



Clinical trial results:

A Phase 2 Study in First Line Metastatic or Unresectable, Recurrent Head and Neck Squamous Cell Carcinoma to Evaluate Intratumoral MK-1454 in Combination with IV Pembrolizumab vs IV Pembrolizumab Monotherapy

Summary

| | |
|--------------------------|-------------------|
| EudraCT number | 2019-003060-42 |
| Trial protocol | NO ES FR GB |
| Global end of trial date | 30 September 2022 |

Results information

| | |
|--------------------------------|-----------------|
| Result version number | v1 |
| This version publication date | 13 October 2023 |
| First version publication date | 13 October 2023 |

Trial information

Trial identification

| | |
|-----------------------|----------|
| Sponsor protocol code | 1454-002 |
|-----------------------|----------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT04220866 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|--|
| Sponsor organisation name | Merck Sharp & Dohme LLC |
| Sponsor organisation address | 126 East Lincoln Avenue,, Rahway, NJ, United States, P.O. Box 2000 |
| Public contact | Clinical Trials Disclosure, Merck Sharp & Dohme LLC, ClinicalTrialsDisclosure@merck.com |
| Scientific contact | Clinical Trials Disclosure, Merck Sharp & Dohme LLC, ClinicalTrialsDisclosure@merck.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 | 30 September 2022 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 30 September 2022 |
| Global end of trial reached? | Yes |
| Global end of trial date | 30 September 2022 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

The purpose of this study is to assess the efficacy and safety of intratumoral (IT) ulevostinag PLUS pembrolizumab (MK-3475) compared to pembrolizumab alone as a first line treatment of adults with metastatic or unresectable, recurrent head and neck squamous cell carcinoma (HNSCC).

The primary study hypotheses are that IT ulevostinag in combination with pembrolizumab results in a superior Objective Response Rate (ORR), per Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST 1.1), compared to pembrolizumab alone:

1. In participants with a tumor that has a programmed cell death-ligand 1 (PD-L1) Combined Positive Scoring (CPS) ≥ 1 , and
2. In participants with a tumor that has a PD-L1 CPS ≥ 20 .

Protection of trial subjects:

This study was conducted in conformance with Good Clinical Practice standards and applicable country and/or local statutes and regulations regarding ethical committee review, informed consent, and the protection of human subjects participating in biomedical research.

Background therapy: -

Evidence for comparator: -

| | |
|---|---------------|
| Actual start date of recruitment | 04 March 2022 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | No |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|-----------------------|
| Country: Number of subjects enrolled | Australia: 1 |
| Country: Number of subjects enrolled | France: 4 |
| Country: Number of subjects enrolled | Israel: 4 |
| Country: Number of subjects enrolled | Korea, Republic of: 1 |
| Country: Number of subjects enrolled | Norway: 1 |
| Country: Number of subjects enrolled | Spain: 3 |
| Country: Number of subjects enrolled | United States: 4 |
| Worldwide total number of subjects | 18 |
| EEA total number of subjects | 8 |

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) | 10 |
| From 65 to 84 years | 8 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Adults with a confirmed diagnosis of metastatic or unresectable, recurrent head and neck squamous cell carcinoma (HNSCC) with a tumor programmed cell death-1 ligand 1 (PD-L1) immunohistochemistry (IHC) combined positive scoring (CPS) ≥ 1 and had at least 1 measurable lesion that was amenable to intratumor (IT) injection were enrolled in this study.

Period 1

| | |
|------------------------------|--------------------------------|
| Period 1 title | Overall Study (overall period) |
| Is this the baseline period? | Yes |
| Allocation method | Randomised - controlled |
| Blinding used | Not blinded |

Arms

| | |
|------------------------------|-----------------------------|
| Are arms mutually exclusive? | Yes |
| Arm title | Ulevostinag + Pembrolizumab |

Arm description:

Participants received ulevostinag 540 ug via intratumoral (IT) injection on Day 1 of every week for two 3-week cycles (Cycles 1-2), then on Day 1 of each 3-week cycle for up to 33 cycles (Cycles 3-35), for a total of 35 cycles PLUS pembrolizumab 200 mg via intravenous (IV) infusion on Day 1 of each 3-week cycle for up to 35 cycles. The total duration of treatment was up to approximately 2 years.

| | |
|--|----------------------|
| Arm type | Experimental |
| Investigational medicinal product name | Pembrolizumab |
| Investigational medicinal product code | |
| Other name | MK-3475 KEYTRUDA® |
| Pharmaceutical forms | Infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

Participants received pembrolizumab 200 mg via IV infusion on Day 1 of each 3-week cycle for up to 35 cycles. The total duration of treatment is up to approximately 2 years

| | |
|--|------------------|
| Investigational medicinal product name | Ulevostinag |
| Investigational medicinal product code | |
| Other name | MK-1454 |
| Pharmaceutical forms | Injection |
| Routes of administration | Intratumoral use |

Dosage and administration details:

Participants received ulevostinag 540 ug via intratumoral (IT) injection on Day 1 of every week for two 3-week cycles (Cycles 1-2), then on Day 1 of each 3-week cycle for up to 33 cycles (Cycles 3-35), for a total of 35 cycles

| | |
|------------------|---------------|
| Arm title | Pembrolizumab |
|------------------|---------------|

Arm description:

Participants received pembrolizumab 200 mg via IV infusion on Day 1 of each 3-week cycle for up to 35 cycles. The total duration of treatment is up to approximately 2 years.

| | |
|----------|-------------------|
| Arm type | Active comparator |
|----------|-------------------|

| | |
|--|-------------------|
| Investigational medicinal product name | Pembrolizumab |
| Investigational medicinal product code | |
| Other name | MK-3475 KEYTRUDA® |
| Pharmaceutical forms | Infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

Participants received pembrolizumab 200 mg via IV infusion on Day 1 of each 3-week cycle for up to 35 cycles. The total duration of treatment is up to approximately 2 years

| Number of subjects in period 1 | Ulevostinag + Pembrolizumab | Pembrolizumab |
|---|-----------------------------|---------------|
| Started | 8 | 10 |
| Completed | 0 | 0 |
| Not completed | 8 | 10 |
| Adverse event, serious fatal | 4 | 5 |
| Participation in the study terminated By Sponsor | 2 | 4 |
| Consent withdrawn by subject | - | 1 |
| Participation at the site terminated By Sponsor | 2 | - |

Baseline characteristics

Reporting groups

| | |
|-----------------------|-----------------------------|
| Reporting group title | Ulevostinag + Pembrolizumab |
|-----------------------|-----------------------------|

Reporting group description:

Participants received ulevostinag 540 ug via intratumoral (IT) injection on Day 1 of every week for two 3-week cycles (Cycles 1-2), then on Day 1 of each 3-week cycle for up to 33 cycles (Cycles 3-35), for a total of 35 cycles PLUS pembrolizumab 200 mg via intravenous (IV) infusion on Day 1 of each 3-week cycle for up to 35 cycles. The total duration of treatment was up to approximately 2 years.

| | |
|-----------------------|---------------|
| Reporting group title | Pembrolizumab |
|-----------------------|---------------|

Reporting group description:

Participants received pembrolizumab 200 mg via IV infusion on Day 1 of each 3-week cycle for up to 35 cycles. The total duration of treatment is up to approximately 2 years.

| Reporting group values | Ulevostinag + Pembrolizumab | Pembrolizumab | Total |
|--|-----------------------------|---------------|-------|
| Number of subjects | 8 | 10 | 18 |
| Age categorical | | | |
| Units: Subjects | | | |
| In utero | 0 | 0 | 0 |
| Preterm newborn infants (gestational age < 37 wks) | 0 | 0 | 0 |
| Newborns (0-27 days) | 0 | 0 | 0 |
| Infants and toddlers (28 days-23 months) | 0 | 0 | 0 |
| Children (2-11 years) | 0 | 0 | 0 |
| Adolescents (12-17 years) | 0 | 0 | 0 |
| Adults (18-64 years) | 3 | 7 | 10 |
| From 65-84 years | 5 | 3 | 8 |
| 85 years and over | 0 | 0 | 0 |
| Age Continuous | | | |
| Units: Years | | | |
| arithmetic mean | 65.3 | 59.8 | - |
| standard deviation | ± 9.8 | ± 9.8 | - |
| Sex: Female, Male | | | |
| Units: | | | |
| Female | 0 | 1 | 1 |
| Male | 8 | 9 | 17 |
| Race (NIH/OMB) | | | |
| Units: Subjects | | | |
| American Indian or Alaska Native | 0 | 0 | 0 |
| Asian | 0 | 1 | 1 |
| Native Hawaiian or Other Pacific Islander | 0 | 0 | 0 |
| Black or African American | 0 | 0 | 0 |
| White | 8 | 9 | 17 |
| More than one race | 0 | 0 | 0 |
| Unknown or Not Reported | 0 | 0 | 0 |
| Ethnicity (NIH/OMB) | | | |
| Units: Subjects | | | |
| Hispanic or Latino | 0 | 0 | 0 |
| Not Hispanic or Latino | 8 | 10 | 18 |

| | | | |
|-------------------------|---|---|---|
| Unknown or Not Reported | 0 | 0 | 0 |
|-------------------------|---|---|---|

End points

End points reporting groups

| | |
|--|-----------------------------|
| Reporting group title | Ulevostinag + Pembrolizumab |
| Reporting group description: Participants received ulevostinag 540 ug via intratumoral (IT) injection on Day 1 of every week for two 3-week cycles (Cycles 1-2), then on Day 1 of each 3-week cycle for up to 33 cycles (Cycles 3-35), for a total of 35 cycles PLUS pembrolizumab 200 mg via intravenous (IV) infusion on Day 1 of each 3-week cycle for up to 35 cycles. The total duration of treatment was up to approximately 2 years. | |
| Reporting group title | Pembrolizumab |
| Reporting group description: Participants received pembrolizumab 200 mg via IV infusion on Day 1 of each 3-week cycle for up to 35 cycles. The total duration of treatment is up to approximately 2 years. | |

Primary: Objective Response Rate (ORR) per Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST 1.1)

| | |
|--|--|
| End point title | Objective Response Rate (ORR) per Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST 1.1) ^[1] |
| End point description: ORR was defined as the percentage of participants in the analysis population who have a Complete Response (CR: Disappearance of all target lesions) or a Partial Response (PR: At least a 30% decrease in the sum of diameters of target lesions) per RECIST 1.1. ORR was assessed by blinded independent central review (BICR), and the 95% confidence interval (CI) was based on the exact method for binomial data. The population analyzed was all randomized participants based on the treatment arm to which they were randomized. | |
| End point type | Primary |
| End point timeframe: Up to 1088.0 days | |
| 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 comparisons between treatment groups were neither planned nor performed for this primary endpoint. | |

| End point values | Ulevostinag + Pembrolizumab | Pembrolizumab | | |
|-----------------------------------|-----------------------------|--------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 8 | 10 | | |
| Units: Percentage of participants | | | | |
| number (confidence interval 95%) | 50.0 (15.7 to 84.3) | 10.0 (0.3 to 44.5) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants discontinuing study treatment due to an AE

| | |
|--|---|
| End point title | Number of participants discontinuing study treatment due to an AE |
| End point description: An AE is any untoward medical occurrence in a participant, temporally associated with the use of study | |

treatment, whether or not considered related to the study treatment. The population analyzed was all randomized participants who received at least 1 dose of study treatment.

| | |
|--------------------------------|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Up to approximately 715.0 days | |

| End point values | Ulevostinag + Pembrolizumab | Pembrolizumab | | |
|-----------------------------|-----------------------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 8 | 10 | | |
| Units: Participants | 3 | 2 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival (OS)

| | |
|--|-----------------------|
| End point title | Overall Survival (OS) |
| End point description: | |
| OS is defined as the time from randomization to the date of death from any cause, and is based on the product-limit (Kaplan-Meier) method for censored data. The population analyzed was all randomized participants based on the treatment arm to which they were randomized. | |
| End point type | Secondary |
| End point timeframe: | |
| Up to 1088.0 days | |

| End point values | Ulevostinag + Pembrolizumab | Pembrolizumab | | |
|----------------------------------|-----------------------------|---------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 8 ^[2] | 10 ^[3] | | |
| Units: Months | | | | |
| median (confidence interval 95%) | 99999 (1.0 to 99999) | 11.1 (0.8 to 99999) | | |

Notes:

[2] - 99999 = Median and upper limit not reached due to insufficient number of participants with an event.

[3] - 99999 = Median and upper limit not reached due to insufficient number of participants with an event.

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants who experienced an Adverse Event (AE)

| | |
|-----------------|--|
| End point title | Number of participants who experienced an Adverse Event (AE) |
|-----------------|--|

End point description:

An AE is any untoward medical occurrence in a participant, temporally associated with the use of study treatment, whether or not considered related to the study treatment. The population analyzed was all randomized participants who received at least 1 dose of study treatment.

| | |
|----------------------|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Up to 1088.0 days | |

| End point values | Ulevostinag + Pembrolizumab | Pembrolizumab | | |
|-----------------------------|-----------------------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 8 | 10 | | |
| Units: Participants | 8 | 10 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Response (DOR) per Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST 1.1)

| | |
|-----------------|--|
| End point title | Duration of Response (DOR) per Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST 1.1) |
|-----------------|--|

End point description:

DOR was defined as the time from the first documented evidence of a Complete Response (CR: Disappearance of all target lesions) or a Partial Response (PR: At least a 30% decrease in the sum of diameters of target lesions) per RECIST 1.1 until Progressive Disease (PD) or death due to any cause, whichever occurs first, in participants demonstrating a CR or PR. Per RECIST 1.1, PD is defined as at least a 20% increase in the sum of diameters of target lesions. In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. The appearance of one or more new lesions is also considered PD. DOR was based on the product-limit (Kaplan-Meier) method for censored data. The population analyzed was all randomized participants based on the treatment arm to which they were randomized.

| | |
|----------------------|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Up to 1088.0 days | |

| End point values | Ulevostinag + Pembrolizumab | Pembrolizumab | | |
|-------------------------------|-----------------------------|------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 8 ^[4] | 10 ^[5] | | |
| Units: Months | | | | |
| median (full range (min-max)) | 99999 (99999 to 99999) | 99999 (99999 to 99999) | | |

Notes:

[4] - .99999 = Results not reached due to insufficient number of responding participants with relapse

[5] - .99999 = Results not reached due to insufficient number of responding participants with relapse

Statistical analyses

No statistical analyses for this end point

Secondary: Progression-free Survival (PFS) per Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST 1.1)

| | |
|-----------------|---|
| End point title | Progression-free Survival (PFS) per Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST 1.1) |
|-----------------|---|

End point description:

PFS was defined as the time from randomization to the first documented progressive disease (PD) or death from any cause, whichever occurs first. Per RECIST 1.1, PD was defined as at least a 20% increase in the sum of diameters of target lesions. In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. The appearance of one or more new lesions was also considered PD. PFS was assessed by BICR and was based on the product-limit (Kaplan-Meier) method for censored data. The population analyzed was all randomized participants based on the treatment arm to which they were randomized.

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

End point timeframe:

Up to 1088.0 days

| End point values | Ulevostinag + Pembrolizumab | Pembrolizumab | | |
|----------------------------------|-----------------------------|--------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 8 ^[6] | 10 ^[7] | | |
| Units: Months | | | | |
| median (confidence interval 95%) | 6.4 (1.0 to 99999) | 1.5 (0.5 to 99999) | | |

Notes:

[6] - 99999 = Upper limit not reached due to insufficient number of participants with an even

[7] - 99999 = Upper limit not reached due to insufficient number of participants with an even

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse Events (AEs): from first treatment up to 1088.0 days. All Cause Mortality (ACM): from randomization up to 1088.0 days.:

Adverse event reporting additional description:

The ACM population consisted of all randomized participants. The AE population consisted of all randomized participants who received at least 1 dose of study treatment. Per protocol the following AE preferred terms not related to the drug were excluded: Neoplasm progression, Malignant neoplasm progression and Disease progression.

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

Dictionary used

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

| | |
|--------------------|------|
| Dictionary version | 25.1 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|---------------|
| Reporting group title | Pembrolizumab |
|-----------------------|---------------|

Reporting group description:

Participants received pembrolizumab 200 mg via IV infusion on Day 1 of each 3-week cycle for up to 35 cycles. The total duration of treatment is up to approximately 2 years

| | |
|-----------------------|-----------------------------|
| Reporting group title | Ulevostinag + Pembrolizumab |
|-----------------------|-----------------------------|

Reporting group description:

Participants received ulevostinag 540 ug via intratumoral (IT) injection on Day 1 of every week for two 3-week cycles (Cycles 1-2), then on Day 1 of each 3-week cycle for up to 33 cycles (Cycles 3-35), for a total of 35 cycles PLUS pembrolizumab 200 mg via intravenous (IV) infusion on Day 1 of each 3-week cycle for up to 35 cycles. The total duration of treatment was up to approximately 2 years.

| Serious adverse events | Pembrolizumab | Ulevostinag + Pembrolizumab | |
|---|-----------------|-----------------------------|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 4 / 10 (40.00%) | 5 / 8 (62.50%) | |
| number of deaths (all causes) | 5 | 4 | |
| number of deaths resulting from adverse events | 0 | 0 | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Tumour haemorrhage | | | |
| subjects affected / exposed | 1 / 10 (10.00%) | 0 / 8 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Injury, poisoning and procedural complications | | | |
| Injection related reaction | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 1 / 8 (12.50%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|--|----------------|----------------|--|
| Wound haemorrhage | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 1 / 8 (12.50%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac disorders | | | |
| Pericarditis | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 1 / 8 (12.50%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nervous system disorders | | | |
| Carotid artery aneurysm | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 1 / 8 (12.50%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| General disorders and administration site conditions | | | |
| Injection site ulcer | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 1 / 8 (12.50%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pyrexia | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 1 / 8 (12.50%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal disorders | | | |
| Constipation | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 1 / 8 (12.50%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Acute respiratory failure | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 1 / 8 (12.50%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pleuritic pain | | | |

| | | | |
|---|-----------------|----------------|--|
| subjects affected / exposed | 1 / 10 (10.00%) | 0 / 8 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Dyspnoea | | | |
| subjects affected / exposed | 1 / 10 (10.00%) | 0 / 8 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumonitis aspiration | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 1 / 8 (12.50%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Infections and infestations | | | |
| COVID-19 pneumonia | | | |
| subjects affected / exposed | 1 / 10 (10.00%) | 0 / 8 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Pneumonia aspiration | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 1 / 8 (12.50%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Sepsis | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 1 / 8 (12.50%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

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

| Non-serious adverse events | Pembrolizumab | Ulevostinag + Pembrolizumab | |
|---|-----------------|-----------------------------|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 9 / 10 (90.00%) | 8 / 8 (100.00%) | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Neoplasm swelling | | | |
| subjects affected / exposed | 1 / 10 (10.00%) | 0 / 8 (0.00%) | |
| occurrences (all) | 1 | 0 | |

| | | | |
|--|----------------------|----------------------|--|
| Skin neoplasm bleeding subjects affected / exposed occurrences (all) | 1 / 10 (10.00%) 1 | 0 / 8 (0.00%) 0 | |
| Tumour inflammation subjects affected / exposed occurrences (all) | 1 / 10 (10.00%) 1 | 0 / 8 (0.00%) 0 | |
| Vascular disorders Hypotension subjects affected / exposed occurrences (all) | 0 / 10 (0.00%) 0 | 1 / 8 (12.50%) 2 | |
| General disorders and administration site conditions Axillary pain subjects affected / exposed occurrences (all) | 0 / 10 (0.00%) 0 | 1 / 8 (12.50%) 1 | |
| Asthenia subjects affected / exposed occurrences (all) | 1 / 10 (10.00%) 1 | 1 / 8 (12.50%) 1 | |
| Chills subjects affected / exposed occurrences (all) | 0 / 10 (0.00%) 0 | 2 / 8 (25.00%) 5 | |
| Swelling face subjects affected / exposed occurrences (all) | 0 / 10 (0.00%) 0 | 1 / 8 (12.50%) 2 | |
| Swelling subjects affected / exposed occurrences (all) | 0 / 10 (0.00%) 0 | 1 / 8 (12.50%) 1 | |
| Pyrexia subjects affected / exposed occurrences (all) | 0 / 10 (0.00%) 0 | 4 / 8 (50.00%) 10 | |
| Injection site swelling subjects affected / exposed occurrences (all) | 0 / 10 (0.00%) 0 | 1 / 8 (12.50%) 2 | |
| Injection site reaction subjects affected / exposed occurrences (all) | 0 / 10 (0.00%) 0 | 1 / 8 (12.50%) 1 | |
| Injection site pain | | | |

| | | | |
|---|-----------------|----------------|--|
| subjects affected / exposed | 0 / 10 (0.00%) | 4 / 8 (50.00%) | |
| occurrences (all) | 0 | 6 | |
| Injection site necrosis | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 1 / 8 (12.50%) | |
| occurrences (all) | 0 | 1 | |
| Injection site erythema | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 1 / 8 (12.50%) | |
| occurrences (all) | 0 | 2 | |
| Influenza like illness | | | |
| subjects affected / exposed | 1 / 10 (10.00%) | 0 / 8 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Fatigue | | | |
| subjects affected / exposed | 2 / 10 (20.00%) | 1 / 8 (12.50%) | |
| occurrences (all) | 2 | 1 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Chronic obstructive pulmonary disease | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 1 / 8 (12.50%) | |
| occurrences (all) | 0 | 1 | |
| Cough | | | |
| subjects affected / exposed | 1 / 10 (10.00%) | 0 / 8 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Dyspnoea | | | |
| subjects affected / exposed | 1 / 10 (10.00%) | 1 / 8 (12.50%) | |
| occurrences (all) | 1 | 1 | |
| Epistaxis | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 2 / 8 (25.00%) | |
| occurrences (all) | 0 | 2 | |
| Nasal cavity mass | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 1 / 8 (12.50%) | |
| occurrences (all) | 0 | 1 | |
| Productive cough | | | |
| subjects affected / exposed | 1 / 10 (10.00%) | 0 / 8 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Rhinorrhoea | | | |

| | | | |
|--|---------------------|---------------------|--|
| subjects affected / exposed occurrences (all) | 0 / 10 (0.00%) 0 | 1 / 8 (12.50%) 1 | |
| Psychiatric disorders | | | |
| Anxiety | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 1 / 8 (12.50%) | |
| occurrences (all) | 0 | 1 | |
| Depression | | | |
| subjects affected / exposed | 1 / 10 (10.00%) | 0 / 8 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Insomnia | | | |
| subjects affected / exposed | 1 / 10 (10.00%) | 1 / 8 (12.50%) | |
| occurrences (all) | 1 | 1 | |
| Investigations | | | |
| Blood alkaline phosphatase increased | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 1 / 8 (12.50%) | |
| occurrences (all) | 0 | 1 | |
| Blood creatinine increased | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 1 / 8 (12.50%) | |
| occurrences (all) | 0 | 1 | |
| Blood thyroid stimulating hormone increased | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 1 / 8 (12.50%) | |
| occurrences (all) | 0 | 1 | |
| Gamma-glutamyltransferase increased | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 1 / 8 (12.50%) | |
| occurrences (all) | 0 | 1 | |
| Liver function test abnormal | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 1 / 8 (12.50%) | |
| occurrences (all) | 0 | 1 | |
| Tri-iodothyronine free increased | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 1 / 8 (12.50%) | |
| occurrences (all) | 0 | 1 | |
| Injury, poisoning and procedural complications | | | |
| Infusion related reaction | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 1 / 8 (12.50%) | |
| occurrences (all) | 0 | 1 | |

| | | | |
|---|---|---|--|
| Stoma site discharge subjects affected / exposed occurrences (all) | 1 / 10 (10.00%) 1 | 0 / 8 (0.00%) 0 | |
| Vascular pseudoaneurysm subjects affected / exposed occurrences (all) | 0 / 10 (0.00%) 0 | 1 / 8 (12.50%) 1 | |
| Congenital, familial and genetic disorders Tracheo-oesophageal fistula subjects affected / exposed occurrences (all) | 0 / 10 (0.00%) 0 | 1 / 8 (12.50%) 1 | |
| Nervous system disorders Anosmia subjects affected / exposed occurrences (all) Dizziness subjects affected / exposed occurrences (all) Dysgeusia subjects affected / exposed occurrences (all) Speech disorder subjects affected / exposed occurrences (all) | 1 / 10 (10.00%) 1 0 / 10 (0.00%) 0 1 / 10 (10.00%) 1 1 / 10 (10.00%) 1 | 0 / 8 (0.00%) 0 1 / 8 (12.50%) 1 0 / 8 (0.00%) 0 0 / 8 (0.00%) 0 | |
| Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all) Leukopenia subjects affected / exposed occurrences (all) Lymphopenia subjects affected / exposed occurrences (all) Lymphadenitis subjects affected / exposed occurrences (all) | 1 / 10 (10.00%) 1 1 / 10 (10.00%) 1 1 / 10 (10.00%) 1 0 / 10 (0.00%) 0 | 1 / 8 (12.50%) 1 0 / 8 (0.00%) 0 1 / 8 (12.50%) 1 1 / 8 (12.50%) 1 | |

| | | | |
|---|--|--|--|
| Ear and labyrinth disorders Vertigo subjects affected / exposed occurrences (all) Hyperacusis subjects affected / exposed occurrences (all) | 1 / 10 (10.00%) 1 1 / 10 (10.00%) 1 | 0 / 8 (0.00%) 0 0 / 8 (0.00%) 0 | |
| Eye disorders Vision blurred subjects affected / exposed occurrences (all) | 1 / 10 (10.00%) 1 | 0 / 8 (0.00%) 0 | |
| Gastrointestinal disorders Vomiting subjects affected / exposed occurrences (all) Palatal disorder subjects affected / exposed occurrences (all) Oral pain subjects affected / exposed occurrences (all) Nausea subjects affected / exposed occurrences (all) Impaired gastric emptying subjects affected / exposed occurrences (all) Gastrooesophageal reflux disease subjects affected / exposed occurrences (all) Dysphagia subjects affected / exposed occurrences (all) Dry mouth subjects affected / exposed occurrences (all) Diarrhoea | 0 / 10 (0.00%) 0 1 / 10 (10.00%) 1 0 / 10 (0.00%) 0 0 / 10 (0.00%) 0 0 / 10 (0.00%) 0 1 / 10 (10.00%) 1 0 / 10 (0.00%) 0 0 / 10 (0.00%) 0 | 2 / 8 (25.00%) 4 0 / 8 (0.00%) 0 1 / 8 (12.50%) 1 3 / 8 (37.50%) 3 1 / 8 (12.50%) 1 1 / 8 (12.50%) 1 0 / 8 (0.00%) 0 1 / 8 (12.50%) 1 | |

| | | | |
|--|-----------------|----------------|--|
| subjects affected / exposed | 0 / 10 (0.00%) | 1 / 8 (12.50%) | |
| occurrences (all) | 0 | 2 | |
| Constipation | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 1 / 8 (12.50%) | |
| occurrences (all) | 0 | 1 | |
| Colitis | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 1 / 8 (12.50%) | |
| occurrences (all) | 0 | 2 | |
| Skin and subcutaneous tissue disorders | | | |
| Pruritus | | | |
| subjects affected / exposed | 3 / 10 (30.00%) | 0 / 8 (0.00%) | |
| occurrences (all) | 3 | 0 | |
| Dry skin | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 1 / 8 (12.50%) | |
| occurrences (all) | 0 | 1 | |
| Drug eruption | | | |
| subjects affected / exposed | 1 / 10 (10.00%) | 0 / 8 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Dermatitis acneiform | | | |
| subjects affected / exposed | 1 / 10 (10.00%) | 0 / 8 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Skin burning sensation | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 1 / 8 (12.50%) | |
| occurrences (all) | 0 | 1 | |
| Sensitive skin | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 1 / 8 (12.50%) | |
| occurrences (all) | 0 | 1 | |
| Rash | | | |
| subjects affected / exposed | 1 / 10 (10.00%) | 1 / 8 (12.50%) | |
| occurrences (all) | 1 | 1 | |
| Renal and urinary disorders | | | |
| Acute kidney injury | | | |
| subjects affected / exposed | 1 / 10 (10.00%) | 1 / 8 (12.50%) | |
| occurrences (all) | 1 | 1 | |
| Haematuria | | | |

| | | | |
|--|----------------------|---------------------|--|
| subjects affected / exposed occurrences (all) | 0 / 10 (0.00%) 0 | 1 / 8 (12.50%) 1 | |
| Proteinuria subjects affected / exposed occurrences (all) | 0 / 10 (0.00%) 0 | 1 / 8 (12.50%) 1 | |
| Renal impairment subjects affected / exposed occurrences (all) | 1 / 10 (10.00%) 1 | 0 / 8 (0.00%) 0 | |
| Endocrine disorders Hypothyroidism subjects affected / exposed occurrences (all) | 0 / 10 (0.00%) 0 | 1 / 8 (12.50%) 1 | |
| Musculoskeletal and connective tissue disorders Back pain subjects affected / exposed occurrences (all) | 0 / 10 (0.00%) 0 | 1 / 8 (12.50%) 1 | |
| Bone pain subjects affected / exposed occurrences (all) | 1 / 10 (10.00%) 1 | 0 / 8 (0.00%) 0 | |
| Musculoskeletal chest pain subjects affected / exposed occurrences (all) | 0 / 10 (0.00%) 0 | 1 / 8 (12.50%) 1 | |
| Neck pain subjects affected / exposed occurrences (all) | 1 / 10 (10.00%) 1 | 1 / 8 (12.50%) 1 | |
| Infections and infestations Urinary tract infection subjects affected / exposed occurrences (all) | 0 / 10 (0.00%) 0 | 1 / 8 (12.50%) 1 | |
| Tongue fungal infection subjects affected / exposed occurrences (all) | 0 / 10 (0.00%) 0 | 1 / 8 (12.50%) 1 | |
| Soft tissue infection subjects affected / exposed occurrences (all) | 0 / 10 (0.00%) 0 | 1 / 8 (12.50%) 1 | |
| Sinusitis | | | |

| | | | |
|------------------------------------|-----------------|----------------|--|
| subjects affected / exposed | 0 / 10 (0.00%) | 1 / 8 (12.50%) | |
| occurrences (all) | 0 | 1 | |
| Relapsing fever | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 1 / 8 (12.50%) | |
| occurrences (all) | 0 | 1 | |
| Pyuria | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 1 / 8 (12.50%) | |
| occurrences (all) | 0 | 1 | |
| Pneumonia | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 1 / 8 (12.50%) | |
| occurrences (all) | 0 | 2 | |
| Hepatitis C | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 1 / 8 (12.50%) | |
| occurrences (all) | 0 | 1 | |
| Cellulitis | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 1 / 8 (12.50%) | |
| occurrences (all) | 0 | 1 | |
| Candida infection | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 1 / 8 (12.50%) | |
| occurrences (all) | 0 | 1 | |
| COVID-19 | | | |
| subjects affected / exposed | 1 / 10 (10.00%) | 1 / 8 (12.50%) | |
| occurrences (all) | 1 | 1 | |
| Bacteriuria | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 1 / 8 (12.50%) | |
| occurrences (all) | 0 | 1 | |
| Bacterial disease carrier | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 1 / 8 (12.50%) | |
| occurrences (all) | 0 | 1 | |
| Metabolism and nutrition disorders | | | |
| Decreased appetite | | | |
| subjects affected / exposed | 1 / 10 (10.00%) | 3 / 8 (37.50%) | |
| occurrences (all) | 1 | 3 | |
| Dehydration | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 1 / 8 (12.50%) | |
| occurrences (all) | 0 | 1 | |

| | | | |
|-----------------------------|-----------------|----------------|--|
| Hypercalcaemia | | | |
| subjects affected / exposed | 1 / 10 (10.00%) | 0 / 8 (0.00%) | |
| occurrences (all) | 2 | 0 | |
| Hyperkalaemia | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 1 / 8 (12.50%) | |
| occurrences (all) | 0 | 1 | |
| Hyperphosphataemia | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 1 / 8 (12.50%) | |
| occurrences (all) | 0 | 1 | |
| Hypoalbuminaemia | | | |
| subjects affected / exposed | 1 / 10 (10.00%) | 0 / 8 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Hypokalaemia | | | |
| subjects affected / exposed | 1 / 10 (10.00%) | 0 / 8 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Hypomagnesaemia | | | |
| subjects affected / exposed | 1 / 10 (10.00%) | 0 / 8 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Hyponatraemia | | | |
| subjects affected / exposed | 2 / 10 (20.00%) | 0 / 8 (0.00%) | |
| occurrences (all) | 2 | 0 | |
| Hypophosphataemia | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 1 / 8 (12.50%) | |
| occurrences (all) | 0 | 2 | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|-------------------|--|
| 09 September 2020 | Amendment 1: To address Health Authority requests, including to provide rationale for minimum creatinine clearance in the eligibility criteria, to add clarification for PD-L1 testing to the protocol, to clarify ongoing safety monitoring during the conduct of the clinical trial, and to provide additional clarifications. |
| 16 August 2021 | Amendment 2: To update the dose modification and toxicity management guidelines for irAEs associated with pembrolizumab. |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported