29%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Skin lesion | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 1 / 344 (0.29%) | 0 / 344 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Skin ulcer | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 0 / 344 (0.00%) | 1 / 344 (0.29%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Stevens-Johnson syndrome | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 1 / 344 (0.29%) | 0 / 344 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Renal and urinary disorders | | | |
| Acute kidney injury | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 1 / 344 (0.29%) | 2 / 344 (0.58%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Haematuria | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 0 / 344 (0.00%) | 1 / 344 (0.29%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Nephrotic syndrome | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 21 (0.00%) | 1 / 344 (0.29%) | 0 / 344 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Renal colic | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 1 / 344 (0.29%) | 0 / 344 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Renal failure | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 1 / 344 (0.29%) | 0 / 344 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Renal impairment | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 1 / 344 (0.29%) | 0 / 344 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Ureteric obstruction | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 0 / 344 (0.00%) | 1 / 344 (0.29%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Urinary retention | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 0 / 344 (0.00%) | 1 / 344 (0.29%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Endocrine disorders | | | |
| Addison's disease | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 1 / 344 (0.29%) | 0 / 344 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Adrenal insufficiency | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 1 / 344 (0.29%) | 0 / 344 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Adrenocortical insufficiency acute | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 21 (0.00%) | 1 / 344 (0.29%) | 0 / 344 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Endocrine disorder | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 1 / 344 (0.29%) | 0 / 344 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hyperthyroidism | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 1 / 344 (0.29%) | 0 / 344 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypophysitis | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 2 / 344 (0.58%) | 0 / 344 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 2 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypopituitarism | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 0 / 344 (0.00%) | 1 / 344 (0.29%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Lymphocytic hypophysitis | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 1 / 344 (0.29%) | 2 / 344 (0.58%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 3 / 3 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Thyroid mass | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 0 / 344 (0.00%) | 1 / 344 (0.29%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Thyroiditis | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 1 / 344 (0.29%) | 0 / 344 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Musculoskeletal and connective tissue disorders | | | |
| Arthralgia | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 21 (0.00%) | 0 / 344 (0.00%) | 1 / 344 (0.29%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Arthritis | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 0 / 344 (0.00%) | 1 / 344 (0.29%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Arthropathy | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 1 / 344 (0.29%) | 0 / 344 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Back pain | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 0 / 344 (0.00%) | 2 / 344 (0.58%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Intervertebral disc degeneration | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 1 / 344 (0.29%) | 0 / 344 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Intervertebral disc protrusion | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 0 / 344 (0.00%) | 2 / 344 (0.58%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Joint effusion | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 0 / 344 (0.00%) | 1 / 344 (0.29%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Lumbar spinal stenosis | | | |
| subjects affected / exposed | 1 / 21 (4.76%) | 0 / 344 (0.00%) | 0 / 344 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Myositis | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 21 (0.00%) | 3 / 344 (0.87%) | 0 / 344 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 3 / 3 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Osteoarthritis | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 1 / 344 (0.29%) | 0 / 344 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pain in extremity | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 0 / 344 (0.00%) | 1 / 344 (0.29%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pathological fracture | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 0 / 344 (0.00%) | 2 / 344 (0.58%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Polyarthritis | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 0 / 344 (0.00%) | 1 / 344 (0.29%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Psoriatic arthropathy | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 0 / 344 (0.00%) | 1 / 344 (0.29%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Spinal pain | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 1 / 344 (0.29%) | 0 / 344 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infections and infestations | | | |
| Abscess | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 1 / 344 (0.29%) | 0 / 344 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Anal abscess | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 21 (0.00%) | 1 / 344 (0.29%) | 0 / 344 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Appendicitis | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 1 / 344 (0.29%) | 0 / 344 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Atypical pneumonia | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 0 / 344 (0.00%) | 1 / 344 (0.29%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| Bronchitis | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 2 / 344 (0.58%) | 1 / 344 (0.29%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Bronchopulmonary aspergillosis | | | |
| subjects affected / exposed | 1 / 21 (4.76%) | 0 / 344 (0.00%) | 0 / 344 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cellulitis | | | |
| subjects affected / exposed | 1 / 21 (4.76%) | 4 / 344 (1.16%) | 4 / 344 (1.16%) |
| occurrences causally related to treatment / all | 0 / 1 | 2 / 4 | 1 / 7 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Chorioretinitis | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 0 / 344 (0.00%) | 1 / 344 (0.29%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Dermo-hypodermitis | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 0 / 344 (0.00%) | 1 / 344 (0.29%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Diverticulitis | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 21 (0.00%) | 1 / 344 (0.29%) | 0 / 344 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Encephalitis | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 0 / 344 (0.00%) | 1 / 344 (0.29%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Erysipelas | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 2 / 344 (0.58%) | 2 / 344 (0.58%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 2 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Escherichia sepsis | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 0 / 344 (0.00%) | 1 / 344 (0.29%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Extradural abscess | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 0 / 344 (0.00%) | 1 / 344 (0.29%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastroenteritis | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 0 / 344 (0.00%) | 1 / 344 (0.29%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Herpes zoster | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 1 / 344 (0.29%) | 0 / 344 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infected cyst | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 1 / 344 (0.29%) | 0 / 344 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infection | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 21 (0.00%) | 0 / 344 (0.00%) | 1 / 344 (0.29%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Influenza | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 0 / 344 (0.00%) | 1 / 344 (0.29%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Localised infection | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 1 / 344 (0.29%) | 0 / 344 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Lower respiratory tract infection | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 0 / 344 (0.00%) | 1 / 344 (0.29%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Lymph gland infection | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 0 / 344 (0.00%) | 1 / 344 (0.29%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Meningitis aseptic | | | |
| subjects affected / exposed | 1 / 21 (4.76%) | 0 / 344 (0.00%) | 0 / 344 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Nasopharyngitis | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 1 / 344 (0.29%) | 0 / 344 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Periorbital cellulitis | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 0 / 344 (0.00%) | 1 / 344 (0.29%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumonia | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 21 (0.00%) | 4 / 344 (1.16%) | 3 / 344 (0.87%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 4 | 2 / 4 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pulmonary sepsis | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 0 / 344 (0.00%) | 1 / 344 (0.29%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 2 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| Postoperative wound infection | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 0 / 344 (0.00%) | 1 / 344 (0.29%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pyelonephritis chronic | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 0 / 344 (0.00%) | 1 / 344 (0.29%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory tract infection | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 1 / 344 (0.29%) | 0 / 344 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Scrotal abscess | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 0 / 344 (0.00%) | 1 / 344 (0.29%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Sinusitis | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 1 / 344 (0.29%) | 1 / 344 (0.29%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Sepsis | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 1 / 344 (0.29%) | 1 / 344 (0.29%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Tooth abscess | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 21 (0.00%) | 0 / 344 (0.00%) | 1 / 344 (0.29%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Tracheobronchitis | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 0 / 344 (0.00%) | 1 / 344 (0.29%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 0 / 344 (0.00%) | 1 / 344 (0.29%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Ureteritis | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 1 / 344 (0.29%) | 0 / 344 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Urinary tract infection | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 3 / 344 (0.87%) | 5 / 344 (1.45%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 3 | 0 / 6 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Urinary tract infection bacterial | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 0 / 344 (0.00%) | 1 / 344 (0.29%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Urosepsis | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 1 / 344 (0.29%) | 1 / 344 (0.29%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| Wound infection | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 0 / 344 (0.00%) | 2 / 344 (0.58%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Metabolism and nutrition disorders | | | |
| Decreased appetite | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 21 (0.00%) | 1 / 344 (0.29%) | 0 / 344 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Dehydration | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 0 / 344 (0.00%) | 1 / 344 (0.29%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Diabetes mellitus | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 0 / 344 (0.00%) | 3 / 344 (0.87%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 3 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Diabetic ketoacidosis | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 0 / 344 (0.00%) | 2 / 344 (0.58%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 2 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypercalcaemia | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 1 / 344 (0.29%) | 0 / 344 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hyperglycaemia | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 2 / 344 (0.58%) | 1 / 344 (0.29%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 2 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hyperkalaemia | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 1 / 344 (0.29%) | 0 / 344 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hyponatraemia | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 3 / 344 (0.87%) | 2 / 344 (0.58%) |
| occurrences causally related to treatment / all | 0 / 0 | 2 / 3 | 1 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Tumour lysis syndrome | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 21 (0.00%) | 1 / 344 (0.29%) | 0 / 344 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Type 1 diabetes mellitus | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 0 / 344 (0.00%) | 1 / 344 (0.29%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Type 2 diabetes mellitus | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 1 / 344 (0.29%) | 0 / 344 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

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

| **Non-serious adverse events** | Phase 1b: Talimogene Laherparepvec + Pembrolizumab | Phase 3: Placebo + Pembrolizumab | Phase 3: Talimogene Laherparepvec + Pembrolizumab |
|---|---|---|---|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 21 / 21 (100.00%) | 305 / 344 (88.66%) | 317 / 344 (92.15%) |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Squamous cell carcinoma | | | |
| subjects affected / exposed | 3 / 21 (14.29%) | 1 / 344 (0.29%) | 1 / 344 (0.29%) |
| occurrences (all) | 3 | 2 | 1 |
| Vascular disorders | | | |
| Hypertension | | | |
| subjects affected / exposed | 1 / 21 (4.76%) | 22 / 344 (6.40%) | 19 / 344 (5.52%) |
| occurrences (all) | 1 | 36 | 36 |
| General disorders and administration site conditions | | | |
| Asthenia | | | |
| subjects affected / exposed | 2 / 21 (9.52%) | 29 / 344 (8.43%) | 27 / 344 (7.85%) |
| occurrences (all) | 2 | 38 | 33 |
| Chills | | | |
| subjects affected / exposed | 8 / 21 (38.10%) | 17 / 344 (4.94%) | 73 / 344 (21.22%) |
| occurrences (all) | 14 | 19 | 153 |
| Face oedema | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 2 / 21 (9.52%) | 0 / 344 (0.00%) | 3 / 344 (0.87%) |
| occurrences (all) | 3 | 0 | 3 |
| Fatigue | | | |
| subjects affected / exposed | 15 / 21 (71.43%) | 94 / 344 (27.33%) | 137 / 344 (39.83%) |
| occurrences (all) | 25 | 128 | 214 |
| Influenza like illness | | | |
| subjects affected / exposed | 5 / 21 (23.81%) | 26 / 344 (7.56%) | 64 / 344 (18.60%) |
| occurrences (all) | 10 | 35 | 143 |
| Injection site pain | | | |
| subjects affected / exposed | 2 / 21 (9.52%) | 14 / 344 (4.07%) | 15 / 344 (4.36%) |
| occurrences (all) | 2 | 24 | 20 |
| Injection site reaction | | | |
| subjects affected / exposed | 2 / 21 (9.52%) | 3 / 344 (0.87%) | 10 / 344 (2.91%) |
| occurrences (all) | 4 | 3 | 14 |
| Oedema peripheral | | | |
| subjects affected / exposed | 5 / 21 (23.81%) | 22 / 344 (6.40%) | 27 / 344 (7.85%) |
| occurrences (all) | 8 | 23 | 35 |
| Pain | | | |
| subjects affected / exposed | 1 / 21 (4.76%) | 18 / 344 (5.23%) | 24 / 344 (6.98%) |
| occurrences (all) | 2 | 23 | 33 |
| Pyrexia | | | |
| subjects affected / exposed | 10 / 21 (47.62%) | 33 / 344 (9.59%) | 128 / 344 (37.21%) |
| occurrences (all) | 29 | 46 | 352 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Cough | | | |
| subjects affected / exposed | 8 / 21 (38.10%) | 44 / 344 (12.79%) | 58 / 344 (16.86%) |
| occurrences (all) | 8 | 49 | 72 |
| Dyspnoea | | | |
| subjects affected / exposed | 4 / 21 (19.05%) | 24 / 344 (6.98%) | 23 / 344 (6.69%) |
| occurrences (all) | 4 | 26 | 37 |
| Pneumonitis | | | |
| subjects affected / exposed | 2 / 21 (9.52%) | 7 / 344 (2.03%) | 18 / 344 (5.23%) |
| occurrences (all) | 2 | 11 | 28 |
| Psychiatric disorders | | | |

| | | | |
|---|---|---|---|
| Anxiety | | | |
| subjects affected / exposed | 2 / 21 (9.52%) | 7 / 344 (2.03%) | 11 / 344 (3.20%) |
| occurrences (all) | 2 | 7 | 13 |
| Insomnia | | | |
| subjects affected / exposed | 3 / 21 (14.29%) | 27 / 344 (7.85%) | 23 / 344 (6.69%) |
| occurrences (all) | 5 | 29 | 27 |
| Investigations | | | |
| Alanine aminotransferase increased | | | |
| subjects affected / exposed | 3 / 21 (14.29%) | 23 / 344 (6.69%) | 26 / 344 (7.56%) |
| occurrences (all) | 6 | 34 | 35 |
| Aspartate aminotransferase increased | | | |
| subjects affected / exposed | 3 / 21 (14.29%) | 16 / 344 (4.65%) | 20 / 344 (5.81%) |
| occurrences (all) | 3 | 25 | 29 |
| Blood alkaline phosphatase increased | | | |
| subjects affected / exposed | 2 / 21 (9.52%) | 7 / 344 (2.03%) | 15 / 344 (4.36%) |
| occurrences (all) | 3 | 9 | 19 |
| Blood iron decreased | | | |
| subjects affected / exposed | 2 / 21 (9.52%) | 1 / 344 (0.29%) | 0 / 344 (0.00%) |
| occurrences (all) | 2 | 1 | 0 |
| Injury, poisoning and procedural complications | | | |
| Contusion | | | |
| subjects affected / exposed | 2 / 21 (9.52%) | 3 / 344 (0.87%) | 4 / 344 (1.16%) |
| occurrences (all) | 2 | 4 | 4 |
| Infusion related reaction | | | |
| subjects affected / exposed | 2 / 21 (9.52%) | 0 / 344 (0.00%) | 4 / 344 (1.16%) |
| occurrences (all) | 2 | 0 | 7 |
| Procedural pain | | | |
| subjects affected / exposed | 2 / 21 (9.52%) | 5 / 344 (1.45%) | 9 / 344 (2.62%) |
| occurrences (all) | 2 | 5 | 9 |
| Nervous system disorders | | | |
| Headache | | | |
| subjects affected / exposed | 9 / 21 (42.86%) | 44 / 344 (12.79%) | 62 / 344 (18.02%) |
| occurrences (all) | 13 | 59 | 144 |
| Neuropathy peripheral | | | |
| subjects affected / exposed | 2 / 21 (9.52%) | 0 / 344 (0.00%) | 4 / 344 (1.16%) |
| occurrences (all) | 2 | 0 | 5 |

| | | | |
|---|---|---|---|
| Paraesthesia | | | |
| subjects affected / exposed | 2 / 21 (9.52%) | 6 / 344 (1.74%) | 13 / 344 (3.78%) |
| occurrences (all) | 3 | 7 | 13 |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 2 / 21 (9.52%) | 26 / 344 (7.56%) | 33 / 344 (9.59%) |
| occurrences (all) | 6 | 45 | 46 |
| Leukopenia | | | |
| subjects affected / exposed | 2 / 21 (9.52%) | 2 / 344 (0.58%) | 0 / 344 (0.00%) |
| occurrences (all) | 2 | 4 | 0 |
| Eye disorders | | | |
| Visual impairment | | | |
| subjects affected / exposed | 2 / 21 (9.52%) | 2 / 344 (0.58%) | 6 / 344 (1.74%) |
| occurrences (all) | 2 | 2 | 7 |
| Gastrointestinal disorders | | | |
| Abdominal pain | | | |
| subjects affected / exposed | 2 / 21 (9.52%) | 24 / 344 (6.98%) | 23 / 344 (6.69%) |
| occurrences (all) | 2 | 26 | 29 |
| Abdominal pain upper | | | |
| subjects affected / exposed | 2 / 21 (9.52%) | 12 / 344 (3.49%) | 7 / 344 (2.03%) |
| occurrences (all) | 2 | 14 | 8 |
| Constipation | | | |
| subjects affected / exposed | 4 / 21 (19.05%) | 28 / 344 (8.14%) | 52 / 344 (15.12%) |
| occurrences (all) | 5 | 36 | 63 |
| Diarrhoea | | | |
| subjects affected / exposed | 13 / 21 (61.90%) | 73 / 344 (21.22%) | 70 / 344 (20.35%) |
| occurrences (all) | 17 | 124 | 118 |
| Dry mouth | | | |
| subjects affected / exposed | 1 / 21 (4.76%) | 19 / 344 (5.52%) | 14 / 344 (4.07%) |
| occurrences (all) | 1 | 21 | 16 |
| Frequent bowel movements | | | |
| subjects affected / exposed | 2 / 21 (9.52%) | 1 / 344 (0.29%) | 0 / 344 (0.00%) |
| occurrences (all) | 2 | 1 | 0 |
| Nausea | | | |
| subjects affected / exposed | 7 / 21 (33.33%) | 61 / 344 (17.73%) | 92 / 344 (26.74%) |
| occurrences (all) | 10 | 78 | 123 |
| Vomiting | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 7 / 21 (33.33%) | 29 / 344 (8.43%) | 56 / 344 (16.28%) |
| occurrences (all) | 8 | 35 | 86 |
| Skin and subcutaneous tissue disorders | | | |
| Actinic keratosis | | | |
| subjects affected / exposed | 2 / 21 (9.52%) | 4 / 344 (1.16%) | 6 / 344 (1.74%) |
| occurrences (all) | 4 | 6 | 6 |
| Alopecia | | | |
| subjects affected / exposed | 3 / 21 (14.29%) | 3 / 344 (0.87%) | 10 / 344 (2.91%) |
| occurrences (all) | 3 | 3 | 11 |
| Erythema | | | |
| subjects affected / exposed | 2 / 21 (9.52%) | 15 / 344 (4.36%) | 15 / 344 (4.36%) |
| occurrences (all) | 2 | 15 | 19 |
| Pruritus | | | |
| subjects affected / exposed | 7 / 21 (33.33%) | 55 / 344 (15.99%) | 61 / 344 (17.73%) |
| occurrences (all) | 9 | 67 | 74 |
| Rash | | | |
| subjects affected / exposed | 9 / 21 (42.86%) | 42 / 344 (12.21%) | 61 / 344 (17.73%) |
| occurrences (all) | 16 | 56 | 99 |
| Rash erythematous | | | |
| subjects affected / exposed | 2 / 21 (9.52%) | 1 / 344 (0.29%) | 4 / 344 (1.16%) |
| occurrences (all) | 12 | 1 | 4 |
| Rash macular | | | |
| subjects affected / exposed | 2 / 21 (9.52%) | 1 / 344 (0.29%) | 6 / 344 (1.74%) |
| occurrences (all) | 7 | 1 | 7 |
| Rash maculo-papular | | | |
| subjects affected / exposed | 3 / 21 (14.29%) | 17 / 344 (4.94%) | 20 / 344 (5.81%) |
| occurrences (all) | 3 | 23 | 29 |
| Skin lesion | | | |
| subjects affected / exposed | 2 / 21 (9.52%) | 2 / 344 (0.58%) | 11 / 344 (3.20%) |
| occurrences (all) | 2 | 2 | 13 |
| Skin mass | | | |
| subjects affected / exposed | 2 / 21 (9.52%) | 2 / 344 (0.58%) | 0 / 344 (0.00%) |
| occurrences (all) | 4 | 2 | 0 |
| Urticaria | | | |
| subjects affected / exposed | 2 / 21 (9.52%) | 2 / 344 (0.58%) | 3 / 344 (0.87%) |
| occurrences (all) | 2 | 3 | 3 |

| | | | |
|---|---|---|---|
| Vitiligo | | | |
| subjects affected / exposed | 5 / 21 (23.81%) | 32 / 344 (9.30%) | 44 / 344 (12.79%) |
| occurrences (all) | 5 | 32 | 47 |
| Endocrine disorders | | | |
| Hyperthyroidism | | | |
| subjects affected / exposed | 3 / 21 (14.29%) | 20 / 344 (5.81%) | 22 / 344 (6.40%) |
| occurrences (all) | 3 | 20 | 22 |
| Hypothyroidism | | | |
| subjects affected / exposed | 6 / 21 (28.57%) | 49 / 344 (14.24%) | 48 / 344 (13.95%) |
| occurrences (all) | 10 | 61 | 60 |
| Musculoskeletal and connective tissue disorders | | | |
| Arthralgia | | | |
| subjects affected / exposed | 8 / 21 (38.10%) | 66 / 344 (19.19%) | 82 / 344 (23.84%) |
| occurrences (all) | 16 | 93 | 140 |
| Back pain | | | |
| subjects affected / exposed | 3 / 21 (14.29%) | 30 / 344 (8.72%) | 35 / 344 (10.17%) |
| occurrences (all) | 6 | 39 | 40 |
| Muscle spasms | | | |
| subjects affected / exposed | 2 / 21 (9.52%) | 5 / 344 (1.45%) | 9 / 344 (2.62%) |
| occurrences (all) | 2 | 6 | 10 |
| Myalgia | | | |
| subjects affected / exposed | 2 / 21 (9.52%) | 16 / 344 (4.65%) | 33 / 344 (9.59%) |
| occurrences (all) | 2 | 22 | 46 |
| Pain in extremity | | | |
| subjects affected / exposed | 4 / 21 (19.05%) | 21 / 344 (6.10%) | 29 / 344 (8.43%) |
| occurrences (all) | 5 | 26 | 37 |
| Infections and infestations | | | |
| Cellulitis | | | |
| subjects affected / exposed | 2 / 21 (9.52%) | 9 / 344 (2.62%) | 14 / 344 (4.07%) |
| occurrences (all) | 2 | 12 | 19 |
| Influenza | | | |
| subjects affected / exposed | 2 / 21 (9.52%) | 7 / 344 (2.03%) | 9 / 344 (2.62%) |
| occurrences (all) | 2 | 9 | 9 |
| Oral herpes | | | |
| subjects affected / exposed | 2 / 21 (9.52%) | 16 / 344 (4.65%) | 15 / 344 (4.36%) |
| occurrences (all) | 2 | 16 | 20 |

| | | | |
|---|---|---|---|
| Nasopharyngitis | | | |
| subjects affected / exposed | 1 / 21 (4.76%) | 23 / 344 (6.69%) | 21 / 344 (6.10%) |
| occurrences (all) | 1 | 27 | 26 |
| Rhinitis | | | |
| subjects affected / exposed | 2 / 21 (9.52%) | 11 / 344 (3.20%) | 7 / 344 (2.03%) |
| occurrences (all) | 2 | 12 | 8 |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 2 / 21 (9.52%) | 17 / 344 (4.94%) | 17 / 344 (4.94%) |
| occurrences (all) | 3 | 20 | 20 |
| Urinary tract infection | | | |
| subjects affected / exposed | 1 / 21 (4.76%) | 17 / 344 (4.94%) | 22 / 344 (6.40%) |
| occurrences (all) | 1 | 22 | 30 |
| Metabolism and nutrition disorders | | | |
| Decreased appetite | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 26 / 344 (7.56%) | 43 / 344 (12.50%) |
| occurrences (all) | 0 | 29 | 53 |
| Hyperglycaemia | | | |
| subjects affected / exposed | 3 / 21 (14.29%) | 11 / 344 (3.20%) | 19 / 344 (5.52%) |
| occurrences (all) | 11 | 16 | 60 |
| Hyperkalaemia | | | |
| subjects affected / exposed | 2 / 21 (9.52%) | 5 / 344 (1.45%) | 2 / 344 (0.58%) |
| occurrences (all) | 2 | 6 | 2 |
| Hypophosphataemia | | | |
| subjects affected / exposed | 2 / 21 (9.52%) | 3 / 344 (0.87%) | 14 / 344 (4.07%) |
| occurrences (all) | 3 | 9 | 18 |

## More information

## Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|---|---|
| 15 May 2015 | •Changed the Phase 2 part to Phase 3 •Included 2 Phase 3 primary endpoints, PFS and OS. The primary analysis of PFS will be based on tumor evaluation by a blinded independent central review (BICR) using RECIST 1.1 with modifications: 1) increased total target lesions to maximum of 10 (max 5 per organ), 2) new skin lesions will be considered in the overall non-target lesion assessment but will not automatically result in a response of PD. •Removed cross-over combination treatment. •Increased sample size of Phase 3 to 660 subjects for formal testing of PFS and OS. •Revised Phase 3 treatment schedule. •Updated Phase 3 prior therapy inclusion criteria. •Use irRC-RECIST for Phase 3 treatment decisions and secondary endpoints. •Added an event-driven analysis of the secondary PFS endpoint based on irRC-RECIST. •Updated Phase 3 measurable disease and tumor sample inclusion criteria. •Skin photographs and radiographs in Phase 3 will be submitted to BICR for evaluation of PFS and secondary response-related endpoints. •Removed option for retreatment. •Added Phase 1b re-analysis time points. •Added 2 interim safety, 1 interim ORR futility, 1 interim efficacy, and 1 interim analysis for OS in Phase 3. •Utilized an independent, external DMC in phase 3 to monitor safety and evaluate futility. •Updated the pembrolizumab-related pneumonitis toxicity management guidelines. •Updated tumor sample collection schedule in Phase 3. •Revised the schedule of safety laboratory assessments. •Secondary objectives of anti-pembrolizumab antibodies, pembrolizumab PK and changes in PD-L1 changed to exploratory objectives. •Ordinal categorical response score and deep response rate endpoints removed. •Moved evaluation of PRO in phase 3 from exploratory to secondary objective. •Clarified the responsibilities of the DLRT in Phase 1b. •Increased follow-up to 60 months after last subject enrolled. •Changed reporting period for pembrolizumab Events of Clinical Interest and the reporting period for SAEs. |

| | |
|---|---|
| 25 September 2015 | •Changed Phase 3 part to be double-blind and added placebo to the pembrolizumab arm.<br>•Reordered sections to separate Phase 1b and Phase 3 throughout.<br>•Updated background information for T-VEC and pembrolizumab to reflect recent data.<br>•Added results of the completed dose level review team (DLRT) evaluation for Phase 1b.<br>•Allowed for more flexibility in frequency of radiographic follow-up for subjects who have reached a confirmed clinical response (CR) in long term follow-up.<br>•Updated contraception language for exclusion criterion and sections related to pembrolizumab.<br>•Shortened period from ending prior adjuvant therapy to 28 days prior to enrollment.<br>•Prior ipilimumab as adjuvant therapy is now allowed.<br>•Added exclusion criteria for allogeneic hematopoietic stem cell transplantation and active tuberculosis.<br>•Updated text related to pembrolizumab events of clinical interest, rescue medications, dose adjustment, overdose, and supportive care guidelines. Immune-related AEs are no longer considered pembrolizumab events of interest.<br>•Combined the schedule of assessments tables for Phase 3 arms 1 and 2.<br>•Injectable investigational product-related AEs during long-term follow-up will be collected.<br>•Updated pregnancy and lactation reporting language.<br>•Updated text for interim analysis and interim ORR futility analysis in Phase 3. If futility is declared on ORR, DCR will also need to have futility declared. This is to prevent the study treatment being declared futile when the ORR may not be adequately improved but the DCR is at the time of the interim analysis.<br>•Updated text pertaining to the analysis for the secondary endpoint of PFS per irRC-RECIST (phase 3) and included text regarding multiplicity adjustment for clarification.<br>•Removed RECIST 1.1 modification that new skin lesions will be considered in the overall non-target lesion assessment but will not automatically result in esponse of PD.<br>•Updated language to clarify the modified response criteria in the appendices. |
| 12 April 2017 | •An event-driven overall survival interim analysis at 282 events (including futility analysis) added to the planned analyses in order to evaluate the efficacy/futility with approximately 70% power of the combination treatment at an earlier time point in order to facilitate regulatory submission if the combination demonstrates significant improvement in overall survival or stopping the study for futility in overall survival.<br>•The interim futility analysis based on overall response rate and disease control rate for the data monitoring committee review was changed from the investigator assessment to a blinded independent central review. Using blinded independent central review assessed responses would provide a robust and consistent assessment of overall response rate and disease control rate as for the primary endpoint of progression free survival, which also utilizes blinded independent central review. The Bayesian priors for the combination arm were also revised to reflect new data available from the phase 1b part of the study.<br>•The fallback procedure to test overall survival and progression free survival dual primaries with the Maurer-Bretz multiple testing procedure was revised.<br>•The secondary objectives were updated to test additional hypotheses per modified irRC-RECIST by blinded independent central review, and overall survival excluding stage IVM1c.<br>•The secondary and exploratory objectives related to patient reported outcomes were updated. |

| | |
|---|---|
| 24 January 2018 | •Replace the Dose Modification Guidelines for Pembrolizumab Related Adverse Events Table with the Pembrolizumab-related Adverse Event Management table to incorporate the new myocarditis risk and management and remove redundant and outdated information about management of pembrolizumab-related AEs.<br>•Update the information and table regarding management of pembrolizumab-related infusion reactions.<br>•Add thyroid testing up to 3 days before dosing and that study treatment can be administered before the results are reported if the subject is asymptomatic.<br>•Clarify the response evaluation criteria used for Phase 1b and Phase 3 endpoints and update the matrix for determining overall response at each assessment.<br>•Clarify the collection of archival biopsy.<br>•Clarify when subjects should undergo safety follow-up procedures.<br>•Allow survival status to be assessed at additional time points not specified in the Schedule of Assessments.<br>•Clarify that for subjects with PD QLQ-C30 is not collected in long-term follow-up; however, EQ-5D-3L will be collected.<br>•Clarify the timing of the beginning of the registry protocol; update the primary completion and end of trial dates.<br>•Update T-VEC and pembrolizumab background information and the rationale for combination therapy.<br>•Clarify timing of safety monitoring by the DMC.<br>•Clarify that both clinical and photographic evaluations must be done for lesions which cannot be evaluated by radiographic imaging.<br>•Clarify that prior tumor vaccines are allowable if administered in the adjuvant setting.<br>•Clarify that subjects should return to the clinic within 3 days after notification of a suspected herpetic lesion.<br>•Clarify that photographs of all visible lesions must be done at baseline to allow for follow-up of lesions during treatment.<br>•Clarify that laboratory assessment up to 3 days prior to administration of study treatment is allowed.<br>•Clarify the PRO analysis set.<br>•Clarify the futility analysis of OS for a non-constant treatment effect. |
| 15 January 2020 | • Update statistical characteristics of the group sequential OS analyses and add a third interim OS analysis planned after 315 events. To optimize the opportunity to observe statistical significance prior to the OS primary analysis (PA) if there is a late survival effect that would not be achieved at OS interim analysis (IA)1 or OS IA2, an additional look at OS IA3 (n = 315) was added prior to the OS PA. The trigger for 315 was selected to achieve approximately half the information gain between n = 282 and n = 346, and is halfway between the expected timings of OS IA2 and OS PA. The protocol is amended to include this additional analysis prior to any formal evaluation of efficacy related to PFS or OS. Appropriate alpha was allocated for all of the efficacy analyses.<br>• Update the background to include the updated OS results from the KEYNOTE-006 and CHECKMATE-067 trials.<br>•Update exploratory objectives to evaluate PROs as assessed by the EORTC QLQ-C30 and EuroQoL-5D-3L (EQ-5D-3L) subscales and add language for PRO population assessment.<br>• An exploratory endpoint assessing lesion level response was added.<br>• Clarify covariates for efficacy in subgroup or multivariate analyses.<br>• Clarify language for interim efficacy analyses including possible hypotheses tests at planned analyses and operating characteristics of the primary analysis of PFS and sequential tests of OS.<br>• Add text to clarify that in the Phase 1b part when nodal disease regresses to below 10 mm, the nodal lesion measurement should be recorded as 0 x 0 mm instead of the actual measurement.<br>• Clarify that no index lesions identified at baseline is associated with "Not applicable (NA)" instead of "Not done" in the matrix for determining overall response. Add "unevaluable (UE) or iUE (unevaluable by modified irRC-RECIST) to the matrix for determining overall response.<br>• Clarify number of days after the date of enrollment for visit response of stable disease by modified irRC-RECIST (iSD) or better. |

Notes:

## Interruptions (globally)

Were there any global interruptions to the trial?  No

## Limitations and caveats

None reported