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	Australia: 10
Country: Number of subjects enrolled	Canada: 1
Country: Number of subjects enrolled	China: 45
Country: Number of subjects enrolled	Israel: 13
Country: Number of subjects enrolled	Japan: 51
Country: Number of subjects enrolled	Korea, Republic of: 19
Country: Number of subjects enrolled	Russian Federation: 38
Country: Number of subjects enrolled	Taiwan: 69
Country: Number of subjects enrolled	United States: 173
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	Hungary: 43
Country: Number of subjects enrolled	Ireland: 3
Country: Number of subjects enrolled	Italy: 19
Country: Number of subjects enrolled	Poland: 16
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	Greece: 23

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/m^2) 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/m^2 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
Death	-	1
No Longer Met Eligibility Criteria	-	1
Withdrawal by subject	2	2
Adverse event, non-fatal	3	-

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/m^2) 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/m^2 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
Death	5	8
Physician decision	2	1
Global Deterioration of Health Status	1	-
Withdrawal by subject	10	4
Adverse event, non-fatal	12	12
Unspecified	2	1
Lost to follow-up	1	1

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/m^2) 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	Cisplastin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intravenous use

Dosage and administration details:

Subjects received Cisplatin 100 mg/m^2 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/m^2 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	Cisplastin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intravenous use

Dosage and administration details:

Subjects received Cisplatin 100 mg/m^2 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
Death	3	8
Physician decision	12	10
Global Deterioration of Health Status	1	-
Withdrawal by subject	11	3
Adverse event, non-fatal	82	81
Unspecified	1	1
Lost to follow-up	1	1
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/m^2) 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/m^2 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
Death	5	8
Global Deterioration of Health Status	1	-
Withdrawal by subject	10	6
Adverse event, non-fatal	5	5
Unspecified	1	-
Lost to follow-up	1	1
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/m^2) 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/m^2 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
Study Terminated by Sponsor	1	6
Progressive disease	60	54
Death	17	11
Non-compliance With Study Drug	1	1
Physician decision	1	1
Global Deterioration of Health Status	14	5
Withdrawal by subject	31	25
Adverse event, non-fatal	24	21
Unspecified	2	1
Lost to follow-up	1	2

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/m^2) 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/m^2 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
Study Terminated by Sponsor	32	50
Death	12	10
Withdrawal by subject	6	2
Unspecified	7	5
Lost to follow-up	1	1

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:

Ssubjects 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/m^2) 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/m^2 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
Study Terminated by Sponsor	187	201
Death	51	31
Withdrawal by subject	7	1
Lost to follow-up	2	4
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/m^2) 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/m^2 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 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/m^2) 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/m^2 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/m^2) 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/m^2 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/m^2) 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/m^2 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.

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Reporting group description:

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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 (>=) 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

No statistical analyses for this end point

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/mm^3,500-200/mm^3;LC increased (inc):grade 3:>20,000/mm^3:NC dec:<LLN-1500/mm^3;<1000-500/mm^3;PC dec:<LLN-75,000/mm^3;<50,000-25,000/mm^3;WBC dec:<LLN-3000/mm^3;<2000-1000/mm^3;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;Hypernatremia:>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

End point type	Secondary

End point timeframe:

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		
Bilurubin 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 (± 10.13)	78.1 (± 10.91)		
Lead in Phase: DBP: Change at Day 1 (n=2,2)	-3.0 (± 4.24)	-8.0 (± 11.31)		
CRT Phase: DBP: Change at Day 1 (n=332,322)	-1.5 (± 9.52)	-2.2 (± 9.91)		
CRT Phase: DBP: Change at Day 8 (n=323,315)	-3.8 (± 10.46)	-3.9 (± 10.99)		
CRT Phase: DBP: Change at Day 22 (n-313,309)	-4.2 (± 11.77)	-5.0 (± 10.95)		
CRT Phase: DBP: Change at Day 25 (n=310,306)	-3.4 (± 11.91)	-3.3 (± 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)	-1.3 (± 15.57)	0.4 (± 13.24)		
EOT(n=223,210)	0.2 (± 14.73)	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 (± 0.17227)	0.0389 (± 0.18732)		
MP: Change at EOT (n=184,187)	-0.0051 (± 0.24528)	0.0074 (± 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 (± 18.20)	74.9 (± 18.24)		
CRT Phase: Change at Day 1 (n=317, 314)	-1.1 (± 13.49)	-1.4 (± 11.39)		
CRT Phase: Change at Day 29 (n=291, 271)	-10.9 (± 19.94)	-9.2 (± 18.70)		
MP: Change at C1D1 (n=272, 277)	-7.7 (± 19.05)	-6.2 (± 18.67)		
MP: Change at C3D1 (n=240, 236)	-1.8 (± 18.00)	-0.7 (± 16.14)		
MP: Change at C7D1 (n=95,113)	-0.6 (± 14.91)	8.6 (± 81.42)		
MP: Change at C7D15 (n=59, 78)	4.8 (± 18.52)	3.1 (± 19.28)		
MP: Change at C11D1 (n=89,108)	0.3 (± 17.60)	4.3 (± 16.10)		
MP: Change at C11D15 (n=37, 40)	10.1 (± 24.69)	2.4 (± 18.20)		
MP: Change at EOT (n=183, 184)	-1.9 (± 22.55)	0.7 (± 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 (mm^2). 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 Cisplastin

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

End point description:

Dose normalized (dn) Cmax was calculated by dividing Cmax by the exact dose of total or free Cisplastin (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 Cisplastin	26.23 (± 36)	25.33 (± 26)		
Free Cisplastin	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 cisplastin (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 Cisplastin	3781 (± 44)	4001 (± 34)		
Free Cisplastin	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 Cisplastin	1.000 (0.500 to 2.40)	1.170 (0.983 to 24.0)		
Free Cisplastin	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/m^2) 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/m^2 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			
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	
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	
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	
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	0 / 0	0 / 1	

treatment / all			
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	
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	
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	
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	
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	

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	
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	
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	
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	
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	
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	
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	
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	
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	
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	
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	
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	
Infections and infestations			
Abdominal 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	
Abscess oral			
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	
Anal abscess			
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	
Appendicitis			
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	
Bacterial 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	
Bronchitis			
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	
Bronchitis bacterial			
subjects affected / exposed	1 / 348 (0.29%)	0 / 344 (0.00%)	
occurrences causally related to	0 / 1	0 / 0	

treatment / all			
deaths causally related to treatment / all	0 / 0	0 / 0	
Candida infection			
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	
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	

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			
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	
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	
Malaise			
subjects affected / exposed	20 / 348 (5.75%)	23 / 344 (6.69%)	
occurrences (all)	39	39	
Oedema peripheral			
subjects affected / exposed	19 / 348 (5.46%)	16 / 344 (4.65%)	
occurrences (all)	27	23	
Mucosal inflammation			
subjects affected / exposed	146 / 348 (41.95%)	131 / 344 (38.08%)	
occurrences (all)	333	289	
Pain			
subjects affected / exposed	23 / 348 (6.61%)	28 / 344 (8.14%)	
occurrences (all)	26	41	
Pyrexia			
subjects affected / exposed	87 / 348 (25.00%)	45 / 344 (13.08%)	
occurrences (all)	140	69	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	26 / 348 (7.47%)	34 / 344 (9.88%)	
occurrences (all)	27	42	
Depression			
subjects affected / exposed	10 / 348 (2.87%)	18 / 344 (5.23%)	
occurrences (all)	10	21	
Insomnia			

subjects affected / exposed	57 / 348 (16.38%)	47 / 344 (13.66%)	
occurrences (all)	67	56	
Injury, poisoning and procedural complications			
Infusion related reaction			
subjects affected / exposed	24 / 348 (6.90%)	6 / 344 (1.74%)	
occurrences (all)	40	18	
Radiation skin injury			
subjects affected / exposed	135 / 348 (38.79%)	136 / 344 (39.53%)	
occurrences (all)	216	223	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	56 / 348 (16.09%)	30 / 344 (8.72%)	
occurrences (all)	92	43	
Amylase increased			
subjects affected / exposed	22 / 348 (6.32%)	10 / 344 (2.91%)	
occurrences (all)	41	11	
Aspartate aminotransferase increased			
subjects affected / exposed	55 / 348 (15.80%)	26 / 344 (7.56%)	
occurrences (all)	87	39	
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	
Neutrophil count decreased			
subjects affected / exposed	64 / 348 (18.39%)	60 / 344 (17.44%)	
occurrences (all)	115	117	
Gamma-glutamyltransferase increased			
subjects affected / exposed	23 / 348 (6.61%)	15 / 344 (4.36%)	
occurrences (all)	49	24	
Lymphocyte count decreased			

subjects affected / exposed	40 / 348 (11.49%)	42 / 344 (12.21%)	
occurrences (all)	153	204	
White blood cell count decreased			
subjects affected / exposed	69 / 348 (19.83%)	64 / 344 (18.60%)	
occurrences (all)	164	203	
Platelet count decreased			
subjects affected / exposed	40 / 348 (11.49%)	33 / 344 (9.59%)	
occurrences (all)	66	75	
Weight decreased			
subjects affected / exposed	157 / 348 (45.11%)	171 / 344 (49.71%)	
occurrences (all)	282	333	
Respiratory, thoracic and mediastinal disorders			
Dysphonia			
subjects affected / exposed	51 / 348 (14.66%)	47 / 344 (13.66%)	
occurrences (all)	64	78	
Cough			
subjects affected / exposed	74 / 348 (21.26%)	63 / 344 (18.31%)	
occurrences (all)	96	85	
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	
Productive cough			
subjects affected / exposed	40 / 348 (11.49%)	31 / 344 (9.01%)	
occurrences (all)	53	37	
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	
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	
Lymphopenia			
subjects affected / exposed	33 / 348 (9.48%)	27 / 344 (7.85%)	
occurrences (all)	164	101	
Neutropenia			
subjects affected / exposed	102 / 348 (29.31%)	98 / 344 (28.49%)	
occurrences (all)	192	169	
Thrombocytopenia			
subjects affected / exposed	45 / 348 (12.93%)	41 / 344 (11.92%)	
occurrences (all)	92	81	
Nervous system disorders			
Dysgeusia			
subjects affected / exposed	106 / 348 (30.46%)	119 / 344 (34.59%)	
occurrences (all)	154	166	
Dizziness			
subjects affected / exposed	41 / 348 (11.78%)	33 / 344 (9.59%)	
occurrences (all)	45	40	
Headache			
subjects affected / exposed	44 / 348 (12.64%)	41 / 344 (11.92%)	
occurrences (all)	55	54	
Neuropathy peripheral			
subjects affected / exposed	11 / 348 (3.16%)	28 / 344 (8.14%)	
occurrences (all)	12	45	
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	
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	
Diarrhoea			
subjects affected / exposed	83 / 348 (23.85%)	66 / 344 (19.19%)	
occurrences (all)	112	92	
Constipation			
subjects affected / exposed	178 / 348 (51.15%)	155 / 344 (45.06%)	
occurrences (all)	280	215	
Odynophagia			
subjects affected / exposed	62 / 348 (17.82%)	48 / 344 (13.95%)	
occurrences (all)	111	67	
Dysphagia			
subjects affected / exposed	143 / 348 (41.09%)	152 / 344 (44.19%)	
occurrences (all)	253	275	
Nausea			
subjects affected / exposed	210 / 348 (60.34%)	199 / 344 (57.85%)	
occurrences (all)	346	340	
Vomiting			
subjects affected / exposed	112 / 348 (32.18%)	121 / 344 (35.17%)	
occurrences (all)	195	210	
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	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	18 / 348 (5.17%)	22 / 344 (6.40%)	
occurrences (all)	42	37	
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	
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	
Erythema			
subjects affected / exposed	24 / 348 (6.90%)	27 / 344 (7.85%)	
occurrences (all)	30	30	
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	
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	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	128 / 348 (36.78%)	124 / 344 (36.05%)	
occurrences (all)	211	194	
Hyperkalaemia			
subjects affected / exposed	34 / 348 (9.77%)	32 / 344 (9.30%)	
occurrences (all)	49	66	
Hyperglycaemia			
subjects affected / exposed	31 / 348 (8.91%)	33 / 344 (9.59%)	
occurrences (all)	65	74	
Dehydration			
subjects affected / exposed	31 / 348 (8.91%)	29 / 344 (8.43%)	
occurrences (all)	38	33	
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	
Hypophosphataemia			
subjects affected / exposed	23 / 348 (6.61%)	32 / 344 (9.30%)	
occurrences (all)	41	46	
Hyponatraemia			
subjects affected / exposed	83 / 348 (23.85%)	68 / 344 (19.77%)	
occurrences (all)	183	164	
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	24 / 348 (6.90%)	21 / 344 (6.10%)	
occurrences (all)	28	23	

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: