



Clinical trial results:

A Randomized Double-blind Phase 3 Study of Avelumab in Combination With Standard of Care Chemoradiotherapy (Cisplatin Plus Definitive Radiation Therapy) Versus Standard of Care Chemoradiotherapy in the Front-line Treatment of Patients With Locally Advanced Squamous cell Carcinoma of The Head and Neck.

Summary

| | |
|--------------------------|-------------------------------------|
| EudraCT number | 2016-001456-21 |
| Trial protocol | GB BE DE PL AT ES IE PT HU FR GR IT |
| Global end of trial date | 25 August 2020 |

Results information

| | |
|--------------------------------|----------------|
| Result version number | v1 (current) |
| This version publication date | 21 August 2021 |
| First version publication date | 21 August 2021 |

Trial information

Trial identification

| | |
|-----------------------|----------|
| Sponsor protocol code | B9991016 |
|-----------------------|----------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT02952586 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|--|
| Sponsor organisation name | Pfizer Inc. |
| Sponsor organisation address | 235 E 42nd Street, New York, United States, |
| Public contact | Pfizer ClinicalTrials.gov Call Center, Pfizer Inc., +1 8007181021, ClinicalTrials.gov_Inquiries@pfizer.com |
| Scientific contact | Pfizer ClinicalTrials.gov Call Center, Pfizer Inc., +1 8007181021, ClinicalTrials.gov_Inquiries@pfizer.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 | 19 February 2021 |
| Is this the analysis of the primary completion data? | No |
| Global end of trial reached? | Yes |
| Global end of trial date | 25 August 2020 |
| Was the trial ended prematurely? | Yes |

Notes:

General information about the trial

Main objective of the trial:

To demonstrate that treatment with avelumab in combination with Standard of Care Chemotherapy (SOC CRT) was superior to SOC CRT alone in prolonging Progression-free Survival (PFS) in front-line subjects with high risk, locally advanced squamous cell carcinoma of the head and neck (LA SCCHN) who were candidates for definitive CRT with cisplatin.

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and in compliance with all International Council for Harmonisation (ICH) Good Clinical Practice (GCP) Guidelines. All the local regulatory requirements pertinent to safety of trial subjects were followed.

Background therapy: -

Evidence for comparator: -

| | |
|---|------------------|
| Actual start date of recruitment | 28 November 2016 |
| Long term follow-up planned | Yes |
| Long term follow-up rationale | Safety |
| Long term follow-up duration | 28 Months |
| Independent data monitoring committee (IDMC) involvement? | Yes |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|------------------------|
| Country: Number of subjects enrolled | Canada: 1 |
| Country: Number of subjects enrolled | United States: 173 |
| Country: Number of subjects enrolled | China: 45 |
| Country: Number of subjects enrolled | Japan: 51 |
| Country: Number of subjects enrolled | Korea, Republic of: 19 |
| Country: Number of subjects enrolled | Taiwan: 69 |
| Country: Number of subjects enrolled | Australia: 10 |
| Country: Number of subjects enrolled | Hungary: 43 |
| Country: Number of subjects enrolled | Poland: 16 |
| Country: Number of subjects enrolled | Russian Federation: 38 |
| Country: Number of subjects enrolled | Israel: 13 |
| Country: Number of subjects enrolled | Austria: 4 |
| Country: Number of subjects enrolled | Belgium: 19 |
| Country: Number of subjects enrolled | France: 53 |
| Country: Number of subjects enrolled | Germany: 8 |
| Country: Number of subjects enrolled | Greece: 23 |
| Country: Number of subjects enrolled | Ireland: 3 |

| | |
|--------------------------------------|--------------------|
| Country: Number of subjects enrolled | Italy: 19 |
| Country: Number of subjects enrolled | Portugal: 30 |
| Country: Number of subjects enrolled | Spain: 31 |
| Country: Number of subjects enrolled | Switzerland: 12 |
| Country: Number of subjects enrolled | United Kingdom: 17 |
| Worldwide total number of subjects | 697 |
| EEA total number of subjects | 249 |

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) | 495 |
| From 65 to 84 years | 201 |
| 85 years and over | 1 |

Subject disposition

Recruitment

Recruitment details:

Study had 3 sequential treatment phases: Lead-in, CRT and Maintenance. There were 3 treatments administered during CRT phase: Blinded therapy (Avelumab/placebo), Cisplatin and IMRT. Only blinded therapy (Avelumab/placebo) was administered during Lead-in and Maintenance phases. Reasons for discontinuation are summarized separately for each treatment.

Pre-assignment

Screening details:

If a subject discontinued all 3 treatments due to death, then death is included as reason for discontinuation in each treatment disposition summary. All deaths that are reported as reason for discontinuation at any phase are included in all-cause mortality summary.

Period 1

| | |
|------------------------------|--------------------------------|
| Period 1 title | Lead-In Phase (7 Days) |
| Is this the baseline period? | Yes |
| Allocation method | Randomised - controlled |
| Blinding used | Double blind |
| Roles blinded | Investigator, Monitor, Subject |

Arms

| | |
|------------------------------|--|
| Are arms mutually exclusive? | Yes |
| Arm title | Avelumab + Standard of Care Chemotherapy (SOC CRT) |

Arm description:

Subjects with locally advanced squamous cell carcinoma of the head and neck (LA SCCHN) were administered with avelumab 10 milligram per kilogram (mg/kg) intravenous (IV) injection on Day 1 of the Lead-in Phase (7 days) and on Days 8, 25 and 39 in CRT phase (63 days). In CRT phase subjects also received SOC CRT: cisplatin 100 milligram per square meter (mg/m²) on Days 1, 22, 43 and intensity-modulated radiation therapy (IMRT) 5 days a week. CRT phase was followed by maintenance phase (12 months) in which subjects received avelumab 10 mg/kg IV injection every 2 weeks. All subjects were followed for safety 30 days after the last study treatment administration or until the time of initiation of new systemic anticancer treatment. If any concern arose subjects were followed up on Day 90 via telephone call thereafter in long term (LT) follow up period every 16 weeks for survival and new systemic anticancer treatment.

| | |
|--|-----------------|
| Arm type | Experimental |
| Investigational medicinal product name | Avelumab |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Injection |
| Routes of administration | Intravenous use |

Dosage and administration details:

Subjects were administered with avelumab 10 mg/kg IV injection on Day 1 of the Lead-in Phase.

| | |
|------------------|-------------------|
| Arm title | Placebo + SOC CRT |
|------------------|-------------------|

Arm description:

Subjects with LA SCCHN were administered with placebo IV injection matched to avelumab on Day 1 of the Lead-in Phase (7 days) and on Days 8, 25 and 39 in CRT phase (63 days). In CRT phase subjects also received SOC CRT: cisplatin mg/m² on Days 1, 22 and 43 + IMRT 5 days a week. CRT phase was followed by maintenance phase (12 months) in which subjects received placebo IV injection every 2 weeks. All subjects were followed for safety 30 days after the last study treatment administration or until the time of initiation of new systemic anticancer treatment. If any concern arose subjects were followed up on Day 90 via telephone call thereafter in long term follow up period every 16 weeks for survival and new systemic anticancer treatment.

| | |
|----------|---------|
| Arm type | Placebo |
|----------|---------|

| | |
|--|-----------------|
| Investigational medicinal product name | Placebo |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Injection |
| Routes of administration | Intravenous use |

Dosage and administration details:

Subjects were administered with placebo IV injection matched to avelumab on Day 1 of the Lead-in Phase (7 days).

| Number of subjects in period 1 | Avelumab + Standard of Care Chemotherapy (SOC CRT) | Placebo + SOC CRT |
|---------------------------------------|---|--------------------------|
| Started | 350 | 347 |
| Safety Analysis Set | 348 | 344 |
| Completed | 345 | 343 |
| Not completed | 5 | 4 |
| Adverse event, non-fatal | 3 | - |
| Death | - | 1 |
| No Longer Met Eligibility Criteria | - | 1 |
| Withdrawal by subject | 2 | 2 |

Period 2

| | |
|------------------------------|---------------------------------------|
| Period 2 title | CRT for Avelumab or Placebo (63 Days) |
| Is this the baseline period? | No |
| Allocation method | Randomised - controlled |
| Blinding used | Double blind |
| Roles blinded | Subject, Investigator, Monitor |

Arms

| | |
|------------------------------|--|
| Are arms mutually exclusive? | Yes |
| Arm title | Avelumab + Standard of Care Chemotherapy (SOC CRT) |

Arm description:

Subjects with locally advanced squamous cell carcinoma of the head and neck (LA SCCHN) were administered with avelumab 10 milligram per kilogram (mg/kg) intravenous (IV) injection on Day 1 of the Lead-in Phase (7 days) and on Days 8, 25 and 39 in CRT phase (63 days). In CRT phase subjects also received SOC CRT: cisplatin 100 milligram per square meter (mg/m²) on Days 1, 22, 43 and intensity-modulated radiation therapy (IMRT) 5 days a week. CRT phase was followed by maintenance phase (12 months) in which subjects received avelumab 10 mg/kg IV injection every 2 weeks. All subjects were followed for safety 30 days after the last study treatment administration or until the time of initiation of new systemic anticancer treatment. If any concern arose subjects were followed up on Day 90 via telephone call thereafter in long term (LT) follow up period every 16 weeks for survival and new systemic anticancer treatment.

| | |
|----------|--------------|
| Arm type | Experimental |
|----------|--------------|

| | |
|---|-------------------|
| Investigational medicinal product name | Avelumab |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Injection |
| Routes of administration | Intravenous use |
| Dosage and administration details: | |
| Subjects were administered with avelumab 10 mg/kg IV injection on Days 8, 25 and 39 in CRT phase. | |
| Arm title | Placebo + SOC CRT |

Arm description:

Subjects with LA SCCHN were administered with placebo IV injection matched to avelumab on Day 1 of the Lead-in Phase (7 days) and on Days 8, 25 and 39 in CRT phase (63 days). In CRT phase subjects also received SOC CRT: cisplatin mg/m² on Days 1, 22 and 43 + IMRT 5 days a week. CRT phase was followed by maintenance phase (12 months) in which subjects received placebo IV injection every 2 weeks. All subjects were followed for safety 30 days after the last study treatment administration or until the time of initiation of new systemic anticancer treatment. If any concern arose subjects were followed up on Day 90 via telephone call thereafter in long term follow up period every 16 weeks for survival and new systemic anticancer treatment.

| | |
|--|-----------------|
| Arm type | Placebo |
| Investigational medicinal product name | Placebo |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Injection |
| Routes of administration | Intravenous use |

Dosage and administration details:

Subjects were administered with avelumab matching placebo 10 mg/kg IV injection on Days 8, 25 and 39 in CRT phase.

| Number of subjects in period 2^[1] | Avelumab + Standard of Care Chemotherapy (SOC CRT) | Placebo + SOC CRT |
|---|---|--------------------------|
| Started | 345 | 340 |
| Completed | 312 | 313 |
| Not completed | 33 | 27 |
| Physician decision | 2 | 1 |
| Adverse event, non-fatal | 12 | 12 |
| Death | 5 | 8 |
| Unspecified | 2 | 1 |
| Lost to follow-up | 1 | 1 |
| Global Deterioration of Health Status | 1 | - |
| Withdrawal by subject | 10 | 4 |

Notes:

[1] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.

Justification: All subjects who did not withdraw from study after Lead-In phase, entered into CRT phase.

Period 3

| | |
|------------------------------|--------------------------------|
| Period 3 title | CRT for Cisplatin (63 Days) |
| Is this the baseline period? | No |
| Allocation method | Randomised - controlled |
| Blinding used | Double blind |
| Roles blinded | Subject, Investigator, Monitor |

Arms

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

| | |
|------------------|--|
| Arm title | Avelumab + Standard of Care Chemotherapy (SOC CRT) |
|------------------|--|

Arm description:

Subjects with locally advanced squamous cell carcinoma of the head and neck (LA SCCHN) were administered with avelumab 10 milligram per kilogram (mg/kg) intravenous (IV) injection on Day 1 of the Lead-in Phase (7 days) and on Days 8, 25 and 39 in CRT phase (63 days). In CRT phase subjects also received SOC CRT: cisplatin 100 milligram per square meter (mg/m²) on Days 1, 22, 43 and intensity-modulated radiation therapy (IMRT) 5 days a week. CRT phase was followed by maintenance phase (12 months) in which subjects received avelumab 10 mg/kg IV injection every 2 weeks. All subjects were followed for safety 30 days after the last study treatment administration or until the time of initiation of new systemic anticancer treatment. If any concern arose subjects were followed up on Day 90 via telephone call thereafter in long term (LT) follow up period every 16 weeks for survival and new systemic anticancer treatment.

| | |
|--|-----------------|
| Arm type | Experimental |
| Investigational medicinal product name | Cisplatin |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Injection |
| Routes of administration | Intravenous use |

Dosage and administration details:

Subjects received Cisplatin 100 mg/m² IV injection on Days 1, 22 and 43 of CRT phase.

| | |
|------------------|-------------------|
| Arm title | Placebo + SOC CRT |
|------------------|-------------------|

Arm description:

Subjects with LA SCCHN were administered with placebo IV injection matched to avelumab on Day 1 of the Lead-in Phase (7 days) and on Days 8, 25 and 39 in CRT phase (63 days). In CRT phase subjects also received SOC CRT: cisplatin mg/m² on Days 1, 22 and 43 + IMRT 5 days a week. CRT phase was followed by maintenance phase (12 months) in which subjects received placebo IV injection every 2 weeks. All subjects were followed for safety 30 days after the last study treatment administration or until the time of initiation of new systemic anticancer treatment. If any concern arose subjects were followed up on Day 90 via telephone call thereafter in long term follow up period every 16 weeks for survival and new systemic anticancer treatment.

| | |
|--|-----------------|
| Arm type | Placebo |
| Investigational medicinal product name | Cisplatin |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Injection |
| Routes of administration | Intravenous use |

Dosage and administration details:

Subjects received Cisplatin 100 mg/m² IV injection on Days 1, 22 and 43 of CRT phase.

| Number of subjects in period 3 | Avelumab + Standard of Care Chemotherapy (SOC CRT) | Placebo + SOC CRT |
|---------------------------------------|--|-------------------|
| Started | 312 | 313 |
| Completed | 234 | 236 |
| Not completed | 111 | 104 |
| Physician decision | 12 | 10 |
| Adverse event, non-fatal | 82 | 81 |
| Death | 3 | 8 |
| Unspecified | 1 | 1 |
| Lost to follow-up | 1 | 1 |
| Global Deterioration of Health Status | 1 | - |
| Withdrawal by subject | 11 | 3 |
| Joined | 33 | 27 |
| Continued in this period | 33 | 27 |

Period 4

| | |
|------------------------------|--------------------------------|
| Period 4 title | CRT for IMRT (63 Days) |
| Is this the baseline period? | No |
| Allocation method | Randomised - controlled |
| Blinding used | Double blind |
| Roles blinded | Subject, Investigator, Monitor |

Arms

| | |
|------------------------------|--|
| Are arms mutually exclusive? | Yes |
| Arm title | Avelumab + Standard of Care Chemotherapy (SOC CRT) |

Arm description:

Subjects with locally advanced squamous cell carcinoma of the head and neck (LA SCCHN) were administered with avelumab 10 milligram per kilogram (mg/kg) intravenous (IV) injection on Day 1 of the Lead-in Phase (7 days) and on Days 8, 25 and 39 in CRT phase (63 days). In CRT phase subjects also received SOC CRT: cisplatin 100 milligram per square meter (mg/m²) on Days 1, 22, 43 and intensity-modulated radiation therapy (IMRT) 5 days a week. CRT phase was followed by maintenance phase (12 months) in which subjects received avelumab 10 mg/kg IV injection every 2 weeks. All subjects were followed for safety 30 days after the last study treatment administration or until the time of initiation of new systemic anticancer treatment. If any concern arose subjects were followed up on Day 90 via telephone call thereafter in long term (LT) follow up period every 16 weeks for survival and new systemic anticancer treatment.

| | |
|---|-------------------|
| Arm type | No intervention |
| No investigational medicinal product assigned in this arm | |
| Arm title | Placebo + SOC CRT |

Arm description:

Subjects with LA SCCHN were administered with placebo IV injection matched to avelumab on Day 1 of the Lead-in Phase (7 days) and on Days 8, 25 and 39 in CRT phase (63 days). In CRT phase subjects also received SOC CRT: cisplatin mg/m² on Days 1, 22 and 43 + IMRT 5 days a week. CRT phase was followed by maintenance phase (12 months) in which subjects received placebo IV injection every 2 weeks. All subjects were followed for safety 30 days after the last study treatment administration or

until the time of initiation of new systemic anticancer treatment. If any concern arose subjects were followed up on Day 90 via telephone call thereafter in long term follow up period every 16 weeks for survival and new systemic anticancer treatment.

| | |
|---|-----------------|
| Arm type | No intervention |
| No investigational medicinal product assigned in this arm | |

| Number of subjects in period 4 | Avelumab + Standard of Care Chemotherapy (SOC CRT) | Placebo + SOC CRT |
|---------------------------------------|--|-------------------|
| Started | 234 | 236 |
| Completed | 322 | 320 |
| Not completed | 23 | 20 |
| Adverse event, non-fatal | 5 | 5 |
| Death | 5 | 8 |
| Unspecified | 1 | - |
| Lost to follow-up | 1 | 1 |
| Global Deterioration of Health Status | 1 | - |
| Withdrawal by subject | 10 | 6 |
| Joined | 111 | 104 |
| Continued in this period | 111 | 104 |

Period 5

| | |
|------------------------------|------------------------------------|
| Period 5 title | Maintenance Phase (MP) (12 Months) |
| Is this the baseline period? | No |
| Allocation method | Randomised - controlled |
| Blinding used | Double blind |
| Roles blinded | Subject, Investigator, Monitor |

Arms

| | |
|------------------------------|--|
| Are arms mutually exclusive? | Yes |
| Arm title | Avelumab + Standard of Care Chemotherapy (SOC CRT) |

Arm description:

Subjects with locally advanced squamous cell carcinoma of the head and neck (LA SCCHN) were administered with avelumab 10 milligram per kilogram (mg/kg) intravenous (IV) injection on Day 1 of the Lead-in Phase (7 days) and on Days 8, 25 and 39 in CRT phase (63 days). In CRT phase subjects also received SOC CRT: cisplatin 100 milligram per square meter (mg/m²) on Days 1, 22, 43 and intensity-modulated radiation therapy (IMRT) 5 days a week. CRT phase was followed by maintenance phase (12 months) in which subjects received avelumab 10 mg/kg IV injection every 2 weeks. All subjects were followed for safety 30 days after the last study treatment administration or until the time of initiation of new systemic anticancer treatment. If any concern arose subjects were followed up on Day 90 via telephone call thereafter in long term (LT) follow up period every 16 weeks for survival and new systemic anticancer treatment.

| | |
|--|-----------------|
| Arm type | Experimental |
| Investigational medicinal product name | Avelumab |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Injection |
| Routes of administration | Intravenous use |

Dosage and administration details:

Subjects received avelumab 10 mg/kg IV injection every 2 weeks for up to 12 months.

| | |
|------------------|-------------------|
| Arm title | Placebo + SOC CRT |
|------------------|-------------------|

Arm description:

Subjects with LA SCCHN were administered with placebo IV injection matched to avelumab on Day 1 of the Lead-in Phase (7 days) and on Days 8, 25 and 39 in CRT phase (63 days). In CRT phase subjects also received SOC CRT: cisplatin mg/m² on Days 1, 22 and 43 + IMRT 5 days a week. CRT phase was followed by maintenance phase (12 months) in which subjects received placebo IV injection every 2 weeks. All subjects were followed for safety 30 days after the last study treatment administration or until the time of initiation of new systemic anticancer treatment. If any concern arose subjects were followed up on Day 90 via telephone call thereafter in long term follow up period every 16 weeks for survival and new systemic anticancer treatment.

| | |
|--|-----------------|
| Arm type | Placebo |
| Investigational medicinal product name | Placebo |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Injection |
| Routes of administration | Intravenous use |

Dosage and administration details:

Subjects received avelumab 10 mg/kg matching placebo IV injection every 2 weeks for up to 12 months.

| Number of subjects in period 5^[2] | Avelumab + Standard of Care Chemotherapy (SOC CRT) | Placebo + SOC CRT |
|---|--|-------------------|
| Started | 291 | 304 |
| Completed | 139 | 177 |
| Not completed | 152 | 127 |
| Physician decision | 1 | 1 |
| Adverse event, non-fatal | 24 | 21 |
| Non-compliance With Study Drug | 1 | 1 |
| Death | 17 | 11 |
| Unspecified | 2 | 1 |
| Study Terminated by Sponsor | 1 | 6 |
| Progressive disease | 60 | 54 |
| Lost to follow-up | 1 | 2 |
| Global Deterioration of Health Status | 14 | 5 |
| Withdrawal by subject | 31 | 25 |

Notes:

[2] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.

Justification: All subjects who did not withdraw from the CRT phase entered MP

Period 6

| | |
|------------------------------|---------------------------------|
| Period 6 title | Follow-Up Phase (FUP) (90 Days) |
| Is this the baseline period? | No |
| Allocation method | Randomised - controlled |
| Blinding used | Double blind |
| Roles blinded | Subject, Investigator, Monitor |

Arms

| | |
|------------------------------|--|
| Are arms mutually exclusive? | Yes |
| Arm title | Avelumab + Standard of Care Chemotherapy (SOC CRT) |

Arm description:

Subjects with locally advanced squamous cell carcinoma of the head and neck (LA SCCHN) were administered with avelumab 10 milligram per kilogram (mg/kg) intravenous (IV) injection on Day 1 of the Lead-in Phase (7 days) and on Days 8, 25 and 39 in CRT phase (63 days). In CRT phase subjects also received SOC CRT: cisplatin 100 milligram per square meter (mg/m²) on Days 1, 22, 43 and intensity-modulated radiation therapy (IMRT) 5 days a week. CRT phase was followed by maintenance phase (12 months) in which subjects received avelumab 10 mg/kg IV injection every 2 weeks. All subjects were followed for safety 30 days after the last study treatment administration or until the time of initiation of new systemic anticancer treatment. If any concern arose subjects were followed up on Day 90 via telephone call thereafter in long term (LT) follow up period every 16 weeks for survival and new systemic anticancer treatment.

| | |
|---|-------------------|
| Arm type | No intervention |
| No investigational medicinal product assigned in this arm | |
| Arm title | Placebo + SOC CRT |

Arm description:

Subjects with LA SCCHN were administered with placebo IV injection matched to avelumab on Day 1 of the Lead-in Phase (7 days) and on Days 8, 25 and 39 in CRT phase (63 days). In CRT phase subjects also received SOC CRT: cisplatin mg/m² on Days 1, 22 and 43 + IMRT 5 days a week. CRT phase was followed by maintenance phase (12 months) in which subjects received placebo IV injection every 2 weeks. All subjects were followed for safety 30 days after the last study treatment administration or until the time of initiation of new systemic anticancer treatment. If any concern arose subjects were followed up on Day 90 via telephone call thereafter in long term follow up period every 16 weeks for survival and new systemic anticancer treatment.

| | |
|---|-----------------|
| Arm type | No intervention |
| No investigational medicinal product assigned in this arm | |

| Number of subjects in period 6 | Avelumab + Standard of Care Chemotherapy (SOC CRT) | Placebo + SOC CRT |
|---------------------------------------|--|-------------------|
| Started | 139 | 177 |
| Completed | 208 | 216 |
| Not completed | 58 | 68 |
| Death | 12 | 10 |
| Unspecified | 7 | 5 |
| Study Terminated by Sponsor | 32 | 50 |
| Lost to follow-up | 1 | 1 |
| Withdrawal by subject | 6 | 2 |

| | | |
|--------------------------|-----|-----|
| Joined | 127 | 107 |
| Continued in this period | 127 | 107 |

Period 7

| | |
|------------------------------|--------------------------------|
| Period 7 title | LT Follow-up (up to 45 months) |
| Is this the baseline period? | No |
| Allocation method | Randomised - controlled |
| Blinding used | Double blind |
| Roles blinded | Subject, Investigator, Monitor |

Arms

| | |
|------------------------------|--|
| Are arms mutually exclusive? | Yes |
| Arm title | Avelumab + Standard of Care Chemotherapy (SOC CRT) |

Arm description:

Subjects with locally advanced squamous cell carcinoma of the head and neck (LA SCCHN) were administered with avelumab 10 milligram per kilogram (mg/kg) intravenous (IV) injection on Day 1 of the Lead-in Phase (7 days) and on Days 8, 25 and 39 in CRT phase (63 days). In CRT phase subjects also received SOC CRT: cisplatin 100 milligram per square meter (mg/m²) on Days 1, 22, 43 and intensity-modulated radiation therapy (IMRT) 5 days a week. CRT phase was followed by maintenance phase (12 months) in which subjects received avelumab 10 mg/kg IV injection every 2 weeks. All subjects were followed for safety 30 days after the last study treatment administration or until the time of initiation of new systemic anticancer treatment. If any concern arose subjects were followed up on Day 90 via telephone call thereafter in long term (LT) follow up period every 16 weeks for survival and new systemic anticancer treatment.

| | |
|---|-------------------|
| Arm type | No intervention |
| No investigational medicinal product assigned in this arm | |
| Arm title | Placebo + SOC CRT |

Arm description:

Subjects with LA SCCHN were administered with placebo IV injection matched to avelumab on Day 1 of the Lead-in Phase (7 days) and on Days 8, 25 and 39 in CRT phase (63 days). In CRT phase subjects also received SOC CRT: cisplatin mg/m² on Days 1, 22 and 43 + IMRT 5 days a week. CRT phase was followed by maintenance phase (12 months) in which subjects received placebo IV injection every 2 weeks. All subjects were followed for safety 30 days after the last study treatment administration or until the time of initiation of new systemic anticancer treatment. If any concern arose subjects were followed up on Day 90 via telephone call thereafter in long term follow up period every 16 weeks for survival and new systemic anticancer treatment.

| | |
|---|-----------------|
| Arm type | No intervention |
| No investigational medicinal product assigned in this arm | |

| Number of subjects in period 7 | Avelumab + Standard of Care Chemotherapy (SOC CRT) | Placebo + SOC CRT |
|--------------------------------|---|-------------------|
| | | |
| Started | 208 | 216 |
| Completed | 0 | 0 |
| Not completed | 247 | 237 |
| Death | 51 | 31 |
| Study Terminated by Sponsor | 187 | 201 |
| Lost to follow-up | 2 | 4 |
| Withdrawal by subject | 7 | 1 |
| Joined | 39 | 21 |
| Continued in this period | 39 | 21 |

Baseline characteristics

Reporting groups

| | |
|-----------------------|--|
| Reporting group title | Avelumab + Standard of Care Chemotherapy (SOC CRT) |
|-----------------------|--|

Reporting group description:

Subjects with locally advanced squamous cell carcinoma of the head and neck (LA SCCHN) were administered with avelumab 10 milligram per kilogram (mg/kg) intravenous (IV) injection on Day 1 of the Lead-in Phase (7 days) and on Days 8, 25 and 39 in CRT phase (63 days). In CRT phase subjects also received SOC CRT: cisplatin 100 milligram per square meter (mg/m²) on Days 1, 22, 43 and intensity-modulated radiation therapy (IMRT) 5 days a week. CRT phase was followed by maintenance phase (12 months) in which subjects received avelumab 10 mg/kg IV injection every 2 weeks. All subjects were followed for safety 30 days after the last study treatment administration or until the time of initiation of new systemic anticancer treatment. If any concern arose subjects were followed up on Day 90 via telephone call thereafter in long term (LT) follow up period every 16 weeks for survival and new systemic anticancer treatment.

| | |
|-----------------------|-------------------|
| Reporting group title | Placebo + SOC CRT |
|-----------------------|-------------------|

Reporting group description:

Subjects with LA SCCHN were administered with placebo IV injection matched to avelumab on Day 1 of the Lead-in Phase (7 days) and on Days 8, 25 and 39 in CRT phase (63 days). In CRT phase subjects also received SOC CRT: cisplatin mg/m² on Days 1, 22 and 43 + IMRT 5 days a week. CRT phase was followed by maintenance phase (12 months) in which subjects received placebo IV injection every 2 weeks. All subjects were followed for safety 30 days after the last study treatment administration or until the time of initiation of new systemic anticancer treatment. If any concern arose subjects were followed up on Day 90 via telephone call thereafter in long term follow up period every 16 weeks for survival and new systemic anticancer treatment.

| Reporting group values | Avelumab + Standard of Care Chemotherapy (SOC CRT) | Placebo + SOC CRT | Total |
|--|--|-------------------|-------|
| Number of subjects | 350 | 347 | 697 |
| Age categorical Units: Subjects | | | |
| In utero | 0 | 0 | 0 |
| Preterm newborn infants (gestational age < 37 wks) | 0 | 0 | 0 |
| Newborns (0-27 days) | 0 | 0 | 0 |
| Infants and toddlers (28 days-23 months) | 0 | 0 | 0 |
| Children (2-11 years) | 0 | 0 | 0 |
| Adolescents (12-17 years) | 0 | 0 | 0 |
| Adults (18-64 years) | 248 | 247 | 495 |
| From 65-84 years | 102 | 99 | 201 |
| 85 years and over | 0 | 1 | 1 |
| Age Continuous Units: years | | | |
| arithmetic mean | 59.36 | 58.88 | - |
| standard deviation | ± 8.56 | ± 9.09 | - |
| Sex: Female, Male Units: subjects | | | |
| Female | 60 | 62 | 122 |
| Male | 290 | 285 | 575 |
| Ethnicity (NIH/OMB) Units: Subjects | | | |
| Hispanic or Latino | 13 | 8 | 21 |

| | | | |
|---|-----|-----|-----|
| Not Hispanic or Latino | 312 | 312 | 624 |
| Unknown or Not Reported | 25 | 27 | 52 |
| Race/Ethnicity, Customized Units: Subjects | | | |
| Black or African American | 9 | 10 | 19 |
| American Indian or Alaska Native | 1 | 0 | 1 |
| Asian | 102 | 86 | 188 |
| Native Hawaiian or Other Pacific Islander | 0 | 1 | 1 |
| White | 224 | 229 | 453 |
| Other | 14 | 21 | 35 |

End points

End points reporting groups

| | |
|-----------------------|--|
| Reporting group title | Avelumab + Standard of Care Chemotherapy (SOC CRT) |
|-----------------------|--|

Reporting group description:

Subjects with locally advanced squamous cell carcinoma of the head and neck (LA SCCHN) were administered with avelumab 10 milligram per kilogram (mg/kg) intravenous (IV) injection on Day 1 of the Lead-in Phase (7 days) and on Days 8, 25 and 39 in CRT phase (63 days). In CRT phase subjects also received SOC CRT: cisplatin 100 milligram per square meter (mg/m²) on Days 1, 22, 43 and intensity-modulated radiation therapy (IMRT) 5 days a week. CRT phase was followed by maintenance phase (12 months) in which subjects received avelumab 10 mg/kg IV injection every 2 weeks. All subjects were followed for safety 30 days after the last study treatment administration or until the time of initiation of new systemic anticancer treatment. If any concern arose subjects were followed up on Day 90 via telephone call thereafter in long term (LT) follow up period every 16 weeks for survival and new systemic anticancer treatment.

| | |
|-----------------------|-------------------|
| Reporting group title | Placebo + SOC CRT |
|-----------------------|-------------------|

Reporting group description:

Subjects with LA SCCHN were administered with placebo IV injection matched to avelumab on Day 1 of the Lead-in Phase (7 days) and on Days 8, 25 and 39 in CRT phase (63 days). In CRT phase subjects also received SOC CRT: cisplatin mg/m² on Days 1, 22 and 43 + IMRT 5 days a week. CRT phase was followed by maintenance phase (12 months) in which subjects received placebo IV injection every 2 weeks. All subjects were followed for safety 30 days after the last study treatment administration or until the time of initiation of new systemic anticancer treatment. If any concern arose subjects were followed up on Day 90 via telephone call thereafter in long term follow up period every 16 weeks for survival and new systemic anticancer treatment.

| | |
|-----------------------|--|
| Reporting group title | Avelumab + Standard of Care Chemotherapy (SOC CRT) |
|-----------------------|--|

Reporting group description:

Subjects with locally advanced squamous cell carcinoma of the head and neck (LA SCCHN) were administered with avelumab 10 milligram per kilogram (mg/kg) intravenous (IV) injection on Day 1 of the Lead-in Phase (7 days) and on Days 8, 25 and 39 in CRT phase (63 days). In CRT phase subjects also received SOC CRT: cisplatin 100 milligram per square meter (mg/m²) on Days 1, 22, 43 and intensity-modulated radiation therapy (IMRT) 5 days a week. CRT phase was followed by maintenance phase (12 months) in which subjects received avelumab 10 mg/kg IV injection every 2 weeks. All subjects were followed for safety 30 days after the last study treatment administration or until the time of initiation of new systemic anticancer treatment. If any concern arose subjects were followed up on Day 90 via telephone call thereafter in long term (LT) follow up period every 16 weeks for survival and new systemic anticancer treatment.

| | |
|-----------------------|-------------------|
| Reporting group title | Placebo + SOC CRT |
|-----------------------|-------------------|

Reporting group description:

Subjects with LA SCCHN were administered with placebo IV injection matched to avelumab on Day 1 of the Lead-in Phase (7 days) and on Days 8, 25 and 39 in CRT phase (63 days). In CRT phase subjects also received SOC CRT: cisplatin mg/m² on Days 1, 22 and 43 + IMRT 5 days a week. CRT phase was followed by maintenance phase (12 months) in which subjects received placebo IV injection every 2 weeks. All subjects were followed for safety 30 days after the last study treatment administration or until the time of initiation of new systemic anticancer treatment. If any concern arose subjects were followed up on Day 90 via telephone call thereafter in long term follow up period every 16 weeks for survival and new systemic anticancer treatment.

| | |
|-----------------------|--|
| Reporting group title | Avelumab + Standard of Care Chemotherapy (SOC CRT) |
|-----------------------|--|

Reporting group description:

Subjects with locally advanced squamous cell carcinoma of the head and neck (LA SCCHN) were administered with avelumab 10 milligram per kilogram (mg/kg) intravenous (IV) injection on Day 1 of the Lead-in Phase (7 days) and on Days 8, 25 and 39 in CRT phase (63 days). In CRT phase subjects also received SOC CRT: cisplatin 100 milligram per square meter (mg/m²) on Days 1, 22, 43 and intensity-modulated radiation therapy (IMRT) 5 days a week. CRT phase was followed by maintenance phase (12 months) in which subjects received avelumab 10 mg/kg IV injection every 2 weeks. All subjects were followed for safety 30 days after the last study treatment administration or until the time of initiation of new systemic anticancer treatment. If any concern arose subjects were followed up on Day 90 via telephone call thereafter in long term (LT) follow up period every 16 weeks for survival and new systemic anticancer treatment.

| | |
|-----------------------|-------------------|
| Reporting group title | Placebo + SOC CRT |
|-----------------------|-------------------|

Reporting group description:

Subjects with LA SCCHN were administered with placebo IV injection matched to avelumab on Day 1 of

the Lead-in Phase (7 days) and on Days 8, 25 and 39 in CRT phase (63 days). In CRT phase subjects also received SOC CRT: cisplatin mg/m² on Days 1, 22 and 43 + IMRT 5 days a week. CRT phase was followed by maintenance phase (12 months) in which subjects received placebo IV injection every 2 weeks. All subjects were followed for safety 30 days after the last study treatment administration or until the time of initiation of new systemic anticancer treatment. If any concern arose subjects were followed up on Day 90 via telephone call thereafter in long term follow up period every 16 weeks for survival and new systemic anticancer treatment.

| | |
|-----------------------|--|
| Reporting group title | Avelumab + Standard of Care Chemotherapy (SOC CRT) |
|-----------------------|--|

Reporting group description:

Subjects with locally advanced squamous cell carcinoma of the head and neck (LA SCCHN) were administered with avelumab 10 milligram per kilogram (mg/kg) intravenous (IV) injection on Day 1 of the Lead-in Phase (7 days) and on Days 8, 25 and 39 in CRT phase (63 days). In CRT phase subjects also received SOC CRT: cisplatin 100 milligram per square meter (mg/m²) on Days 1, 22, 43 and intensity-modulated radiation therapy (IMRT) 5 days a week. CRT phase was followed by maintenance phase (12 months) in which subjects received avelumab 10 mg/kg IV injection every 2 weeks. All subjects were followed for safety 30 days after the last study treatment administration or until the time of initiation of new systemic anticancer treatment. If any concern arose subjects were followed up on Day 90 via telephone call thereafter in long term (LT) follow up period every 16 weeks for survival and new systemic anticancer treatment.

| | |
|-----------------------|-------------------|
| Reporting group title | Placebo + SOC CRT |
|-----------------------|-------------------|

Reporting group description:

Subjects with LA SCCHN were administered with placebo IV injection matched to avelumab on Day 1 of the Lead-in Phase (7 days) and on Days 8, 25 and 39 in CRT phase (63 days). In CRT phase subjects also received SOC CRT: cisplatin mg/m² on Days 1, 22 and 43 + IMRT 5 days a week. CRT phase was followed by maintenance phase (12 months) in which subjects received placebo IV injection every 2 weeks. All subjects were followed for safety 30 days after the last study treatment administration or until the time of initiation of new systemic anticancer treatment. If any concern arose subjects were followed up on Day 90 via telephone call thereafter in long term follow up period every 16 weeks for survival and new systemic anticancer treatment.

| | |
|-----------------------|--|
| Reporting group title | Avelumab + Standard of Care Chemotherapy (SOC CRT) |
|-----------------------|--|

Reporting group description:

Subjects with locally advanced squamous cell carcinoma of the head and neck (LA SCCHN) were administered with avelumab 10 milligram per kilogram (mg/kg) intravenous (IV) injection on Day 1 of the Lead-in Phase (7 days) and on Days 8, 25 and 39 in CRT phase (63 days). In CRT phase subjects also received SOC CRT: cisplatin 100 milligram per square meter (mg/m²) on Days 1, 22, 43 and intensity-modulated radiation therapy (IMRT) 5 days a week. CRT phase was followed by maintenance phase (12 months) in which subjects received avelumab 10 mg/kg IV injection every 2 weeks. All subjects were followed for safety 30 days after the last study treatment administration or until the time of initiation of new systemic anticancer treatment. If any concern arose subjects were followed up on Day 90 via telephone call thereafter in long term (LT) follow up period every 16 weeks for survival and new systemic anticancer treatment.

| | |
|-----------------------|-------------------|
| Reporting group title | Placebo + SOC CRT |
|-----------------------|-------------------|

Reporting group description:

Subjects with LA SCCHN were administered with placebo IV injection matched to avelumab on Day 1 of the Lead-in Phase (7 days) and on Days 8, 25 and 39 in CRT phase (63 days). In CRT phase subjects also received SOC CRT: cisplatin mg/m² on Days 1, 22 and 43 + IMRT 5 days a week. CRT phase was followed by maintenance phase (12 months) in which subjects received placebo IV injection every 2 weeks. All subjects were followed for safety 30 days after the last study treatment administration or until the time of initiation of new systemic anticancer treatment. If any concern arose subjects were followed up on Day 90 via telephone call thereafter in long term follow up period every 16 weeks for survival and new systemic anticancer treatment.

| | |
|-----------------------|--|
| Reporting group title | Avelumab + Standard of Care Chemotherapy (SOC CRT) |
|-----------------------|--|

Reporting group description:

Subjects with locally advanced squamous cell carcinoma of the head and neck (LA SCCHN) were administered with avelumab 10 milligram per kilogram (mg/kg) intravenous (IV) injection on Day 1 of the Lead-in Phase (7 days) and on Days 8, 25 and 39 in CRT phase (63 days). In CRT phase subjects also received SOC CRT: cisplatin 100 milligram per square meter (mg/m²) on Days 1, 22, 43 and intensity-modulated radiation therapy (IMRT) 5 days a week. CRT phase was followed by maintenance phase (12 months) in which subjects received avelumab 10 mg/kg IV injection every 2 weeks. All subjects were followed for safety 30 days after the last study treatment administration or until the time of initiation of new systemic anticancer treatment. If any concern arose subjects were followed up on Day 90 via telephone call thereafter in long term (LT) follow up period every 16 weeks for survival and new systemic anticancer treatment.

| | |
|-----------------------|-------------------|
| Reporting group title | Placebo + SOC CRT |
|-----------------------|-------------------|

Reporting group description:

Subjects with LA SCCHN were administered with placebo IV injection matched to avelumab on Day 1 of the Lead-in Phase (7 days) and on Days 8, 25 and 39 in CRT phase (63 days). In CRT phase subjects also received SOC CRT: cisplatin mg/m² on Days 1, 22 and 43 + IMRT 5 days a week. CRT phase was followed by maintenance phase (12 months) in which subjects received placebo IV injection every 2 weeks. All subjects were followed for safety 30 days after the last study treatment administration or until the time of initiation of new systemic anticancer treatment. If any concern arose subjects were followed up on Day 90 via telephone call thereafter in long term follow up period every 16 weeks for survival and new systemic anticancer treatment.

| | |
|-----------------------|--|
| Reporting group title | Avelumab + Standard of Care Chemotherapy (SOC CRT) |
|-----------------------|--|

Reporting group description:

Subjects with locally advanced squamous cell carcinoma of the head and neck (LA SCCHN) were administered with avelumab 10 milligram per kilogram (mg/kg) intravenous (IV) injection on Day 1 of the Lead-in Phase (7 days) and on Days 8, 25 and 39 in CRT phase (63 days). In CRT phase subjects also received SOC CRT: cisplatin 100 milligram per square meter (mg/m²) on Days 1, 22, 43 and intensity-modulated radiation therapy (IMRT) 5 days a week. CRT phase was followed by maintenance phase (12 months) in which subjects received avelumab 10 mg/kg IV injection every 2 weeks. All subjects were followed for safety 30 days after the last study treatment administration or until the time of initiation of new systemic anticancer treatment. If any concern arose subjects were followed up on Day 90 via telephone call thereafter in long term (LT) follow up period every 16 weeks for survival and new systemic anticancer treatment.

| | |
|-----------------------|-------------------|
| Reporting group title | Placebo + SOC CRT |
|-----------------------|-------------------|

Reporting group description:

Subjects with LA SCCHN were administered with placebo IV injection matched to avelumab on Day 1 of the Lead-in Phase (7 days) and on Days 8, 25 and 39 in CRT phase (63 days). In CRT phase subjects also received SOC CRT: cisplatin mg/m² on Days 1, 22 and 43 + IMRT 5 days a week. CRT phase was followed by maintenance phase (12 months) in which subjects received placebo IV injection every 2 weeks. All subjects were followed for safety 30 days after the last study treatment administration or until the time of initiation of new systemic anticancer treatment. If any concern arose subjects were followed up on Day 90 via telephone call thereafter in long term follow up period every 16 weeks for survival and new systemic anticancer treatment.

Primary: Progression-free Survival (PFS) per Modified Response Evaluation Criteria in Solid Tumors v1.1 (RECIST v1.1) as Assessed by Investigator

| | |
|-----------------|--|
| End point title | Progression-free Survival (PFS) per Modified Response Evaluation Criteria in Solid Tumors v1.1 (RECIST v1.1) as Assessed by Investigator |
|-----------------|--|

End point description:

PFS= Time (in months) from date of randomization to first documented objective PD per modified RECIST v1.1 as assessed by Investigator or death (by any cause), whichever occurred first. Analysis was performed by Kaplan Meier method. PD=any of following: 1) Locoregional PD confirmed by pathology to verify radiographic changes represent true tumor progression and not radiation effects or non-malignant contrast enhancement. 2) Locoregional clinically detectable progression confirmed by pathology. 3) Salvage of primary tumor with tumor present on final pathology. 4) Salvage neck dissection >20 weeks after completion of CRT with tumor present on final pathology. 5) Metastatic PD. PFS data was censored on date of last adequate tumor assessment for subjects with no PFS event. FAS used. 99999=Median and upper limit of 95% CI were not reached at time of PCD. At time of pre-specified interim analysis for endpoint, futility boundaries for Avelumab +SOC CRT arm was crossed and study terminated.

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

End point timeframe:

From randomization until documented PD or death, censored date, whichever occurred first (up to 37 months)

| End point values | Avelumab + Standard of Care Chemotherapy (SOC CRT) | Placebo + SOC CRT | | |
|----------------------------------|--|-----------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 350 | 347 | | |
| Units: months | | | | |
| median (confidence interval 95%) | 99999 (16.9 to 99999) | 99999 (23.0 to 99999) | | |

Statistical analyses

| | |
|---|--|
| Statistical analysis title | PFS analysis (Avelumab+SOC CRT Vs Placebo+SOC CRT) |
| Comparison groups | Placebo + SOC CRT v Avelumab + Standard of Care Chemotherapy (SOC CRT) |
| Number of subjects included in analysis | 697 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.9199 ^[1] |
| Method | Logrank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 1.21 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.928 |
| upper limit | 1.573 |

Notes:

[1] - The treatment arms were compared using a stratified, 1-sided, log rank Test. The three stratification factors were tumor (T) stage (< T4 vs T4), Nodal (N) stage (N0 /N1/N2a/N2b vs N2c/N3), Human papillomavirus (HPV) status (Positive vs Negative).

Secondary: Overall Survival (OS)

| | |
|------------------------|--|
| End point title | Overall Survival (OS) |
| End point description: | Overall survival was defined as the time (in months) from the date of randomization to the date of death due to any cause. Subjects last known to be alive were censored at date of last contact. Analysis was performed using Kaplan Meier method. FAS included all randomized subjects. 99999=Median and 95% CI were not reached at the time of primary completion date. At the time of pre-specified interim analysis for the endpoint, the futility boundaries for the Avelumab +SOC CRT arm was crossed and the study was terminated. |
| End point type | Secondary |
| End point timeframe: | From randomization to the date of death or censored date, whichever occurred first (up to 37 months) |

| End point values | Avelumab + Standard of Care Chemotherapy (SOC CRT) | Placebo + SOC CRT | | |
|----------------------------------|--|------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 350 | 347 | | |
| Units: months | | | | |
| median (confidence interval 95%) | 99999 (99999 to 99999) | 99999 (99999 to 99999) | | |

Statistical analyses

| | |
|---|--|
| Statistical analysis title | OS analysis (Avelumab+SOC CRT Vs Placebo+SOC CRT) |
| Comparison groups | Avelumab + Standard of Care Chemotherapy (SOC CRT) v Placebo + SOC CRT |
| Number of subjects included in analysis | 697 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.9372 ^[2] |
| Method | Logrank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 1.31 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.927 |
| upper limit | 1.849 |

Notes:

[2] - The treatment arms were compared using a stratified, 1-sided, log rank Test. The three stratification factors were tumor (T) stage (< T4 vs T4), Nodal (N) stage (N0 /N1/N2a/N2b vs N2c/N3), Human papillomavirus (HPV) status (Positive vs Negative).

Secondary: Pathologic Complete Response (pCR) Rate in Subjects With Salvage Surgery at the Primary Site

| | |
|--|--|
| End point title | Pathologic Complete Response (pCR) Rate in Subjects With Salvage Surgery at the Primary Site |
| End point description: | pCR was defined as the absence of histologically identifiable residual cancer in any resected specimen. The pCR rate at primary site was estimated by dividing the number of subjects with pCR recorded at any visit from randomization until PD per modified RECIST v1.1 or death due to any cause by the number of subjects randomised who had salvage surgery at the primary site. All randomized subjects who had salvage surgery at the primary site. |
| End point type | Secondary |
| End point timeframe: | |
| From randomization until PD or death (up to 37 months) | |

| End point values | Avelumab + Standard of Care Chemotherapy (SOC CRT) | Placebo + SOC CRT | | |
|----------------------------------|--|--------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 6 | 7 | | |
| Units: percentage of subjects | | | | |
| number (confidence interval 95%) | 0 (0.0 to 45.9) | 14.3 (0.4 to 57.9) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Locoregional Failure per Modified RECIST v1.1 as Assessed by Investigator

| | |
|-----------------|---|
| End point title | Time to Locoregional Failure per Modified RECIST v1.1 as Assessed by Investigator |
|-----------------|---|

End point description:

Locoregional failure was defined as the time from the date of randomization to the date of the first documentation of locoregional recurrence per modified RECIST v1.1 as assessed by Investigator or death due to any cause , whichever occurred first. Analysis was performed using Kaplan Meier method. Here, "99999" indicated median and upper limit of 95% CI were not reached. FAS included all randomized subjects.

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

End point timeframe:

From the date of randomization to the date of the first documentation of locoregional recurrence or death, whichever occurred first (up to 37 months)

| End point values | Avelumab + Standard of Care Chemotherapy (SOC CRT) | Placebo + SOC CRT | | |
|----------------------------------|--|-----------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 350 | 347 | | |
| Units: months | | | | |
| median (confidence interval 95%) | 99999 (22.4 to 99999) | 99999 (25.0 to 99999) | | |

Statistical analyses

| | |
|-----------------------------------|--|
| Statistical analysis title | Avelumab + SOC CRT Vs Placebo + SOC CRT |
| Comparison groups | Avelumab + Standard of Care Chemotherapy (SOC CRT) v Placebo + SOC CRT |

| | |
|---|-------------------------|
| Number of subjects included in analysis | 697 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.9316 ^[3] |
| Method | Logrank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 1.25 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.93 |
| upper limit | 1.694 |

Notes:

[3] - The treatment arms were compared using a stratified, 1-sided, log rank Test. The three stratification factors were tumor (T) stage (< T4 vs T4), Nodal (N) stage (N0 /N1/N2a/N2b vs N2c/N3), Human papillomavirus (HPV) status (Positive vs Negative).

Secondary: Objective Response Rate (ORR) per Modified RECIST v1.1 as Assessed by Investigator

| | |
|-----------------|--|
| End point title | Objective Response Rate (ORR) per Modified RECIST v1.1 as Assessed by Investigator |
|-----------------|--|

End point description:

Objective response (OR) was defined as a complete response (CR) or partial response (PR) per RECIST v1.1 recorded from randomization until disease progression per modified RECIST v1.1 or death due to any cause. A subject was considered to have achieved an OR if the subject had a CR or PR which did not need to be confirmed at a subsequent assessment. CR for target disease: complete disappearance of all target lesions with the exception of nodal disease. All target nodes must decrease to normal size (short axis less than [$<$] 10 millimeter [mm]). CR for non-target disease: disappearance of all non-target lesions and normalization of tumor marker levels. All lymph nodes must be 'normal' in size ($<$ 10 mm short axis). PR: Greater than or equal to (\geq) 30% decrease under baseline of the sum of diameters of all target measurable lesions. The ORR was estimated by dividing the number of subjects with OR (CR or PR) by the number of subjects randomized. FAS included all randomized subjects.

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

End point timeframe:

From randomization until disease progression or death, whichever occurred first (up to 37 months)

| End point values | Avelumab + Standard of Care Chemotherapy (SOC CRT) | Placebo + SOC CRT | | |
|----------------------------------|--|---------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 350 | 347 | | |
| Units: percentage of subjects | | | | |
| number (confidence interval 95%) | 74.0 (69.1 to 78.5) | 74.9 (70.0 to 79.4) | | |

Statistical analyses

| | |
|----------------------------|--|
| Statistical analysis title | ORR analysis (Avelumab+SOC CRT Vs Placebo+SOC CRT) |
| Comparison groups | Avelumab + Standard of Care Chemotherapy (SOC CRT) v Placebo + SOC CRT |

| | |
|---|-------------------------|
| Number of subjects included in analysis | 697 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.6229 [4] |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 0.947 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.663 |
| upper limit | 1.352 |

Notes:

[4] - The treatment arms were compared using a stratified, 1-sided, Cochran-Mantel-Haenszel Test. The 3 stratification factors were tumor stage (< T4 vs T4), Nodal stage (N0 /N1/N2a/N2b vs N2c/N3), HPV status (Positive vs Negative).

Secondary: Time to Distant Metastatic Failure per Modified RECIST v1.1 as Assessed by Investigator

| | |
|-----------------|---|
| End point title | Time to Distant Metastatic Failure per Modified RECIST v1.1 as Assessed by Investigator |
|-----------------|---|

End point description:

Time to distant metastatic failure or distant metastasis (DM) was defined as the time from the date of randomization to the date of the first documentation of distant metastasis or death due to any cause, whichever occurred first. Distant metastatic disease was defined as new tumor identified at a site distant from the head and neck anatomic region or draining lymph nodes. Analysis was performed using Kaplan Meier method. FAS included all randomized subjects. 99999=Median and upper limit of 95% CI were not reached at the time of primary completion date. At the time of pre-specified interim analysis for the outcome measure, the futility boundaries for the Avelumab +SOC CRT arm was crossed and the study was terminated.

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

End point timeframe:

From the date of randomization to the date of the first documentation of distant metastatic or death (up to 37 months)

| End point values | Avelumab + Standard of Care Chemotherapy (SOC CRT) | Placebo + SOC CRT | | |
|----------------------------------|--|------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 350 | 347 | | |
| Units: months | | | | |
| median (confidence interval 95%) | 99999 (22.8 to 99999) | 99999 (99999 to 99999) | | |

Statistical analyses

| | |
|----------------------------|--|
| Statistical analysis title | Avelumab + SOC CRT Vs Placebo + SOC CRT |
| Comparison groups | Avelumab + Standard of Care Chemotherapy (SOC CRT) v Placebo + SOC CRT |

| | |
|---|-------------------------|
| Number of subjects included in analysis | 697 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.9061 ^[5] |
| Method | Logrank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 1.21 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.909 |
| upper limit | 1.624 |

Notes:

[5] - The treatment arms were compared using a stratified, 1-sided, log rank Test. The three stratification factors were tumor stage (< T4 vs T4), Nodal stage (N0 /N1/N2a/N2b vs N2c/N3), HPV status (Positive vs Negative).

Secondary: Duration of Response (DOR) per modified RECIST v1.1 as Assessed by Investigator

| | |
|-----------------|---|
| End point title | Duration of Response (DOR) per modified RECIST v1.1 as Assessed by Investigator |
|-----------------|---|

End point description:

DOR:time from 1st documentation of objective tumor response (CR/PR) to first documentation of PD/death (any cause),whichever occurred first.PR:>=30% decrease under baseline of sum of diameters of all target measurable lesions. CR(Target disease):Complete disappearance of all target lesions with exception of nodal disease.CR(non-target disease):disappearance of all non-target lesions and normalization of tumor marker levels PD is anyone:1)Locoregional PD confirmed by pathology to verify radiographic changes denote true tumor progression and not radiation effects or non-malignant contrast boost.2)Locoregional clinically detectable progression confirmed by pathology.3)Surgical removal of primary tumor with tumor present on final pathology.4)Salvage neck dissection >20 weeks after completion of CRT with tumor present on final pathology.5)Metastatic PD.DOR data censored on date of last adequate tumor assessment for subject with no overall response.All randomized with unconfirmed CR or PR.

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

End point timeframe:

From the first documentation of objective tumor response to the first documentation of PD or death or censored date, whichever occurred first (up to 37 months)

| End point values | Avelumab + Standard of Care Chemotherapy (SOC CRT) | Placebo + SOC CRT | | |
|----------------------------------|--|------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 259 | 260 | | |
| Units: months | | | | |
| median (confidence interval 95%) | 99999 (99999 to 99999) | 99999 (99999 to 99999) | | |

Statistical analyses

Secondary: Number of Subjects With Treatment-Emergent Adverse Events (TEAEs) as Graded by National Cancer Institute Common Terminology Criteria (NCI-CTCAE), Version 4.03

| | |
|-----------------|--|
| End point title | Number of Subjects With Treatment-Emergent Adverse Events (TEAEs) as Graded by National Cancer Institute Common Terminology Criteria (NCI-CTCAE), Version 4.03 |
|-----------------|--|

End point description:

Adverse event (AE) was any untoward medical occurrence in a subject who received study drug without regard to possibility of causal relationship. As per NCI-CTCAE version 4.03, severity was graded as Grade 1: asymptomatic/mild symptoms, clinical/diagnostic observations only, intervention not indicated; Grade 2: moderate, minimal, local/noninvasive intervention indicated, limiting age-appropriate instrumental activities of daily life (ADL); Grade 3: severe/medically significant but not immediately life-threatening, hospitalization/prolongation of existing hospitalization indicated, disabling, limiting self-care ADL; Grade 4: life-threatening consequence, urgent intervention indicated; Grade 5: death related to AE. TEAE was defined as event with onset dates occurring during the on-treatment period. Safety analysis set included all subjects who received at least one dose of study drug.

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

End point timeframe:

Baseline up to 44 months

| End point values | Avelumab + Standard of Care Chemotherapy (SOC CRT) | Placebo + SOC CRT | | |
|-----------------------------|--|-------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 348 | 344 | | |
| Units: subjects | | | | |
| Grade 1 | 10 | 8 | | |
| Grade 2 | 30 | 53 | | |
| Grade 3 | 224 | 215 | | |
| Grade 4 | 59 | 49 | | |
| Grade 5 | 22 | 17 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects with Shift From Baseline in Clinical Laboratory Parameters

| | |
|-----------------|---|
| End point title | Number of Subjects with Shift From Baseline in Clinical Laboratory Parameters |
|-----------------|---|

End point description:

Grade 1 and 3 ranges: Anemia:Hb:<LLN-10.0,<8.0 g/dL;LC decreased (dec):<LLN-800/mm³,500-200/mm³;LC increased (inc):grade 3:>20,000/mm³:NC dec:<LLN-1500/mm³; <1000-500/mm³;PC dec:<LLN-75,000/mm³; <50,000-25,000/mm³;WBC dec:<LLN-3000/mm³; <2000-1000/mm³;ALT inc:>ULN-3.0*ULN;>5.0-20.0*ULN;ALP & GGT inc:>ULN-2.5*ULN;>5.0-20.0*ULN;AST inc:>ULN-3.0*ULN;>5.0-20.0*ULN;BB inc:>ULN-1.5*ULN;>3.0-10.0*ULN;CH high:>ULN-300 mg/dL;>400-500 mg/dL;Hypercalcemia:>ULN-11.5;>12.5-13.5mg/dL;Hyperglycemia:>ULN-160; >250-500mg/dL;Hyperkalemia:>ULN-5.5;>6.0-7.0mmol/L;Hypermagnesemia:>ULN-3.0;>3.0-8.0

mg/dL; Hyponatremia: >ULN-150; >155-160 mmol/L; Hypertriglyceridemia; 150-300; >500-1000 mg/dL; Hypoalbuminemia: <LLN-3; <2g/dL; Hypocalcemia: <LLN-8.0; <8.0-7.0mg/dL; Hypokalemia: <LLN-3.0; <3.0-2.5mmol/L; Hypomagnesemia; <LLN-1.2; <0.9-0.7 mg/dL; Hyponatremia: <LLN-130; <130-120mmol/L; Hypophosphatemia: <LLN-2.5; <2.0-1.0mg/dL. Safety. N=subjects evaluable for this endpoint, n=subjects evaluable for each specified category.

| | |
|--------------------------|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Baseline up to 15 months | |

| End point values | Avelumab + Standard of Care Chemotherapy (SOC CRT) | Placebo + SOC CRT | | |
|---|--|-------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 346 | 340 | | |
| Units: subjects | | | | |
| Anemia: New/worsened (N/W) grade ≥ 1 (n =346,340) | 314 | 311 | | |
| Anemia: N/W to grade ≥ 3 (n =346, 340) | 42 | 49 | | |
| LC Dec: N/W to grade ≥ 1 (n =346, 340) | 336 | 330 | | |
| LC Decreased: N/W to grade ≥ 3 (n =346, 340) | 279 | 284 | | |
| LC Increased: N/W to grade ≥ 1 (n =346, 340) | 7 | 7 | | |
| LC increased: N/W to grade ≥ 3 (n =346, 340) | 0 | 0 | | |
| NC Decreased: N/W to grade ≥ 1 (n =346, 340) | 257 | 237 | | |
| NC Decreased N/W to grade ≥ 3 (n =346, 340) | 120 | 101 | | |
| PC Decreased : N/W to grade ≥ 1 (n =346, 340) | 157 | 154 | | |
| PC Decreased: N/W to grade ≥ 3 (n =346, 340) | 20 | 7 | | |
| WBC Decreased: N/W to grade ≥ 1 (n =346, 340) | 309 | 307 | | |
| WBC Decreased: N/W to grade ≥ 3 (n =346, 340) | 121 | 129 | | |
| ALT increased: N/W to grade ≥ 1 (n =346, 340) | 152 | 135 | | |
| ALT increased: N/W to grade ≥ 3 (n =346, 340) | 13 | 2 | | |
| ALP: N/W to grade ≥ 1 (n =346, 340) | 72 | 49 | | |
| ALP increased: N/W to grade ≥ 3 (n =346, 340) | 1 | 1 | | |
| AST increased: N/W to grade ≥ 1 (n =345, 340) | 146 | 111 | | |
| AST increased: N/W to grade ≥ 3 (n =345, 340) | 11 | 4 | | |
| Bilirubin increased: N/W to grade ≥ 1 (n =346,340) | 58 | 54 | | |
| Bilirubin increased: N/W to grade ≥ 3 (n=346, 340) | 9 | 4 | | |
| Cholesterol (CH) high:N/W to grade ≥ 1 (n=161,164) | 25 | 21 | | |

| | | | | |
|--|-----|-----|--|--|
| CH high: N/W to grade ≥ 3 (n=161,164) | 0 | 0 | | |
| CPK increased: N/W grade ≥ 1 (n=160,156) | 7 | 7 | | |
| CPK increased: N/W to grade ≥ 3 (n=160,156) | 0 | 1 | | |
| Creatinine increased: N/W to grade ≥ 1 (n=346,340) | 334 | 325 | | |
| Creatinine increased: N/W to grade ≥ 3 (n=346,340) | 36 | 37 | | |
| GGT increased: N/W to grade ≥ 1 (n=191,193) | 37 | 23 | | |
| GGT increased: N/W to grade ≥ 3 (n=191,193) | 10 | 5 | | |
| Hypercalcemia: N/W to grade ≥ 1 (n=346,340) | 67 | 59 | | |
| Hypercalcemia: N/W to grade ≥ 3 (n=346,340) | 1 | 5 | | |
| Hyperglycemia: N/W to grade ≥ 1 (n=345,340) | 144 | 137 | | |
| Hyperglycemia: N/W to grade ≥ 3 (n=345,340) | 28 | 29 | | |
| Hyperkalemia: N/W to grade ≥ 1 (n=346,340) | 106 | 113 | | |
| Hyperkalemia: N/W to grade ≥ 3 (n=346,340) | 9 | 17 | | |
| Hypermagnesemia: N/W to grade ≥ 1 (n=346,339) | 39 | 40 | | |
| Hypermagnesemia: N/W to grade ≥ 3 (n=346,339) | 10 | 10 | | |
| Hypernatremia: N/W to grade ≥ 1 (n=346,340) | 22 | 20 | | |
| Hypernatremia: N/W to grade ≥ 3 (n=346,340) | 1 | 0 | | |
| Hypertriglyceridemia: N/W to grade ≥ 1 (n=162,161) | 35 | 26 | | |
| Hypertriglyceridemia: N/W to grade ≥ 3 (n=162,161) | 1 | 2 | | |
| Hypoalbuminemia: N/W to grade ≥ 1 (n=346,340) | 195 | 170 | | |
| Hypoalbuminemia: N/W to grade ≥ 3 (n=346,340) | 7 | 5 | | |
| Hypocalcemia: N/W to grade ≥ 1 (n=346,340) | 82 | 88 | | |
| Hypocalcemia: N/W to grade ≥ 3 (n=346,340) | 8 | 14 | | |
| Hypoglycemia: N/W to grade ≥ 1 (n=345,340) | 56 | 44 | | |
| Hypoglycemia: N/W to grade ≥ 3 (n=345,340) | 2 | 2 | | |
| Hypokalemia: N/W to grade ≥ 1 (n=346,340) | 140 | 122 | | |
| Hypokalemia: N/W to grade ≥ 3 (n=346,340) | 55 | 49 | | |
| Hypomagnesemia: N/W to grade ≥ 1 (n=346,339) | 180 | 158 | | |
| Hypomagnesemia: N/W to grade ≥ 3 (n=346,339) | 8 | 12 | | |
| Hyponatremia: N/W to grade ≥ 1 (n=346,340) | 232 | 212 | | |
| Hyponatremia: N/W to grade ≥ 3 (n=346,340) | 74 | 70 | | |

| | | | | |
|--|-----|-----|--|--|
| Hypophosphatemia: N/W to grade ≥ 1 (n=340,339) | 108 | 100 | | |
| Hypophosphatemia: N/W to grade ≥ 3 (n=340,339) | 21 | 19 | | |
| Lipase increased: N/W to grade ≥ 1 (n=161,154) | 19 | 13 | | |
| Lipase increased: N/W to grade ≥ 3 (n=161,154) | 11 | 3 | | |
| Serum amylase increased: N/W Grade ≥ 1 (n=159,152) | 13 | 10 | | |
| Serum amylase increased: N/W grade ≥ 3 (n=159,152) | 9 | 5 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Vital Sign - Systolic and Diastolic Blood Pressure

| | |
|-----------------|--|
| End point title | Change From Baseline in Vital Sign - Systolic and Diastolic Blood Pressure |
|-----------------|--|

End point description:

Change from baseline in systolic blood pressure (SBP) and diastolic blood pressure (DBP) measured in sitting position were reported. Safety analysis set included all subjects who received at least one dose of study drug. Here, "Overall Number of Subjects Analysed" signifies number of subjects evaluable for this endpoint and "n" signifies subjects evaluable for each specified category at each specified time point. Maintenance Phase =MP

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

End point timeframe:

Baseline, Lead-in phase: Day1; CRT Phase: Days 1, 8, 22, 25, 39, and 43; Maintenance phase: on Days 1 and 15 in Cycles 1 to 13 and EOT (3 days after the last dose of study drug)

| End point values | Avelumab + Standard of Care Chemotherapy (SOC CRT) | Placebo + SOC CRT | | |
|--|--|----------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 342 | 336 | | |
| Units: millimeter of mercury | | | | |
| arithmetic mean (standard deviation) | | | | |
| DBP: Baseline (n=342, 336) | 77.8 (\pm 10.13) | 78.1 (\pm 10.91) | | |
| Lead in Phase: DBP: Change at Day 1 (n=2,2) | -3.0 (\pm 4.24) | -8.0 (\pm 11.31) | | |
| CRT Phase: DBP: Change at Day 1 (n=332,322) | -1.5 (\pm 9.52) | -2.2 (\pm 9.91) | | |
| CRT Phase: DBP: Change at Day 8 (n=323,315) | -3.8 (\pm 10.46) | -3.9 (\pm 10.99) | | |
| CRT Phase: DBP: Change at Day 22 (n- 313,309) | -4.2 (\pm 11.77) | -5.0 (\pm 10.95) | | |
| CRT Phase: DBP: Change at Day 25 (n=310,306) | -3.4 (\pm 11.91) | -3.3 (\pm 11.44) | | |

| | | | | |
|---|--------------------|--------------------|--|--|
| CRT Phase: DBP: Change at Day 39 (n=309,302) | -5.7 (± 11.83) | -5.1 (± 12.14) | | |
| CRT Phase: DBP: Change at Day 43 (n=293,283) | -5.0 (± 11.49) | -4.7 (± 11.76) | | |
| Maintenance Phase: DBP: Change at C1D1 (n=282,290) | -4.8 (± 11.43) | -4.3 (± 11.67) | | |
| MP: DBP: Change at C1D15 (n=265,279) | -3.7 (± 11.78) | -4.0 (± 10.96) | | |
| MP: DBP: Change at C2D1(n=266,277) | -3.3 (± 11.74) | -3.3 (± 12.31) | | |
| MP:DBP:Change at C2D15 (n=255,272) | -2.7 (± 11.05) | -2.3 (± 11.82) | | |
| MP:DBP: Change at C3D1(n=249,262) | -2.7 (± 11.37) | -3.6 (± 11.42) | | |
| MP: DBP: Change at C3D15 (n=234,255) | -2.7 (± 11.09) | -3.4 (± 11.10) | | |
| MP: DBP: Change at C4D1 (n=222,247) | -2.2 (± 12.07) | -3.4 (± 11.42) | | |
| MP: DBP: Change at C4D15(n=216,240) | -2.4 (± 11.38) | -3.3 (± 11.54) | | |
| MP: DBP: Change at C5D1(n=210,241) | -2.8 (± 11.61) | -3.2 (± 10.88) | | |
| MP: DBP: Change at C5D15(n=204,232) | -2.5 (± 11.89) | -3.5 (± 10.69) | | |
| MP: DBP: Change at C6D1(n=201,226) | -3.1 (± 11.21) | -3.8 (± 11.28) | | |
| MP: DBP: Change at C6D15(n=198,230) | -3.8 (± 12.20) | -4.6 (± 11.43) | | |
| MP: DBP: Change at C7D1(n=190,220) | -4.1 (± 11.48) | -4.2 (± 11.52) | | |
| MP: DBP: Change at C7D15 (n=185,214) | -3.8 (± 12.05) | -3.8 (± 10.88) | | |
| MP: DBP: Change at C8D1(n=173,209) | -2.9 (± 11.29) | -4.1 (± 10.95) | | |
| MP: DBP: Change at C8D15 (n=167,194) | -3.4 (± 11.48) | -4.0 (± 12.29) | | |
| MP: DBP: Change at C9D1(n=169,198) | -3.1 (± 11.78) | -4.2 (± 10.98) | | |
| MP: DBP: Change at C9D15(n=162,194) | -2.1 (± 11.52) | -3.7 (± 12.07) | | |
| MP: DBP: Change at C10D1 (n=161,192) | -2.2 (± 11.58) | -3.5 (± 11.54) | | |
| MP: DBP: Change at C10D15 (n=159,191) | -2.5 (± 10.90) | -4.4 (± 11.69) | | |
| MP: DBP: Change at C11D1(n=146,179) | -2.7 (± 11.01) | -4.6 (± 11.23) | | |
| MP: DBP: Change at C11D15(n=139,162) | -2.9 (± 10.37) | -3.9 (± 10.22) | | |
| MP: DBP: Change at C12D1(n=125,156) | -2.1 (± 9.51) | -3.5 (± 11.40) | | |
| MP: DBP: Change at C12D15(n=115,146) | -3.3 (± 11.78) | -4.6 (± 11.19) | | |
| MP: DBP: Change at C13D1(n=105,132) | -2.0 (± 9.60) | -3.3 (± 11.49) | | |
| MP: DBP: Change at C13D15(n=92,118) | -1.1 (± 10.22) | -3.8 (± 11.44) | | |
| DBP: EOT(n=225,210) | -2.4 (± 11.96) | -3.2 (± 11.17) | | |
| SBP: Baseline (n=342,336) | 129.8 (± 16.42) | 130.5 (± 17.44) | | |
| Lead in Phase:SBP: Change at Day 1(n=2,2) | -5.5 (± 2.12) | 12.5 (± 6.36) | | |
| CRT Phase: SBP: Change at Day 1(n=332,322) | -2.5 (± 15.32) | -3.5 (± 14.82) | | |
| CRT Phase: SBP: Change at Day 8(n=323,315) | -8.3 (± 17.78) | -8.0 (± 17.58) | | |
| CRT Phase: SBP: Change at Day 22(n=313,309) | -8.9 (± 18.54) | -8.4 (± 17.55) | | |
| CRT Phase: SBP: Change at Day 25(n=310,306) | -7.9 (± 19.06) | -5.8 (± 19.51) | | |
| CRT Phase: SBP: Change at Day 39(n=309,302) | -10.6 (± 20.51) | -10.3 (± 19.05) | | |
| CRT Phase: SBP: Change at Day 43(n=293,283) | -9.6 (± 18.53) | -9.2 (± 19.52) | | |
| MP: SBP: Change at C1D1 (n=282,290) | -9.4 (± 17.97) | -9.4 (± 20.19) | | |

| | | | | |
|--|----------------|----------------|--|--|
| MP: SBP: Change at C1D15(n=265, 279) | -9.5 (± 17.73) | -8.2 (± 19.58) | | |
| MP: SBP: Change at C2D1(n=266,277) | -7.0 (± 18.03) | -7.8 (± 20.09) | | |
| MP: SBP: Change at C2D15(n=255,272) | -7.9 (± 18.55) | -6.6 (± 19.73) | | |
| MP: SBP: Change at C3D1(n=249,262) | -7.3 (± 18.93) | -8.5 (± 18.04) | | |
| MP: SBP: Change at C3D15(n=234,255) | -8.3 (± 17.79) | -7.1 (± 19.90) | | |
| Maintenance Phase: SBP: Change at C4D1(n=222,247) | -8.4 (± 18.01) | -8.9 (± 18.41) | | |
| Maintenance Phase: SBP: Change at C4D15(n=216,240) | -6.2 (± 18.20) | -8.2 (± 19.62) | | |
| MP: SBP: Change at C5D1(n=210,241) | -7.6 (± 17.57) | -7.7 (± 18.69) | | |
| MP: SBP: Change at C5D15(n=204,232) | -8.4 (± 18.69) | -7.5 (± 18.49) | | |
| MP: SBP: Change at C6D1(n=201,206) | -7.6 (± 17.67) | -8.3 (± 18.96) | | |
| MP: SBP: Change at C6D15(n=198,230) | -7.1 (± 19.35) | -9.4 (± 19.56) | | |
| MP: SBP: Change at C7D1(n=190,220) | -9.0 (± 18.30) | -8.9 (± 18.96) | | |
| MP: SBP: Change at C7D15(n=185,214) | -8.7 (± 18.10) | -6.8 (± 18.73) | | |
| MP: SBP: Change at C8D1(n=173,209) | -6.5 (± 17.00) | -9.4 (± 18.65) | | |
| MP: SBP: Change at C8D15(n=167,194) | -6.8 (± 16.69) | -7.9 (± 18.21) | | |
| MP: SBP: Change at C9D1(n=169,198) | -6.1 (± 18.49) | -8.1 (± 18.41) | | |
| MP: SBP: Change at C9D15(n=162,194) | -6.3 (± 19.00) | -6.7 (± 20.28) | | |
| MP: SBP: Change at C10D1(n=161,192) | -6.1 (± 19.24) | -7.2 (± 18.63) | | |
| MP: SBP: Change at C10D15(n=159,191) | -5.6 (± 17.07) | -7.7 (± 18.76) | | |
| MP: SBP: Change at C11D1(n=146,179) | -6.3 (± 19.44) | -7.7 (± 18.86) | | |
| MP: SBP: Change at C11D15(n=139,162) | -6.3 (± 18.99) | -7.4 (± 18.65) | | |
| MP: SBP: Change at C12D1(n=125,156) | -6.8 (± 18.25) | -6.1 (± 20.21) | | |
| MP: SBP: Change at C12D15(n=115,146) | -7.1 (± 19.34) | -7.8 (± 19.12) | | |
| MP: SBP: Change at C13D1(n=105,132) | -5.8 (± 20.04) | -6.2 (± 18.54) | | |
| MP: SBP: Change at C13D15(n=92,118) | -4.9 (± 18.82) | -5.6 (± 19.00) | | |
| MP: SBP: EOT(n=225,210) | -7.0 (± 19.83) | -4.9 (± 17.97) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Vital Sign - Pulse Rate

| | |
|--|---|
| End point title | Change From Baseline in Vital Sign - Pulse Rate |
| End point description: | |
| Change from baseline in pulse rate in sitting position in beats per minute was reported. Here, "Overall Number of Subjects Analysed" signifies number of subjects evaluable for this endpoint and "n" signifies subjects evaluable for each specified category at each specified time point. | |
| End point type | Secondary |
| End point timeframe: | |
| Baseline, Lead-in phase: Day1; CRT Phase: Days 1, 8, 22, 25, 39, and 43; Maintenance phase: on Days 1 and 15 in Cycles 1 to 13 and EOT (3 days after the last dose of study drug) | |

| End point values | Avelumab + Standard of Care Chemotherapy (SOC CRT) | Placebo + SOC CRT | | |
|---|--|----------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 342 | 336 | | |
| Units: beats per minute | | | | |
| arithmetic mean (standard deviation) | | | | |
| Baseline (n=342,336) | 79.9 (± 13.72) | 86.0 (± 43.0) | | |
| Lead in Phase: Change at Day 1 (n=2,2) | -3.5 (± 0.71) | -8.5 (± 19.09) | | |
| CRT Phase: Change at Day 1 (n=331,322) | 0.7 (± 11.70) | 1.3 (± 10.92) | | |
| CRT Phase: Change at Day 8 (n=323,315) | 1.5 (± 13.15) | 2.2 (± 12.42) | | |
| CRT Phase: Change at Day 22(n=314,309) | 0.5 (± 13.86) | 2.6 (± 12.24) | | |
| CRT Phase: Change at Day 25(n=310,306) | -1.6 (± 14.87) | -1.2 (± 13.90) | | |
| CRT Phase: Change at Day 29(n=10,8) | -11.0 (± 20.47) | 3.6 (± 21.29) | | |
| CRT Phase: Change at Day 39(n=310,301) | 4.0 (± 15.46) | 4.3 (± 14.71) | | |
| CRT Phase: Change at Day 43(n=293,283) | 4.7 (± 16.82) | 6.1 (± 14.78) | | |
| Maintenance Phase: Change at C1D1 1(n=282,291) | 5.1 (± 16.23) | 7.5 (± 14.43) | | |
| Maintenance Phase: Change at C1D15(n=265,279) | 3.8 (± 15.04) | 6.3 (± 13.65) | | |
| Maintenance Phase: Change at C2D1(n=266,277) | 3.5 (± 15.30) | 5.9 (± 14.74) | | |
| Maintenance Phase: Change at C2D15(n=254,272) | 4.1 (± 15.32) | 4.9 (± 13.94) | | |
| Maintenance Phase: Change at C3D1(n=249,262) | 3.5 (± 14.49) | 3.9 (± 14.37) | | |
| Maintenance Phase: Change at C3D15(n=234,255) | 2.8 (± 14.73) | 2.8 (± 14.14) | | |
| Maintenance Phase: Change at C4D1(n=222,247) | 1.8 (± 14.79) | 3.8 (± 14.95) | | |
| MP: Change at C4D15(n=216,240) | 1.6 (± 14.80) | 3.8 (± 15.02) | | |
| MP: Change at C5D1(n=210,241) | 2.6 (± 13.88) | 2.9 (± 14.82) | | |
| MP: Change at C5D15(n=204,232) | 1.6 (± 15.11) | 3.3 (± 13.74) | | |
| MP: Change at C6D1(n=201,226) | 1.6 (± 15.42) | 2.7 (± 15.72) | | |
| MP: Change at C6D15(n=198,230) | 0.4 (± 14.04) | 1.4 (± 13.66) | | |
| MP: Change at C7D1(n=190,220) | -0.1 (± 14.47) | 2.5 (± 14.18) | | |
| MP: Change at C7D15(n=185,214) | -0.1 (± 14.24) | 1.4 (± 14.33) | | |
| MP: Change at C8D1(n=173,209) | -0.2 (± 13.84) | 1.0 (± 13.67) | | |
| MP: Change at C8D15(n=167,194) | -1.5 (± 14.52) | 1.5 (± 14.86) | | |
| MP: Change at C9D1(n=169,198) | -1.0 (± 14.29) | -0.1 (± 14.06) | | |
| MP: Change at C9D15(n=162,194) | -1.0 (± 14.20) | 0.2 (± 14.44) | | |
| MP: Change at C10D1(n=161,192) | -0.9 (± 13.40) | 0.7 (± 14.52) | | |
| MP: Change at C10D15(n=159,191) | -0.5 (± 15.33) | 0.7 (± 14.66) | | |
| MP: Change at C11D1(n=145,178) | -1.6 (± 14.57) | 0.2 (± 14.01) | | |
| MP: Change at C11D15(n=139,162) | -0.2 (± 13.23) | 0.3 (± 12.93) | | |
| MP: Change at C12D1(n=125,156) | -0.3 (± 13.92) | 0.4 (± 13.67) | | |
| MP: Change at C12D15(n=115,146) | -1.4 (± 14.92) | -0.5 (± 12.47) | | |
| MP: Change at C13D1(n=105,132) | -1.4 (± 14.09) | -0.1 (± 12.22) | | |

| | | | | |
|--|---------------------------------|--------------------------------|--|--|
| MP: Change at C13D15(n=92,118) EOT(n=223,210) | -1.3 (± 15.57) 0.2 (± 14.73) | 0.4 (± 13.24) 1.9 (± 14.09) | | |
|--|---------------------------------|--------------------------------|--|--|

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in the European Quality of Life- 5 Dimension-5 Levels (EQ-5D-5L) Index Score at CRT Phase and Maintenance Phase

| | |
|-----------------|--|
| End point title | Change from Baseline in the European Quality of Life- 5 Dimension-5 Levels (EQ-5D-5L) Index Score at CRT Phase and Maintenance Phase |
|-----------------|--|

End point description:

EQ-5D-5L is a standardized subject completed questionnaire that measures health status in terms of a single index value or utility score. EQ-5D-5L consisted of two components: a health state profile (descriptive system) and a visual analogue scale (VAS) in which subjects rate their overall health status from 0 (worst imaginable) to 100 (best imaginable), where higher scores indicated better health status. EQ-5D health state profile is comprised of 5 dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each dimension has 5 response levels: 1=no problems, 2=slight problems, 3=moderate problems, 4=severe problems and 5=extreme problems. EQ-5D-5L health status index score range between 0 to 1. Higher score indicated better health status. FAS included all randomized subjects. Overall Number of Subjects Analysed=subjects evaluable for this endpoint and "n" signifies subjects evaluable for each specified category at each specified time point.

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

End point timeframe:

Baseline, CRT Phase: Days 1 and 29; Maintenance phase: Cycle 1/Day 1, Cycle 3/Day 1, Cycle 7/Day 1, Cycle 7/Day 15, Cycle 11/Day 1, Cycle 11/Day 15, EOT (3 days after the last dose of study drug)

| End point values | Avelumab + Standard of Care Chemotherapy (SOC CRT) | Placebo + SOC CRT | | |
|--|--|---------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 334 | 333 | | |
| Units: units on a scale | | | | |
| arithmetic mean (standard deviation) | | | | |
| Baseline: (n=334, 333) | 0.7718 (± 0.17822) | 0.7615 (± 0.18517) | | |
| CRT Phase: Change at Day 1: (n=321, 318) | -0.0078 (± 0.13269) | 0.0176 (± 0.14066) | | |
| CRT Phase: Change at Day 2 (n=293, 276) | -0.0915 (± 0.22053) | -0.0487 (± 0.19175) | | |
| MP: Change at C1D1 (n=272, 279) | -0.0749 (± 0.22126) | -0.0519 (± 0.17253) | | |
| MP: Change at C3D1 (n=239, 243) | -0.0203 (± 0.21340) | -0.0160 (± 0.18179) | | |
| MP: Change at C7D1 (n=95,113) | 0.0088 (± 0.16690) | 0.0140 (± 0.16240) | | |
| MP: Change at C7D15 (n=59, 79) | 0.0552 (± 0.18544) | 0.0472 (± 0.17990) | | |
| MP: Change at C11D1 (n=90,111) | 0.0376 (± 0.21078) | 0.0792 (± 0.19287) | | |

| | | | | |
|---------------------------------|--------------------------|-------------------------|--|--|
| MP: Change at C11D15 (n=36, 40) | 0.0673 (\pm 0.17227) | 0.0389 (\pm 0.18732) | | |
| MP: Change at EOT (n=184,187) | -0.0051 (\pm 0.24528) | 0.0074 (\pm 0.24874) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in the European Quality of Life- 5 Dimension-5 Levels (EQ-5D-5L) VAS Score at CRT Phase and Maintenance Phase

| | |
|-----------------|--|
| End point title | Change From Baseline in the European Quality of Life- 5 Dimension-5 Levels (EQ-5D-5L) VAS Score at CRT Phase and Maintenance Phase |
|-----------------|--|

End point description:

EQ-5D-5L is a standardized subject completed questionnaire that measures health status in terms of a single index value or utility score. EQ-5D-5L consisted of two components: a health state profile (descriptive system) and a visual analogue scale (VAS). EQ-5D health state profile is comprised of 5 dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each dimension has 5 response levels: 1=no problems, 2=slight problems, 3=moderate problems, 4=severe problems and 5=extreme problems. EQ-5D-5L health status index score range between 0 to 1. Higher score indicated worse health status. In VAS subjects rate their overall health status from 0 (worst imaginable) to 100 (best imaginable), where higher scores indicated better health status. FAS included all randomized subjects. "Overall Number of subjects Analysed" signifies subjects evaluable for this endpoint and "n" signifies subjects evaluable at each specified time point.

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

End point timeframe:

Baseline, CRT Phase: Days 1 and 29; Maintenance phase: Cycle 1/Day 1, Cycle 3/Day 1, Cycle 7/Day 1, Cycle 7/Day 15, Cycle 11/Day 1, Cycle 11/Day 15, EOT (3 days after the last dose of study drug)

| End point values | Avelumab + Standard of Care Chemotherapy (SOC CRT) | Placebo + SOC CRT | | |
|--|---|---------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 333 | 330 | | |
| Units: units on a scale | | | | |
| arithmetic mean (standard deviation) | | | | |
| Baseline: (n=333, 330) | 75.8 (\pm 18.20) | 74.9 (\pm 18.24) | | |
| CRT Phase: Change at Day 1 (n=317, 314) | -1.1 (\pm 13.49) | -1.4 (\pm 11.39) | | |
| CRT Phase: Change at Day 29 (n=291, 271) | -10.9 (\pm 19.94) | -9.2 (\pm 18.70) | | |
| MP: Change at C1D1 (n=272, 277) | -7.7 (\pm 19.05) | -6.2 (\pm 18.67) | | |
| MP: Change at C3D1 (n=240, 236) | -1.8 (\pm 18.00) | -0.7 (\pm 16.14) | | |
| MP: Change at C7D1 (n=95,113) | -0.6 (\pm 14.91) | 8.6 (\pm 81.42) | | |
| MP: Change at C7D15 (n=59, 78) | 4.8 (\pm 18.52) | 3.1 (\pm 19.28) | | |
| MP: Change at C11D1 (n=89,108) | 0.3 (\pm 17.60) | 4.3 (\pm 16.10) | | |
| MP: Change at C11D15 (n=37, 40) | 10.1 (\pm 24.69) | 2.4 (\pm 18.20) | | |
| MP: Change at EOT (n=183, 184) | -1.9 (\pm 22.55) | 0.7 (\pm 19.28) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in National Cancer Comprehensive Network Head and Neck Symptom Index-22 Item Scores (NCCN FHNSI-22) at CRT Phase and Maintenance Phase

| | |
|-----------------|---|
| End point title | Change From Baseline in National Cancer Comprehensive Network Head and Neck Symptom Index-22 Item Scores (NCCN FHNSI-22) at CRT Phase and Maintenance Phase |
|-----------------|---|

End point description:

The NCCN FHNSI-22 questionnaire measured disease symptoms, treatment side effects and overall quality of life in participants with head and neck cancer. The questionnaire contained 22 items with 5-point Likert scales ranging from 0 to 4 as follows: 'not at all = 0', a little bit = 1, somewhat = 2, quite a bit = 3 and very much = 4. Total score ranged from 0 to 88 where, higher scores represented better symptomatology, quality of life or functioning. FAS included all randomized subjects. Here, "Overall Number of Subjects Analysed" signifies number of subjects evaluable for this endpoint and "n" signifies subjects evaluable for each specified category at each specified time point.

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

End point timeframe:

Baseline, CRT Phase: Days 1 and 29; Maintenance phase: Cycle 1/Day 1, Cycle 3/Day 1, Cycle 7/Day 1, Cycle 7/Day 15, Cycle 11/Day 1, Cycle 11/Day 15, EOT (3 days after the last dose of study drug)

| End point values | Avelumab + Standard of Care Chemotherapy (SOC CRT) | Placebo + SOC CRT | | |
|--|---|-------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 333 | 331 | | |
| Units: units on a scale | | | | |
| arithmetic mean (standard deviation) | | | | |
| Baseline: (n=333, 331) | 60.56 (± 13.731) | 61.05 (± 13.155) | | |
| CRT Phase: Change at Day 1: (n=318, 317) | -0.59 (± 8.719) | -0.14 (± 9.136) | | |
| CRT Phase: Change at Day 29 (n=294, 275) | -14.34 (± 16.847) | -14.56 (± 15.470) | | |
| MP: Change at C1D1 (n=272, 281) | -11.33 (± 16.054) | -12.08 (± 14.950) | | |
| MP: Change at C3D1 (n=241, 241) | -3.81 (± 14.017) | -2.26 (± 13.625) | | |
| MP: Change at C7D1 (n=96,113) | -0.86 (± 12.503) | -0.51 (± 14.585) | | |
| MP: Change at C7D15 (n=61, 78) | 3.96 (± 14.035) | 0.92 (± 14.454) | | |
| MP: Change at C11D1 (n=88,110) | 2.68 (± 13.367) | 4.90 (± 14.207) | | |

| | | | | |
|---------------------------------|------------------|-----------------|--|--|
| MP: Change at C11D15 (n=37, 40) | 3.96 (± 14.322) | 3.37 (± 12.689) | | |
| MP: Change at EOT (n=184, 187) | -2.35 (± 17.428) | 0.79 (± 16.509) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Programmed Death Receptor-1 Ligand-1 (PD-L1) Biomarker Expression in Tumor Tissue as Assessed by Immunohistochemistry (IHC)

| | |
|-----------------|---|
| End point title | Programmed Death Receptor-1 Ligand-1 (PD-L1) Biomarker Expression in Tumor Tissue as Assessed by Immunohistochemistry (IHC) |
|-----------------|---|

End point description:

PD-L1 biomarker expression in tumor tissue as assessed by IHC in the form of positive immune cells and tumor staining cells. Biomarker analysis set was a subset of the safety analysis set included subjects who had at least one screening biomarker assessment. Here, "Overall Number of Subjects Analysed" signifies number of subjects evaluable for this endpoint.

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

End point timeframe:

Baseline (prior to first dose)

| End point values | Avelumab + Standard of Care Chemotherapy (SOC CRT) | Placebo + SOC CRT | | |
|--------------------------------------|--|-------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 299 | 307 | | |
| Units: % of PD-L1+ cells | | | | |
| arithmetic mean (standard deviation) | | | | |
| Positive Immune Cells | 7.4 (± 7.06) | 8.3 (± 8.47) | | |
| Tumor Staining Cells | 12.7 (± 24.90) | 18.3 (± 31.12) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Percentage (%) of Total Tumor Area Occupied by Cluster of Differentiation 8 (CD8+) Cells

| | |
|-----------------|---|
| End point title | Mean Percentage (%) of Total Tumor Area Occupied by Cluster of Differentiation 8 (CD8+) Cells |
|-----------------|---|

End point description:

Description: CD8+ cells are the type of T-lymphocytes. Mean percentage of total tumor area occupied by CD8+ Cells has been reported. Area was measured in millimeter square (mm²). Biomarker analysis set was a subset of the safety analysis set included subjects who had at least one screening biomarker assessment. Here, "Overall Number of Subjects Analysed" signifies number of subjects evaluable for this endpoint.

| | |
|--------------------------------|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Baseline (prior to first dose) | |

| End point values | Avelumab + Standard of Care Chemotherapy (SOC CRT) | Placebo + SOC CRT | | |
|---|--|-------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 289 | 294 | | |
| Units: % of tumor area occupied by CD8+ cells | | | | |
| arithmetic mean (standard deviation) | 4.9 (± 6.03) | 5.8 (± 6.55) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With Positive and Negative Pathology of Neck Dissection

| | |
|-----------------|--|
| End point title | Percentage of Subjects With Positive and Negative Pathology of Neck Dissection |
|-----------------|--|

End point description:

Percentage of subjects with positive and negative pathology of neck dissection were reported. Positive pathology included live tumor cells present or 10% or greater vital tumor tissues. Negative pathology included no live tumor cells present, complete tumor regression, no evidence of vital tumor tissues, less than 10% vital tumor tissue, or not consistent with disease under study. Analysis population included all subjects who had received at least one dose of study drug and who had salvage neck dissection.

| | |
|--|-----------|
| End point type | Secondary |
| End point timeframe: | |
| From randomization until PD as per investigator assessment (up to 37 months) | |

| End point values | Avelumab + Standard of Care Chemotherapy (SOC CRT) | Placebo + SOC CRT | | |
|-------------------------------|--|-------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 14 | 15 | | |
| Units: percentage of subjects | | | | |
| number (not applicable) | | | | |
| Negative Pathology | 7.14 | 26.70 | | |
| Positive pathology | 71.43 | 40.00 | | |
| Pathology not reported | 21.43 | 33.30 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Maximum Plasma Concentration (Cmax) of Avelumab

| | |
|-----------------|--|
| End point title | Maximum Plasma Concentration (Cmax) of Avelumab ^[6] |
|-----------------|--|

End point description:

Maximum observed plasma concentration (Cmax) of Avelumab is reported. PK concentration analysis was a subset of the safety analysis set and included subjects who had at least one post-dose concentration measurement above the lower limit of quantitation (LLQ) for avelumab or cisplatin. Here 'overall number of subjects analysed' signifies subjects evaluable for this endpoint and 'n' signifies subjects evaluable at specified time point.

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

End point timeframe:

Pre-dose and end of infusion on Day 1 of lead-in phase, Days 8, 25 of CRT phase, Day 1 of Cycle 1 and 2 (each cycle 28 days)

Notes:

[6] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint was planned to be analyzed for the arms specified

| End point values | Avelumab + Standard of Care Chemotherapy (SOC CRT) | | | |
|---|--|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 236 | | | |
| Units: nanogram per milliliter | | | | |
| geometric mean (geometric coefficient of variation) | | | | |
| Lead-in/Day 1 (n= 236) | 203.6 (± 31) | | | |
| CRT/Day 8 (n= 207) | 190.9 (± 66) | | | |
| CRT/Day 25 (n= 189) | 162.4 (± 114) | | | |
| Cycle 1 Day 1 (n= 152) | 142 (± 117) | | | |
| Cycle 2 Day 1 (n= 128) | 154.9 (± 97) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Predose Plasma Concentration (Ctrough) of Avelumab

| | |
|-----------------|---|
| End point title | Predose Plasma Concentration (Ctrough) of Avelumab ^[7] |
|-----------------|---|

End point description:

Ctrough refers to plasma concentration of Avelumab observed just before treatment administration. PK concentration analysis was a subset of the safety analysis set and included subjects who had at least

one post-dose concentration measurement above the lower limit of quantitation (LLQ) for avelumab or cisplatin. Here 'overall number of subjects analysed' signifies subjects evaluable for this endpoint and 'n' signifies subjects evaluable at specified time point.

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

End point timeframe:

Pre-dose on Day 1 of lead-in phase, Days 8, 25 of CRT phase, Day 1 of Cycle 1, 2, 5, 8, 11 (each cycle 28 days)

Notes:

[7] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: This endpoint was planned to be analyzed for the arms specified

| | | | | |
|---|--|--|--|--|
| End point values | Avelumab + Standard of Care Chemotherapy (SOC CRT) | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 267 | | | |
| Units: microgram per milliliter | | | | |
| geometric mean (geometric coefficient of variation) | | | | |
| Lead-in/Day 1 (n =263) | 2.988 (± 1590) | | | |
| CRT/Day 8 (n =267) | 11.9 (± 63) | | | |
| CRT/Day 25 (n =251) | 6.284 (± 138) | | | |
| Cycle 1/Day 1 (n =183) | 2.354 (± 131) | | | |
| Cycle 2/Day 1 (n =198) | 17.56 (± 70) | | | |
| Cycle 5/Day 1 (n =147) | 24.35 (± 66) | | | |
| Cycle 8/Day 1 (n =125) | 29.59 (± 69) | | | |
| Cycle 11/Day 1 (n =113) | 30.85 (± 79) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Dose Normalized Maximum Plasma Concentration (Cmax [dn]) of Total and Free Cisplatin

| | |
|-----------------|--|
| End point title | Dose Normalized Maximum Plasma Concentration (Cmax [dn]) of Total and Free Cisplatin |
|-----------------|--|

End point description:

Dose normalized (dn) Cmax was calculated by dividing Cmax by the exact dose of total or free Cisplatin (in mg) administered to a subject. PK concentration analysis was a subset of the safety analysis set and included subjects who had at least one post-dose concentration measurement above the lower limit of quantitation (LLQ) for avelumab or cisplatin. Here 'overall number of subjects analysed' signifies subjects evaluable for this endpoint.

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

End point timeframe:

Pre-dose, mid-infusion, end of infusion, 3, 4, and 24 hours post dose on Day 1 of CRT phase

| End point values | Avelumab + Standard of Care Chemotherapy (SOC CRT) | Placebo + SOC CRT | | |
|---|--|-------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 12 | 23 | | |
| Units: nanogram per milliliter per milligram | | | | |
| geometric mean (geometric coefficient of variation) | | | | |
| Total Cisplatin | 26.23 (± 36) | 25.33 (± 26) | | |
| Free Cisplatin | 11.84 (± 29) | 7.286 (± 96) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Dose Normalized Area Under the Curve From Time Zero to Last Quantifiable Concentration (AUClast[dn]) of Total and Free Cisplatin

| | |
|-----------------|--|
| End point title | Dose Normalized Area Under the Curve From Time Zero to Last Quantifiable Concentration (AUClast[dn]) of Total and Free Cisplatin |
|-----------------|--|

End point description:

Area under the plasma concentration time-curve from time zero to the time of last measured concentration (AUClast). AUClast (dn) was calculated by dividing AUClast by the exact dose of cisplatin (in mg) administered to a subject. PK concentration analysis was a subset of the safety analysis set and included subjects who had at least one post-dose concentration measurement above the lower limit of quantitation (LLQ) for avelumab or cisplatin. Here, 'overall number of subjects analysed' signifies subjects evaluable for this endpoint.

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

End point timeframe:

Pre-dose, mid-infusion, end of infusion, 3, 4, and 24 hours post dose on Day 1 of CRT phase

| End point values | Avelumab + Standard of Care Chemotherapy (SOC CRT) | Placebo + SOC CRT | | |
|---|--|-------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 10 | 20 | | |
| Units: nanogram*hour/milliliter/milligram | | | | |
| geometric mean (geometric coefficient of variation) | | | | |
| Total Cisplatin | 299.1 (± 30) | 332.7 (± 17) | | |
| Free Cisplatin | 36.53 (± 51) | 29.08 (± 49) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Maximum Plasma Concentration (Cmax) of Total and Free Cisplatin

| | |
|-----------------|---|
| End point title | Maximum Plasma Concentration (Cmax) of Total and Free Cisplatin |
|-----------------|---|

End point description:

Maximum observed plasma concentration (Cmax) of total and free Cisplatin is reported. PK concentration analysis was a subset of the safety analysis set and included subjects who had at least one post-dose concentration measurement above the lower limit of quantitation (LLQ) for avelumab or cisplatin. Here 'overall number of subjects analysed' signifies subjects evaluable for this endpoint.

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

End point timeframe:

Pre-dose, mid-infusion, end of infusion, 3, 4, and 24 hours post dose on Day 1 of CRT phase

| End point values | Avelumab + Standard of Care Chemotherapy (SOC CRT) | Placebo + SOC CRT | | |
|---|--|-------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 12 | 23 | | |
| Units: nanogram per milliliter | | | | |
| geometric mean (geometric coefficient of variation) | | | | |
| Total Cisplatin | 3781 (± 44) | 4001 (± 34) | | |
| Free Cisplatin | 1710 (± 53) | 1151 (± 109) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Attain Maximum Observed Plasma Concentration (Tmax) of Total and Free Cisplatin

| | |
|-----------------|---|
| End point title | Time to Attain Maximum Observed Plasma Concentration (Tmax) of Total and Free Cisplatin |
|-----------------|---|

End point description:

Time to reach maximum observed plasma concentration (Tmax) of total and free Cisplatin. PK concentration analysis was a subset of the safety analysis set and included subjects who had at least one post-dose concentration measurement above the lower limit of quantitation (LLQ) for avelumab or cisplatin. Here 'overall number of subjects analysed' signifies subjects evaluable for this endpoint.

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

End point timeframe:

Pre-dose, mid-infusion, end of infusion, 3, 4, and 24 hours post dose on Day 1 of CRT phase

| End point values | Avelumab + Standard of Care Chemotherapy (SOC CRT) | Placebo + SOC CRT | | |
|-------------------------------|--|-----------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 12 | 23 | | |
| Units: hour | | | | |
| median (full range (min-max)) | | | | |
| Total Cisplatin | 1.000 (0.500 to 2.40) | 1.170 (0.983 to 24.0) | | |
| Free Cisplatin | 1.000 (0.500 to 1.17) | 1.000 (0.500 to 2.12) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Anti-Drug Antibodies (ADA) Against Avelumab by Never and Ever Positive Status

| | |
|-----------------|--|
| End point title | Number of Subjects With Anti-Drug Antibodies (ADA) Against Avelumab by Never and Ever Positive Status ^[8] |
|-----------------|--|

End point description:

ADA never-positive was defined as no positive ADA results at any time point; ADA-negative subjects (titer less than < cut point) and ADA ever-positive was defined as at least one positive ADA result at any time point; ADA-positive subjects (titer greater than or equal to cut point). Immunogenicity analysis set was a subset of the safety analysis set which included subjects who had at least 1 ADA/nAb sample collected for avelumab in Avelumab + Standard of Care Chemotherapy (SOC CRT) arm.

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

End point timeframe:

pre-dose on Day 1 up to 30 Days after the end of treatment

Notes:

[8] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: This endpoint was planned to be analyzed for the arms specified

| End point values | Avelumab + Standard of Care Chemotherapy (SOC CRT) | | | |
|-----------------------------|--|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 331 | | | |
| Units: subjects | | | | |
| ADA never-positive | 277 | | | |
| ADA ever-positive | 54 | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Neutralizing Antibodies (nAb) Against Avelumab by Never and Ever Positive Status

| | |
|-----------------|--|
| End point title | Number of Subjects With Neutralizing Antibodies (nAb) Against Avelumab by Never and Ever Positive Status |
|-----------------|--|

End point description:

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

End point timeframe:

Day 1 of lead-in phase and on Days 8 and 25 of CRT phase

| End point values | Avelumab + Standard of Care Chemotherapy (SOC CRT) | Placebo + SOC CRT | | |
|-----------------------------|--|----------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 0 ^[9] | 0 ^[10] | | |
| Units: subjects | | | | |

Notes:

[9] - Due to study termination and program decision data for nAb was not collected and analyzed.

[10] - Due to study termination and program decision data for nAb was not collected and analyzed.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Baseline up to 44 months

Adverse event reporting additional description:

Same event may appear as AE, serious AE, here distinct events are presented. Event may be serious in 1 participant and non-serious in another or 1 subject may have experienced both serious, non-serious event. Safety analysis set evaluated.

| | |
|-----------------|----------------|
| Assessment type | Non-systematic |
|-----------------|----------------|

Dictionary used

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

| | |
|--------------------|------|
| Dictionary version | 23.0 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|--|
| Reporting group title | Avelumab + Standard of Care Chemotherapy (SOC CRT) |
|-----------------------|--|

Reporting group description:

Participants with locally advanced squamous cell carcinoma of the head and neck (LA SCCHN) were administered with avelumab 10 milligram per kilogram (mg/kg) intravenous (IV) injection on Day 1 of the Lead-in Phase (7 days) and on Days 8, 25 and 39 in CRT phase (63 days). In CRT phase participants also received SOC CRT: cisplatin 100 milligram per square meter (mg/m²) on Days 1, 22, 43 and intensity-modulated radiation therapy (IMRT) 5 days a week. CRT phase was followed by maintenance phase (12 months) in which participants received avelumab 10 mg/kg IV injection every 2 weeks. All participants were followed for safety 30 days after the last study treatment administration or until the time of initiation of new systemic anticancer treatment. If any concern arose participants were followed up on Day 90 via telephone call thereafter in long term (LT) follow up period every 16 weeks for survival and new systemic anticancer treatment.

| | |
|-----------------------|-------------------|
| Reporting group title | Placebo + SOC CRT |
|-----------------------|-------------------|

Reporting group description:

Participants with LA SCCHN were administered with placebo IV injection matched to avelumab on Day 1 of the Lead-in Phase (7 days) and on Days 8, 25 and 39 in CRT phase (63 days). In CRT phase participants also received SOC CRT: cisplatin mg/m² on Days 1, 22 and 43 + IMRT 5 days a week. CRT phase was followed by maintenance phase (12 months) in which participants received placebo IV injection every 2 weeks. All participants were followed for safety 30 days after the last study treatment administration or until the time of initiation of new systemic anticancer treatment. If any concern arose participants were followed up on Day 90 via telephone call thereafter in long term follow up period every 16 weeks for survival and new systemic anticancer treatment.

| Serious adverse events | Avelumab + Standard of Care Chemotherapy (SOC CRT) | Placebo + SOC CRT | |
|---|--|--------------------|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 184 / 348 (52.87%) | 177 / 344 (51.45%) | |
| number of deaths (all causes) | 86 | 62 | |
| number of deaths resulting from adverse events | | | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Malignant melanoma | | | |
| subjects affected / exposed | 0 / 348 (0.00%) | 1 / 344 (0.29%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|-----------------|-----------------|--|
| Non-small cell lung cancer subjects affected / exposed | 1 / 348 (0.29%) | 0 / 344 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Oesophageal neoplasm subjects affected / exposed | 1 / 348 (0.29%) | 0 / 344 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Oesophageal carcinoma subjects affected / exposed | 0 / 348 (0.00%) | 1 / 344 (0.29%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Transitional cell cancer of the renal pelvis and ureter subjects affected / exposed | 1 / 348 (0.29%) | 0 / 344 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Plasmacytoma subjects affected / exposed | 0 / 348 (0.00%) | 1 / 344 (0.29%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Tumour haemorrhage subjects affected / exposed | 4 / 348 (1.15%) | 4 / 344 (1.16%) | |
| occurrences causally related to treatment / all | 0 / 4 | 1 / 5 | |
| deaths causally related to treatment / all | 0 / 2 | 0 / 3 | |
| Vascular disorders Capillary leak syndrome subjects affected / exposed | 0 / 348 (0.00%) | 1 / 344 (0.29%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Circulatory collapse subjects affected / exposed | 0 / 348 (0.00%) | 1 / 344 (0.29%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |

| | | | |
|---|-----------------|-----------------|--|
| Embolism | | | |
| subjects affected / exposed | 1 / 348 (0.29%) | 0 / 344 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Haematoma | | | |
| subjects affected / exposed | 0 / 348 (0.00%) | 1 / 344 (0.29%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Haemorrhage | | | |
| subjects affected / exposed | 1 / 348 (0.29%) | 1 / 344 (0.29%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 2 | 0 / 0 | |
| Lymphorrhoea | | | |
| subjects affected / exposed | 0 / 348 (0.00%) | 1 / 344 (0.29%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypotension | | | |
| subjects affected / exposed | 2 / 348 (0.57%) | 4 / 344 (1.16%) | |
| occurrences causally related to treatment / all | 1 / 2 | 2 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Shock | | | |
| subjects affected / exposed | 1 / 348 (0.29%) | 0 / 344 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Phlebitis superficial | | | |
| subjects affected / exposed | 1 / 348 (0.29%) | 0 / 344 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vascular rupture | | | |
| subjects affected / exposed | 1 / 348 (0.29%) | 0 / 344 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 1 / 1 | 0 / 0 | |
| Vasculitis | | | |

| | | | |
|--|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 348 (0.29%) | 0 / 344 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Venous haemorrhage | | | |
| subjects affected / exposed | 0 / 348 (0.00%) | 1 / 344 (0.29%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Surgical and medical procedures | | | |
| Gastrostomy | | | |
| subjects affected / exposed | 1 / 348 (0.29%) | 0 / 344 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| General disorders and administration site conditions | | | |
| Asthenia | | | |
| subjects affected / exposed | 2 / 348 (0.57%) | 6 / 344 (1.74%) | |
| occurrences causally related to treatment / all | 2 / 2 | 5 / 6 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Chest pain | | | |
| subjects affected / exposed | 2 / 348 (0.57%) | 1 / 344 (0.29%) | |
| occurrences causally related to treatment / all | 2 / 3 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Chills | | | |
| subjects affected / exposed | 2 / 348 (0.57%) | 0 / 344 (0.00%) | |
| occurrences causally related to treatment / all | 2 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Condition aggravated | | | |
| subjects affected / exposed | 1 / 348 (0.29%) | 0 / 344 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Death | | | |
| subjects affected / exposed | 2 / 348 (0.57%) | 1 / 344 (0.29%) | |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 1 | |
| deaths causally related to treatment / all | 1 / 2 | 0 / 2 | |

| | | | |
|---|-----------------|-----------------|--|
| Fatigue | | | |
| subjects affected / exposed | 2 / 348 (0.57%) | 2 / 344 (0.58%) | |
| occurrences causally related to treatment / all | 1 / 2 | 2 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Disease progression | | | |
| subjects affected / exposed | 1 / 348 (0.29%) | 1 / 344 (0.29%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| General physical health deterioration | | | |
| subjects affected / exposed | 1 / 348 (0.29%) | 6 / 344 (1.74%) | |
| occurrences causally related to treatment / all | 1 / 1 | 6 / 6 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hyperpyrexia | | | |
| subjects affected / exposed | 1 / 348 (0.29%) | 0 / 344 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hyperthermia | | | |
| subjects affected / exposed | 0 / 348 (0.00%) | 2 / 344 (0.58%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypothermia | | | |
| subjects affected / exposed | 0 / 348 (0.00%) | 1 / 344 (0.29%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ill-defined disorder | | | |
| subjects affected / exposed | 0 / 348 (0.00%) | 1 / 344 (0.29%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Malaise | | | |
| subjects affected / exposed | 0 / 348 (0.00%) | 1 / 344 (0.29%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Mucosal inflammation | | | |

| | | | |
|---|------------------|-----------------|--|
| subjects affected / exposed | 5 / 348 (1.44%) | 6 / 344 (1.74%) | |
| occurrences causally related to treatment / all | 6 / 6 | 6 / 6 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pain | | | |
| subjects affected / exposed | 0 / 348 (0.00%) | 2 / 344 (0.58%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Performance status decreased | | | |
| subjects affected / exposed | 0 / 348 (0.00%) | 1 / 344 (0.29%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pyrexia | | | |
| subjects affected / exposed | 12 / 348 (3.45%) | 3 / 344 (0.87%) | |
| occurrences causally related to treatment / all | 5 / 15 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Sudden death | | | |
| subjects affected / exposed | 0 / 348 (0.00%) | 1 / 344 (0.29%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Swelling | | | |
| subjects affected / exposed | 1 / 348 (0.29%) | 0 / 344 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Reproductive system and breast disorders | | | |
| Scrotal oedema | | | |
| subjects affected / exposed | 0 / 348 (0.00%) | 1 / 344 (0.29%) | |
| 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 distress syndrome | | | |
| subjects affected / exposed | 1 / 348 (0.29%) | 0 / 344 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|-----------------|-----------------|--|
| Acute respiratory failure | | | |
| subjects affected / exposed | 2 / 348 (0.57%) | 1 / 344 (0.29%) | |
| occurrences causally related to treatment / all | 0 / 2 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 2 | 1 / 1 | |
| Asphyxia | | | |
| subjects affected / exposed | 1 / 348 (0.29%) | 2 / 344 (0.58%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 1 | |
| Aspiration | | | |
| subjects affected / exposed | 1 / 348 (0.29%) | 1 / 344 (0.29%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Atelectasis | | | |
| subjects affected / exposed | 0 / 348 (0.00%) | 1 / 344 (0.29%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Chronic obstructive pulmonary disease | | | |
| subjects affected / exposed | 0 / 348 (0.00%) | 1 / 344 (0.29%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cough | | | |
| subjects affected / exposed | 0 / 348 (0.00%) | 1 / 344 (0.29%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Dyspnoea | | | |
| subjects affected / exposed | 5 / 348 (1.44%) | 7 / 344 (2.03%) | |
| occurrences causally related to treatment / all | 1 / 5 | 3 / 9 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Haemoptysis | | | |
| subjects affected / exposed | 2 / 348 (0.57%) | 3 / 344 (0.87%) | |
| occurrences causally related to treatment / all | 0 / 2 | 1 / 4 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 1 | |
| Hypoxia | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 348 (0.29%) | 3 / 344 (0.87%) | |
| occurrences causally related to treatment / all | 1 / 1 | 1 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Laryngeal haemorrhage | | | |
| subjects affected / exposed | 0 / 348 (0.00%) | 1 / 344 (0.29%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Laryngeal inflammation | | | |
| subjects affected / exposed | 2 / 348 (0.57%) | 0 / 344 (0.00%) | |
| occurrences causally related to treatment / all | 2 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Laryngeal oedema | | | |
| subjects affected / exposed | 5 / 348 (1.44%) | 4 / 344 (1.16%) | |
| occurrences causally related to treatment / all | 7 / 7 | 4 / 5 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Laryngeal necrosis | | | |
| subjects affected / exposed | 0 / 348 (0.00%) | 1 / 344 (0.29%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Laryngeal stenosis | | | |
| subjects affected / exposed | 2 / 348 (0.57%) | 0 / 344 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Obstructive airways disorder | | | |
| subjects affected / exposed | 0 / 348 (0.00%) | 1 / 344 (0.29%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Oropharyngeal pain | | | |
| subjects affected / exposed | 1 / 348 (0.29%) | 2 / 344 (0.58%) | |
| occurrences causally related to treatment / all | 1 / 1 | 3 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pharyngeal haemorrhage | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 2 / 348 (0.57%) | 2 / 344 (0.58%) | |
| occurrences causally related to treatment / all | 1 / 2 | 1 / 2 | |
| deaths causally related to treatment / all | 1 / 1 | 0 / 1 | |
| Pharyngeal inflammation | | | |
| subjects affected / exposed | 2 / 348 (0.57%) | 0 / 344 (0.00%) | |
| occurrences causally related to treatment / all | 2 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pharyngeal necrosis | | | |
| subjects affected / exposed | 1 / 348 (0.29%) | 0 / 344 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pharyngeal oedema | | | |
| subjects affected / exposed | 1 / 348 (0.29%) | 0 / 344 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pharyngeal stenosis | | | |
| subjects affected / exposed | 1 / 348 (0.29%) | 0 / 344 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pharyngeal ulceration | | | |
| subjects affected / exposed | 2 / 348 (0.57%) | 0 / 344 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumonia aspiration | | | |
| subjects affected / exposed | 5 / 348 (1.44%) | 5 / 344 (1.45%) | |
| occurrences causally related to treatment / all | 1 / 5 | 3 / 5 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Pneumonitis | | | |
| subjects affected / exposed | 6 / 348 (1.72%) | 1 / 344 (0.29%) | |
| occurrences causally related to treatment / all | 5 / 6 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Pneumothorax | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 348 (0.29%) | 2 / 344 (0.58%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Productive cough | | | |
| subjects affected / exposed | 1 / 348 (0.29%) | 1 / 344 (0.29%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pulmonary embolism | | | |
| subjects affected / exposed | 2 / 348 (0.57%) | 0 / 344 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Respiratory arrest | | | |
| subjects affected / exposed | 0 / 348 (0.00%) | 1 / 344 (0.29%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Respiratory distress | | | |
| subjects affected / exposed | 2 / 348 (0.57%) | 1 / 344 (0.29%) | |
| occurrences causally related to treatment / all | 2 / 2 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory failure | | | |
| subjects affected / exposed | 0 / 348 (0.00%) | 2 / 344 (0.58%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 2 | 0 / 2 | |
| Respiratory tract oedema | | | |
| subjects affected / exposed | 1 / 348 (0.29%) | 0 / 344 (0.00%) | |
| occurrences causally related to treatment / all | 2 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Stridor | | | |
| subjects affected / exposed | 1 / 348 (0.29%) | 1 / 344 (0.29%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Tonsillar haemorrhage | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 348 (0.29%) | 0 / 344 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Tracheal stenosis | | | |
| subjects affected / exposed | 1 / 348 (0.29%) | 1 / 344 (0.29%) | |
| occurrences causally related to treatment / all | 1 / 1 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Psychiatric disorders | | | |
| Confusional state | | | |
| subjects affected / exposed | 3 / 348 (0.86%) | 0 / 344 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Delirium | | | |
| subjects affected / exposed | 1 / 348 (0.29%) | 1 / 344 (0.29%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Suicidal ideation | | | |
| subjects affected / exposed | 0 / 348 (0.00%) | 1 / 344 (0.29%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Suicide attempt | | | |
| subjects affected / exposed | 0 / 348 (0.00%) | 1 / 344 (0.29%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Product issues | | | |
| Device malfunction | | | |
| subjects affected / exposed | 1 / 348 (0.29%) | 0 / 344 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Device dislocation | | | |
| subjects affected / exposed | 1 / 348 (0.29%) | 3 / 344 (0.87%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Embedded device | | | |

| | | | |
|--|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 348 (0.00%) | 1 / 344 (0.29%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Investigations | | | |
| Alanine aminotransferase increased | | | |
| subjects affected / exposed | 1 / 348 (0.29%) | 0 / 344 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Blood creatinine increased | | | |
| subjects affected / exposed | 7 / 348 (2.01%) | 6 / 344 (1.74%) | |
| occurrences causally related to treatment / all | 6 / 7 | 6 / 7 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| C-reactive protein increased | | | |
| subjects affected / exposed | 0 / 348 (0.00%) | 1 / 344 (0.29%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Eastern Cooperative Oncology Group performance status worsened | | | |
| subjects affected / exposed | 0 / 348 (0.00%) | 1 / 344 (0.29%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 1 / 1 | |
| Hepatic enzyme increased | | | |
| subjects affected / exposed | 1 / 348 (0.29%) | 0 / 344 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Liver function test abnormal | | | |
| subjects affected / exposed | 0 / 348 (0.00%) | 1 / 344 (0.29%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Liver function test increased | | | |
| subjects affected / exposed | 1 / 348 (0.29%) | 0 / 344 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lymphocyte count decreased | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 348 (0.00%) | 1 / 344 (0.29%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Neutrophil count decreased | | | |
| subjects affected / exposed | 4 / 348 (1.15%) | 1 / 344 (0.29%) | |
| occurrences causally related to treatment / all | 5 / 5 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Oxygen saturation decreased | | | |
| subjects affected / exposed | 1 / 348 (0.29%) | 0 / 344 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Weight decreased | | | |
| subjects affected / exposed | 6 / 348 (1.72%) | 3 / 344 (0.87%) | |
| occurrences causally related to treatment / all | 4 / 6 | 3 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| White blood cell count decreased | | | |
| subjects affected / exposed | 0 / 348 (0.00%) | 1 / 344 (0.29%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Injury, poisoning and procedural complications | | | |
| Femoral neck fracture | | | |
| subjects affected / exposed | 1 / 348 (0.29%) | 0 / 344 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Femur fracture | | | |
| subjects affected / exposed | 1 / 348 (0.29%) | 0 / 344 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrostomy failure | | | |
| subjects affected / exposed | 1 / 348 (0.29%) | 0 / 344 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infusion related reaction | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 2 / 348 (0.57%) | 0 / 344 (0.00%) | |
| occurrences causally related to treatment / all | 2 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nerve injury | | | |
| subjects affected / exposed | 0 / 348 (0.00%) | 1 / 344 (0.29%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Overdose | | | |
| subjects affected / exposed | 1 / 348 (0.29%) | 0 / 344 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pancreatic injury | | | |
| subjects affected / exposed | 0 / 348 (0.00%) | 1 / 344 (0.29%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Post procedural fever | | | |
| subjects affected / exposed | 1 / 348 (0.29%) | 0 / 344 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Post procedural haemorrhage | | | |
| subjects affected / exposed | 2 / 348 (0.57%) | 1 / 344 (0.29%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Radiation associated pain | | | |
| subjects affected / exposed | 0 / 348 (0.00%) | 1 / 344 (0.29%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Radiation fibrosis | | | |
| subjects affected / exposed | 1 / 348 (0.29%) | 0 / 344 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Radiation injury | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 348 (0.00%) | 1 / 344 (0.29%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Radiation mucositis | | | |
| subjects affected / exposed | 0 / 348 (0.00%) | 2 / 344 (0.58%) | |
| occurrences causally related to treatment / all | 0 / 0 | 2 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Radiation necrosis | | | |
| subjects affected / exposed | 0 / 348 (0.00%) | 1 / 344 (0.29%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Radiation skin injury | | | |
| subjects affected / exposed | 3 / 348 (0.86%) | 2 / 344 (0.58%) | |
| occurrences causally related to treatment / all | 6 / 6 | 3 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Stoma site inflammation | | | |
| subjects affected / exposed | 0 / 348 (0.00%) | 1 / 344 (0.29%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Stoma site pain | | | |
| subjects affected / exposed | 0 / 348 (0.00%) | 1 / 344 (0.29%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Subdural haemorrhage | | | |
| subjects affected / exposed | 1 / 348 (0.29%) | 0 / 344 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Thermal burn | | | |
| subjects affected / exposed | 0 / 348 (0.00%) | 1 / 344 (0.29%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Tracheal obstruction | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 348 (0.29%) | 0 / 344 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Tracheal haemorrhage | | | |
| subjects affected / exposed | 2 / 348 (0.57%) | 0 / 344 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Osteoradionecrosis | | | |
| subjects affected / exposed | 0 / 348 (0.00%) | 1 / 344 (0.29%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac disorders | | | |
| Acute coronary syndrome | | | |
| subjects affected / exposed | 1 / 348 (0.29%) | 0 / 344 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Angina pectoris | | | |
| subjects affected / exposed | 0 / 348 (0.00%) | 1 / 344 (0.29%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Acute myocardial infarction | | | |
| subjects affected / exposed | 1 / 348 (0.29%) | 1 / 344 (0.29%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Atrial fibrillation | | | |
| subjects affected / exposed | 0 / 348 (0.00%) | 1 / 344 (0.29%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bradycardia | | | |
| subjects affected / exposed | 1 / 348 (0.29%) | 2 / 344 (0.58%) | |
| occurrences causally related to treatment / all | 0 / 1 | 2 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac arrest | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 348 (0.29%) | 0 / 344 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 2 | 0 / 0 | |
| Cardiac failure | | | |
| subjects affected / exposed | 1 / 348 (0.29%) | 2 / 344 (0.58%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 2 | |
| Cardiac failure congestive | | | |
| subjects affected / exposed | 1 / 348 (0.29%) | 0 / 344 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardio-respiratory arrest | | | |
| subjects affected / exposed | 1 / 348 (0.29%) | 0 / 344 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Sinus tachycardia | | | |
| subjects affected / exposed | 0 / 348 (0.00%) | 1 / 344 (0.29%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Supraventricular tachycardia | | | |
| subjects affected / exposed | 2 / 348 (0.57%) | 0 / 344 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Tachycardia | | | |
| subjects affected / exposed | 0 / 348 (0.00%) | 1 / 344 (0.29%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nervous system disorders | | | |
| Brain hypoxia | | | |
| subjects affected / exposed | 1 / 348 (0.29%) | 0 / 344 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Cerebral ischaemia | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 348 (0.00%) | 1 / 344 (0.29%) | |
| 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 | 1 / 348 (0.29%) | 1 / 344 (0.29%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Coma | | | |
| subjects affected / exposed | 1 / 348 (0.29%) | 0 / 344 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Depressed level of consciousness | | | |
| subjects affected / exposed | 0 / 348 (0.00%) | 1 / 344 (0.29%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Epilepsy | | | |
| subjects affected / exposed | 1 / 348 (0.29%) | 1 / 344 (0.29%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Dizziness | | | |
| subjects affected / exposed | 0 / 348 (0.00%) | 1 / 344 (0.29%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Headache | | | |
| subjects affected / exposed | 1 / 348 (0.29%) | 0 / 344 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Presyncope | | | |
| subjects affected / exposed | 0 / 348 (0.00%) | 1 / 344 (0.29%) | |
| 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 / 348 (0.00%) | 1 / 344 (0.29%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Subacute combined cord degeneration | | | |
| subjects affected / exposed | 0 / 348 (0.00%) | 1 / 344 (0.29%) | |
| occurrences causally related to treatment / all | 0 / 0 | 2 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Syncope | | | |
| subjects affected / exposed | 2 / 348 (0.57%) | 0 / 344 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 8 / 348 (2.30%) | 12 / 344 (3.49%) | |
| occurrences causally related to treatment / all | 7 / 9 | 10 / 12 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Febrile neutropenia | | | |
| subjects affected / exposed | 9 / 348 (2.59%) | 5 / 344 (1.45%) | |
| occurrences causally related to treatment / all | 9 / 9 | 6 / 6 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bone marrow failure | | | |
| subjects affected / exposed | 2 / 348 (0.57%) | 1 / 344 (0.29%) | |
| occurrences causally related to treatment / all | 2 / 2 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lymphadenopathy | | | |
| subjects affected / exposed | 0 / 348 (0.00%) | 1 / 344 (0.29%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Leukopenia | | | |
| subjects affected / exposed | 1 / 348 (0.29%) | 0 / 344 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Neutropenia | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 5 / 348 (1.44%) | 3 / 344 (0.87%) | |
| occurrences causally related to treatment / all | 5 / 5 | 3 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Splenic haematoma | | | |
| subjects affected / exposed | 1 / 348 (0.29%) | 0 / 344 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Thrombocytopenia | | | |
| subjects affected / exposed | 1 / 348 (0.29%) | 0 / 344 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ear and labyrinth disorders | | | |
| Deafness | | | |
| subjects affected / exposed | 1 / 348 (0.29%) | 0 / 344 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Tinnitus | | | |
| subjects affected / exposed | 0 / 348 (0.00%) | 1 / 344 (0.29%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vertigo | | | |
| subjects affected / exposed | 1 / 348 (0.29%) | 0 / 344 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Eye disorders | | | |
| Pterygium | | | |
| subjects affected / exposed | 0 / 348 (0.00%) | 1 / 344 (0.29%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Retinal detachment | | | |
| subjects affected / exposed | 0 / 348 (0.00%) | 1 / 344 (0.29%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal disorders | | | |

| | | | |
|---|------------------|------------------|--|
| Abdominal pain | | | |
| subjects affected / exposed | 0 / 348 (0.00%) | 2 / 344 (0.58%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Colitis | | | |
| subjects affected / exposed | 1 / 348 (0.29%) | 2 / 344 (0.58%) | |
| occurrences causally related to treatment / all | 2 / 2 | 2 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Diarrhoea | | | |
| subjects affected / exposed | 1 / 348 (0.29%) | 2 / 344 (0.58%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Constipation | | | |
| subjects affected / exposed | 1 / 348 (0.29%) | 1 / 344 (0.29%) | |
| occurrences causally related to treatment / all | 0 / 1 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Dry mouth | | | |
| subjects affected / exposed | 0 / 348 (0.00%) | 1 / 344 (0.29%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Duodenal ulcer perforation | | | |
| subjects affected / exposed | 1 / 348 (0.29%) | 0 / 344 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Dyspepsia | | | |
| subjects affected / exposed | 1 / 348 (0.29%) | 0 / 344 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Dysphagia | | | |
| subjects affected / exposed | 15 / 348 (4.31%) | 13 / 344 (3.78%) | |
| occurrences causally related to treatment / all | 13 / 19 | 11 / 14 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Faecaloma | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 348 (0.00%) | 1 / 344 (0.29%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastric perforation | | | |
| subjects affected / exposed | 1 / 348 (0.29%) | 1 / 344 (0.29%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Haematemesis | | | |
| subjects affected / exposed | 1 / 348 (0.29%) | 1 / 344 (0.29%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Haematochezia | | | |
| subjects affected / exposed | 1 / 348 (0.29%) | 0 / 344 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Large intestinal obstruction | | | |
| subjects affected / exposed | 0 / 348 (0.00%) | 1 / 344 (0.29%) | |
| 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 | 2 / 348 (0.57%) | 2 / 344 (0.58%) | |
| occurrences causally related to treatment / all | 0 / 2 | 1 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Mouth swelling | | | |
| subjects affected / exposed | 0 / 348 (0.00%) | 1 / 344 (0.29%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nausea | | | |
| subjects affected / exposed | 7 / 348 (2.01%) | 9 / 344 (2.62%) | |
| occurrences causally related to treatment / all | 9 / 9 | 10 / 11 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Odynophagia | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 3 / 348 (0.86%) | 1 / 344 (0.29%) | |
| occurrences causally related to treatment / all | 2 / 3 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Oesophageal obstruction | | | |
| subjects affected / exposed | 1 / 348 (0.29%) | 0 / 344 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Oesophagitis | | | |
| subjects affected / exposed | 1 / 348 (0.29%) | 1 / 344 (0.29%) | |
| occurrences causally related to treatment / all | 1 / 1 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Oral pain | | | |
| subjects affected / exposed | 1 / 348 (0.29%) | 2 / 344 (0.58%) | |
| occurrences causally related to treatment / all | 1 / 1 | 1 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumoperitoneum | | | |
| subjects affected / exposed | 1 / 348 (0.29%) | 0 / 344 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Salivary hypersecretion | | | |
| subjects affected / exposed | 1 / 348 (0.29%) | 0 / 344 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Stomatitis | | | |
| subjects affected / exposed | 7 / 348 (2.01%) | 4 / 344 (1.16%) | |
| occurrences causally related to treatment / all | 10 / 10 | 4 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Tongue ulceration | | | |
| subjects affected / exposed | 1 / 348 (0.29%) | 0 / 344 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Tongue haemorrhage | | | |

| | | | |
|---|------------------|------------------|--|
| subjects affected / exposed | 2 / 348 (0.57%) | 0 / 344 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Upper gastrointestinal haemorrhage | | | |
| subjects affected / exposed | 1 / 348 (0.29%) | 0 / 344 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vomiting | | | |
| subjects affected / exposed | 11 / 348 (3.16%) | 13 / 344 (3.78%) | |
| occurrences causally related to treatment / all | 14 / 14 | 12 / 15 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hepatobiliary disorders | | | |
| Cholelithiasis | | | |
| subjects affected / exposed | 0 / 348 (0.00%) | 1 / 344 (0.29%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hepatitis | | | |
| subjects affected / exposed | 1 / 348 (0.29%) | 0 / 344 (0.00%) | |
| occurrences causally related to treatment / all | 3 / 3 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hepatotoxicity | | | |
| subjects affected / exposed | 1 / 348 (0.29%) | 0 / 344 (0.00%) | |
| occurrences causally related to treatment / all | 2 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Skin and subcutaneous tissue disorders | | | |
| Erythema multiforme | | | |
| subjects affected / exposed | 1 / 348 (0.29%) | 0 / 344 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Rash | | | |
| subjects affected / exposed | 1 / 348 (0.29%) | 0 / 344 (0.00%) | |
| occurrences causally related to treatment / all | 2 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal and urinary disorders | | | |

| | | | |
|---|------------------|------------------|--|
| Acute kidney injury | | | |
| subjects affected / exposed | 12 / 348 (3.45%) | 11 / 344 (3.20%) | |
| occurrences causally related to treatment / all | 11 / 12 | 11 / 11 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hydronephrosis | | | |
| subjects affected / exposed | 1 / 348 (0.29%) | 0 / 344 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nephritis | | | |
| subjects affected / exposed | 1 / 348 (0.29%) | 0 / 344 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Oliguria | | | |
| subjects affected / exposed | 0 / 348 (0.00%) | 1 / 344 (0.29%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal disorder | | | |
| subjects affected / exposed | 1 / 348 (0.29%) | 0 / 344 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal failure | | | |
| subjects affected / exposed | 0 / 348 (0.00%) | 4 / 344 (1.16%) | |
| occurrences causally related to treatment / all | 0 / 0 | 2 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal tubular necrosis | | | |
| subjects affected / exposed | 1 / 348 (0.29%) | 0 / 344 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Urinary retention | | | |
| subjects affected / exposed | 0 / 348 (0.00%) | 1 / 344 (0.29%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Endocrine disorders | | | |

| | | | |
|---|-----------------|-----------------|--|
| Hyperthyroidism | | | |
| subjects affected / exposed | 0 / 348 (0.00%) | 1 / 344 (0.29%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Adrenal insufficiency | | | |
| subjects affected / exposed | 0 / 348 (0.00%) | 1 / 344 (0.29%) | |
| 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 | | | |
| Arthritis | | | |
| subjects affected / exposed | 1 / 348 (0.29%) | 0 / 344 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Back pain | | | |
| subjects affected / exposed | 0 / 348 (0.00%) | 1 / 344 (0.29%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Haematoma muscle | | | |
| subjects affected / exposed | 0 / 348 (0.00%) | 1 / 344 (0.29%) | |
| 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 | 1 / 348 (0.29%) | 1 / 344 (0.29%) | |
| occurrences causally related to treatment / all | 1 / 1 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Oligoarthritis | | | |
| subjects affected / exposed | 1 / 348 (0.29%) | 0 / 344 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Osteonecrosis of jaw | | | |
| subjects affected / exposed | 0 / 348 (0.00%) | 1 / 344 (0.29%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|--|-----------------------------------|-----------------------------------|--|
| Infections and infestations Abdominal abscess subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | 1 / 348 (0.29%) 0 / 1 0 / 0 | 0 / 344 (0.00%) 0 / 0 0 / 0 | |
| Abscess oral subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | 0 / 348 (0.00%) 0 / 0 0 / 0 | 1 / 344 (0.29%) 0 / 1 0 / 0 | |
| Anal abscess subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | 0 / 348 (0.00%) 0 / 0 0 / 0 | 1 / 344 (0.29%) 0 / 1 0 / 0 | |
| Appendicitis subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | 0 / 348 (0.00%) 0 / 0 0 / 0 | 1 / 344 (0.29%) 0 / 1 0 / 0 | |
| Bacterial infection subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | 0 / 348 (0.00%) 0 / 0 0 / 0 | 1 / 344 (0.29%) 1 / 1 0 / 0 | |
| Bronchitis subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | 1 / 348 (0.29%) 1 / 1 0 / 0 | 1 / 344 (0.29%) 0 / 1 0 / 0 | |
| Bronchitis bacterial subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | 1 / 348 (0.29%) 0 / 1 0 / 0 | 0 / 344 (0.00%) 0 / 0 0 / 0 | |
| Candida infection subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | 1 / 348 (0.29%) 0 / 1 0 / 0 | 0 / 344 (0.00%) 0 / 0 0 / 0 | |
| Cellulitis | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 3 / 348 (0.86%) | 2 / 344 (0.58%) | |
| occurrences causally related to treatment / all | 2 / 4 | 1 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Device related infection | | | |
| subjects affected / exposed | 2 / 348 (0.57%) | 1 / 344 (0.29%) | |
| occurrences causally related to treatment / all | 0 / 2 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Device related sepsis | | | |
| subjects affected / exposed | 1 / 348 (0.29%) | 0 / 344 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Endocarditis | | | |
| subjects affected / exposed | 0 / 348 (0.00%) | 1 / 344 (0.29%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Endocarditis candida | | | |
| subjects affected / exposed | 1 / 348 (0.29%) | 0 / 344 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Enterocolitis infectious | | | |
| subjects affected / exposed | 2 / 348 (0.57%) | 0 / 344 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Epididymitis | | | |
| subjects affected / exposed | 1 / 348 (0.29%) | 0 / 344 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Epiglottitis | | | |
| subjects affected / exposed | 1 / 348 (0.29%) | 0 / 344 (0.00%) | |
| occurrences causally related to treatment / all | 2 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Herpes zoster | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 348 (0.29%) | 0 / 344 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infection | | | |
| subjects affected / exposed | 1 / 348 (0.29%) | 3 / 344 (0.87%) | |
| occurrences causally related to treatment / all | 1 / 1 | 1 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infectious pleural effusion | | | |
| subjects affected / exposed | 0 / 348 (0.00%) | 1 / 344 (0.29%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Localised infection | | | |
| subjects affected / exposed | 1 / 348 (0.29%) | 0 / 344 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lower respiratory tract infection | | | |
| subjects affected / exposed | 2 / 348 (0.57%) | 2 / 344 (0.58%) | |
| occurrences causally related to treatment / all | 1 / 3 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lung abscess | | | |
| subjects affected / exposed | 1 / 348 (0.29%) | 0 / 344 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lower respiratory tract infection bacterial | | | |
| subjects affected / exposed | 0 / 348 (0.00%) | 1 / 344 (0.29%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Neutropenic infection | | | |
| subjects affected / exposed | 1 / 348 (0.29%) | 0 / 344 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Neutropenic sepsis | | | |

| | | | |
|---|------------------|------------------|--|
| subjects affected / exposed | 1 / 348 (0.29%) | 0 / 344 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Oesophageal candidiasis | | | |
| subjects affected / exposed | 1 / 348 (0.29%) | 0 / 344 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Oral candidiasis | | | |
| subjects affected / exposed | 0 / 348 (0.00%) | 1 / 344 (0.29%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Parotitis | | | |
| subjects affected / exposed | 2 / 348 (0.57%) | 1 / 344 (0.29%) | |
| occurrences causally related to treatment / all | 2 / 2 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Oral infection | | | |
| subjects affected / exposed | 0 / 348 (0.00%) | 1 / 344 (0.29%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pharyngitis | | | |
| subjects affected / exposed | 0 / 348 (0.00%) | 2 / 344 (0.58%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumococcal sepsis | | | |
| subjects affected / exposed | 1 / 348 (0.29%) | 0 / 344 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumonia | | | |
| subjects affected / exposed | 25 / 348 (7.18%) | 20 / 344 (5.81%) | |
| occurrences causally related to treatment / all | 8 / 30 | 8 / 21 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 2 | |
| Pneumonia bacterial | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 2 / 348 (0.57%) | 0 / 344 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 2 | 0 / 0 | |
| Respiratory tract infection | | | |
| subjects affected / exposed | 4 / 348 (1.15%) | 0 / 344 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 4 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Sepsis | | | |
| subjects affected / exposed | 7 / 348 (2.01%) | 5 / 344 (1.45%) | |
| occurrences causally related to treatment / all | 3 / 9 | 3 / 5 | |
| deaths causally related to treatment / all | 1 / 2 | 0 / 0 | |
| Sinusitis | | | |
| subjects affected / exposed | 1 / 348 (0.29%) | 0 / 344 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Skin infection | | | |
| subjects affected / exposed | 1 / 348 (0.29%) | 0 / 344 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Soft tissue infection | | | |
| subjects affected / exposed | 1 / 348 (0.29%) | 1 / 344 (0.29%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Staphylococcal sepsis | | | |
| subjects affected / exposed | 1 / 348 (0.29%) | 0 / 344 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Stoma site abscess | | | |
| subjects affected / exposed | 1 / 348 (0.29%) | 0 / 344 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Stoma site infection | | | |

| | | | |
|---|-----------------|------------------|--|
| subjects affected / exposed | 1 / 348 (0.29%) | 1 / 344 (0.29%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Urinary tract infection | | | |
| subjects affected / exposed | 2 / 348 (0.57%) | 1 / 344 (0.29%) | |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vascular device infection | | | |
| subjects affected / exposed | 1 / 348 (0.29%) | 0 / 344 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Osteomyelitis | | | |
| subjects affected / exposed | 0 / 348 (0.00%) | 1 / 344 (0.29%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Metabolism and nutrition disorders | | | |
| Adult failure to thrive | | | |
| subjects affected / exposed | 0 / 348 (0.00%) | 1 / 344 (0.29%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cachexia | | | |
| subjects affected / exposed | 2 / 348 (0.57%) | 2 / 344 (0.58%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 2 | 0 / 1 | |
| Decreased appetite | | | |
| subjects affected / exposed | 5 / 348 (1.44%) | 3 / 344 (0.87%) | |
| occurrences causally related to treatment / all | 7 / 7 | 3 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Dehydration | | | |
| subjects affected / exposed | 9 / 348 (2.59%) | 15 / 344 (4.36%) | |
| occurrences causally related to treatment / all | 7 / 10 | 9 / 15 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Diabetes mellitus inadequate control | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 348 (0.29%) | 0 / 344 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Diabetic ketoacidosis | | | |
| subjects affected / exposed | 0 / 348 (0.00%) | 1 / 344 (0.29%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Electrolyte imbalance | | | |
| subjects affected / exposed | 1 / 348 (0.29%) | 0 / 344 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Failure to thrive | | | |
| subjects affected / exposed | 2 / 348 (0.57%) | 1 / 344 (0.29%) | |
| occurrences causally related to treatment / all | 1 / 2 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Fluid overload | | | |
| subjects affected / exposed | 1 / 348 (0.29%) | 0 / 344 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypercalcaemia | | | |
| subjects affected / exposed | 1 / 348 (0.29%) | 1 / 344 (0.29%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hyperglycaemia | | | |
| subjects affected / exposed | 2 / 348 (0.57%) | 0 / 344 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hyperglycaemic hyperosmolar nonketotic syndrome | | | |
| subjects affected / exposed | 1 / 348 (0.29%) | 0 / 344 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypoalbuminaemia | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 348 (0.00%) | 1 / 344 (0.29%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypocalcaemia | | | |
| subjects affected / exposed | 0 / 348 (0.00%) | 2 / 344 (0.58%) | |
| occurrences causally related to treatment / all | 0 / 0 | 2 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypoglycaemia | | | |
| subjects affected / exposed | 0 / 348 (0.00%) | 1 / 344 (0.29%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypokalaemia | | | |
| subjects affected / exposed | 4 / 348 (1.15%) | 3 / 344 (0.87%) | |
| occurrences causally related to treatment / all | 4 / 4 | 2 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hyponatraemia | | | |
| subjects affected / exposed | 4 / 348 (1.15%) | 7 / 344 (2.03%) | |
| occurrences causally related to treatment / all | 3 / 4 | 6 / 10 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypophagia | | | |
| subjects affected / exposed | 1 / 348 (0.29%) | 0 / 344 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ketoacidosis | | | |
| subjects affected / exposed | 0 / 348 (0.00%) | 1 / 344 (0.29%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Malnutrition | | | |
| subjects affected / exposed | 2 / 348 (0.57%) | 3 / 344 (0.87%) | |
| occurrences causally related to treatment / all | 0 / 2 | 3 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Metabolic disorder | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 348 (0.00%) | 1 / 344 (0.29%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

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

| Non-serious adverse events | Avelumab + Standard of Care Chemotherapy (SOC CRT) | Placebo + SOC CRT | |
|---|---|--------------------|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 344 / 348 (98.85%) | 340 / 344 (98.84%) | |
| Vascular disorders | | | |
| Hypertension | | | |
| subjects affected / exposed | 32 / 348 (9.20%) | 28 / 344 (8.14%) | |
| occurrences (all) | 63 | 54 | |
| Hypotension | | | |
| subjects affected / exposed | 22 / 348 (6.32%) | 14 / 344 (4.07%) | |
| occurrences (all) | 26 | 16 | |
| Lymphoedema | | | |
| subjects affected / exposed | 18 / 348 (5.17%) | 15 / 344 (4.36%) | |
| occurrences (all) | 19 | 17 | |
| General disorders and administration site conditions | | | |
| Chills | | | |
| subjects affected / exposed | 39 / 348 (11.21%) | 7 / 344 (2.03%) | |
| occurrences (all) | 43 | 8 | |
| Asthenia | | | |
| subjects affected / exposed | 63 / 348 (18.10%) | 58 / 344 (16.86%) | |
| occurrences (all) | 124 | 102 | |
| Fatigue | | | |
| subjects affected / exposed | 116 / 348 (33.33%) | 127 / 344 (36.92%) | |
| occurrences (all) | 227 | 232 | |
| Localised oedema | | | |
| subjects affected / exposed | 22 / 348 (6.32%) | 20 / 344 (5.81%) | |
| occurrences (all) | 24 | 25 | |
| Malaise | | | |

| | | | |
|---|--------------------|--------------------|--|
| subjects affected / exposed | 20 / 348 (5.75%) | 23 / 344 (6.69%) | |
| occurrences (all) | 39 | 39 | |
| Mucosal inflammation | | | |
| subjects affected / exposed | 146 / 348 (41.95%) | 131 / 344 (38.08%) | |
| occurrences (all) | 333 | 289 | |
| Oedema peripheral | | | |
| subjects affected / exposed | 19 / 348 (5.46%) | 16 / 344 (4.65%) | |
| occurrences (all) | 27 | 23 | |
| Pyrexia | | | |
| subjects affected / exposed | 87 / 348 (25.00%) | 45 / 344 (13.08%) | |
| occurrences (all) | 140 | 69 | |
| Pain | | | |
| subjects affected / exposed | 23 / 348 (6.61%) | 28 / 344 (8.14%) | |
| occurrences (all) | 26 | 41 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Cough | | | |
| subjects affected / exposed | 74 / 348 (21.26%) | 63 / 344 (18.31%) | |
| occurrences (all) | 96 | 85 | |
| Dysphonia | | | |
| subjects affected / exposed | 51 / 348 (14.66%) | 47 / 344 (13.66%) | |
| occurrences (all) | 64 | 78 | |
| Dyspnoea | | | |
| subjects affected / exposed | 33 / 348 (9.48%) | 33 / 344 (9.59%) | |
| occurrences (all) | 39 | 36 | |
| Hiccups | | | |
| subjects affected / exposed | 26 / 348 (7.47%) | 23 / 344 (6.69%) | |
| occurrences (all) | 33 | 32 | |
| Pharyngeal inflammation | | | |
| subjects affected / exposed | 24 / 348 (6.90%) | 23 / 344 (6.69%) | |
| occurrences (all) | 48 | 35 | |
| Oropharyngeal pain | | | |
| subjects affected / exposed | 75 / 348 (21.55%) | 92 / 344 (26.74%) | |
| occurrences (all) | 131 | 150 | |
| Productive cough | | | |

| | | | |
|--|-------------------------|------------------------|--|
| subjects affected / exposed occurrences (all) | 40 / 348 (11.49%) 53 | 31 / 344 (9.01%) 37 | |
| Psychiatric disorders | | | |
| Anxiety | | | |
| subjects affected / exposed | 26 / 348 (7.47%) | 34 / 344 (9.88%) | |
| occurrences (all) | 27 | 42 | |
| Insomnia | | | |
| subjects affected / exposed | 57 / 348 (16.38%) | 47 / 344 (13.66%) | |
| occurrences (all) | 67 | 56 | |
| Depression | | | |
| subjects affected / exposed | 10 / 348 (2.87%) | 18 / 344 (5.23%) | |
| occurrences (all) | 10 | 21 | |
| Investigations | | | |
| Alanine aminotransferase increased | | | |
| subjects affected / exposed | 56 / 348 (16.09%) | 30 / 344 (8.72%) | |
| occurrences (all) | 92 | 43 | |
| Aspartate aminotransferase increased | | | |
| subjects affected / exposed | 55 / 348 (15.80%) | 26 / 344 (7.56%) | |
| occurrences (all) | 87 | 39 | |
| Amylase increased | | | |
| subjects affected / exposed | 22 / 348 (6.32%) | 10 / 344 (2.91%) | |
| occurrences (all) | 41 | 11 | |
| Blood creatinine increased | | | |
| subjects affected / exposed | 88 / 348 (25.29%) | 73 / 344 (21.22%) | |
| occurrences (all) | 196 | 167 | |
| Blood alkaline phosphatase increased | | | |
| subjects affected / exposed | 22 / 348 (6.32%) | 9 / 344 (2.62%) | |
| occurrences (all) | 36 | 21 | |
| Blood urea increased | | | |
| subjects affected / exposed | 18 / 348 (5.17%) | 17 / 344 (4.94%) | |
| occurrences (all) | 26 | 33 | |
| Gamma-glutamyltransferase increased | | | |
| subjects affected / exposed | 23 / 348 (6.61%) | 15 / 344 (4.36%) | |
| occurrences (all) | 49 | 24 | |
| Lymphocyte count decreased | | | |

| | | | |
|--|---------------------------|---------------------------|--|
| subjects affected / exposed occurrences (all) | 40 / 348 (11.49%) 153 | 42 / 344 (12.21%) 204 | |
| Neutrophil count decreased subjects affected / exposed occurrences (all) | 64 / 348 (18.39%) 115 | 60 / 344 (17.44%) 117 | |
| Weight decreased subjects affected / exposed occurrences (all) | 157 / 348 (45.11%) 282 | 171 / 344 (49.71%) 333 | |
| Platelet count decreased subjects affected / exposed occurrences (all) | 40 / 348 (11.49%) 66 | 33 / 344 (9.59%) 75 | |
| White blood cell count decreased subjects affected / exposed occurrences (all) | 69 / 348 (19.83%) 164 | 64 / 344 (18.60%) 203 | |
| Injury, poisoning and procedural complications | | | |
| Infusion related reaction subjects affected / exposed occurrences (all) | 24 / 348 (6.90%) 40 | 6 / 344 (1.74%) 18 | |
| Radiation skin injury subjects affected / exposed occurrences (all) | 135 / 348 (38.79%) 216 | 136 / 344 (39.53%) 223 | |
| Nervous system disorders | | | |
| Dizziness subjects affected / exposed occurrences (all) | 41 / 348 (11.78%) 45 | 33 / 344 (9.59%) 40 | |
| Dysgeusia subjects affected / exposed occurrences (all) | 106 / 348 (30.46%) 154 | 119 / 344 (34.59%) 166 | |
| Neuropathy peripheral subjects affected / exposed occurrences (all) | 11 / 348 (3.16%) 12 | 28 / 344 (8.14%) 45 | |
| Headache subjects affected / exposed occurrences (all) | 44 / 348 (12.64%) 55 | 41 / 344 (11.92%) 54 | |
| Blood and lymphatic system disorders | | | |

| | | | |
|-----------------------------|--------------------|--------------------|--|
| Leukopenia | | | |
| subjects affected / exposed | 64 / 348 (18.39%) | 46 / 344 (13.37%) | |
| occurrences (all) | 172 | 123 | |
| Anaemia | | | |
| subjects affected / exposed | 206 / 348 (59.20%) | 192 / 344 (55.81%) | |
| occurrences (all) | 531 | 490 | |
| Neutropenia | | | |
| subjects affected / exposed | 102 / 348 (29.31%) | 98 / 344 (28.49%) | |
| occurrences (all) | 192 | 169 | |
| Lymphopenia | | | |
| subjects affected / exposed | 33 / 348 (9.48%) | 27 / 344 (7.85%) | |
| occurrences (all) | 164 | 101 | |
| Thrombocytopenia | | | |
| subjects affected / exposed | 45 / 348 (12.93%) | 41 / 344 (11.92%) | |
| occurrences (all) | 92 | 81 | |
| Ear and labyrinth disorders | | | |
| Ear pain | | | |
| subjects affected / exposed | 23 / 348 (6.61%) | 12 / 344 (3.49%) | |
| occurrences (all) | 26 | 12 | |
| Hypoacusis | | | |
| subjects affected / exposed | 29 / 348 (8.33%) | 30 / 344 (8.72%) | |
| occurrences (all) | 36 | 33 | |
| Tinnitus | | | |
| subjects affected / exposed | 59 / 348 (16.95%) | 66 / 344 (19.19%) | |
| occurrences (all) | 70 | 74 | |
| Gastrointestinal disorders | | | |
| Abdominal pain upper | | | |
| subjects affected / exposed | 14 / 348 (4.02%) | 18 / 344 (5.23%) | |
| occurrences (all) | 16 | 24 | |
| Abdominal pain | | | |
| subjects affected / exposed | 11 / 348 (3.16%) | 20 / 344 (5.81%) | |
| occurrences (all) | 13 | 22 | |
| Constipation | | | |
| subjects affected / exposed | 178 / 348 (51.15%) | 155 / 344 (45.06%) | |
| occurrences (all) | 280 | 215 | |
| Diarrhoea | | | |

| | | | |
|--|--------------------|--------------------|--|
| subjects affected / exposed | 83 / 348 (23.85%) | 66 / 344 (19.19%) | |
| occurrences (all) | 112 | 92 | |
| Dry mouth | | | |
| subjects affected / exposed | 151 / 348 (43.39%) | 158 / 344 (45.93%) | |
| occurrences (all) | 217 | 215 | |
| Dyspepsia | | | |
| subjects affected / exposed | 23 / 348 (6.61%) | 21 / 344 (6.10%) | |
| occurrences (all) | 34 | 22 | |
| Nausea | | | |
| subjects affected / exposed | 210 / 348 (60.34%) | 199 / 344 (57.85%) | |
| occurrences (all) | 346 | 340 | |
| Dysphagia | | | |
| subjects affected / exposed | 143 / 348 (41.09%) | 152 / 344 (44.19%) | |
| occurrences (all) | 253 | 275 | |
| Odynophagia | | | |
| subjects affected / exposed | 62 / 348 (17.82%) | 48 / 344 (13.95%) | |
| occurrences (all) | 111 | 67 | |
| Oral pain | | | |
| subjects affected / exposed | 39 / 348 (11.21%) | 43 / 344 (12.50%) | |
| occurrences (all) | 69 | 78 | |
| Stomatitis | | | |
| subjects affected / exposed | 92 / 348 (26.44%) | 96 / 344 (27.91%) | |
| occurrences (all) | 167 | 184 | |
| Vomiting | | | |
| subjects affected / exposed | 112 / 348 (32.18%) | 121 / 344 (35.17%) | |
| occurrences (all) | 195 | 210 | |
| Skin and subcutaneous tissue disorders | | | |
| Alopecia | | | |
| subjects affected / exposed | 22 / 348 (6.32%) | 20 / 344 (5.81%) | |
| occurrences (all) | 23 | 20 | |
| Dermatitis | | | |
| subjects affected / exposed | 52 / 348 (14.94%) | 42 / 344 (12.21%) | |
| occurrences (all) | 88 | 67 | |
| Dry skin | | | |
| subjects affected / exposed | 18 / 348 (5.17%) | 24 / 344 (6.98%) | |
| occurrences (all) | 19 | 28 | |

| | | | |
|---|-------------------|-------------------|--|
| Erythema | | | |
| subjects affected / exposed | 24 / 348 (6.90%) | 27 / 344 (7.85%) | |
| occurrences (all) | 30 | 30 | |
| Pruritus | | | |
| subjects affected / exposed | 38 / 348 (10.92%) | 24 / 344 (6.98%) | |
| occurrences (all) | 51 | 38 | |
| Rash | | | |
| subjects affected / exposed | 43 / 348 (12.36%) | 36 / 344 (10.47%) | |
| occurrences (all) | 67 | 51 | |
| Renal and urinary disorders | | | |
| Acute kidney injury | | | |
| subjects affected / exposed | 18 / 348 (5.17%) | 22 / 344 (6.40%) | |
| occurrences (all) | 42 | 37 | |
| Endocrine disorders | | | |
| Hyperthyroidism | | | |
| subjects affected / exposed | 24 / 348 (6.90%) | 7 / 344 (2.03%) | |
| occurrences (all) | 28 | 7 | |
| Hypothyroidism | | | |
| subjects affected / exposed | 51 / 348 (14.66%) | 45 / 344 (13.08%) | |
| occurrences (all) | 64 | 51 | |
| Musculoskeletal and connective tissue disorders | | | |
| Arthralgia | | | |
| subjects affected / exposed | 17 / 348 (4.89%) | 20 / 344 (5.81%) | |
| occurrences (all) | 18 | 25 | |
| Neck pain | | | |
| subjects affected / exposed | 30 / 348 (8.62%) | 25 / 344 (7.27%) | |
| occurrences (all) | 45 | 28 | |
| Infections and infestations | | | |
| Oral candidiasis | | | |
| subjects affected / exposed | 25 / 348 (7.18%) | 31 / 344 (9.01%) | |
| occurrences (all) | 36 | 40 | |
| Pneumonia | | | |
| subjects affected / exposed | 36 / 348 (10.34%) | 25 / 344 (7.27%) | |
| occurrences (all) | 43 | 31 | |
| Upper respiratory tract infection | | | |

| | | | |
|--|------------------------|------------------------|--|
| subjects affected / exposed occurrences (all) | 24 / 348 (6.90%) 28 | 21 / 344 (6.10%) 23 | |
| Metabolism and nutrition disorders | | | |
| Decreased appetite | | | |
| subjects affected / exposed | 128 / 348 (36.78%) | 124 / 344 (36.05%) | |
| occurrences (all) | 211 | 194 | |
| Dehydration | | | |
| subjects affected / exposed | 31 / 348 (8.91%) | 29 / 344 (8.43%) | |
| occurrences (all) | 38 | 33 | |
| Hyperglycaemia | | | |
| subjects affected / exposed | 31 / 348 (8.91%) | 33 / 344 (9.59%) | |
| occurrences (all) | 65 | 74 | |
| Hyperkalaemia | | | |
| subjects affected / exposed | 34 / 348 (9.77%) | 32 / 344 (9.30%) | |
| occurrences (all) | 49 | 66 | |
| Hypoalbuminaemia | | | |
| subjects affected / exposed | 42 / 348 (12.07%) | 36 / 344 (10.47%) | |
| occurrences (all) | 88 | 73 | |
| Hypocalcaemia | | | |
| subjects affected / exposed | 29 / 348 (8.33%) | 23 / 344 (6.69%) | |
| occurrences (all) | 42 | 37 | |
| Hypokalaemia | | | |
| subjects affected / exposed | 87 / 348 (25.00%) | 71 / 344 (20.64%) | |
| occurrences (all) | 179 | 130 | |
| Hypomagnesaemia | | | |
| subjects affected / exposed | 93 / 348 (26.72%) | 84 / 344 (24.42%) | |
| occurrences (all) | 178 | 173 | |
| Hyponatraemia | | | |
| subjects affected / exposed | 83 / 348 (23.85%) | 68 / 344 (19.77%) | |
| occurrences (all) | 183 | 164 | |
| Hypophosphataemia | | | |
| subjects affected / exposed | 23 / 348 (6.61%) | 32 / 344 (9.30%) | |
| occurrences (all) | 41 | 46 | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

| |
|---|
| If a subject discontinued all 3 treatments of CRT phase due to death then death is included as discontinuation reason in each treatment disposition summary. Deaths reported as reason of discontinuation at any phase are included in all-cause mortality. |
|---|

Notes: