



## Clinical trial results:

### A Phase II Clinical Trial of Single Agent Pembrolizumab (MK-3475) in Subjects with Recurrent or Metastatic Head and Neck Squamous Cell Carcinoma (HNSCC) Who Have Failed Platinum and Cetuximab

#### Summary

|                          |                |
|--------------------------|----------------|
| EudraCT number           | 2014-002447-18 |
| Trial protocol           | NO DK          |
| Global end of trial date | 18 June 2021   |

#### Results information

|                                |              |
|--------------------------------|--------------|
| Result version number          | v2 (current) |
| This version publication date  | 27 July 2022 |
| First version publication date | 11 June 2022 |
| Version creation reason        |              |

#### Trial information

##### Trial identification

|                       |          |
|-----------------------|----------|
| Sponsor protocol code | 3475-055 |
|-----------------------|----------|

##### Additional study identifiers

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT02255097 |
| WHO universal trial number (UTN)   | -           |

Notes:

#### Sponsors

|                              |  |
|------------------------------|--|
| Sponsor organisation name    | Merck Sharp & Dohme LLC  |
| Sponsor organisation address | 126 East Lincoln Avenue, P.O. Box 2000, Rahway, NJ, United States, 07065                   |
| Public contact               | Clinical Trials Disclosure, Merck Sharp & Dohme LLC,<br>ClinicalTrialsDisclosure@merck.com |
| Scientific contact           | Clinical Trials Disclosure, Merck Sharp & Dohme LLC,<br>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                       | 18 June 2021  |
| Is this the analysis of the primary completion data? | Yes           |
| Primary completion date                              | 22 April 2016 |
| Global end of trial reached?                         | Yes           |
| Global end of trial date                             | 18 June 2021  |
| Was the trial ended prematurely?                     | No            |

Notes:

## General information about the trial

Main objective of the trial:

This is a study of single-agent pembrolizumab (MK-3475) in participants with recurrent and/or metastatic head and neck squamous cell carcinoma (HNSCC) who have progressed on platinum-based and cetuximab therapy. The primary study hypothesis is that pembrolizumab will provide a clinically meaningful objective response rate (ORR).

With protocol amendment 05 (02-Jan-2018), once study participants have achieved the study objective or the study has ended, participants will be discontinued from this study and enrolled in an extension study to continue protocol-defined assessments and treatment.

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                          | 24 October 2014 |
| 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 | Denmark: 3         |
| Country: Number of subjects enrolled | Norway: 3          |
| Country: Number of subjects enrolled | United States: 166 |
| Worldwide total number of subjects   | 172                |
| EEA total number of subjects         | 6                  |

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)      | 108 |
| From 65 to 84 years       | 63  |
| 85 years and over         | 1   |

## Subject disposition

### Recruitment

Recruitment details:

Participants were eligible to receive second course treatment with pembrolizumab if they met criteria for re-treatment. Per protocol, data collected during the second course were not counted towards efficacy or safety outcome measures.

### Pre-assignment

Screening details:

Final analyses for all primary outcome measures were done at the protocol-specified primary outcome measure met date. The analyses for all secondary outcome measures and the collection of adverse events were done at the end of study date.

One participant allocated to receive pembrolizumab was not treatment and was not eligible for analysis.

### Period 1

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

### Arms

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

Arm description:

Participants received pembrolizumab 200 mg by intravenous (IV) infusion on Day 1 of each 3-week cycle for up to 24 months. Participants who stopped pembrolizumab as a result of obtaining a CR or those who stopped after receiving pembrolizumab for 24 months for reasons other than disease progression or intolerability, were eligible for up to an additional 1 year of treatment after progressive disease if they met the criteria for retreatment.

|  |                                 |
|--|---------------------------------|
| Arm type                               | Experimental                    |
| Investigational medicinal product name | Pembrolizumab                   |
| Investigational medicinal product code |                                 |
| Other name                             | KEYTRUDA®                       |
| Pharmaceutical forms                   | Solution for injection/infusion |
| Routes of administration               | Intravenous use                 |

Dosage and administration details:

200 mg administered by IV infusion on Day 1 of each 3-week cycle for up to 24 months

| Number of subjects in period 1          | Pembrolizumab |
|---|---------------|
| Started                                 | 172           |
| Treated                                 | 171           |
| Received Second Course of Pembrolizumab | 3             |
| Completed                               | 0             |
| Not completed                           | 172           |
| Adverse event, serious fatal            | 151           |
| Consent withdrawn by subject            | 7             |
| Allocated but not treated               | 1             |
| Lost to follow-up                       | 5             |

|   |   |
|---|---|
| Participation in Study Discontinued<br>by Sponsor | 8 |
|---|---|

## Baseline characteristics

### Reporting groups

|                       |               |
|-----------------------|---------------|
| Reporting group title | Overall Study |
|-----------------------|---------------|

Reporting group description:

Participants received pembrolizumab 200 mg by intravenous (IV) infusion on Day 1 of each 3-week cycle for up to 24 months. Participants who stopped pembrolizumab as a result of obtaining a CR or those who stopped after receiving pembrolizumab for 24 months for reasons other than disease progression or intolerability, were eligible for up to an additional 1 year of treatment after progressive disease if they met the criteria for retreatment.

| Reporting group values                              | Overall Study | Total |  |
|---|---------------|-------|--|
| Number of subjects                                  | 172           | 172   |  |
| Age categorical                                     |               |       |  |
| Units: Participants                                 |               |       |  |
| In utero  | 0             | 0     |  |
| Preterm newborn infants (gestational age < 37 wks)  | 0             | 0     |  |
| Newborns (0-27 days)                                | 0             | 0     |  |
| Infants and toddlers (28 days-23 months)            | 0             | 0     |  |
| Children (2-11 years)                               | 0             | 0     |  |
| Adolescents (12-17 years)                           | 0             | 0     |  |
| Adults (18-64 years)                                | 108           | 108   |  |
| From 65-84 years                                    | 63            | 63    |  |
| 85 years and over                                   | 1             | 1     |  |
| Age Continuous                                      |               |       |  |
| Units: years  |               |       |  |
| arithmetic mean                                     | 61.1          |       |  |
| standard deviation                                  | ± 9.9         | -     |  |
| Sex: Female, Male                                   |               |       |  |
| Units: Participants                                 |               |       |  |
| Female  | 34            | 34    |  |
| Male  | 138           | 138   |  |
| Race (NIH/OMB)                                      |               |       |  |
| Units: Subjects                                     |               |       |  |
| American Indian or Alaska Native                    | 1             | 1     |  |
| Asian   | 7             | 7     |  |
| Native Hawaiian or Other Pacific Islander           | 0             | 0     |  |
| Black or African American                           | 11            | 11    |  |
| White   | 153           | 153   |  |
| More than one race                                  | 0             | 0     |  |
| Unknown or Not Reported                             | 0             | 0     |  |
| Ethnicity (NIH/OMB)                                 |               |       |  |
| Units: Subjects                                     |               |       |  |
| Hispanic or Latino                                  | 9             | 9     |  |
| Not Hispanic or Latino                              | 153           | 153   |  |
| Unknown or Not Reported                             | 10            | 10    |  |
| Programmed Cell Death-Ligand 1 (PD-L1) Tumor Status |               |       |  |

Participants were assessed for their PD-L1 tumor expression status by immunohistochemistry assay using tumor tissue from an archival or newly obtained biopsy. Participants with a tumor proportion score (TPS) were classified as follows:  $\geq 50\%$  = PD-L1 strongly positive; 1-49% = PD-L1 weakly positive; and  $< 1\%$  = PD-L1 negative.

| Units: Subjects   |    |    |  |
|-------------------|----|----|--|
| $\geq 50\%$       | 44 | 44 |  |
| $\geq 1 - < 50\%$ | 77 | 77 |  |
| $< 1\%$           | 46 | 46 |  |
| Unknown           | 5  | 5  |  |

## End points

### End points reporting groups

|   |  |
|---|--|
| Reporting group title   | Pembrolizumab                          |
| Reporting group description:<br>Participants received pembrolizumab 200 mg by intravenous (IV) infusion on Day 1 of each 3-week cycle for up to 24 months. Participants who stopped pembrolizumab as a result of obtaining a CR or those who stopped after receiving pembrolizumab for 24 months for reasons other than disease progression or intolerability, were eligible for up to an additional 1 year of treatment after progressive disease if they met the criteria for retreatment.  |  |
| Subject analysis set title  | Pembrolizumab                          |
| Subject analysis set type   | Per protocol                           |
| Subject analysis set description:<br>Participants received pembrolizumab 200 mg by IV infusion on Day 1 of each 3-week cycle for up to 24 months. Participants who stopped pembrolizumab as a result of obtaining a CR or those who stopped after receiving pembrolizumab for 24 months for reasons other than disease progression or intolerability, were eligible for up to an additional 1 year of treatment after progressive disease if they met the criteria for re-treatment.  |  |
| Subject analysis set title  | Pembrolizumab First Course             |
| Subject analysis set type   | Safety analysis                        |
| Subject analysis set description:<br>Participants received pembrolizumab 200 mg by IV infusion on Day 1 of each 3-week cycle for up to 24 months. Participants who stopped pembrolizumab as a result of obtaining a CR or those who stopped after receiving pembrolizumab for 24 months for reasons other than disease progression or intolerability, were eligible for up to an additional 1 year of treatment after progressive disease if they met the criteria for re-treatment.  |  |
| Subject analysis set title  | Pembrolizumab Second Course            |
| Subject analysis set type   | Safety analysis                        |
| Subject analysis set description:<br>Participants who met the criteria for retreatment received pembrolizumab 200 mg by IV infusion on Day 1 of each 3-week cycle for up to 1 year of treatment.  |  |
| Subject analysis set title  | Strong PD-L1 TPS Positive Participants |
| Subject analysis set type   | Sub-group analysis                     |
| Subject analysis set description:<br>Participants with strong programmed cell death ligand 1 (PD-L1) positive expression status, defined as a PD-L1 tumor proportion score (TPS) $\geq 50\%$ , received pembrolizumab 200 mg by IV infusion on Day 1 of each 3-week cycle for up to 24 months. Participants who stopped pembrolizumab as a result of obtaining a CR or those who stopped after receiving pembrolizumab for 24 months for reasons other than disease progression or intolerability, were eligible for up to an additional 1 year of treatment after progressive disease if they met the criteria for re-treatment. |  |
| Subject analysis set title  | PD-L1 TPS Positive Participants        |
| Subject analysis set type   | Sub-group analysis                     |
| Subject analysis set description:<br>Participants with programmed cell death ligand 1 (PD-L1) positive expression status, defined as a PD-L1 tumor proportion score (TPS) $\geq 1\%$ , received pembrolizumab 200 mg by IV infusion on Day 1 of each 3-week cycle for up to 24 months. Participants who stopped pembrolizumab as a result of obtaining a CR or those who stopped after receiving pembrolizumab for 24 months for reasons other than disease progression or intolerability, were eligible for up to an additional 1 year of treatment after progressive disease if they met the criteria for re-treatment.         |  |
| Subject analysis set title  | PD-L1 CPS Positive Participants        |
| Subject analysis set type   | Sub-group analysis                     |
| Subject analysis set description:<br>Participants with programmed cell death ligand 1 (PD-L1) positive expression status, defined as a PD-L1 combined positive score (CPS) $\geq 1\%$ , received pembrolizumab 200 mg by IV infusion on Day 1 of each 3-week cycle for up to 24 months. Participants who stopped pembrolizumab as a result of obtaining a CR or those who stopped after receiving pembrolizumab for 24 months for reasons other than disease progression or intolerability, were eligible for up to an additional 1 year of treatment after progressive disease if they met the criteria for re-treatment.        |  |



|                            |   |
|----------------------------|---|
| Subject analysis set title | Participants With a HPV-positive Tumor Biopsy |
| Subject analysis set type  | Sub-group analysis                            |

Subject analysis set description:

Participants with a human papillomavirus (HPV) tumor biopsy received pembrolizumab 200 mg by IV infusion on Day 1 of each 3-week cycle for up to 24 months. Participants who stopped pembrolizumab as a result of obtaining a CR or those who stopped after receiving pembrolizumab for 24 months for reasons other than disease progression or intolerability, were eligible for up to an additional 1 year of treatment after progressive disease if they met the criteria for re-treatment.

|                            |                             |
|----------------------------|-----------------------------|
| Subject analysis set title | Duplicate Pembrolizumab Arm |
| Subject analysis set type  | Sub-group analysis          |

Subject analysis set description:

Participants received pembrolizumab 200 mg by IV infusion on Day 1 of each 3-week cycle for up to 24 months. Participants who stopped pembrolizumab as a result of obtaining a CR or those who stopped after receiving pembrolizumab for 24 months for reasons other than disease progression or intolerability, were eligible for up to an additional 1 year of treatment after progressive disease if they met the criteria for re-treatment. This duplicate arm is added as a workaround to accommodate the statistical analysis of the single arm to a fixed efficacy target within the electronic application.

|                            |  |
|----------------------------|--|
| Subject analysis set title | Duplicate Strong PD-L1 TPS Positive Participants |
| Subject analysis set type  | Sub-group analysis                               |

Subject analysis set description:

Participants with strong programmed cell death ligand 1 (PD-L1) positive expression status, defined as a PD-L1 tumor proportion score (TPS)  $\geq 50\%$ , received pembrolizumab 200 mg by IV infusion on Day 1 of each 3-week cycle for up to 24 months. Participants who stopped pembrolizumab as a result of obtaining a CR or those who stopped after receiving pembrolizumab for 24 months for reasons other than disease progression or intolerability, were eligible for up to an additional 1 year of treatment after progressive disease if they met the criteria for re-treatment. This duplicate arm is added as a workaround to accommodate the statistical analysis of the single arm to a fixed efficacy target within the electronic application.

|                            |   |
|----------------------------|---|
| Subject analysis set title | Duplicate PD-L1 TPS Positive Participants |
| Subject analysis set type  | Sub-group analysis                        |

Subject analysis set description:

Participants with programmed cell death ligand 1 (PD-L1) positive expression status, defined as a PD-L1 tumor proportion score (TPS)  $\geq 1\%$ , received pembrolizumab 200 mg by IV infusion on Day 1 of each 3-week cycle for up to 24 months. Participants who stopped pembrolizumab as a result of obtaining a CR or those who stopped after receiving pembrolizumab for 24 months for reasons other than disease progression or intolerability, were eligible for up to an additional 1 year of treatment after progressive disease if they met the criteria for re-treatment. This duplicate arm is added as a workaround to accommodate the statistical analysis of the single arm to a fixed efficacy target within the electronic application.

|                            |   |
|----------------------------|---|
| Subject analysis set title | Duplicate Participants With a HPV-positive Tumor Biopsy |
| Subject analysis set type  | Sub-group analysis                                      |

Subject analysis set description:

Participants with a human papillomavirus (HPV) tumor biopsy received pembrolizumab 200 mg by IV infusion on Day 1 of each 3-week cycle for up to 24 months. Participants who stopped pembrolizumab as a result of obtaining a CR or those who stopped after receiving pembrolizumab for 24 months for reasons other than disease progression or intolerability, were eligible for up to an additional 1 year of treatment after progressive disease if they met the criteria for re-treatment. This duplicate arm is added as a workaround to accommodate the statistical analysis of the single arm to a fixed efficacy target within the electronic application.

### Primary: Objective Response Rate (ORR) by Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST 1.1) in All Participants

|                 |  |
|-----------------|--|
| End point title | Objective Response Rate (ORR) by Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST 1.1) in All Participants |
|-----------------|--|

End point description:

ORR was assessed by RECIST 1.1 by performing imaging every 6-9 weeks after the first dose of treatment. ORR was defined as the percentage of participants in the analysis population who had a Complete Response (CR) defined as a disappearance of all target lesions with pathological lymph nodes having a reduction in short axis to  $<10$  mm or Partial Response (PR) defined as at least a 30% decrease in the sum of diameters (SPD) of target lesions, using the baseline SPD as a reference. Participants with missing data were considered non-responders. The analysis included all participants who received  $\geq 1$

dose of study treatment.

|                      |         |
|----------------------|---------|
| End point type       | Primary |
| End point timeframe: |         |
| Up to 36 months      |         |

| End point values                  | Pembrolizumab        | Duplicate<br>Pembrolizumab<br>Arm |  |  |
|-----------------------------------|----------------------|-----------------------------------|--|--|
| Subject group type                | Subject analysis set | Subject analysis set              |  |  |
| Number of subjects analysed       | 171                  | 171                               |  |  |
| Units: Percentage of participants |                      |                                   |  |  |
| number (confidence interval 95%)  | 16.4 (11.2 to 22.8)  | 16.4 (11.2 to 22.8)               |  |  |

## Statistical analyses

|   |   |
|---|---|
| Statistical analysis title  | ORR Comparison to Fixed Efficacy Target     |
| Statistical analysis description:   |   |
| ORR was evaluated statistically by comparing the ORR for pembrolizumab to a fixed efficacy target of 5% using an exact test of binomial distribution. |   |
| Comparison groups   | Pembrolizumab v Duplicate Pembrolizumab Arm |
| Number of subjects included in analysis   | 342   |
| Analysis specification  | Pre-specified                               |
| Analysis type   | superiority                                 |
| P-value   | < 0.001 <sup>[1]</sup>                      |
| Method  | exact binomial distribution                 |

Notes:

[1] - null hypothesis (H0):  $p \leq 0.05$  versus alternate hypothesis (H1):  $p > 0.05$

## Primary: Objective Response Rate (ORR) by Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST 1.1) in Strong Programmed Cell Death Ligand 1 (PD-L1) Positive Participants

|                 |   |
|-----------------|---|
| End point title | Objective Response Rate (ORR) by Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST 1.1) in Strong Programmed Cell Death Ligand 1 (PD-L1) Positive Participants |
|-----------------|---|

End point description:

Participants with a strong PD-L1 expression status were evaluated for ORR by RECIST 1.1. The expression of PD-L1 was determined by immunohistochemistry (IHC) and strong PD-L1 positive was defined as a PD-L1 tumor proportion score (TPS)  $\geq 50\%$ . ORR was assessed by performing imaging every 6-9 weeks after the first dose of treatment. ORR was defined as the percentage of participants in the analysis population who had a CR defined as a disappearance of all target lesions with pathological lymph nodes having a reduction in short axis to  $< 10$  mm or PR defined as at least a 30% decrease in the SPD of target lesions, using the baseline SPD as a reference. Participants with missing data were considered non-responders. The analysis included all participants who received  $\geq 1$  dose of study treatment with a TPS  $\geq 50\%$ .

|                      |         |
|----------------------|---------|
| End point type       | Primary |
| End point timeframe: |         |
| Up to 36 months      |         |

| End point values                  | Strong PD-L1<br>TPS Positive<br>Participants | Duplicate<br>Strong PD-L1<br>TPS Positive<br>Participants |  |  |
|-----------------------------------|--|---|--|--|
| Subject group type                | Subject analysis set                         | Subject analysis set                                      |  |  |
| Number of subjects analysed       | 44   | 44  |  |  |
| Units: Percentage of participants |  |   |  |  |
| number (confidence interval 95%)  | 27.3 (15.0 to<br>42.8)                       | 27.3 (15.0 to<br>42.8)                                    |  |  |

## Statistical analyses

| Statistical analysis title  | ORR Comparison to Fixed Efficacy Target   |
|---|---|
| Statistical analysis description:   |   |
| ORR was evaluated statistically by comparing the ORR for pembrolizumab to a fixed efficacy target of 5% using an exact test of binomial distribution. |   |
| Comparison groups   | Strong PD-L1 TPS Positive Participants v Duplicate Strong PD-L1 TPS Positive Participants |
| Number of subjects included in analysis   | 88  |
| Analysis specification  | Pre-specified   |
| Analysis type   | superiority   |
| P-value   | < 0.001 [2]   |
| Method  | exact binomial distribution   |

Notes:

[2] - null hypothesis (H0):  $p \leq 0.05$  versus alternate hypothesis (H1):  $p > 0.05$

## Primary: Number of Participants Discontinuing Study Drug Due to an AE

| End point title   | Number of Participants Discontinuing Study Drug Due to an |
|---|---|
| End point description:  |   |
| An AE was defined as any untoward medical occurrence in a participant administered a pharmaceutical product and which did not necessarily have to have a causal relationship with treatment. An AE could therefore be any unfavorable and unintended sign, symptom, or disease temporally associated with the use of the product, whether or not considered related to the product. Worsening of a preexisting condition temporally associated with the use of the product was also an AE. A serious adverse event was an AE that resulted in death, was life threatening, resulted in persistent or significant disability/incapacity, resulted in or prolonged an existing inpatient hospitalization, was a congenital anomaly/birth defect, was a cancer, was associated with an overdose, or was another important medical event. Per protocol, analysis for this outcome measure was performed during the initial (first) course of therapy. The analysis included all participants who received $\geq 1$ dose of study treatment. |   |
| End point type  | Primary   |
| End point timeframe:  |   |
| Up to 24 months   |   |

Notes:

[3] - 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: There was no statistical analysis planned for this endpoint.

|                             |                      |  |  |  |
|-----------------------------|----------------------|--|--|--|
| <b>End point values</b>     | Pembrolizumab        |  |  |  |
| Subject group type          | Subject analysis set |  |  |  |
| Number of subjects analysed | 171                  |  |  |  |
| Units: Participants         | 24                   |  |  |  |

## Statistical analyses

No statistical analyses for this end point

### Primary: Number of Participants Experiencing an Adverse Event (AE)

|                 |  |
|-----------------|--|
| End point title | Number of Participants Experiencing an Adverse Event (AE) <sup>[4]</sup> |
|-----------------|--|

End point description:

An AE was defined as any untoward medical occurrence in a participant administered a pharmaceutical product and which did not necessarily have to have a causal relationship with treatment. An AE could therefore be any unfavorable and unintended sign, symptom, or disease temporally associated with the use of the product, whether or not considered related to the product. Worsening of a preexisting condition temporally associated with the use of the product was also an AE. A serious adverse event was an AE that resulted in death, was life threatening, resulted in persistent or significant disability/incapacity, resulted in or prolonged an existing inpatient hospitalization, was a congenital anomaly/birth defect, was a cancer, was associated with an overdose, or was another important medical event. Per protocol, analysis for this outcome measure was performed during the initial (first) course of therapy. The analysis included all participants who received  $\geq 1$  dose of study treatment.

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

End point timeframe:

Up to 27 months

Notes:

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

Justification: There was no statistical analysis planned for this endpoint.

|                             |                      |  |  |  |
|-----------------------------|----------------------|--|--|--|
| <b>End point values</b>     | Pembrolizumab        |  |  |  |
| Subject group type          | Subject analysis set |  |  |  |
| Number of subjects analysed | 171                  |  |  |  |
| Units: Participants         | 166                  |  |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Objective Response Rate (ORR) by Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST 1.1) in Human Papillomavirus (HPV) Positive Tumors

|                 |  |
|-----------------|--|
| End point title | Objective Response Rate (ORR) by Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST 1.1) in Human Papillomavirus (HPV) Positive Tumors |
|-----------------|--|

End point description:

Participants with a HPV-positive tumor biopsy were evaluated for ORR by RECIST 1.1. ORR was assessed by performing imaging every 6-9 weeks after the first dose of treatment. ORR was defined as the percentage of participants in the analysis population who had a CR defined as a disappearance of all target lesions with pathological lymph nodes having a reduction in short axis to  $<10$  mm or PR defined as at least a 30% decrease in the SPD of target lesions, using the baseline SPD as a reference. Participants with missing data were considered non-responders. The analysis included all participants

who received  $\geq 1$  dose of study treatment with a HPV-positive tumor.

|                      |           |
|----------------------|-----------|
| End point type       | Secondary |
| End point timeframe: |           |
| Up to 76.9 months    |           |

| End point values                  | Participants With a HPV-positive Tumor Biopsy | Duplicate Participants With a HPV-positive Tumor Biopsy |  |  |
|-----------------------------------|---|---|--|--|
| Subject group type                | Subject analysis set                          | Subject analysis set                                    |  |  |
| Number of subjects analysed       | 71  | 71  |  |  |
| Units: Percentage of participants |   |   |  |  |
| number (confidence interval 95%)  | 14.1 (7.0 to 24.4)                            | 14.1 (7.0 to 24.4)                                      |  |  |

## Statistical analyses

|   |   |
|---|---|
| Statistical analysis title  | ORR Comparison to Fixed Efficacy Target   |
| Statistical analysis description:   |   |
| ORR was evaluated statistically by comparing the ORR for pembrolizumab to a fixed efficacy target of 5% using an exact test of binomial distribution. |   |
| Comparison groups   | Participants With a HPV-positive Tumor Biopsy v Duplicate Participants With a HPV-positive Tumor Biopsy |
| Number of subjects included in analysis   | 142   |
| Analysis specification  | Pre-specified   |
| Analysis type   | superiority   |
| P-value   | = 0.0027 [5]  |
| Method  | exact binomial distribution   |

Notes:

[5] - null hypothesis (H0):  $p \leq 0.05$  versus alternate hypothesis (H1):  $p > 0.05$

## Secondary: Objective Response Rate (ORR) by Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST 1.1) in Programmed Cell Death Ligand 1 (PD-L1) Positive Participants

|                 |  |
|-----------------|--|
| End point title | Objective Response Rate (ORR) by Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST 1.1) in Programmed Cell Death Ligand 1 (PD-L1) Positive Participants |
|-----------------|--|

End point description:

Participants with a positive PD-L1 expression status were evaluated for ORR by RECIST 1.1. PD-L1 expression was determined by IHC and PD-L1 positive was defined as a PD-L1 TPS  $\geq 1\%$ . ORR was assessed by performing imaging every 6-9 weeks after the first dose of treatment. ORR was defined as the percentage of participants in the analysis population who had a CR defined as a disappearance of all target lesions with pathological lymph nodes having a reduction in short axis to  $< 10$  mm or PR defined as at least a 30% decrease in the SPD of target lesions, using the baseline SPD as a reference. Participants with missing data were considered non-responders. The analysis included all participants who received  $\geq 1$  dose of study treatment with a TPS  $\geq 1\%$ .

|                      |           |
|----------------------|-----------|
| End point type       | Secondary |
| End point timeframe: |           |
| Up to 76.9 months    |           |

| End point values                  | PD-L1 TPS Positive Participants | Duplicate PD-L1 TPS Positive Participants |  |  |
|-----------------------------------|---------------------------------|---|--|--|
| Subject group type                | Subject analysis set            | Subject analysis set                      |  |  |
| Number of subjects analysed       | 121                             | 121                                       |  |  |
| Units: Percentage of participants |                                 |   |  |  |
| number (confidence interval 95%)  | 18.2 (11.8 to 26.2)             | 18.2 (11.8 to 26.2)                       |  |  |

## Statistical analyses

| Statistical analysis title  | ORR Comparison to Fixed Efficacy Target                                     |
|---|---|
| Statistical analysis description:   |   |
| ORR was evaluated statistically by comparing the ORR for pembrolizumab to a fixed efficacy target of 5% using an exact test of binomial distribution. |   |
| Comparison groups   | PD-L1 TPS Positive Participants v Duplicate PD-L1 TPS Positive Participants |
| Number of subjects included in analysis   | 242   |
| Analysis specification  | Pre-specified   |
| Analysis type   | superiority   |
| P-value   | < 0.001 <sup>[6]</sup>  |
| Method  | exact binomial distribution   |

Notes:

[6] - null hypothesis (H0):  $p \leq 0.05$  versus alternate hypothesis (H1):  $p > 0.05$

## Secondary: Objective Response Rate (ORR) by Modified Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST 1.1) in All Participants

|                 |   |
|-----------------|---|
| End point title | Objective Response Rate (ORR) by Modified Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST 1.1) in All Participants |
|-----------------|---|

End point description:

ORR was assessed by modified RECIST 1.1 by performing imaging every 6-9 weeks after the first dose. ORR was defined as the percentage of participants who had a CR defined as a disappearance of all target lesions with pathological lymph nodes having a reduction in short axis to <10 mm or PR defined as at least a 30% decrease in the sum of diameters of target lesions, using the baseline SPD as a reference. If imaging shows disease progression (PD) imaging was repeated 4 weeks later for confirmation. PD was defined as  $\geq 20\%$  increase in SPD of target lesions and new measurable lesions, taking as reference the smallest sum recorded since treatment started. Participants with missing data were considered non-responders. The analysis included all participants who received  $\geq 1$  dose of study treatment.

|                      |           |
|----------------------|-----------|
| End point type       | Secondary |
| End point timeframe: |           |
| Up to 76.9 months    |           |

| End point values                  | Pembrolizumab        | Duplicate Pembrolizumab Arm |  |  |
|-----------------------------------|----------------------|-----------------------------|--|--|
| Subject group type                | Subject analysis set | Subject analysis set        |  |  |
| Number of subjects analysed       | 171                  | 171                         |  |  |
| Units: Percentage of participants |                      |                             |  |  |
| number (confidence interval 95%)  | 16.4 (11.2 to 22.8)  | 16.4 (11.2 to 22.8)         |  |  |

## Statistical analyses

| Statistical analysis title  | ORR Comparison to Fixed Efficacy Target     |
|---|---|
| Statistical analysis description:   |   |
| ORR was evaluated statistically by comparing the ORR for pembrolizumab to a fixed efficacy target of 5% using an exact test of binomial distribution. |   |
| Comparison groups   | Pembrolizumab v Duplicate Pembrolizumab Arm |
| Number of subjects included in analysis   | 342   |
| Analysis specification  | Pre-specified                               |
| Analysis type   | superiority                                 |
| P-value   | < 0.001 [7]                                 |
| Method  | exact binomial distribution                 |

Notes:

[7] - null hypothesis (H0):  $p \leq 0.05$  versus alternate hypothesis (H1):  $p > 0.05$

## Secondary: Objective Response Rate (ORR) by Modified Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST 1.1) in Programmed Cell Death Ligand 1 (PD-L1) Positive Participants

|                 |   |
|-----------------|---|
| End point title | Objective Response Rate (ORR) by Modified Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST 1.1) in Programmed Cell Death Ligand 1 (PD-L1) Positive Participants |
|-----------------|---|

End point description:

Participants with a positive PD-L1 expression status were evaluated for ORR by modified RECIST 1.1. PD-L1 expression was determined by IHC and PD-L1 positive was defined as a TPS  $\geq 1\%$ . ORR was assessed by imaging every 6-9 weeks after the first dose. ORR was defined as the percentage of participants who had a CR defined as a disappearance of all target lesions with pathological lymph nodes having a reduction in short axis to  $< 10$  mm or PR defined as at least a 30% decrease in the SPD of target lesions, using the baseline SPD as a reference. If imaging shows PD imaging was repeated 4 weeks later for confirmation. PD was defined as  $\geq 20\%$  increase in the SPD of target lesions and new measurable lesions, taking as reference the smallest sum recorded since treatment started. Participants with missing data were considered non-responders. The analysis included all participants who received  $\geq 1$  dose of study treatment with a tumor proportion score  $\geq 1\%$ .

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

End point timeframe:

Up to 76.9 months

| End point values                  | PD-L1 TPS Positive Participants | Duplicate PD-L1 TPS Positive Participants |  |  |
|-----------------------------------|---------------------------------|---|--|--|
| Subject group type                | Subject analysis set            | Subject analysis set                      |  |  |
| Number of subjects analysed       | 121                             | 121                                       |  |  |
| Units: Percentage of participants |                                 |   |  |  |
| number (confidence interval 95%)  | 18.2 (11.8 to 26.2)             | 18.2 (11.8 to 26.2)                       |  |  |

## Statistical analyses

| Statistical analysis title  | ORR Comparison to Fixed Efficacy Target                                     |
|---|---|
| Statistical analysis description:   |   |
| ORR was evaluated statistically by comparing the ORR for pembrolizumab to a fixed efficacy target of 5% using an exact test of binomial distribution. |   |
| Comparison groups   | PD-L1 TPS Positive Participants v Duplicate PD-L1 TPS Positive Participants |
| Number of subjects included in analysis   | 242   |
| Analysis specification  | Pre-specified   |
| Analysis type   | superiority   |
| P-value   | < 0.001 <sup>[8]</sup>  |
| Method  | exact binomial distribution   |

Notes:

[8] - null hypothesis (H0):  $p \leq 0.05$  versus alternate hypothesis (H1):  $p > 0.05$

## Secondary: Objective Response Rate (ORR) by Modified Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST 1.1) in Strong Programmed Cell Death Ligand 1 (PD-L1) Positive Participants

|                 |  |
|-----------------|--|
| End point title | Objective Response Rate (ORR) by Modified Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST 1.1) in Strong Programmed Cell Death Ligand 1 (PD-L1) Positive Participants |
|-----------------|--|

End point description:

Participants with a strong positive PD-L1 expression status were evaluated for ORR by modified RECIST 1.1. PD-L1 expression was determined by IHC and strong PD-L1 positive was defined as a TPS  $\geq 50\%$ . ORR was assessed by imaging every 6-9 weeks after the first dose. ORR was defined as the percentage of participants who had a CR defined as a disappearance of all target lesions with pathological lymph nodes having a reduction in short axis to  $< 10$  mm or PR defined as at least a 30% decrease in the SPD of target lesions, using the baseline SPD as a reference. If imaging shows PD imaging was repeated 4 weeks later for confirmation. PD was defined as  $\geq 20\%$  increase in the SPD of target lesions and new measurable lesions, taking as reference the smallest sum recorded since treatment started. Participants with missing data were considered non-responders. The analysis included all participants who received  $\geq 1$  dose of study treatment with a tumor proportion score  $\geq 50\%$ .

|                      |           |
|----------------------|-----------|
| End point type       | Secondary |
| End point timeframe: |           |
| Up to 76.9 months    |           |



| End point values                  | Strong PD-L1<br>TPS Positive<br>Participants | Duplicate<br>Strong PD-L1<br>TPS Positive<br>Participants |  |  |
|-----------------------------------|--|---|--|--|
| Subject group type                | Subject analysis set                         | Subject analysis set                                      |  |  |
| Number of subjects analysed       | 44   | 44  |  |  |
| Units: Percentage of participants |  |   |  |  |
| number (confidence interval 95%)  | 27.3 (15.0 to<br>42.8)                       | 27.3 (15.0 to<br>42.8)                                    |  |  |

## Statistical analyses

| Statistical analysis title   | ORR Comparison to Fixed Efficacy Target   |
|--|---|
| Statistical analysis description:<br>ORR was evaluated statistically by comparing the ORR for pembrolizumab to a fixed efficacy target of 5% using an exact test of binomial distribution. |   |
| Comparison groups  | Strong PD-L1 TPS Positive Participants v Duplicate Strong PD-L1 TPS Positive Participants |
| Number of subjects included in analysis  | 88  |
| Analysis specification   | Pre-specified   |
| Analysis type  | superiority   |
| P-value  | < 0.001 <sup>[9]</sup>  |
| Method   | exact binomial distribution   |

Notes:

[9] - null hypothesis (H0):  $p \leq 0.05$  versus alternate hypothesis (H1):  $p > 0.05$

## Secondary: Response Duration (DOR) by Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST 1.1) in All Participants

| End point title   | Response Duration (DOR) by Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST 1.1) in All Participants |
|---|--|
| End point description:<br>DOR was based on RECIST 1.1 and measured from the time of CR/PR (whichever was first recorded) until the first date that recurrent or PD was documented (taking as reference for PD the smallest measurements recorded on study). DOR was censored at the last tumor assessment date if a responder did not have PD or death. Non-responders were not included in the analysis. The lower and upper limits were estimated at the time of data cutoff. DOR was analyzed by the Kaplan-Meier method for censored data and reported in months. 9999=Upper limit not reached at time of data cut-off due to insufficient number of responding participants with relapse. The analysis included all participants who received $\geq 1$ dose of study treatment with a best overall response as confirmed CR or PR. |  |
| End point type  | Secondary  |
| End point timeframe:<br>Up to 76.9 months   |  |

| End point values              | Pembrolizumab         |  |  |  |
|-------------------------------|-----------------------|--|--|--|
| Subject group type            | Subject analysis set  |  |  |  |
| Number of subjects analysed   | 28                    |  |  |  |
| Units: Months                 |                       |  |  |  |
| median (full range (min-max)) | 15.7 (2.8 to<br>9999) |  |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Response Duration (DOR) by Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST 1.1) in Programmed Cell Death Ligand 1 (PD-L1) Positive Participants

|   |  |
|---|--|
| End point title   | Response Duration (DOR) by Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST 1.1) in Programmed Cell Death Ligand 1 (PD-L1) Positive Participants |
| End point description:<br>Participants with a positive PD-L1 expression status were evaluated for DOR based on RECIST 1.1. PD-L1 expression was determined by IHC and PD-L1 positive was defined as a PD-L1 combined positive score $\geq 1\%$ . DOR was measured from the time of CR/PR (whichever was first recorded) until the first date that recurrent or PD was documented (taking as reference for PD the smallest measurements recorded on study). DOR was censored at the last tumor assessment date if a responder did not have PD or death. Non-responders were not included in the analysis. The lower and upper limits were estimated at the time of data cutoff. DOR was analyzed by the Kaplan-Meier method for censored data and reported in months. 9999=Upper limit not reached at time of data cut-off due to insufficient number of responding participants with relapse. The analysis included all participants who received $\geq 1$ dose of study treatment with a combined positive score $\geq 1\%$ and a best overall response as confirmed CR or PR. |  |
| End point type  | Secondary  |
| End point timeframe:<br>Up to 76.9 months   |  |

| End point values              | PD-L1 CPS Positive Participants |  |  |  |
|-------------------------------|---------------------------------|--|--|--|
| Subject group type            | Subject analysis set            |  |  |  |
| Number of subjects analysed   | 25                              |  |  |  |
| Units: Months                 |                                 |  |  |  |
| median (full range (min-max)) | 15.7 (2.8 to 9999)              |  |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Response Duration (DOR) by Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST 1.1) in Strong Programmed Cell Death Ligand 1 (PD-L1) Positive Participants

|                 |   |
|-----------------|---|
| End point title | Response Duration (DOR) by Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST 1.1) in Strong Programmed Cell Death Ligand 1 (PD-L1) Positive Participants |
|-----------------|---|

---

**End point description:**

Participants with a strong PD-L1 expression status were evaluated for DOR based on RECIST 1.1. PD-L1 expression was determined by IHC and strong PD-L1 positive was defined as a PD-L1 tumor proportion score  $\geq 50\%$ . DOR was measured from the time of CR/PR (whichever was first recorded) until the first date that recurrent or PD was documented (taking as reference for PD the smallest measurements recorded on study). DOR was censored at the last tumor assessment date if a responder did not have PD or death. Non-responders were not included in the analysis. The lower and upper limits were estimated at the time of data cutoff. DOR was analyzed by the Kaplan-Meier method for censored data and reported in months. 9999=Upper limit not reached at time of data cut-off due to insufficient number of responding participants with relapse. The analysis included all participants who received  $\geq 1$  dose of study treatment with a tumor proportion score  $\geq 50\%$  and a best overall response as confirmed CR or PR.

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

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End point timeframe:

Up to 76.9 months

---

|                               |  |  |  |  |
|-------------------------------|--|--|--|--|
| <b>End point values</b>       | Strong PD-L1<br>TPS Positive<br>Participants |  |  |  |
| Subject group type            | Subject analysis set                         |  |  |  |
| Number of subjects analysed   | 12   |  |  |  |
| Units: Months                 |  |  |  |  |
| median (full range (min-max)) | 22.8 (4.2 to<br>9999)                        |  |  |  |

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**Statistical analyses**

No statistical analyses for this end point

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**Secondary: Progression-free Survival (PFS) by Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST 1.1) in All Participants**

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

---

End point description:

PFS was defined as the time from the first day of study treatment to the first documented PD per RECIST 1.1 or death due to any cause, whichever occurred first. Using RECIST 1.1, PD was defined as either a 20% relative increase in the sum of diameters of target lesions, taking as reference the smallest sum on study OR an absolute increase of  $>5$  mm the sum of lesions, OR the appearance of new lesions. PFS was analyzed by the Kaplan-Meier method for censored data and reported in months. Participant data were censored at last assessment. The analysis included all participants who received  $\geq 1$  dose of study treatment.

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

---

End point timeframe:

Up to 76.9 months

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|                                  |                      |  |  |  |
|----------------------------------|----------------------|--|--|--|
| <b>End point values</b>          | Pembrolizumab        |  |  |  |
| Subject group type               | Subject analysis set |  |  |  |
| Number of subjects analysed      | 171                  |  |  |  |
| Units: Months                    |                      |  |  |  |
| median (confidence interval 95%) | 2.1 (2.1 to 2.1)     |  |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Progression-free Survival (PFS) by Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST 1.1) in Strong Programmed Cell Death Ligand 1 (PD-L1) Positive Participants

|                 |   |
|-----------------|---|
| End point title | Progression-free Survival (PFS) by Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST 1.1) in Strong Programmed Cell Death Ligand 1 (PD-L1) Positive Participants |
|-----------------|---|

End point description:

Participants with a strong PD-L1 expression status were evaluated for PFS by modified RECIST 1.1. PD-L1 expression was determined by IHC and strong PD-L1 positive was defined as a PD-L1 tumor proportion score  $\geq 50\%$ . PFS was defined as the time from the first day of study treatment to the first documented PD per RECIST 1.1 or death due to any cause, whichever occurred first. Using RECIST 1.1, PD was defined as either a 20% relative increase in the sum of diameters of target lesions, taking as reference the smallest sum on study OR an absolute increase of  $>5$  mm the sum of lesions, OR the appearance of new lesions. PFS was analyzed by the Kaplan-Meier method for censored data and reported in months. Participant data were censored at last assessment. The analysis included all participants who received  $\geq 1$  dose of study treatment with a tumor proportion score  $\geq 50\%$ .

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

End point timeframe:

Up to 76.9 months

|                                  |  |  |  |  |
|----------------------------------|--|--|--|--|
| <b>End point values</b>          | Strong PD-L1<br>TPS Positive<br>Participants |  |  |  |
| Subject group type               | Subject analysis set                         |  |  |  |
| Number of subjects analysed      | 44   |  |  |  |
| Units: Months                    |  |  |  |  |
| median (confidence interval 95%) | 2.1 (1.8 to 3.6)                             |  |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Progression-free Survival (PFS) by Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST 1.1) in Programmed Cell Death Ligand 1 (PD-L1) Positive Participants

|                 |  |
|-----------------|--|
| End point title | Progression-free Survival (PFS) by Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST 1.1) in Programmed Cell Death Ligand 1 (PD-L1) Positive Participants |
|-----------------|--|

**End point description:**

Participants with a positive PD-L1 expression status were evaluated for PFS. PD-L1 expression was determined by IHC and PD-L1 positive was defined as a PD-L1 combined positive score  $\geq 1\%$ . PFS was defined as the time from the first day of study treatment to the first documented PD per RECIST 1.1 or death due to any cause, whichever occurred first. Using RECIST 1.1, PD was defined as either a 20% relative increase in the sum of diameters of target lesions, taking as reference the smallest sum on study OR an absolute increase of  $>5$  mm the sum of lesions, OR the appearance of new lesions. PFS was analyzed by the Kaplan-Meier method for censored data and reported in months. Participant data were censored at last assessment. The analysis included all participants who received  $\geq 1$  dose of study treatment with a combined positive score  $\geq 1\%$ .

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

End point timeframe:

Up to 76.9 months

| End point values                 | PD-L1 CPS Positive Participants |  |  |  |
|----------------------------------|---------------------------------|--|--|--|
| Subject group type               | Subject analysis set            |  |  |  |
| Number of subjects analysed      | 141                             |  |  |  |
| Units: Months                    |                                 |  |  |  |
| median (confidence interval 95%) | 2.1 (2.0 to 2.1)                |  |  |  |

**Statistical analyses**

No statistical analyses for this end point

**Secondary: Overall Survival (OS) in Programmed Cell Death Ligand 1 (PD-L1) Positive Participants**

|                 |   |
|-----------------|---|
| End point title | Overall Survival (OS) in Programmed Cell Death Ligand 1 (PD-L1) Positive Participants |
|-----------------|---|

**End point description:**

Participants with a positive PD-L1 expression status were evaluated for OS. PD-L1 expression was determined by IHC and PD-L1 positive was defined as a PD-L1 combined positive score  $\geq 1\%$ . OS was defined as the time from the first day of study treatment to death due to any cause. OS was analyzed by the Kaplan-Meier method for censored data and reported in months. Participant data were censored at last assessment. The analysis included all participants who received  $\geq 1$  dose of study treatment with a combined positive score  $\geq 1\%$ .

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

End point timeframe:

Up to 76.9 months

| End point values                 | PD-L1 CPS Positive Participants |  |  |  |
|----------------------------------|---------------------------------|--|--|--|
| Subject group type               | Subject analysis set            |  |  |  |
| Number of subjects analysed      | 141                             |  |  |  |
| Units: Months                    |                                 |  |  |  |
| median (confidence interval 95%) | 9.0 (6.2 to 11.8)               |  |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Overall Survival (OS) in All Participants

|                 |   |
|-----------------|---|
| End point title | Overall Survival (OS) in All Participants |
|-----------------|---|

End point description:

OS was defined as the time from the first day of study treatment to death due to any cause. OS was analyzed by the Kaplan-Meier method for censored data and reported in months. Participant data were censored at last assessment. The analysis included all participants who received  $\geq 1$  dose of study treatment.

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

End point timeframe:

Up to 76.9 months

| End point values                 | Pembrolizumab        |  |  |  |
|----------------------------------|----------------------|--|--|--|
| Subject group type               | Subject analysis set |  |  |  |
| Number of subjects analysed      | 171                  |  |  |  |
| Units: Months                    |                      |  |  |  |
| median (confidence interval 95%) | 8.5 (6.6 to 11.1)    |  |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Overall Survival (OS) in Strong Programmed Cell Death Ligand 1 (PD-L1) Positive Participants

|                 |  |
|-----------------|--|
| End point title | Overall Survival (OS) in Strong Programmed Cell Death Ligand 1 (PD-L1) Positive Participants |
|-----------------|--|

End point description:

Participants with a strong PD-L1 expression status were evaluated for OS. PD-L1 expression was determined by IHC and strong PD-L1 positive was defined as a PD-L1 tumor proportion score  $\geq 50\%$ . OS was defined as the time from the first day of study treatment to death due to any cause. OS was analyzed by the Kaplan-Meier method for censored data and reported in months. Participant data were censored at last assessment. The analysis included all participants who received  $\geq 1$  dose of study treatment with a tumor proportion score  $\geq 50\%$ .

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

End point timeframe:

Up to 76.9 months

|                                  |  |  |  |  |
|----------------------------------|--|--|--|--|
| <b>End point values</b>          | Strong PD-L1<br>TPS Positive<br>Participants |  |  |  |
| Subject group type               | Subject analysis set                         |  |  |  |
| Number of subjects analysed      | 44   |  |  |  |
| Units: Months                    |  |  |  |  |
| median (confidence interval 95%) | 6.9 (4.0 to<br>11.8)                         |  |  |  |

### Statistical analyses

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No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

First Course: Up to 76.9 months

Second Course: Up to 53.3 months

First and second course dosing occurred concurrently

Adverse event reporting additional description:

All-cause mortality (ACM)=all allocated participants (n=172); AEs=all participants who received ≥1 dose of study treatment (n=171). Per protocol, Medical Dictionary for Regulatory Activities (MedDRA) terms neoplasm progression (NP), malignant NP, and disease progression not related to treatment were excluded.

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

### Dictionary used

|                    |        |
|--------------------|--------|
| Dictionary name    | MedDRA |
| Dictionary version | 24.0   |

### Reporting groups

|                       |                             |
|-----------------------|-----------------------------|
| Reporting group title | Pembrolizumab Second Course |
|-----------------------|-----------------------------|

Reporting group description:

Participants who met the criteria for retreatment received pembrolizumab 200 mg by IV infusion on Day 1 of each 3-week cycle for up to 1 year of treatment.

|                       |                            |
|-----------------------|----------------------------|
| Reporting group title | Pembrolizumab First Course |
|-----------------------|----------------------------|

Reporting group description:

Participants received pembrolizumab 200 mg by IV infusion on Day 1 of each 3-week cycle for up to 24 months. Participants who stopped pembrolizumab as a result of obtaining a CR or those who stopped after receiving pembrolizumab for 24 months for reasons other than disease progression or intolerability, were eligible for up to an additional 1 year of treatment after progressive disease if they met the criteria for re-treatment.

| Serious adverse events  | Pembrolizumab Second Course | Pembrolizumab First Course |  |
|---|-----------------------------|----------------------------|--|
| Total subjects affected by serious adverse events                   |                             |                            |  |
| subjects affected / exposed   | 1 / 3 (33.33%)              | 87 / 171 (50.88%)          |  |
| number of deaths (all causes)                                       | 2                           | 153                        |  |
| number of deaths resulting from adverse events                      | 0                           | 2                          |  |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |                             |                            |  |
| Infected neoplasm   |                             |                            |  |
| subjects affected / exposed   | 0 / 3 (0.00%)               | 1 / 171 (0.58%)            |  |
| occurrences causally related to treatment / all                     | 0 / 0                       | 0 / 1                      |  |
| deaths causally related to treatment / all                          | 0 / 0                       | 0 / 0                      |  |
| Basal cell carcinoma  |                             |                            |  |
| subjects affected / exposed   | 0 / 3 (0.00%)               | 1 / 171 (0.58%)            |  |
| occurrences causally related to treatment / all                     | 0 / 0                       | 0 / 1                      |  |
| deaths causally related to treatment / all                          | 0 / 0                       | 0 / 0                      |  |



|   |               |                 |  |
|---|---------------|-----------------|--|
| Appendix cancer                                 |               |                 |  |
| subjects affected / exposed                     | 0 / 3 (0.00%) | 1 / 171 (0.58%) |  |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0           |  |
| Cancer pain                                     |               |                 |  |
| subjects affected / exposed                     | 0 / 3 (0.00%) | 1 / 171 (0.58%) |  |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0           |  |
| Malignant melanoma                              |               |                 |  |
| subjects affected / exposed                     | 0 / 3 (0.00%) | 2 / 171 (1.17%) |  |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0           |  |
| Squamous cell carcinoma of skin                 |               |                 |  |
| subjects affected / exposed                     | 0 / 3 (0.00%) | 1 / 171 (0.58%) |  |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0           |  |
| Keratoacanthoma                                 |               |                 |  |
| subjects affected / exposed                     | 0 / 3 (0.00%) | 1 / 171 (0.58%) |  |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0           |  |
| Tumour associated fever                         |               |                 |  |
| subjects affected / exposed                     | 0 / 3 (0.00%) | 1 / 171 (0.58%) |  |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0           |  |
| Vascular disorders                              |               |                 |  |
| Hypotension                                     |               |                 |  |
| subjects affected / exposed                     | 0 / 3 (0.00%) | 1 / 171 (0.58%) |  |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0           |  |
| Deep vein thrombosis                            |               |                 |  |
| subjects affected / exposed                     | 0 / 3 (0.00%) | 1 / 171 (0.58%) |  |
| 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                                 |               |                 |  |  |
| Death   |               |                 |  |  |
| subjects affected / exposed                     | 0 / 3 (0.00%) | 3 / 171 (1.75%) |  |  |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 3           |  |  |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 3           |  |  |
| Malaise   |               |                 |  |  |
| subjects affected / exposed                     | 0 / 3 (0.00%) | 1 / 171 (0.58%) |  |  |
| occurrences causally related to treatment / all | 0 / 0         | 1 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0           |  |  |
| Facial pain                                     |               |                 |  |  |
| subjects affected / exposed                     | 0 / 3 (0.00%) | 1 / 171 (0.58%) |  |  |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0           |  |  |
| Systemic inflammatory response syndrome         |               |                 |  |  |
| subjects affected / exposed                     | 0 / 3 (0.00%) | 1 / 171 (0.58%) |  |  |
| occurrences causally related to treatment / all | 0 / 0         | 1 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0           |  |  |
| Oedema peripheral                               |               |                 |  |  |
| subjects affected / exposed                     | 0 / 3 (0.00%) | 1 / 171 (0.58%) |  |  |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0           |  |  |
| Pyrexia   |               |                 |  |  |
| subjects affected / exposed                     | 0 / 3 (0.00%) | 2 / 171 (1.17%) |  |  |
| occurrences causally related to treatment / all | 0 / 0         | 1 / 2           |  |  |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0           |  |  |
| Swelling face                                   |               |                 |  |  |
| subjects affected / exposed                     | 0 / 3 (0.00%) | 2 / 171 (1.17%) |  |  |
| occurrences causally related to treatment / all | 0 / 0         | 1 / 2           |  |  |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0           |  |  |
| Multiple organ dysfunction syndrome             |               |                 |  |  |
| subjects affected / exposed                     | 0 / 3 (0.00%) | 1 / 171 (0.58%) |  |  |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 1           |  |  |

|   |               |                 |  |
|---|---------------|-----------------|--|
| Chills  |               |                 |  |
| subjects affected / exposed                     | 0 / 3 (0.00%) | 1 / 171 (0.58%) |  |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0           |  |
| Immune system disorders                         |               |                 |  |
| Hypersensitivity                                |               |                 |  |
| subjects affected / exposed                     | 0 / 3 (0.00%) | 1 / 171 (0.58%) |  |
| 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 / 3 (0.00%) | 3 / 171 (1.75%) |  |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 3           |  |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 1           |  |
| Chronic obstructive pulmonary disease           |               |                 |  |
| subjects affected / exposed                     | 0 / 3 (0.00%) | 1 / 171 (0.58%) |  |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 1           |  |
| Haemoptysis                                     |               |                 |  |
| subjects affected / exposed                     | 0 / 3 (0.00%) | 2 / 171 (1.17%) |  |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0           |  |
| Dyspnoea  |               |                 |  |
| subjects affected / exposed                     | 0 / 3 (0.00%) | 2 / 171 (1.17%) |  |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 3           |  |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0           |  |
| Increased upper airway secretion                |               |                 |  |
| subjects affected / exposed                     | 0 / 3 (0.00%) | 1 / 171 (0.58%) |  |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0           |  |
| Laryngeal haemorrhage                           |               |                 |  |

|   |               |                 |  |
|---|---------------|-----------------|--|
| subjects affected / exposed                     | 0 / 3 (0.00%) | 1 / 171 (0.58%) |  |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0           |  |
| Pneumonitis                                     |               |                 |  |
| subjects affected / exposed                     | 0 / 3 (0.00%) | 3 / 171 (1.75%) |  |
| occurrences causally related to treatment / all | 0 / 0         | 3 / 3           |  |
| deaths causally related to treatment / all      | 0 / 0         | 1 / 1           |  |
| Pneumonia aspiration                            |               |                 |  |
| subjects affected / exposed                     | 0 / 3 (0.00%) | 8 / 171 (4.68%) |  |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 8           |  |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 3           |  |
| Pleural effusion                                |               |                 |  |
| subjects affected / exposed                     | 0 / 3 (0.00%) | 4 / 171 (2.34%) |  |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 4           |  |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0           |  |
| Stridor   |               |                 |  |
| subjects affected / exposed                     | 0 / 3 (0.00%) | 1 / 171 (0.58%) |  |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0           |  |
| Respiratory failure                             |               |                 |  |
| subjects affected / exposed                     | 0 / 3 (0.00%) | 2 / 171 (1.17%) |  |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 2           |  |
| Pulmonary embolism                              |               |                 |  |
| subjects affected / exposed                     | 0 / 3 (0.00%) | 4 / 171 (2.34%) |  |
| occurrences causally related to treatment / all | 0 / 0         | 1 / 4           |  |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0           |  |
| Pneumothorax                                    |               |                 |  |
| subjects affected / exposed                     | 0 / 3 (0.00%) | 2 / 171 (1.17%) |  |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0           |  |
| Aspiration                                      |               |                 |  |

|   |               |                 |  |
|---|---------------|-----------------|--|
| subjects affected / exposed                     | 0 / 3 (0.00%) | 1 / 171 (0.58%) |  |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0           |  |
| Hypoxia   |               |                 |  |
| subjects affected / exposed                     | 0 / 3 (0.00%) | 1 / 171 (0.58%) |  |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0           |  |
| Psychiatric disorders                           |               |                 |  |
| Completed suicide                               |               |                 |  |
| subjects affected / exposed                     | 0 / 3 (0.00%) | 1 / 171 (0.58%) |  |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 1           |  |
| Mental status changes                           |               |                 |  |
| subjects affected / exposed                     | 0 / 3 (0.00%) | 1 / 171 (0.58%) |  |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0           |  |
| Product issues                                  |               |                 |  |
| Device dislocation                              |               |                 |  |
| subjects affected / exposed                     | 0 / 3 (0.00%) | 2 / 171 (1.17%) |  |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0           |  |
| Investigations                                  |               |                 |  |
| Clostridium test positive                       |               |                 |  |
| subjects affected / exposed                     | 0 / 3 (0.00%) | 1 / 171 (0.58%) |  |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0           |  |
| Injury, poisoning and procedural complications  |               |                 |  |
| Fall  |               |                 |  |
| subjects affected / exposed                     | 0 / 3 (0.00%) | 1 / 171 (0.58%) |  |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0           |  |
| Post procedural haemorrhage                     |               |                 |  |

|   |               |                 |  |
|---|---------------|-----------------|--|
| subjects affected / exposed                     | 0 / 3 (0.00%) | 2 / 171 (1.17%) |  |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0           |  |
| Tracheal obstruction                            |               |                 |  |
| subjects affected / exposed                     | 0 / 3 (0.00%) | 1 / 171 (0.58%) |  |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0           |  |
| Radiation oesophagitis                          |               |                 |  |
| subjects affected / exposed                     | 0 / 3 (0.00%) | 1 / 171 (0.58%) |  |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0           |  |
| Gastrointestinal stoma complication             |               |                 |  |
| subjects affected / exposed                     | 0 / 3 (0.00%) | 1 / 171 (0.58%) |  |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 1           |  |
| Subdural haematoma                              |               |                 |  |
| subjects affected / exposed                     | 0 / 3 (0.00%) | 1 / 171 (0.58%) |  |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 1           |  |
| Traumatic fracture                              |               |                 |  |
| subjects affected / exposed                     | 0 / 3 (0.00%) | 1 / 171 (0.58%) |  |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0           |  |
| Cardiac disorders                               |               |                 |  |
| Cardiac arrest                                  |               |                 |  |
| subjects affected / exposed                     | 0 / 3 (0.00%) | 2 / 171 (1.17%) |  |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 2           |  |
| Atrial fibrillation                             |               |                 |  |
| subjects affected / exposed                     | 0 / 3 (0.00%) | 3 / 171 (1.75%) |  |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 3           |  |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0           |  |
| Myocardial infarction                           |               |                 |  |

|   |               |                 |  |
|---|---------------|-----------------|--|
| subjects affected / exposed                     | 0 / 3 (0.00%) | 3 / 171 (1.75%) |  |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 3           |  |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 1           |  |
| Pericardial effusion                            |               |                 |  |
| subjects affected / exposed                     | 0 / 3 (0.00%) | 1 / 171 (0.58%) |  |
| occurrences causally related to treatment / all | 0 / 0         | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0           |  |
| Acute coronary syndrome                         |               |                 |  |
| subjects affected / exposed                     | 0 / 3 (0.00%) | 1 / 171 (0.58%) |  |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0           |  |
| Nervous system disorders                        |               |                 |  |
| Altered state of consciousness                  |               |                 |  |
| subjects affected / exposed                     | 0 / 3 (0.00%) | 1 / 171 (0.58%) |  |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0           |  |
| Cerebrovascular accident                        |               |                 |  |
| subjects affected / exposed                     | 0 / 3 (0.00%) | 1 / 171 (0.58%) |  |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 1           |  |
| Cerebral haemorrhage                            |               |                 |  |
| subjects affected / exposed                     | 0 / 3 (0.00%) | 1 / 171 (0.58%) |  |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0           |  |
| Depressed level of consciousness                |               |                 |  |
| subjects affected / exposed                     | 0 / 3 (0.00%) | 1 / 171 (0.58%) |  |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0           |  |
| Cranial nerve paralysis                         |               |                 |  |
| subjects affected / exposed                     | 0 / 3 (0.00%) | 1 / 171 (0.58%) |  |
| occurrences causally related to treatment / all | 0 / 0         | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0           |  |
| Dizziness                                       |               |                 |  |

|   |               |                 |  |
|---|---------------|-----------------|--|
| subjects affected / exposed                     | 0 / 3 (0.00%) | 1 / 171 (0.58%) |  |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0           |  |
| Headache  |               |                 |  |
| subjects affected / exposed                     | 0 / 3 (0.00%) | 1 / 171 (0.58%) |  |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0           |  |
| Seizure   |               |                 |  |
| subjects affected / exposed                     | 0 / 3 (0.00%) | 1 / 171 (0.58%) |  |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0           |  |
| Spinal cord compression                         |               |                 |  |
| subjects affected / exposed                     | 0 / 3 (0.00%) | 1 / 171 (0.58%) |  |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0           |  |
| Syncope   |               |                 |  |
| subjects affected / exposed                     | 0 / 3 (0.00%) | 4 / 171 (2.34%) |  |
| occurrences causally related to treatment / all | 0 / 0         | 1 / 4           |  |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0           |  |
| Amyotrophic lateral sclerosis                   |               |                 |  |
| subjects affected / exposed                     | 0 / 3 (0.00%) | 1 / 171 (0.58%) |  |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 1           |  |
| Blood and lymphatic system disorders            |               |                 |  |
| Neutropenia                                     |               |                 |  |
| subjects affected / exposed                     | 0 / 3 (0.00%) | 1 / 171 (0.58%) |  |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0           |  |
| Anaemia   |               |                 |  |
| subjects affected / exposed                     | 0 / 3 (0.00%) | 1 / 171 (0.58%) |  |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0           |  |
| Febrile neutropenia                             |               |                 |  |



|   |                |                 |  |
|---|----------------|-----------------|--|
| subjects affected / exposed                     | 1 / 3 (33.33%) | 0 / 171 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Gastrointestinal disorders                      |                |                 |  |
| Colitis   |                |                 |  |
| subjects affected / exposed                     | 0 / 3 (0.00%)  | 1 / 171 (0.58%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Constipation                                    |                |                 |  |
| subjects affected / exposed                     | 0 / 3 (0.00%)  | 2 / 171 (1.17%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Diarrhoea                                       |                |                 |  |
| subjects affected / exposed                     | 0 / 3 (0.00%)  | 2 / 171 (1.17%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 1 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Impaired gastric emptying                       |                |                 |  |
| subjects affected / exposed                     | 0 / 3 (0.00%)  | 1 / 171 (0.58%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Dysphagia                                       |                |                 |  |
| subjects affected / exposed                     | 0 / 3 (0.00%)  | 3 / 171 (1.75%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 3           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Nausea  |                |                 |  |
| subjects affected / exposed                     | 0 / 3 (0.00%)  | 3 / 171 (1.75%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 3           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Pancreatitis                                    |                |                 |  |
| subjects affected / exposed                     | 0 / 3 (0.00%)  | 1 / 171 (0.58%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Mouth haemorrhage                               |                |                 |  |

|   |               |                 |  |
|---|---------------|-----------------|--|
| subjects affected / exposed                     | 0 / 3 (0.00%) | 1 / 171 (0.58%) |  |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0           |  |
| Vomiting  |               |                 |  |
| subjects affected / exposed                     | 0 / 3 (0.00%) | 1 / 171 (0.58%) |  |
| occurrences causally related to treatment / all | 0 / 0         | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0           |  |
| Salivary duct inflammation                      |               |                 |  |
| subjects affected / exposed                     | 0 / 3 (0.00%) | 1 / 171 (0.58%) |  |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0           |  |
| Upper gastrointestinal haemorrhage              |               |                 |  |
| subjects affected / exposed                     | 0 / 3 (0.00%) | 1 / 171 (0.58%) |  |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0           |  |
| Hepatobiliary disorders                         |               |                 |  |
| Bile duct stenosis                              |               |                 |  |
| subjects affected / exposed                     | 0 / 3 (0.00%) | 1 / 171 (0.58%) |  |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0           |  |
| Hepatitis                                       |               |                 |  |
| subjects affected / exposed                     | 0 / 3 (0.00%) | 1 / 171 (0.58%) |  |
| occurrences causally related to treatment / all | 0 / 0         | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0           |  |
| Skin and subcutaneous tissue disorders          |               |                 |  |
| Angioedema                                      |               |                 |  |
| subjects affected / exposed                     | 0 / 3 (0.00%) | 1 / 171 (0.58%) |  |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0           |  |
| Endocrine disorders                             |               |                 |  |
| Adrenal insufficiency                           |               |                 |  |
| subjects affected / exposed                     | 0 / 3 (0.00%) | 1 / 171 (0.58%) |  |
| occurrences causally related to treatment / all | 0 / 0         | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0           |  |

|   |               |                 |  |
|---|---------------|-----------------|--|
| Hyperthyroidism                                 |               |                 |  |
| subjects affected / exposed                     | 0 / 3 (0.00%) | 1 / 171 (0.58%) |  |
| occurrences causally related to treatment / all | 0 / 0         | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0           |  |
| Musculoskeletal and connective tissue disorders |               |                 |  |
| Muscular weakness                               |               |                 |  |
| subjects affected / exposed                     | 0 / 3 (0.00%) | 1 / 171 (0.58%) |  |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0           |  |
| Neck pain                                       |               |                 |  |
| subjects affected / exposed                     | 0 / 3 (0.00%) | 1 / 171 (0.58%) |  |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0           |  |
| Arthritis                                       |               |                 |  |
| subjects affected / exposed                     | 0 / 3 (0.00%) | 1 / 171 (0.58%) |  |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0           |  |
| Infections and infestations                     |               |                 |  |
| Cellulitis                                      |               |                 |  |
| subjects affected / exposed                     | 0 / 3 (0.00%) | 3 / 171 (1.75%) |  |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 3           |  |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0           |  |
| Clostridium difficile colitis                   |               |                 |  |
| subjects affected / exposed                     | 0 / 3 (0.00%) | 1 / 171 (0.58%) |  |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0           |  |
| Empyema   |               |                 |  |
| subjects affected / exposed                     | 0 / 3 (0.00%) | 1 / 171 (0.58%) |  |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0           |  |
| Endocarditis bacterial                          |               |                 |  |
| subjects affected / exposed                     | 0 / 3 (0.00%) | 1 / 171 (0.58%) |  |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0           |  |

|   |               |                  |  |
|---|---------------|------------------|--|
| Osteomyelitis                                   |               |                  |  |
| subjects affected / exposed                     | 0 / 3 (0.00%) | 1 / 171 (0.58%)  |  |
| occurrences causally related to treatment / all | 0 / 0         | 1 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0            |  |
| Pneumonia                                       |               |                  |  |
| subjects affected / exposed                     | 0 / 3 (0.00%) | 15 / 171 (8.77%) |  |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 18           |  |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 1            |  |
| Septic shock                                    |               |                  |  |
| subjects affected / exposed                     | 0 / 3 (0.00%) | 2 / 171 (1.17%)  |  |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 1            |  |
| Sepsis  |               |                  |  |
| subjects affected / exposed                     | 0 / 3 (0.00%) | 2 / 171 (1.17%)  |  |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0            |  |
| Pneumonia staphylococcal                        |               |                  |  |
| subjects affected / exposed                     | 0 / 3 (0.00%) | 2 / 171 (1.17%)  |  |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 1            |  |
| Soft tissue infection                           |               |                  |  |
| subjects affected / exposed                     | 0 / 3 (0.00%) | 1 / 171 (0.58%)  |  |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0            |  |
| Staphylococcal bacteraemia                      |               |                  |  |
| subjects affected / exposed                     | 0 / 3 (0.00%) | 2 / 171 (1.17%)  |  |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0            |  |
| Staphylococcal sepsis                           |               |                  |  |
| subjects affected / exposed                     | 0 / 3 (0.00%) | 1 / 171 (0.58%)  |  |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0            |  |
| Tracheitis                                      |               |                  |  |

|   |                |                 |  |
|---|----------------|-----------------|--|
| subjects affected / exposed                     | 0 / 3 (0.00%)  | 1 / 171 (0.58%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Tracheobronchitis                               |                |                 |  |
| subjects affected / exposed                     | 1 / 3 (33.33%) | 1 / 171 (0.58%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Wound infection                                 |                |                 |  |
| subjects affected / exposed                     | 0 / 3 (0.00%)  | 1 / 171 (0.58%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Urinary tract infection                         |                |                 |  |
| subjects affected / exposed                     | 0 / 3 (0.00%)  | 1 / 171 (0.58%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Pneumonia escherichia                           |                |                 |  |
| subjects affected / exposed                     | 0 / 3 (0.00%)  | 1 / 171 (0.58%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Pseudomonas infection                           |                |                 |  |
| subjects affected / exposed                     | 0 / 3 (0.00%)  | 1 / 171 (0.58%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Vascular device infection                       |                |                 |  |
| subjects affected / exposed                     | 0 / 3 (0.00%)  | 1 / 171 (0.58%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Metabolism and nutrition disorders              |                |                 |  |
| Cachexia  |                |                 |  |
| subjects affected / exposed                     | 0 / 3 (0.00%)  | 1 / 171 (0.58%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Dehydration                                     |                |                 |  |

|   |               |                 |  |
|---|---------------|-----------------|--|
| subjects affected / exposed                     | 0 / 3 (0.00%) | 5 / 171 (2.92%) |  |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 6           |  |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0           |  |
| Diabetes mellitus                               |               |                 |  |
| subjects affected / exposed                     | 0 / 3 (0.00%) | 2 / 171 (1.17%) |  |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 1           |  |
| Diabetic ketoacidosis                           |               |                 |  |
| subjects affected / exposed                     | 0 / 3 (0.00%) | 1 / 171 (0.58%) |  |
| occurrences causally related to treatment / all | 0 / 0         | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0         | 1 / 1           |  |
| Decreased appetite                              |               |                 |  |
| subjects affected / exposed                     | 0 / 3 (0.00%) | 1 / 171 (0.58%) |  |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0           |  |
| Hypernatraemia                                  |               |                 |  |
| subjects affected / exposed                     | 0 / 3 (0.00%) | 1 / 171 (0.58%) |  |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0           |  |
| Hyperkalaemia                                   |               |                 |  |
| subjects affected / exposed                     | 0 / 3 (0.00%) | 1 / 171 (0.58%) |  |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0           |  |
| Hypercalcaemia                                  |               |                 |  |
| subjects affected / exposed                     | 0 / 3 (0.00%) | 5 / 171 (2.92%) |  |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 5           |  |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0           |  |
| Hypoglycaemia                                   |               |                 |  |
| subjects affected / exposed                     | 0 / 3 (0.00%) | 2 / 171 (1.17%) |  |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0           |  |
| Hypokalaemia                                    |               |                 |  |

|   |               |                 |  |
|---|---------------|-----------------|--|
| subjects affected / exposed                     | 0 / 3 (0.00%) | 1 / 171 (0.58%) |  |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0           |  |
| Type 1 diabetes mellitus                        |               |                 |  |
| subjects affected / exposed                     | 0 / 3 (0.00%) | 1 / 171 (0.58%) |  |
| occurrences causally related to treatment / all | 0 / 0         | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0           |  |
| Hyponatraemia                                   |               |                 |  |
| subjects affected / exposed                     | 0 / 3 (0.00%) | 3 / 171 (1.75%) |  |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 3           |  |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0           |  |

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

| <b>Non-serious adverse events</b>                     | Pembrolizumab<br>Second Course | Pembrolizumab First<br>Course |  |
|---|--------------------------------|-------------------------------|--|
| Total subjects affected by non-serious adverse events |                                |                               |  |
| subjects affected / exposed                           | 3 / 3 (100.00%)                | 158 / 171 (92.40%)            |  |
| Vascular disorders                                    |                                |                               |  |
| Hypotension   |                                |                               |  |
| subjects affected / exposed                           | 0 / 3 (0.00%)                  | 16 / 171 (9.36%)              |  |
| occurrences (all)                                     | 0                              | 17                            |  |
| Hypertension  |                                |                               |  |
| subjects affected / exposed                           | 0 / 3 (0.00%)                  | 11 / 171 (6.43%)              |  |
| occurrences (all)                                     | 0                              | 17                            |  |
| Lymphoedema   |                                |                               |  |
| subjects affected / exposed                           | 1 / 3 (33.33%)                 | 2 / 171 (1.17%)               |  |
| occurrences (all)                                     | 1                              | 2                             |  |
| General disorders and administration site conditions  |                                |                               |  |
| Fatigue   |                                |                               |  |
| subjects affected / exposed                           | 0 / 3 (0.00%)                  | 67 / 171 (39.18%)             |  |
| occurrences (all)                                     | 0                              | 71                            |  |
| Pyrexia   |                                |                               |  |
| subjects affected / exposed                           | 0 / 3 (0.00%)                  | 10 / 171 (5.85%)              |  |
| occurrences (all)                                     | 0                              | 11                            |  |
| Oedema peripheral                                     |                                |                               |  |

|  |   |  |  |
|--|---|--|--|
| subjects affected / exposed<br>occurrences (all)   | 0 / 3 (0.00%)<br>0  | 11 / 171 (6.43%)<br>13   |  |
| Respiratory, thoracic and mediastinal disorders<br>Cough<br>subjects affected / exposed<br>occurrences (all)<br><br>Dyspnoea<br>subjects affected / exposed<br>occurrences (all)<br><br>Rhinitis allergic<br>subjects affected / exposed<br>occurrences (all)  | 0 / 3 (0.00%)<br>0<br><br>1 / 3 (33.33%)<br>1<br><br>1 / 3 (33.33%)<br>1  | 38 / 171 (22.22%)<br>39<br><br>23 / 171 (13.45%)<br>26<br><br>2 / 171 (1.17%)<br>2   |  |
| Psychiatric disorders<br>Insomnia<br>subjects affected / exposed<br>occurrences (all)<br><br>Depression<br>subjects affected / exposed<br>occurrences (all)  | 0 / 3 (0.00%)<br>0<br><br>1 / 3 (33.33%)<br>1   | 18 / 171 (10.53%)<br>19<br><br>7 / 171 (4.09%)<br>7  |  |
| Investigations<br>Alanine aminotransferase increased<br>subjects affected / exposed<br>occurrences (all)<br><br>Aspartate aminotransferase increased<br>subjects affected / exposed<br>occurrences (all)<br><br>Weight decreased<br>subjects affected / exposed<br>occurrences (all)<br><br>Lymphocyte count decreased<br>subjects affected / exposed<br>occurrences (all)<br><br>Blood alkaline phosphatase increased<br>subjects affected / exposed<br>occurrences (all) | 0 / 3 (0.00%)<br>0<br><br>0 / 3 (0.00%)<br>0<br><br>0 / 3 (0.00%)<br>0<br><br>0 / 3 (0.00%)<br>0<br><br>1 / 3 (33.33%)<br>1 | 11 / 171 (6.43%)<br>13<br><br>19 / 171 (11.11%)<br>20<br><br>33 / 171 (19.30%)<br>33<br><br>10 / 171 (5.85%)<br>10<br><br>9 / 171 (5.26%)<br>9 |  |
| Injury, poisoning and procedural   |   |  |  |



|                                      |                |                   |  |
|--------------------------------------|----------------|-------------------|--|
| complications                        |                |                   |  |
| Fall                                 |                |                   |  |
| subjects affected / exposed          | 0 / 3 (0.00%)  | 9 / 171 (5.26%)   |  |
| occurrences (all)                    | 0              | 10                |  |
| Stoma site erythema                  |                |                   |  |
| subjects affected / exposed          | 1 / 3 (33.33%) | 0 / 171 (0.00%)   |  |
| occurrences (all)                    | 1              | 0                 |  |
| Nervous system disorders             |                |                   |  |
| Dizziness                            |                |                   |  |
| subjects affected / exposed          | 0 / 3 (0.00%)  | 18 / 171 (10.53%) |  |
| occurrences (all)                    | 0              | 21                |  |
| Neuropathy peripheral                |                |                   |  |
| subjects affected / exposed          | 0 / 3 (0.00%)  | 9 / 171 (5.26%)   |  |
| occurrences (all)                    | 0              | 9                 |  |
| Headache                             |                |                   |  |
| subjects affected / exposed          | 0 / 3 (0.00%)  | 20 / 171 (11.70%) |  |
| occurrences (all)                    | 0              | 20                |  |
| Blood and lymphatic system disorders |                |                   |  |
| Anaemia                              |                |                   |  |
| subjects affected / exposed          | 0 / 3 (0.00%)  | 32 / 171 (18.71%) |  |
| occurrences (all)                    | 0              | 35                |  |
| Gastrointestinal disorders           |                |                   |  |
| Constipation                         |                |                   |  |
| subjects affected / exposed          | 1 / 3 (33.33%) | 42 / 171 (24.56%) |  |
| occurrences (all)                    | 1              | 46                |  |
| Dry mouth                            |                |                   |  |
| subjects affected / exposed          | 0 / 3 (0.00%)  | 12 / 171 (7.02%)  |  |
| occurrences (all)                    | 0              | 12                |  |
| Diarrhoea                            |                |                   |  |
| subjects affected / exposed          | 0 / 3 (0.00%)  | 24 / 171 (14.04%) |  |
| occurrences (all)                    | 0              | 38                |  |
| Dysphagia                            |                |                   |  |
| subjects affected / exposed          | 0 / 3 (0.00%)  | 23 / 171 (13.45%) |  |
| occurrences (all)                    | 0              | 24                |  |
| Vomiting                             |                |                   |  |
| subjects affected / exposed          | 0 / 3 (0.00%)  | 15 / 171 (8.77%)  |  |
| occurrences (all)                    | 0              | 15                |  |

|  |                     |                         |  |
|--|---------------------|-------------------------|--|
| Nausea<br>subjects affected / exposed<br>occurrences (all)   | 0 / 3 (0.00%)<br>0  | 34 / 171 (19.88%)<br>37 |  |
| Abdominal pain<br>subjects affected / exposed<br>occurrences (all)                                     | 0 / 3 (0.00%)<br>0  | 9 / 171 (5.26%)<br>13   |  |
| Lip dry<br>subjects affected / exposed<br>occurrences (all)  | 1 / 3 (33.33%)<br>1 | 0 / 171 (0.00%)<br>0    |  |
| Mouth haemorrhage<br>subjects affected / exposed<br>occurrences (all)                                  | 1 / 3 (33.33%)<br>1 | 1 / 171 (0.58%)<br>1    |  |
| Skin and subcutaneous tissue disorders<br>Pruritus<br>subjects affected / exposed<br>occurrences (all) | 0 / 3 (0.00%)<br>0  | 14 / 171 (8.19%)<br>14  |  |
| Rash<br>subjects affected / exposed<br>occurrences (all)   | 0 / 3 (0.00%)<br>0  | 17 / 171 (9.94%)<br>20  |  |
| Psoriasis<br>subjects affected / exposed<br>occurrences (all)  | 1 / 3 (33.33%)<br>1 | 0 / 171 (0.00%)<br>0    |  |
| Rash maculo-papular<br>subjects affected / exposed<br>occurrences (all)                                | 1 / 3 (33.33%)<br>1 | 6 / 171 (3.51%)<br>7    |  |
| Dermatitis acneiform<br>subjects affected / exposed<br>occurrences (all)                               | 1 / 3 (33.33%)<br>1 | 4 / 171 (2.34%)<br>4    |  |
| Decubitus ulcer<br>subjects affected / exposed<br>occurrences (all)                                    | 1 / 3 (33.33%)<br>1 | 2 / 171 (1.17%)<br>2    |  |
| Endocrine disorders<br>Hypothyroidism<br>subjects affected / exposed<br>occurrences (all)              | 0 / 3 (0.00%)<br>0  | 32 / 171 (18.71%)<br>34 |  |
| Musculoskeletal and connective tissue disorders  |                     |                         |  |

|                                    |                |                   |  |
|------------------------------------|----------------|-------------------|--|
| Arthralgia                         |                |                   |  |
| subjects affected / exposed        | 0 / 3 (0.00%)  | 27 / 171 (15.79%) |  |
| occurrences (all)                  | 0              | 33                |  |
| Myalgia                            |                |                   |  |
| subjects affected / exposed        | 0 / 3 (0.00%)  | 13 / 171 (7.60%)  |  |
| occurrences (all)                  | 0              | 13                |  |
| Neck pain                          |                |                   |  |
| subjects affected / exposed        | 0 / 3 (0.00%)  | 13 / 171 (7.60%)  |  |
| occurrences (all)                  | 0              | 14                |  |
| Back pain                          |                |                   |  |
| subjects affected / exposed        | 0 / 3 (0.00%)  | 9 / 171 (5.26%)   |  |
| occurrences (all)                  | 0              | 9                 |  |
| Infections and infestations        |                |                   |  |
| Herpes zoster                      |                |                   |  |
| subjects affected / exposed        | 1 / 3 (33.33%) | 2 / 171 (1.17%)   |  |
| occurrences (all)                  | 1              | 2                 |  |
| Pneumonia                          |                |                   |  |
| subjects affected / exposed        | 0 / 3 (0.00%)  | 12 / 171 (7.02%)  |  |
| occurrences (all)                  | 0              | 15                |  |
| Metabolism and nutrition disorders |                |                   |  |
| Decreased appetite                 |                |                   |  |
| subjects affected / exposed        | 0 / 3 (0.00%)  | 30 / 171 (17.54%) |  |
| occurrences (all)                  | 0              | 36                |  |
| Hyperglycaemia                     |                |                   |  |
| subjects affected / exposed        | 0 / 3 (0.00%)  | 14 / 171 (8.19%)  |  |
| occurrences (all)                  | 0              | 23                |  |
| Hypercalcaemia                     |                |                   |  |
| subjects affected / exposed        | 0 / 3 (0.00%)  | 13 / 171 (7.60%)  |  |
| occurrences (all)                  | 0              | 15                |  |
| Dehydration                        |                |                   |  |
| subjects affected / exposed        | 0 / 3 (0.00%)  | 16 / 171 (9.36%)  |  |
| occurrences (all)                  | 0              | 20                |  |
| Hyponatraemia                      |                |                   |  |
| subjects affected / exposed        | 1 / 3 (33.33%) | 29 / 171 (16.96%) |  |
| occurrences (all)                  | 1              | 41                |  |
| Hypomagnesaemia                    |                |                   |  |

|                             |                |                  |  |
|-----------------------------|----------------|------------------|--|
| subjects affected / exposed | 0 / 3 (0.00%)  | 14 / 171 (8.19%) |  |
| occurrences (all)           | 0              | 17               |  |
| Hypokalaemia                |                |                  |  |
| subjects affected / exposed | 0 / 3 (0.00%)  | 11 / 171 (6.43%) |  |
| occurrences (all)           | 0              | 16               |  |
| Hypoalbuminaemia            |                |                  |  |
| subjects affected / exposed | 1 / 3 (33.33%) | 11 / 171 (6.43%) |  |
| occurrences (all)           | 1              | 16               |  |
| Hypoglycaemia               |                |                  |  |
| subjects affected / exposed | 1 / 3 (33.33%) | 1 / 171 (0.58%)  |  |
| occurrences (all)           | 1              | 2                |  |
| Hypocalcaemia               |                |                  |  |
| subjects affected / exposed | 0 / 3 (0.00%)  | 11 / 171 (6.43%) |  |
| occurrences (all)           | 0              | 13               |  |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date             | Amendment  |
|------------------|--|
| 19 December 2014 | Amendment 01 removed the option to discontinue pharmacokinetics (PK) sampling after the assessment of the first 65-70 participants and instituted PK analysis for all participants. In addition, language was added to clarify that PK samples will also be used to explore the exposure-response relationships for pembrolizumab and measures of anti-tumor activity/efficacy, toxicity, and pharmacodynamics in the proposed population of participants. |
| 06 May 2015      | Amendment 02 modified the objective response rate (ORR) endpoint to specify analyses in a Programmed Cell Death Ligand-1 (PD-L1) strong positive subgroup instead of any PD-L1 positivity. The analysis of any PD-L1 positivity is now a secondary objective.  |
| 22 March 2016    | Amendment 03 unblinded the Sponsor to the PD-L1 data, after the cut-point for PD-L1 strong positive was determined, in support of the upcoming analyses.   |
| 08 December 2017 | Amendment 04 revised the survival status activities to enable flexibility and ensure that current and complete survival data are available at the time of database locks. In addition, the dose modification guidelines were replaced to provide current comprehensive guidelines for management of immune-related adverse events associated with pembrolizumab.   |
| 04 April 2018    | Amendment 05 made a correction to the trial diagram.   |

Notes:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported