Clinical trial results:
A Phase III, Open-label, Multicenter Trial of Avelumab (MSB0010718C) Versus Platinum-based Doublet as a First-line Treatment of Recurrent or Stage IV PD-L1+NSCLC

Summary

EudraCT number	2015-001537-24
Trial protocol	SK DE PT LT BE CZ GB ES HU PL NL FR DK BG HR CY GR IT
Global end of trial date	29 January 2024

Results information

Result version number	v1 (current)
This version publication date	06 February 2025
First version publication date	06 February 2025

Trial information

Trial identification

Sponsor protocol code	EMR 100070-005

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02576574
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Merck Healthcare KGaA
Sponsor organisation address	Frankfurter Strasse 250, Darmstadt, Germany, 64293
Public contact	Communication Center, Merck KGaA, Darmstadt, Germany, +49 6151725200, service@merckgroup.com
Scientific contact	Communication Center, Merck KGaA, Darmstadt, Germany, +49 6151725200, service@merckgroup.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	29 January 2024
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	29 January 2024
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The purpose of this study was to demonstrate superiority with regard to Overall Survival (OS) or Progression Free Survival (PFS) of avelumab versus platinum-based doublet, based on an Independent Review Committee assessment, in Non-small cell lung cancer (NSCLC) participants with Programmed death ligand 1+ (PD-L1+) tumors.

Protection of trial subjects:

Subject protection was ensured by following high medical and ethical standards in accordance with the principles laid down in the Declaration of Helsinki, and that are consistent with Good Clinical Practice and applicable regulations

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	29 October 2015
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Canada: 1
Country: Number of subjects enrolled	United States: 26
Country: Number of subjects enrolled	Brazil: 34
Country: Number of subjects enrolled	Chile: 15
Country: Number of subjects enrolled	Colombia: 1
Country: Number of subjects enrolled	Peru: 8
Country: Number of subjects enrolled	Belgium: 4
Country: Number of subjects enrolled	Germany: 3
Country: Number of subjects enrolled	Denmark: 9
Country: Number of subjects enrolled	Spain: 75
Country: Number of subjects enrolled	France: 44
Country: Number of subjects enrolled	Greece: 24
Country: Number of subjects enrolled	United Kingdom: 5
Country: Number of subjects enrolled	Ireland: 1
Country: Number of subjects enrolled	Italy: 11
Country: Number of subjects enrolled	Netherlands: 8
Country: Number of subjects enrolled	Portugal: 19
Country: Number of subjects enrolled	Bulgaria: 7
Country: Number of subjects enrolled	Czechia: 6

Country: Number of subjects enrolled	Estonia: 1
Country: Number of subjects enrolled	Croatia: 6
Country: Number of subjects enrolled	Hungary: 54
Country: Number of subjects enrolled	Lithuania: 6
Country: Number of subjects enrolled	Poland: 58
Country: Number of subjects enrolled	Romania: 65
Country: Number of subjects enrolled	Russian Federation: 116
Country: Number of subjects enrolled	Serbia: 51
Country: Number of subjects enrolled	Slovakia: 2
Country: Number of subjects enrolled	Ukraine: 58
Country: Number of subjects enrolled	Australia: 49
Country: Number of subjects enrolled	New Zealand: 53
Country: Number of subjects enrolled	China: 28
Country: Number of subjects enrolled	Japan: 31
Country: Number of subjects enrolled	Korea, Democratic People's Republic of: 133
Country: Number of subjects enrolled	Singapore: 12
Country: Number of subjects enrolled	Thailand: 20
Country: Number of subjects enrolled	Taiwan: 13
Country: Number of subjects enrolled	South Africa: 2
Country: Number of subjects enrolled	Israel: 10
Country: Number of subjects enrolled	Lebanon: 7
Country: Number of subjects enrolled	Türkiye: 138
Worldwide total number of subjects	1214
EEA total number of subjects	403

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)	1214
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

A total of 3423 subjects were screened out of which 1214 subjects received the study treatments.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Avelumab Biweekly

Arm description:

Subjects received Avelumab at a dose of 10 milligrams per kilogram (mg/kg) as a 1-hour (-10/+20 minutes) intravenous (IV) infusion once every 2 weeks until disease progression or unacceptable toxicities.

Arm type	Experimental
Investigational medicinal product name	Avelumab
Investigational medicinal product code	
Other name	MSB0010718C
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Subjects received Avelumab at a dose of 10 milligrams per kilogram (mg/kg) as a 1-hour (-10/+20 minutes) intravenous (IV) infusion once every 2 weeks until disease progression or unacceptable toxicities.

Arm title	Avelumab Weekly

Arm description:

Subjects received Avelumab at a dose of 10 mg/kg as a 1-hour (-10/+20 minutes) IV infusion every week for 12 consecutive weeks, followed by Avelumab at a dose of 10 mg/kg once every 2 weeks until disease progression or unacceptable toxicities.

Arm type	Experimental
Investigational medicinal product name	Avelumab
Investigational medicinal product code	
Other name	MSB0010718C
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Subjects received Avelumab at a dose of 10 mg/kg as a 1-hour (-10/+20 minutes) IV infusion every week for 12 consecutive weeks.

Investigational medicinal product name	Cisplatin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Subjects received Cisplatin 75 mg/m^2 by IV infusion in 3-Week cycle up to a maximum of 6 cycles of IV injection until disease progression or unacceptable toxicities.

Arm title	Chemotherapy

Arm description:

Subjects received Pemetrexed (500 milligrams per square meter [mg/m^2]) in combination with Cisplatin (75 mg/m^2) administered on Day1 of each cycle or pemetrexed (500 mg/m^2) in combination with carboplatin (area under the concentration curve [AUC] 6 milligrams per milliliter [mg/mL] * minutes administered on Day 1 of each cycle). Subjects assigned pemetrexed could continue to receive pemetrexed as a maintenance therapy after 4 cycles of platinum-based chemotherapy if their disease had not progressed. Subjects with tumor of squamous histology received Paclitaxel (200 mg/m^2) plus carboplatin (AUC 6 mg/mL * min administered on Day 1 of each cycle) or Gemcitabine (1250 mg/m^2 administered on Day 1 and Day 8 of each cycle) plus cisplatin (75 mg/m^2) or Gemcitabine (1000 mg/m^2 administered on Day 1 and Day 8 of each cycle) plus carboplatin (AUC 5 mg/mL * min) in 3-week cycles up to a maximum of 6 cycles of IV injection or until disease progression or unacceptable toxicities.

Arm type	Experimental
Investigational medicinal product name	Paclitaxel
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Subjects received Paclitaxel 200 mg/m^2 by IV infusion on Day 1 of 3-Week cycle up to a maximum of 6 cycles of IV injection until disease progression or unacceptable toxicities.

Investigational medicinal product name	Pemetrexed
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate and solvent for concentrate for solution for infusion, Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Subjects received Pemetrexed 500 milligrams per square meter (mg/m^2) by IV infusion on Day 1 of 3-Week cycle up to a maximum of 6 cycles of IV injection until disease progression or unacceptable toxicities.

Number of subjects in period 1	Avelumab Biweekly	Avelumab Weekly	Chemotherapy
Started	366	322	526
Completed	366	322	526

Baseline characteristics

Reporting groups	
Reporting group title	Avelumab Biweekly
Reporting group description:	
Subjects received Avelumab at a dose of 10 milligrams per kilogram (mg/kg) as a 1-hour (-10/+20 minutes) intravenous (IV) infusion once every 2 weeks until disease progression or unacceptable toxicities.	
Reporting group title	Avelumab Weekly
Reporting group description:	
Subjects received Avelumab at a dose of 10 mg/kg as a 1-hour (-10/+20 minutes) IV infusion every week for 12 consecutive weeks, followed by Avelumab at a dose of 10 mg/kg once every 2 weeks until disease progression or unacceptable toxicities.	
Reporting group title	Chemotherapy
Reporting group description:	
Subjects received Pemetrexed (500 milligrams per square meter [mg/m^2]) in combination with Cisplatin (75 mg/m^2) administered on Day1 of each cycle or pemetrexed (500 mg/m^2) in combination with carboplatin (area under the concentration curve [AUC] 6 milligrams per milliliter [mg/mL] * minutes administered on Day 1 of each cycle). Subjects assigned pemetrexed could continue to receive pemetrexed as a maintenance therapy after 4 cycles of platinum-based chemotherapy if their disease had not progressed. Subjects with tumor of squamous histology received Paclitaxel (200 mg/m^2) plus carboplatin (AUC 6 mg/mL * min administered on Day 1 of each cycle) or Gemcitabine (1250 mg/m^2 administered on Day 1 and Day 8 of each cycle) plus cisplatin (75 mg/m^2) or Gemcitabine (1000 mg/m^2 administered on Day 1 and Day 8 of each cycle) plus carboplatin (AUC 5 mg/mL * min) in 3-week cycles up to a maximum of 6 cycles of IV injection or until disease progression or unacceptable toxicities.	

Reporting group values	Avelumab Biweekly	Avelumab Weekly	Chemotherapy
Number of subjects	366	322	526
Age Categorical Units: subjects			
<=18 years	0	0	0
Between 18 and 65 years	190	168	289
>=65 years	176	154	237
Sex: Female, Male Units: subjects			
Female	84	69	145
Male	282	253	381
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	85	53	104
Native Hawaiian or Other Pacific Islander	1	0	0
Black or African American	1	2	4
White	254	250	375
More than one race	0	0	0
Unknown or Not Reported	25	17	43
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	14	20	38
Not Hispanic or Latino	338	296	466
Unknown or Not Reported	14	6	22

Reporting group values	Total		
Number of subjects	1214		
Age Categorical Units: subjects			
<=18 years	0		
Between 18 and 65 years	647		
>=65 years	567		
Sex: Female, Male Units: subjects			
Female	298		
Male	916		
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0		
Asian	242		
Native Hawaiian or Other Pacific Islander	1		
Black or African American	7		
White	879		
More than one race	0		
Unknown or Not Reported	85		
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	72		
Not Hispanic or Latino	1100		
Unknown or Not Reported	42		

End points

End points reporting groups

Reporting group title	Avelumab Biweekly
Reporting group description:	
Subjects received Avelumab at a dose of 10 milligrams per kilogram (mg/kg) as a 1-hour (-10/+20 minutes) intravenous (IV) infusion once every 2 weeks until disease progression or unacceptable toxicities.	

Reporting group title	Avelumab Weekly
Reporting group description:	
Subjects received Avelumab at a dose of 10 mg/kg as a 1-hour (-10/+20 minutes) IV infusion every week for 12 consecutive weeks, followed by Avelumab at a dose of 10 mg/kg once every 2 weeks until disease progression or unacceptable toxicities.	

Reporting group title	Chemotherapy
Reporting group description:	
Subjects received Pemetrexed (500 milligrams per square meter [mg/m^2]) in combination with Cisplatin (75 mg/m^2) administered on Day1 of each cycle or pemetrexed (500 mg/m^2) in combination with carboplatin (area under the concentration curve [AUC] 6 milligrams per milliliter [mg/mL] * minutes administered on Day 1 of each cycle). Subjects assigned pemetrexed could continue to receive pemetrexed as a maintenance therapy after 4 cycles of platinum-based chemotherapy if their disease had not progressed. Subjects with tumor of squamous histology received Paclitaxel (200 mg/m^2) plus carboplatin (AUC 6 mg/mL * min administered on Day 1 of each cycle) or Gemcitabine (1250 mg/m^2 administered on Day 1 and Day 8 of each cycle) plus cisplatin (75 mg/m^2) or Gemcitabine (1000 mg/m^2 administered on Day 1 and Day 8 of each cycle) plus carboplatin (AUC 5 mg/mL * min) in 3-week cycles up to a maximum of 6 cycles of IV injection or until disease progression or unacceptable toxicities.	

Primary: Progression Free Survival (PFS) According to Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1) Assessed by Independent Review Committee (IRC) in High Programmed Death Ligand 1 (PD-L1) + Full Analysis Set (FAS)

End point title	Progression Free Survival (PFS) According to Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1) Assessed by Independent Review Committee (IRC) in High Programmed Death Ligand 1 (PD-L1) + Full Analysis Set (FAS)[1]
End point description:	
PFS is defined as the time from date of randomization until date of the first documentation of progressive disease (PD) or death due to any cause in the absence of documented PD, whichever occurs first. PD is defined as at least a 20 percent (%) increase in the sum of the longest diameter (SLD), taking as reference the smallest SLD recorded from baseline or the appearance of 1 or more new lesions. PFS was measured using Kaplan-Meier (KM) estimates. High PD-L1+ FAS included all high expression PD-L1+ subjects who were randomized to study intervention. High expression PD-L1+ subjects with greater than or equal to (>=) 80 percent (%) of tumor cells deemed positive for PD-L1 expression at any staining intensity (1+, 2+, or 3+).	

End point type	Primary
End point timeframe:	
Time from date of randomization up to data cutoff (assessed up to approximately 71.5 months)	

Notes:

[1] - 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: Endpoint only compares the data of Avelumab and Chemotherapy groups

End point values	Avelumab Biweekly	Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	151	216		
Units: months				
median (confidence interval 95%)	8.4 (5.4 to 12.6)	5.6 (5.4 to 6.8)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Avelumab Biweekly v Chemotherapy
Number of subjects included in analysis	367
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.007
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.71
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.54
upper limit	0.93

Primary: Progression Free Survival (PFS) According to Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1) Assessed by Independent Review Committee (IRC) in High Programmed Death Ligand 1 (PD-L1) + Modified Full Analysis Set (mFAS)

End point title	Progression Free Survival (PFS) According to Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1) Assessed by Independent Review Committee (IRC) in High Programmed Death Ligand 1 (PD-L1) + Modified Full Analysis Set (mFAS)[2]

End point description:

PFS is defined as the time from date of randomization until date of the first documentation of progressive disease (PD) or death due to any cause in the absence of documented PD, whichever occurs first. PD is defined as at least a 20 percent (%) increase in the sum of the longest diameter (SLD), taking as reference the smallest SLD recorded from baseline or the appearance of 1 or more new lesions. PFS was measured using Kaplan-Meier (KM) estimates. High PD-L1+ mFAS included all high expression PD-L1+ subjects who were randomized to study intervention after weekly Avelumab was included into the randomization allocation. The PDL1+ subjects with >= 80% of tumor cells deemed positive for PD-L1 expression at any staining intensity (1+, 2+, or 3+).

End point type	Primary

End point timeframe:

Time from date of randomization up to data cutoff (assessed up to approximately 71.5 months)

Notes:

[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Endpoint only compares the data of Avelumab and Chemotherapy groups

End point values	Avelumab Weekly	Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	130	129		
Units: months				
median (confidence interval 95%)	7.5 (4.2 to 11.1)	5.6 (5.0 to 6.8)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Avelumab Weekly v Chemotherapy
Number of subjects included in analysis	259
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0196
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.72
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.52
upper limit	0.98

Primary: Overall Survival (OS) in High Programmed Death Ligand 1 (PD-L1) + Full Analysis Set (FAS)

End point title	Overall Survival (OS) in High Programmed Death Ligand 1 (PD-L1) + Full Analysis Set (FAS)[3]

End point description:

OS is defined as the time from randomization to the date of death, regardless of the actual cause of the subjects death. The subjects who were still alive at the time of data analysis or who were lost to follow-up OS time was censored at the last recorded date that the participant was known to be alive before the data cutoff date. OS was measured using Kaplan-Meier (KM) estimates. High PD-L1+ FAS included all high expression PD-L1+ subjects who were randomized to study intervention. High expression PD-L1+ subjects with greater than or equal to (>=) 80 percent (%) of tumor cells deemed positive for PD-L1 expression at any staining intensity (1+, 2+, or 3+).

End point type	Primary

End point timeframe:

Time from date of randomization up to data cutoff (assessed up to approximately 71.5 months)

Notes:

[3] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Endpoint only compares the data of Avelumab and Chemotherapy groups

End point values	Avelumab Biweekly	Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	151	216		
Units: months				
median (confidence interval 95%)	20.1 (15.0 to 24.3)	14.9 (11.8 to 18.6)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Avelumab Biweekly v Chemotherapy
Number of subjects included in analysis	367
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.1032
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.85
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.67
upper limit	1.09

Primary: Overall Survival (OS) in High Programmed Death Ligand 1 (PD-L1)+ Modified Full Analysis Set (mFAS)

End point title	Overall Survival (OS) in High Programmed Death Ligand 1 (PD-L1)+ Modified Full Analysis Set (mFAS)[4]

End point description:

OS is defined as the time from randomization to the date of death, regardless of the actual cause of the subjects death. The subjects who were still alive at the time of data analysis or who were lost to follow-up OS time was censored at the last recorded date that the subject was known to be alive before the data cutoff date. OS was measured using Kaplan-Meier (KM) estimates. High PD-L1+ mFAS included all high expression PD-L1+ subjects who were randomized to study intervention after weekly Avelumab was included into the randomization allocation. The PDL1+ subjects with >= 80% of tumor cells deemed positive for PD-L1 expression at any staining intensity (1+, 2+, or 3+).

End point type	Primary

End point timeframe:

Time from date of randomization up to data cutoff (assessed up to approximately 71.5 months)

Notes:

[4] - 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: Endpoint only compares the data of Avelumab and Chemotherapy groups

End point values	Avelumab Weekly	Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	130	129		
Units: months				
median (confidence interval 95%)	19.3 (14.0 to 28.1)	15.3 (11.6 to 19.1)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Avelumab Weekly v Chemotherapy
Number of subjects included in analysis	259
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.063
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.79
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.59
upper limit	1.07

Secondary: Progression Free Survival (PFS) According to Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1) Assessed by Independent Review Committee (IRC) in Moderate and High Programmed Death Ligand 1 (PD-L1)+ Full Analysis Set (FAS)

End point title	Progression Free Survival (PFS) According to Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1) Assessed by Independent Review Committee (IRC) in Moderate and High Programmed Death Ligand 1 (PD-L1)+ Full Analysis Set (FAS)[5]

End point description:

PFS is defined as the time from date of randomization until date of the first documentation of progressive disease (PD) or death due to any cause in the absence of documented PD, whichever occurs first. PD is defined as at least a 20 percent (%) increase in the sum of the longest diameter (SLD), taking as reference the smallest SLD recorded from baseline or the appearance of 1 or more new lesions. PFS was measured using Kaplan-Meier (KM) estimates. Moderate and High PD-L1+ FAS included all high expression PDL-L1+ subjects who were randomized to study intervention. The PD-L1+ subjects with >= 50% of tumor cells deemed positive for PD-L1 expression at any staining intensity (1+, 2+, or 3+).

End point type	Secondary

End point timeframe:

Time from date of randomization up to data cutoff (assessed up to approximately 71.5 months)

Notes:

[5] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Endpoint only compares the data of Avelumab and Chemotherapy groups

End point values	Avelumab Biweekly	Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	218	304		
Units: months				
median (confidence interval 95%)	6.9 (5.4 to 9.6)	5.6 (5.5 to 6.6)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Avelumab Biweekly v Chemotherapy
Number of subjects included in analysis	522
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0147
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.78
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.62
upper limit	0.98

Secondary: Progression Free Survival (PFS) According to Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1) Assessed by Independent Review Committee (IRC) in Moderate and High Programmed Death Ligand 1 (PD-L1)+ Modified Full Analysis Set (mFAS)

End point title	Progression Free Survival (PFS) According to Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1) Assessed by Independent Review Committee (IRC) in Moderate and High Programmed Death Ligand 1 (PD-L1)+ Modified Full Analysis Set (mFAS)[6]

End point description:

PFS is defined as the time from date of randomization until date of the first documentation of progressive disease (PD) or death due to any cause in the absence of documented PD, whichever occurs first. PD is defined as at least a 20 percent (%) increase in the sum of the longest diameter (SLD), taking as reference the smallest SLD recorded from baseline or the appearance of 1 or more new lesions. PFS was measured using Kaplan-Meier (KM) estimates. Moderate and High PD-L1+ mFAS included all high expression PD-L1+ subjects who were randomized to study intervention after weekly avelumab was included into the randomization allocation. The PD-L1+ subjects with >= 50% of tumor cells deemed positive for PD-L1 expression at any staining intensity (1+, 2+, or 3+).

End point type	Secondary

End point timeframe:

Time from date of randomization up to data cutoff (assessed up to approximately 71.5 months)

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: Endpoint only compares the data of Avelumab and Chemotherapy groups

End point values	Avelumab Weekly	Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	183	183		
Units: months				
median (confidence interval 95%)	5.6 (2.8 to 8.2)	5.6 (5.5 to 6.6)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Avelumab Weekly v Chemotherapy
Number of subjects included in analysis	366
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.1753
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.88
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.67
upper limit	1.15

Secondary: Overall Survival (OS) in Moderate and High Programmed Death Ligand 1 (PD-L1)+ Full Analysis Set (FAS)

End point title	Overall Survival (OS) in Moderate and High Programmed Death Ligand 1 (PD-L1)+ Full Analysis Set (FAS)[7]

End point description:

OS is defined as the time from randomization to the date of death, regardless of the actual cause of the subjects death. The subjects who were still alive at the time of data analysis or who were lost to follow-up OS time was censored at the last recorded date that the subject was known to be alive before the data cutoff date. OS was measured using Kaplan-Meier (KM) estimates. Moderate and High PD-L1+ FAS included all high expression PD-L1+ subjects who were randomized to study intervention. The PD-L1+ subjects with >= 50% of tumor cells deemed positive for PD-L1 expression at any staining intensity (1+, 2+, or 3+).

End point type	Secondary

End point timeframe:

Time from date of randomization up to data cutoff (assessed up to approximately 71.5 months)

Notes:

[7] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Endpoint only compares the data of Avelumab and Chemotherapy groups

End point values	Avelumab Biweekly	Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	218	304		
Units: months				
median (confidence interval 95%)	18.7 (14.6 to 21.7)	13.3 (11.4 to 16.6)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Avelumab Biweekly v Chemotherapy
Number of subjects included in analysis	522
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0257
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.82
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.66
upper limit	1

Secondary: Overall Survival (OS) in Moderate and High Programmed Death Ligand 1 (PD-L1)+ Modified Full Analysis Set (mFAS)

End point title	Overall Survival (OS) in Moderate and High Programmed Death Ligand 1 (PD-L1)+ Modified Full Analysis Set (mFAS)[8]

End point description:

OS is defined as the time from randomization to the date of death, regardless of the actual cause of the subjects death. The subjects who were still alive at the time of data analysis or who were lost to follow-up OS time was censored at the last recorded date that the subject was known to be alive before the data cutoff date. OS was measured using Kaplan-Meier (KM) estimates. Moderate and High PD-L1+ mFAS included all high expression PD-L1+ subjects who were randomized to study intervention after weekly avelumab was included into the randomization allocation. The PD-L1+ subjects with >= 50% of tumor cells deemed positive for PD-L1 expression at any staining intensity (1+, 2+, or 3+).

End point type	Secondary

End point timeframe:

Time from date of randomization up to data cutoff (assessed up to approximately 71.5 months)

Notes:

[8] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Endpoint only compares the data of Avelumab and Chemotherapy groups

End point values	Avelumab Weekly	Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	183	183		
Units: months				
median (confidence interval 95%)	16.8 (12.5 to 21.3)	13.0 (11.1 to 17.0)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Avelumab Weekly v Chemotherapy
Number of subjects included in analysis	366
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0809
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.84
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.66
upper limit	1.07

Secondary: Overall Survival (OS) in Full Analysis Set (FAS)

End point title	Overall Survival (OS) in Full Analysis Set (FAS)[9]

End point description:

OS is defined as the time from randomization to the date of death, regardless of the actual cause of the subjects death. The subjects who were still alive at the time of data analysis or who were lost to follow-up OS time was censored at the last recorded date that the participant was known to be alive before the data cutoff date. OS was measured using Kaplan-Meier (KM) estimates. FAS included all subjects who were randomized to study intervention.

End point type	Secondary

End point timeframe:

Time from date of randomization up to data cutoff (assessed up to approximately 71.5 months)

Notes:

[9] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Endpoint only compares the data of Avelumab and Chemotherapy groups

End point values	Avelumab Biweekly	Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	366	526		
Units: months				
median (confidence interval 95%)	15.0 (12.5 to 19.1)	14.3 (11.8 to 15.6)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Avelumab Biweekly v Chemotherapy
Number of subjects included in analysis	892
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.1294
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.92
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.78
upper limit	1.07

Secondary: Percentage of Subjects With Confirmed Objective Response According to Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST v1.1) as Assessed by Independent Review Committee (IRC) in High PD-L1+ Full Analysis Set

End point title	Percentage of Subjects With Confirmed Objective Response According to Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST v1.1) as Assessed by Independent Review Committee (IRC) in High PD-L1+ Full Analysis Set[10]

End point description:

Confirmed objective response was defined as the percentage of subjects with a confirmed objective response of complete response (CR) or partial response (PR). CR: Disappearance of all evidence of target and non-target lesions. PR: At least 30% reduction from baseline in the sum of the longest diameter (SLD) of all lesions. High PD-L1+ FAS included all high expression PD-L1+ participants who were randomized to study intervention. High expression PD-L1+ subjects with greater than or equal to (>=) 80 percent (%) of tumor cells deemed positive for PD-L1 expression at any staining intensity (1+, 2+, or 3+).

End point type	Secondary

End point timeframe:

Time from date of randomization up to data cutoff (assessed up to approximately 71.5 months)

Notes:

[10] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Endpoint only compares the data of Avelumab and Chemotherapy groups

End point values	Avelumab Biweekly	Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	151	216		
Units: percentage of subjects				
number (confidence interval 95%)	37.7 (30.0 to 46.0)	30.1 (24.1 to 36.7)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Avelumab Biweekly v Chemotherapy
Number of subjects included in analysis	367
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.064
Method	Cochran-Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Point estimate	1.41
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.91
upper limit	2.18

Secondary: Overall Survival (OS) in Modified Full Analysis Set (mFAS)

End point title	Overall Survival (OS) in Modified Full Analysis Set (mFAS)[11]

End point description:

OS is defined as the time from randomization to the date of death, regardless of the actual cause of the subjects death. The subjects who were still alive at the time of data analysis or who were lost to follow-up OS time was censored at the last recorded date that the subject was known to be alive before the data cutoff date. OS was measured using Kaplan-Meier (KM) estimates. mFAS included all subjects who were randomized to study intervention after weekly avelumab was included into the randomization allocation.

End point type	Secondary

End point timeframe:

Time from date of randomization up to data cutoff (assessed up to approximately 71.5 months)

Notes:

[11] - 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: Endpoint only compares the data of Avelumab and Chemotherapy groups

End point values	Avelumab Weekly	Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	322	321		
Units: months				
median (confidence interval 95%)	15.4 (12.1 to 18.1)	14.8 (11.6 to 16.4)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Avelumab Weekly v Chemotherapy
Number of subjects included in analysis	643
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.2618
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.94
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.79
upper limit	1.13

Secondary: Percentage of Subjects With Confirmed Objective Response According to Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST v1.1) as Assessed by Independent Review Committee (IRC) in High PD-L1+ Modified Full Analysis Set

End point title	Percentage of Subjects With Confirmed Objective Response According to Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST v1.1) as Assessed by Independent Review Committee (IRC) in High PD-L1+ Modified Full Analysis Set[12]

End point description:

Confirmed objective response was defined as the percentage of subjects with a confirmed objective response of complete response (CR) or partial response (PR). CR: Disappearance of all evidence of target and non-target lesions. PR: At least 30% reduction from baseline in the sum of the longest diameter (SLD) of all lesions. High PD-L1+ mFAS included all high expression PD-L1+ subjects who were randomized to study intervention after weekly Avelumab was included into the randomization allocation. The PDL1+ subjects with >= 80% of tumor cells deemed positive for PD-L1 expression at any staining intensity (1+, 2+, or 3+).

End point type	Secondary

End point timeframe:

Time from date of randomization up to data cutoff (assessed up to approximately 71.5 months)

Notes:

[12] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Endpoint only compares the data of Avelumab and Chemotherapy groups

End point values	Avelumab Weekly	Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	130	129		
Units: percentage of subjects				
median (confidence interval 95%)	34.6 (26.5 to 43.5)	30.2 (22.5 to 38.9)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Avelumab Weekly v Chemotherapy
Number of subjects included in analysis	259
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.2217
Method	Cochran-Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Point estimate	1.23
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.73
upper limit	2.07

Secondary: Percentage of Subjects With Confirmed Objective Response According to Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST v1.1) as Assessed by Independent Review Committee (IRC) in Moderate and High PD-L1+ Full Analysis Set

End point title	Percentage of Subjects With Confirmed Objective Response According to Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST v1.1) as Assessed by Independent Review Committee (IRC) in Moderate and High PD-L1+ Full Analysis Set[13]

End point description:

Confirmed objective response was defined as the percentage of subjects with a confirmed objective response of complete response (CR) or partial response (PR). CR: Disappearance of all evidence of target and non-target lesions. PR: At least 30% reduction from baseline in the sum of the longest diameter (SLD) of all lesions. Moderate and High PD-L1+ FAS included all high expression PD-L1+ subjects who were randomized to study intervention. The PD-L1+ subjects with >= 50% of tumor cells deemed positive for PD-L1 expression at any staining intensity (1+, 2+, or 3+).

End point type	Secondary

End point timeframe:

Time from date of randomization up to data cutoff (assessed up to approximately 71.5 months)

Notes:

[13] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Endpoint only compares the data of Avelumab and Chemotherapy groups

End point values	Avelumab Biweekly	Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	218	304		
Units: percentage of subjects				
number (confidence interval 95%)	33.5 (27.3 to 40.2)	30.3 (25.1 to 35.8)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Avelumab Biweekly v Chemotherapy
Number of subjects included in analysis	522
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.1912
Method	Cochran-Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Point estimate	1.18
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.81
upper limit	1.72

Secondary: Percentage of Subjects With Confirmed Objective Response According to Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST v1.1) as Assessed by Independent Review Committee (IRC) in Moderate and High PD-L1+ Modified Full Analysis Set

End point title	Percentage of Subjects With Confirmed Objective Response According to Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST v1.1) as Assessed by Independent Review Committee (IRC) in Moderate and High PD-L1+ Modified Full Analysis Set[14]

End point description:

Confirmed objective response was defined as the percentage of subjects with a confirmed objective response of complete response (CR) or partial response (PR). CR: Disappearance of all evidence of target and non-target lesions. PR: At least 30% reduction from baseline in the sum of the longest diameter (SLD) of all lesions. Moderate and High PD-L1+ mFAS included all high expression PD-L1+ subjects who were randomized to study intervention after weekly avelumab was included into the randomization allocation. The PD-L1+ subjects with >= 50% of tumor cells deemed positive for PD-L1 expression at any staining intensity (1+, 2+, or 3+).

End point type	Secondary

End point timeframe:

Time from date of randomization up to data cutoff (assessed up to approximately 71.5 months)

Notes:

[14] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Endpoint only compares the data of Avelumab and Chemotherapy groups

End point values	Avelumab Weekly	Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	183	183		
Units: percentage of subjects				
number (confidence interval 95%)	30.6 (24.0 to 37.8)	30.6 (24.0 to 37.8)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Avelumab Weekly v Chemotherapy
Number of subjects included in analysis	366
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.4951
Method	Cochran-Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Point estimate	1
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.64
upper limit	1.57

Secondary: Duration of Response (DOR) According to Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST v1.1) as Assessed by Independent Review Committee (IRC) in High Programmed Death Ligand 1 (PD-L1)+ Full Analysis Set (FAS)

End point title	Duration of Response (DOR) According to Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST v1.1) as Assessed by Independent Review Committee (IRC) in High Programmed Death Ligand 1 (PD-L1)+ Full Analysis Set (FAS)[15]

End point description:

DOR was defined for subjects with confirmed response, as the time from first documentation of objective response (Complete Response [CR] or Partial Response [PR]) to the date of first documentation of progression disease (PD) or death due to any cause, whichever occurred first. CR: Disappearance of all evidence of target and non-target lesions. PR: At least 30% reduction from baseline in the SLD of all lesions. PD: At least a 20 percent (%) increase in the sum of the longest diameter (SLD), taking as reference the smallest SLD recorded from baseline or the appearance of 1 or more new lesions. High PD-L1+ FAS was used. Here, "Overall Number of Subjects Analyzed" signifies those participants who were evaluable for this outcome measure.

End point type	Secondary

End point timeframe:

Time from date of randomization up to data cutoff (assessed up to approximately 71.5 months)

Notes:

[15] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Endpoint only compares the data of Avelumab and Chemotherapy groups

End point values	Avelumab Biweekly	Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	57	65		
Units: months				
median (full range (min-max))	35.9 (1.4 to 60.8)	8.4 (1.0 to 63.9)		

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Response (DOR) According to Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST v1.1) as Assessed by Independent Review Committee (IRC) in High Programmed Death Ligand 1 (PD-L1)+ Modified Full Analysis Set (mFAS)

End point title	Duration of Response (DOR) According to Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST v1.1) as Assessed by Independent Review Committee (IRC) in High Programmed Death Ligand 1 (PD-L1)+ Modified Full Analysis Set (mFAS)[16]

End point description:

DOR was defined for subjects with confirmed response, as the time from first documentation of objective response (Complete Response [CR] or Partial Response [PR]) to the date of first documentation of progression disease (PD) or death due to any cause, whichever occurred first. CR: Disappearance of all evidence of target and non-target lesions. PR: At least 30% reduction from baseline in the SLD of all lesions. PD: At least a 20 percent (%) increase in the sum of the longest diameter (SLD), taking as reference the smallest SLD recorded from baseline or the appearance of 1 or more new lesions. High PD-L1+ mFAS was used. Here, "Overall Number of Subjects Analyzed" signifies those subjects who were evaluable for this outcome measure.

End point type	Secondary

End point timeframe:

Time from date of randomization up to data cutoff (assessed up to approximately 71.5 months)

Notes:

[16] - 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: Endpoint only compares the data of Avelumab and Chemotherapy groups

End point values	Avelumab Weekly	Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	45	39		
Units: months				
median (full range (min-max))	19.4 (3.8 to 43.9)	8.4 (1.0 to 35.9)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in European Quality Of Life 5-dimensions (EQ-5D-5L) Visual Analog Scale (VAS) in High PD-L1+ Health-related Quality of Life

(HRQoL) Analysis Set at End of Treatment

End point title	Change from Baseline in European Quality Of Life 5-dimensions (EQ-5D-5L) Visual Analog Scale (VAS) in High PD-L1+ Health-related Quality of Life (HRQoL) Analysis Set at End of Treatment[17]

End point description:

EQ-5D-5L is comprised of the following 5 subject-reported dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension has 5 levels: no problems, slight problems, moderate problems, severe problems, and extreme problems. The responses are used to derive overall score using a visual analog scale (VAS) that ranged from 0 to 100 millimeter (mm), where 0 is the worst health you can imagine and 100 is the best health you can imagine. High PD-L1+HRQoL analysis set includes all high expression PD-L1+ FAS participants who have 1 baseline HRQoL assessment and have >=1 post-baseline HRQoL questionnaire complete. The high expression PDL1+ participants were with >= 80% of tumor cells deemed positive for PD-L1 expression at any staining intensity (1+, 2+, or 3+). Here, "Overall Number of Subjects Analyzed" signifies those subjects who were evaluable for this outcome measure.

End point type	Secondary

End point timeframe:

Baseline, End of treatment (up to Week 283.9)

Notes:

[17] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Endpoint only compares the data of Avelumab and Chemotherapy groups

End point values	Avelumab Biweekly	Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	56	107		
Units: millimeter (mm)				
arithmetic mean (standard deviation)	-6.2 (± 23.61)	-5.2 (± 20.48)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in European Quality Of Life 5-dimensions (EQ-5D-5L) Visual Analog Scale (VAS) in High Programmed Death Ligand 1 (PD-L1)+ Modified HRQoL Analysis Set

End point title	Change from Baseline in European Quality Of Life 5-dimensions (EQ-5D-5L) Visual Analog Scale (VAS) in High Programmed Death Ligand 1 (PD-L1)+ Modified HRQoL Analysis Set[18]

End point description:

EQ-5D-5L is comprised of the following 5 subject-reported dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension has 5 levels: no problems, slight problems, moderate problems, severe problems, and extreme problems. The responses are used to derive overall score using a visual analog scale (VAS) that ranged from 0 to 100 millimeter (mm), where 0 is the worst health you can imagine and 100 is the best health you can imagine. High PD-L1+ Modified HRQoL Analysis Set included all mFAS subjects who have 1 baseline HRQoL assessment and have >=1 post-baseline HRQoL questionnaire completed. The high expression PDL1+ subjects were with >= 80% of tumor cells deemed positive for PD-L1 expression at any staining intensity (1+, 2+, or 3+). Here, "Overall Number of Subjects Analyzed" signifies those subjects who were evaluable for this outcome measure.

End point type	Secondary

End point timeframe:

Baseline, End of treatment (Week 283.9)

Notes:

[18] - 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: Endpoint only compares the data of Avelumab and Chemotherapy groups

End point values	Avelumab Weekly	Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	53	70		
Units: millimeter				
arithmetic mean (standard deviation)	-10.3 (± 22.49)	-3.9 (± 20.21)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in European Organization for the Research and Treatment of Cancer Quality of Life (EORTC QLQ-C30) Global Health Status at End of Treatment (EOT) in High Programmed Death Ligand 1 (PD-L1)+ HRQoL Analysis Set

End point title	Change From Baseline in European Organization for the Research and Treatment of Cancer Quality of Life (EORTC QLQ-C30) Global Health Status at End of Treatment (EOT) in High Programmed Death Ligand 1 (PD-L1)+ HRQoL Analysis Set[19]

End point description:

EORTC QLQ-C30 was a 30-question tool used to assess the overall quality of life (QoL) in cancer subjects. It consisted of 15 domains: 1 global health status (GHS) scale, 5 functional scales (Physical, role, cognitive, emotional, social), and 9 symptom scales/items (Fatigue, nausea and vomiting, pain, dyspnea, sleep disturbance, appetite loss, constipation, diarrhea, financial impact). The EORTC QLQ-C30 GHS/QoL score ranged from 0 to 100; High score indicated better GHS/QoL. Score 0 represents: very poor physical condition and QoL. Score 100 represents: excellent overall physical condition and QoL. High PD-L1+HRQoL analysis set includes all high expression PD-L1 FAS subjects who have 1 baseline HRQoL assessment and have >=1 post-baseline HRQoL questionnaire complete. The high expression PDL1+ subjects were with >= 80% of tumor cells deemed positive for PD-L1 expression at any staining intensity (1+, 2+, or 3+).

End point type	Secondary

End point timeframe:

Baseline, End of treatment (up to Week 283.9)

Notes:

[19] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Endpoint only compares the data of Avelumab and Chemotherapy groups

End point values	Avelumab Biweekly	Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	56	108		
Units: score on a scale				
arithmetic mean (standard deviation)	-0.3 (± 22.30)	-6.1 (± 24.55)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire Lung Cancer 13 (EORTC QLQ-LC13) at End of Treatment (EOT) in High Programmed Death Ligand 1 (PD-L1)+ HRQoL Analysis Set

End point title	Change From Baseline in European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire Lung Cancer 13 (EORTC QLQ-LC13) at End of Treatment (EOT) in High Programmed Death Ligand 1 (PD-L1)+ HRQoL Analysis Set[20]

End point description:

EORTC QLQ-LC13 consists 13 questions relating to disease symptoms specific to lung cancer and treatment side effects typical of treatment with chemotherapy and radiotherapy. The EORTC QLQ-LC13 generated one multiple-item score assessing dyspnea and a series of single item scores assessing coughing, hemoptysis, sore mouth, dysphagia, peripheral neuropathy, alopecia, pain in chest, pain in arms or shoulder and pain in other parts. Score range: 0 (no burden of symptom domain or single symptom item) to 100 (highest burden of symptoms for symptom domains and single items). High PD-L1+ HRQoL analysis set includes all high expression PD-L1+ FAS subjects who have 1 baseline HRQoL assessment and have >=1 post-baseline HRQoL questionnaire complete. The high expression PDL1+ subjects were with >= 80% of tumor cells deemed positive for PD-L1 expression at any staining intensity (1+, 2+, or 3+).

End point type	Secondary

End point timeframe:

Baseline, End of treatment (up to Week 283.9)

Notes:

[20] - 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: Endpoint only compares the data of Avelumab and Chemotherapy groups

End point values	Avelumab Biweekly	Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	56	108		
Units: score on a scale				
arithmetic mean (standard deviation)				
Dyspnea	7.3 (± 24.10)	5.2 (± 19.66)		
Coughing	2.4 (± 29.04)	-4.3 (± 27.01)		
Hemoptysis	-1.8 (± 21.48)	1.5 (± 13.95)		
Sore mouth	3.0 (± 18.28)	1.9 (± 21.77)		
Dysphagia	3.0 (± 19.36)	-0.6 (± 21.36)		
Peripheral neuropathy	3.6 (± 17.60)	10.8 (± 24.46)		
Alopecia	0.0 (± 8.98)	14.2 (± 32.93)		
Pain in chest	-4.2 (± 22.96)	-1.5 (± 26.33)		
Pain in arm or shoulder	0.6 (± 32.71)	1.9 (± 26.50)		
Pain in other parts	1.8 (± 33.29)	1.5 (± 30.36)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in European Organization for the Research and Treatment of Cancer Quality of Life (EORTC QLQ-C30) Global Health Status at End of Treatment (EOT) in High Programmed Death Ligand 1 (PD-L1)+ Modified HRQoL Analysis Set

End point title	Change From Baseline in European Organization for the Research and Treatment of Cancer Quality of Life (EORTC QLQ-C30) Global Health Status at End of Treatment (EOT) in High Programmed Death Ligand 1 (PD-L1)+ Modified HRQoL Analysis Set[21]

End point description:

EORTC QLQ-C30 a 30-question tool used to assess the QoL in cancer subjects. It consisted of 15 domains: 1 GHS scale, 5 functional scales (Physical, role, cognitive, emotional, social), and 9 symptom scales/items (Fatigue, nausea and vomiting, pain, dyspnea, sleep disturbance, appetite loss, constipation, diarrhea, financial impact). The EORTC QLQ-C30 GHS/QoL score ranged from 0 to 100; High score indicated better GHS/QoL. Score 0 represents: very poor physical condition and QoL. Score 100 represents: excellent overall physical condition and QoL. High PD-L1+modified HRQoL analysis set includes all high expression PD-l1+ mFAS subjects who have 1 baseline HRQoL assessment and have ≥1 post-baseline HRQoL questionnaire completed. The high expression PDL1+ subjects were with >= 80% of tumor cells deemed positive for PD-L1 expression at any staining intensity (1+, 2+, or 3+). Here, "Overall Number of Subjects Analyzed" signifies those subjects who were evaluable for this outcome measure.

End point type	Secondary

End point timeframe:

Baseline, End of treatment (Week 283.9)

Notes:

[21] - 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: Endpoint only compares the data of Avelumab and Chemotherapy groups

End point values	Avelumab Weekly	Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	53	71		
Units: score on a scale				
arithmetic mean (standard deviation)	-12.9 (± 21.03)	-4.5 (± 23.30)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire Lung Cancer 13 (EORTC QLQ-LC13) at End of Treatment (EOT) in High Programmed Death Ligand 1 (PD-L1)+ Modified HRQoL Analysis Set

End point title	Change From Baseline in European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire Lung Cancer 13 (EORTC QLQ-LC13) at End of Treatment (EOT) in High Programmed Death Ligand 1 (PD-L1)+ Modified HRQoL Analysis Set[22]

End point description:

EORTC QLQ-LC13 consisted of 13 questions relating to disease symptoms specific to lung cancer and treatment side effects typical of treatment with chemotherapy and radiotherapy. The EORTC QLQ-LC13 module generated one multiple-item score assessing dyspnea and a series of single item scores assessing coughing, hemoptysis, sore mouth, dysphagia, peripheral neuropathy, alopecia, pain in chest, pain in arms or shoulder and pain in other parts. Score range: 0 (no burden of symptom domain or single symptom item) to 100 (highest burden of symptoms for symptom domains and single items).

High PD-L1+ modified HRQoL analysis set was used. Here, "Overall Number of Subjects Analyzed" signifies those subjects who were evaluable for this outcome measure and "number analyzed" signifies those subjects who were evaluable for specified categories.

End point type	Secondary

End point timeframe:

Baseline, End of treatment (up to Week 283.9)

Notes:

[22] - 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: Endpoint only compares the data of Avelumab and Chemotherapy groups

End point values	Avelumab Weekly	Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	53	71		
Units: score on a scale				
arithmetic mean (standard deviation)				
Dyspnea	6.1 (± 27.19)	4.9 (± 18.77)		
Coughing	-0.6 (± 28.87)	-5.2 (± 24.34)		
Hemoptysis	-0.6 (± 17.89)	0.0 (± 12.59)		
Sore mouth	0.6 (± 13.97)	1.9 (± 17.71)		
Dysphagia	3.8 (± 14.10)	-0.5 (± 22.88)		
Peripheral neuropathy	0.6 (± 21.17)	9.9 (± 23.49)		
Alopecia	-2.5 (± 17.11)	15.0 (± 29.70)		
Pain in chest	2.5 (± 29.13)	-0.5 (± 25.50)		
Pain in arm or shoulder	4.4 (± 30.69)	1.4 (± 25.46)		
Pain in other parts	10.1 (± 28.93)	1.4 (± 28.97)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects with Shift From Baseline to Greater Than or Equal to (>=) Grade 3 in Laboratory Parameter Values Based on National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE), Version 4.03

End point title	Number of Subjects with Shift From Baseline to Greater Than or Equal to (>=) Grade 3 in Laboratory Parameter Values Based on National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE), Version 4.03

End point description:

Number of subjects with shifts from Baseline values (Grade 0/1/2/3) to abnormal post-baseline values (shift to >= Grade 4) were reported as per NCI-CTCAE, v4.03 graded from Grade 1 to 5. Grade 1: Mild; Grade 2: Moderate; Grade 3: Severe; Grade 4: Life-threatening; Grade 5: Death. Shifts in laboratory parameter (anemia, lymphocyte count decreased, neutrophil count decreased, platelet count decreased, white blood cell count decreased, alanine aminotransferase increased, alkaline phosphatase increased, aspartate aminotransferase increased, blood bilirubin increased, creatine phosphokinase increased, creatinine increased and Hyperglycemia) were reported. The Safety analysis set (Safety-AS) included all randomized subjects who were administered at least one dose of the study medication, that is (i.e.) avelumab or chemotherapy.

End point type	Secondary

End point timeframe:

Time from date of randomization up to data cutoff (assessed up to approximately 71.5 months)

End point values	Avelumab Biweekly	Avelumab Weekly	Chemotherapy	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	361	318	500	
Units: subjects				
Anemia: Grade 0 to Grade 3	4	2	58	
Anemia: Grade 1 to Grade 3	4	5	30	
Anemia: Grade 2 to Grade 3	4	6	6	
Lymphocyte count decreased: Grade 0 to Grade 3	16	15	31	
Lymphocyte count decreased: Grade 0 to Grade 4	1	2	3	
Lymphocyte count decreased: Grade 1 to Grade 3	2	10	12	
Lymphocyte count decreased: Grade 2 to Grade 3	7	6	12	
Lymphocyte count decreased: Grade 2 to Grade 4	0	0	1	
Lymphocyte count decreased: Grade 3 to Grade 4	0	0	1	
Neutrophil count decreased: Grade 0 to Grade 3	4	4	65	
Neutrophil count decreased: Grade 0 to Grade 4	0	3	25	
Neutrophil count decreased: Grade 1 to Grade 3	1	0	1	
Platelet count decreased: Grade 0 to Grade 3	0	1	18	
Platelet count decreased: Grade 0 to Grade 4	0	3	20	
Platelet count decreased: Grade 1 to Grade 3	0	1	0	
WBC count decreased:Grade0 to Grade3	0	3	24	
WBC count decreased: Grade 0 to Grade 4	0	1	11	
Alanineaminotransferase increased:Grade0 to 3	12	8	5	
Alanineaminotransferase increased: Grade0 to 4	1	1	3	
Alanineaminotransferase increased: Grade 1 to 3	1	0	2	
Alkaline phosphatase increased: Grade 0 to Grade 3	0	3	1	
Alkaline phosphatase increased: Grade 1 to Grade 3	1	3	1	
Alkaline phosphatase increased: Grade 1 to Grade 4	0	0	1	
Alkaline phosphatase increased: Grade 2 to Grade 3	0	1	0	
Aspartate aminotransferase increased: Grade 0 to 3	7	4	3	
Aspartate aminotransferase increased: Grade 0 to 4	1	2	2	
Aspartate aminotransferase increased: Grade 1 to 3	0	0	1	

Blood bilirubin increased: Grade 0 to Grade 3	0	4	3	
Blood bilirubin increased: Grade 0 to Grade 4	0	1	0	
Creatine phosphokinase increased: Grade 0 to 3	6	5	1	
Creatine phosphokinase increased: Grade 0 to 4	5	0	0	
Creatine phosphokinase increased: Grade 1 to 4	0	1	0	
Creatine phosphokinase increased: Grade 2 to 3	0	1	0	
Creatinine increased: Grade 0 to Grade 3	6	4	4	
Creatinine increased: Grade 1 to Grade 3	0	0	1	
Hyperglycemia: Grade 0 to Grade 3	21	20	35	
Hyperglycemia: Grade 0 to Grade 4	0	0	3	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Treatment-Emergent Adverse Events (TEAEs) and AEs of Special Interest (AESIs)

End point title	Number of Subjects With Treatment-Emergent Adverse Events (TEAEs) and AEs of Special Interest (AESIs)

End point description:

Adverse event (AE) was defined as any untoward medical occurrence in a subject, which does not necessarily have causal relationship with treatment. A serious AE was defined as an AE that resulted in any of the following outcomes: death; life threatening; persistent/significant disability/incapacity; initial or prolonged in subject hospitalization; congenital anomaly/birth defect or was otherwise considered medically important. Any AE that was suspicious to be a potential Immune-related adverse event (irAE) including infusion related reactions were considered AESIs. Number of subjects with TEAEs and AESIs were reported. High PD-L1+ modified HRQoL analysis set was used. Here, "Overall Number of Subjects Analyzed" signifies those subjects who were evaluable for this outcome measure and "number analyzed" signifies those subjects who were evaluable for specified categories.

End point type	Secondary

End point timeframe:

Time from date of randomization up to data cutoff (assessed up to approximately 71.5 months)

End point values	Avelumab Biweekly	Avelumab Weekly	Chemotherapy	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	361	318	500	
Units: subjects				
TEAEs	346	308	484	
AESIs	158	160	173	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects with Maximal On-Treatment Changes From Baseline in Vital Signs - Maximal Body Temperature Increase

End point title	Number of Subjects with Maximal On-Treatment Changes From Baseline in Vital Signs - Maximal Body Temperature Increase

End point description:

The number of subjects with changes from baseline in increased Body Temperature (degree Celsius [°C]) were reported by using criteria: Baseline temperature (temp.) less than (<) 37°C, on treatment change <1°C, 1 - <2°C, 2 - <3°C, greater than or equal to (>=)3°C and missing; Baseline temp. 37 - <38°C, on treatment change <1°C, 1 - <2°C, 2 - <3°C, >=3°C and missing; Baseline temp. 38 - <39°C, on treatment change <1°C, 1 - <2°C, 2 - <3°C, >=3°C and missing; Baseline temp. 39-<40°C, on treatment change <1°C, 1 - <2°C, 2 - <3°C, >=3°C and missing; Baseline temp. >=40°C, on treatment change <1°C, 1 - <2°C, 2 - <3°C, >=3°C and missing; Baseline temp. missing, on treatment change missing. The Safety analysis set (Safety-AS) included all randomized subjects who were administered at least one dose of the study medication, that is (i.e.) avelumab or chemotherapy.

End point type	Secondary

End point timeframe:

Time from date of randomization up to data cutoff (assessed up to approximately 71.5 months)

End point values	Avelumab Biweekly	Avelumab Weekly	Chemotherapy	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	361	318	500	
Units: subjects				
Baseline temp.<37°C, on treatment change<1°C	271	256	403	
Baseline temp.<37°C, on treatment change 1 - <2°C	45	32	33	
Baseline temp.<37°C, on treatment change2-<3°C	3	2	0	
Baseline temp.<37°C,on treatment change>=3°C	0	1	0	
Baseline temp.<37°C,on treatment change missing	16	6	21	
Baseline temp.37-<38°C, on treatment change<1°C	23	19	37	
Baseline temp.37-<38°C, on treatment change1-<2°C	1	2	1	
Baseline temp.37-<38°C, on treatment change2-<3°C	0	0	0	
Baseline temp.37-<38°C, on treatment change >=3°C	0	0	0	
Baseline temp.37-<38°C,treatment change missing	1	0	3	
Baseline temp.38-<39°C, on treatment change <1°C	0	0	0	
Baseline temp.38-<39°C, on treatment change1<2°C	0	0	0	
Baseline temp.38-<39°C, on treatment change2-<3°C	0	0	0	
Baseline temp.38-<39°C,on treatment change>=3°C	0	0	0	
Baseline temp.38-<39°C, treatment change missing	0	0	0	

Baseline temp.39-<40°C, on treatment change<1°C	1	0	0	
Baseline temp.39-<40°C, on treatment change1-<2°C	0	0	0	
Baseline temp.39-<40°C, on treatment change2-<3°C	0	0	0	
Baseline temp.39-<40°C, on treatment change>=3°C	0	0	0	
Baseline temp.39-<40°C,treatment change missing	0	0	0	
Baseline temp.>=40°C, on treatment change<1°C	0	0	0	
Baseline temp.>=40°C, on treatment change1-<2°C	0	0	0	
Baseline temp.>=40°C, on treatment change2-<3°C	0	0	0	
Baseline temp.>=40°C, on treatment change>=3°C	0	0	0	
Baseline temp.>=40°C, on treatment change missing	0	0	0	
Baseline temp. missing, treatment change missing	0	0	2	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects with Maximal On-Treatment Changes From Baseline in Vital Signs - Maximal Weight Increase/Decrease

End point title	Number of Subjects with Maximal On-Treatment Changes From Baseline in Vital Signs - Maximal Weight Increase/Decrease

End point description:

The number of subjects with maximal on-treatment changes from baseline in Increase (Ic.)/Decrease (Dc.) in maximal weight were reported by using criteria: Ic./Dc. From baseline, on treatment (TR) change <10 percentage (%), >=10% and missing. The Safety analysis set (Safety-AS) included all randomized subjects who were administered at least one dose of the study medication, that is (i.e.) avelumab or chemotherapy.

End point type	Secondary

End point timeframe:

Time from date of randomization up to data cutoff (assessed up to approximately 71.5 months)

End point values	Avelumab Biweekly	Avelumab Weekly	Chemotherapy	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	361	318	500	
Units: subjects				
Ic. from baseline, on TR change <10%	302	280	436	
Ic. from baseline, on TR change >=10%	38	28	39	
Ic. from baseline, on TR change missing	21	10	25	
Dc. from baseline, on TR change <10%	296	258	423	
Dc. from baseline, on TR change >=10%	44	50	52	

Dc. from baseline, on TR change missing	21	10	25	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Maximal On-Treatment Changes From Baseline in Vital Signs - Maximal Heart Rate Increase/Decrease

End point title	Number of Subjects With Maximal On-Treatment Changes From Baseline in Vital Signs - Maximal Heart Rate Increase/Decrease

End point description:

The number of subjects with maximal on-treatment (TR) changes from baseline (BS) in Increase (Ic.)/Decrease (Dc.) heart rate (HR) (beats per minute [bpm]) were reported by using criteria: Ic./Dc. BS HR <100/>=100 bpm, on treatment change =<20 bpm, >20 - =<40 bpm, >40 bpm and missing; Ic./Dc. BS HR missing, on treatment change missing. The Safety analysis set (Safety-AS) included all randomized subjects who were administered at least one dose of the study medication, that is (i.e.) avelumab or chemotherapy.

End point type	Secondary

End point timeframe:

Time from date of randomization up to data cutoff (assessed up to approximately 71.5 months)

End point values	Avelumab Biweekly	Avelumab Weekly	Chemotherapy	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	361	318	500	
Units: subjects				
Ic. BS HR <100 bpm, on TR change =<20 bpm	206	202	332	
Ic. BS HR <100 bpm, on TR change >20 - =<40 bpm	86	66	85	
Ic. BS HR <100 bpm, on TR change >40 bpm	21	12	9	
Ic. BS HR <100 bpm, on TR change missing	14	5	16	
Ic. BS HR >= 100 bpm, on TR change =<20 bpm	31	30	46	
Ic. BS HR >= 100 bpm, on TR change >20 - =<40 bpm	0	2	3	
Ic. BS HR >= 100 bpm, on TR change >40 bpm	0	0	0	
Ic. BS HR >= 100 bpm, on TR change missing	3	1	7	
Ic. BS HR missing, on TR change missing	0	0	2	
Dc. BS HR <100 bpm, on TR change =<20 bpm	267	227	385	
Dc. BS HR <100 bpm, on TR change >20 - =<40 bpm	44	52	40	
Dc. BS HR <100 bpm, on TR change >40 bpm	2	1	1	

Dc. BS HR <100 bpm, on TR change missing	14	5	16	
Dc. BS HR >= 100 bpm, on TR change =<20 bpm	14	13	20	
Dc. BS HR >= 100 bpm, on TR change >20 - =<40 bpm	6	12	26	
Dc. BS HR >= 100 bpm, on TR change >40 bpm	11	7	3	
Dc. BS HR >= 100 bpm, on TR change missing	3	1	7	
Dc. BS HR missing, on TR change missing	0	0	2	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Maximal On-Treatment Changes From Baseline in Vital Signs - Maximal Systolic Blood Pressure Increase/Decrease and Maximal Diastolic Blood Pressure Increase/Decrease

End point title	Number of Subjects With Maximal On-Treatment Changes From Baseline in Vital Signs - Maximal Systolic Blood Pressure Increase/Decrease and Maximal Diastolic Blood Pressure Increase/Decrease

End point description:

The number of subjects with maximal on-treatment changes from baseline (BS) in Increase (Ic.)/Decrease (Dc.) Systolic Blood Pressure (SBP) and diastolic blood pressure (DBP) (millimeter of mercury [mmHg]) were reported by using criteria: Ic./Dc. BS SBP <140 mmHg and >=140 mmHg, on maximal treatment (TR) change =<20 mmHg, >20 - =<40 mmHg, >40 mmHg and missing; Ic./Dc. BS SBP missing, on maximal treatment (TR) change missing; Ic./Dc. BS DBP <90 mmHg and >= 90 mmHg, on maximal TR change =<20 mmHg, >20 - =<40 mmHg, >40 mmHg and missing; Ic./Dc. BS DBP missing on maximal TR change missing. The Safety analysis set (Safety-AS) included all randomized subjects who were administered at least one dose of the study medication, that is (i.e.) avelumab or chemotherapy.

End point type	Secondary

End point timeframe:

Time from date of randomization up to data cutoff (assessed up to approximately 71.5 months)

End point values	Avelumab Biweekly	Avelumab Weekly	Chemotherapy	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	361	318	500	
Units: subjects				
Ic. BS SBP <140 mmHg, on TR change =<20 mmHg	219	209	278	
Ic. BS SBP <140 mmHg, on TR change >20 - =<40 mmHg	61	56	104	
Ic. BS SBP <140 mmHg, on TR change >40 mmHg	16	16	10	
Ic. BS SBP <140 mmHg, on TR change missing	14	4	21	
Ic. BS SBP >=140 mmHg, on TR change =<20 mmHg	41	26	78	

Ic. BS SBP>=140mmHg,onTR change>20-=<40mmHg	7	5	5	
Ic. BS SBP >=140 mmHg, on TR change >40 mmHg	0	0	1	
Ic. BS SBP > = 140 mmHg, on TR change missing	3	2	2	
Ic. BS SBP missing, on TR change missing	0	0	1	
Dc. BS SBP <140 mmHg, on TR change =<20 mmHg	220	204	322	
Dc. BS SBP <140 mmHg, on TR change >20 - =<40 mmHg	70	70	69	
Dc. BS SBP <140 mmHg, on TR change >40 mmHg	6	7	1	
Dc. BS SBP <140 mmHg, on TR change missing	14	4	21	
Dc. BS SBP >=140 mmHg, on TR change =<20 mmHg	11	6	32	
Dc. BS SBP>=140 mmHg, on TR change>20-=<40mmHg	25	15	34	
Dc. BS SBP >=140 mmHg, on TR change >40 mmHg	12	10	18	
Dc. BS SBP > = 140 mmHg, on TR change missing	3	2	2	
Dc. BS SBP missing, on TR change missing	0	0	1	
Ic. BS DBP <90 mmHg, on TR change =<20 mmHg	272	260	402	
Ic. BS DBP <90 mmHg, on TR change >20 - =<40 mmHg	48	37	45	
Ic. BS DBP <90 mmHg, on TR change >40 mmHg	0	1	1	
Ic. BS DBP <90 mmHg, on TR change missing	17	5	23	
Ic. BS DBP missing, on TR change missing	0	0	1	
Ic. BS DBP >=90 mmHg, on TR change =<20 mmHg	24	12	28	
Ic. BS DBP >=90 mmHg, on TR change >20 - =<40 mmHg	0	1	0	
Ic. BS DBP >=90 mmHg, on TR change >40 mmHg	0	1	0	
Ic. BS DBP >=90 mmHg, on TR change missing	0	1	0	
Dc. BS DBP <90 mmHg, on TR change =<20 mmHg	279	264	415	
Dc. BS DBP <90 mmHg, on TR change >20 - =<40 mmHg	38	33	32	
Dc. BS DBP <90 mmHg, on TR change >40 mmHg	3	1	1	
Dc. BS DBP <90 mmHg, on TR change missing	17	5	23	
Dc. BS DBP >=90 mmHg, on TR change =<20 mmHg	11	5	18	
Dc. BS DBP >=90 mmHg,on TR change >20 - =<40 mmHg	12	9	10	
Dc. BS DBP >=90 mmHg, on TR change >40 mmHg	1	0	0	
Dc. BS DBP >=90 mmHg, on TR change missing	0	1	0	
Dc. BS DBP missing, on TR change missing	0	0	1	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Maximal On-Treatment Changes From Baseline in Vital Signs - Maximal Respiration Rate Increase/Decrease

End point title	Number of Subjects With Maximal On-Treatment Changes From Baseline in Vital Signs - Maximal Respiration Rate Increase/Decrease

End point description:

The number of subjects with maximal on-treatment (TR) changes from baseline (BS) in Increase (Ic.)/Decrease (Dc.) maximal Respiration Rate (RR) were reported by using criteria: Ic./Dc. BS RR <20 breaths per minute (breaths/min), on TR change =<5 breaths/min, >5 - =<10 breaths/min, >10 breaths/min and missing. Ic./Dc. BS RR missing, on TR change missing. Ic./Dc. BS RR >=20 breaths/min, on TR change(chge) =<5 breaths/min, >5 - =<10 breaths/min, >10 breaths/min and missing. The Safety analysis set (Safety-AS) included all randomized subjects who were administered at least one dose of the study medication, that is (i.e.) avelumab or chemotherapy.

End point type	Secondary

End point timeframe:

Time from date of randomization up to data cutoff (assessed up to 71.5 months)

End point values	Avelumab Biweekly	Avelumab Weekly	Chemotherapy	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	361	318	500	
Units: subjects				
Ic.BS RR<20breaths/min, onTRchge=<5breath/min	221	224	306	
Ic.BS RR<20breaths/min, onTRchge>5-=<10breath/min	18	13	26	
Ic.BS RR<20breaths/min, onTRchge>10breath/min	1	1	2	
Ic.BS RR<20breaths/min, onTRchge missing	11	4	14	
Ic.BS RR>=20breaths/min,onTRchge=<5brea	89	68	124	
Ic.BS RR>=20breath/min,on TRchge>5-=<10breath/min	5	4	2	
Ic.BS RR>=20breath/min,on TRchge >10breath/min	3	1	0	
Ic. BS RR >=20 breath/min, on TR change missing	7	2	15	
Ic. BS RR missing, on TR change missing	6	1	11	
Dc.BS RR<20 breath/min,onTRchge=<5breaths/min	232	236	325	
Dc.BSRR<20 breath/min,onTR chge>5-=<10breath/min	8	2	8	

Dc.BSRR<20breath/min, onTRchge>10 breath/min	0	0	1	
Dc.BSRR<20breaths/min,onTRchange missing	11	4	14	
Dc.BSRR>=20breath/min,on TRch=<5 breath/min	79	58	101	
Dc.BSRR>=20breath/min,onTRchge>5-=<10breath/min	14	13	22	
Dc.BS RR>=20breath/min,onTRchge>10	4	2	3	
Dc.BS RR>=20breaths/min,onTRchange missing	7	2	15	
Dc.BS RRmissing, onTR change missing	6	1	11	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Potentially Clinically Significant Abnormalities (PCSA) in Electrocardiogram (ECG) Parameters

End point title	Number of Subjects With Potentially Clinically Significant Abnormalities (PCSA) in Electrocardiogram (ECG) Parameters

End point description:

ECG parameters included heart rate, PR interval, QRS interval, corrected QT interval using Bazett's formula (QTcB) and corrected QT interval using Fridericia's formula (QTcF). PCSA criteria for abnormal value of ECG parameters: any heart rate <= 50 bpm and decrease from baseline >=20 bpm , any hear rate >= 120 bpm and increase from baseline >= 20 bpm; PR interval: >= 220 milliseconds (ms) and increase from baseline >= 20 ms; QRS interval >= 120 ms; QTcF > 450 ms, > 480 ms, > 500 ms, QTcF increase from baseline > 30 ms and QTcF increase from baseline > 60 ms; QTcB > 450 ms, > 480 ms, > 500 ms, QTcB increase from baseline > 30 ms and QTcB increase from baseline > 60 ms. The Safety analysis set (Safety-AS) included all randomized subjects who were administered at least one dose of the study medication, that is (i.e.) avelumab or chemotherapy.

End point type	Secondary

End point timeframe:

Time from date of randomization up to data cutoff (assessed up to approximately 71.5 months)

End point values	Avelumab Biweekly	Avelumab Weekly	Chemotherapy	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	264	223	399	
Units: subjects				
Heart Rate<=50bpm&decrease from baseline>=20bpm	1	1	0	
Heart Rate>=120bpm&decrease from baseline>=20bpm	10	6	7	
PRinterval>=220ms&increase from baseline >=20ms	0	5	3	
QRS interval >= 120 ms	18	10	15	
QTcF > 450 ms	19	13	24	
QTcF > 480 ms	5	4	11	
QTcF > 500 ms	3	1	5	
QTcF increase from baseline > 30 ms	20	12	39	

QTcF increase from baseline > 60 ms	6	1	13	
QTcB > 450 ms	49	31	70	
QTcB > 480 ms	13	11	24	
QTcB > 500 ms	6	5	16	
QTcB increase from baseline > 30 ms	32	25	49	
QTcB increase from baseline > 60 ms	11	7	19	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Eastern Cooperative Oncology Group (ECOG) Performance: Baseline Score Versus (Vs) Worst Post-baseline Score

End point title	Number of Subjects With Eastern Cooperative Oncology Group (ECOG) Performance: Baseline Score Versus (Vs) Worst Post-baseline Score

End point description:

ECOG performance status measured to assess subjects performance status on a scale of 0 to 5, where 0 = Fully active, able to carry on all pre-disease activities without restriction; 1 = Restricted in physically strenuous activity, ambulatory and able to carry out light or sedentary work; 2 = Ambulatory and capable of all selfcare but unable to carry out any work activities; 3 = Capable of only limited self-care, confined to bed/chair for more than 50 percent of waking hours; 4 = Completely disabled, cannot carry on any self-care, totally confined to bed/chair; 5 = dead. ECOG performance status was reported in terms of number of participants with baseline value vs worst post-baseline value (that is [i.e.] highest score). The Safety analysis set (Safety-AS) included all randomized subjects who were administered at least one dose of the study medication, that is (i.e.) avelumab or chemotherapy.

End point type	Secondary

End point timeframe:

Time from date of randomization up to data cutoff (assessed up to approximately 71.5 months)

End point values	Avelumab Biweekly	Avelumab Weekly	Chemotherapy	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	361	318	500	
Units: subjects				
Baseline score0,worst post-baseline score0	50	35	84	
Baseline score0,worst post-baseline score1	56	49	83	
Baseline score0,worst post-baseline score2	8	9	11	
Baseline score0,worst post-baseline score3	1	7	4	
Baseline score0,worst post-baseline score4	1	0	0	
Baseline score0,worst post-baseline score5	0	0	1	
Baseline score0,worst post-baseline scoreMissing	6	4	4	
Baseline score1,worst post-baselinescore0	1	2	4	
Baseline score1,worst post-baseline score1	168	153	233	

Baseline score1,worst post-baseline score2	35	32	46	
Baseline score1,worst post-baseline score3	16	18	6	
Baseline score1,worst post-baseline score4	3	1	4	
Baseline score1,worst post-baseline score5	5	1	3	
Baseline score1, worst post-baselinescoreMissing	10	6	16	
Baseline score>=2,worst post-baseline score0	0	0	0	
Baseline score>=2,worst post-baseline score1	0	0	0	
Baseline score>=2,worst post-baseline score2	0	0	0	
Baseline score>=2,worst post-baseline score3	1	0	0	
Baseline score>=2,worst post-baseline score4	0	0	0	
Baseline score>=2,worst post-baseline score5	0	1	0	
Baseline score>=2,worst post-baseline scoremissing	0	0	0	
Baseline score missing,worst post-baseline score0	0	0	0	
Baseline score missing,worst post-baseline score1	0	0	1	
Baseline score missing,worst post-baseline score2	0	0	0	
Baseline score missing,worst post-baseline score3	0	0	0	
Baseline score missing,worst post-baseline score4	0	0	0	
Baseline score missing,worst post-baseline score5	0	0	0	
Baseline score&worst post-baselinescoremissing	0	0	0	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With At Least One Positive Anti-Drug Antibodies (ADAs) and Neutralizing Antibodies (NAbs) for Avelumab

End point title	Number of Subjects With At Least One Positive Anti-Drug Antibodies (ADAs) and Neutralizing Antibodies (NAbs) for Avelumab[23]

End point description:

Serum samples were analyzed by a validated electrochemiluminesce immunoassay to detect the presence of antidrug antibodies (ADA). Samples that screened positive were subsequently tested in a confirmatory assay were tested for neutralizing antibodies (nAb). Number of subjects with ADA or nAb positive results for Avelumab were reported. The Safety analysis set (Safety-AS) included all randomized subjects who were administered at least one dose of the study medication, that is (i.e.) avelumab or chemotherapy.

End point type	Secondary

End point timeframe:

Time from date of randomization up to data cutoff (assessed up to approximately 71.5 months)

Notes:

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

Justification: Endpoint only compares the data of Avelumab and Chemotherapy groups

End point values	Avelumab Biweekly	Avelumab Weekly		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	360	318		
Units: subjects				
ADAs to Avelumab	66	38		
NAbs to Avelumab	43	18		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Time from date of randomization up to data cutoff (assessed up to approximately 71.5 months)

Adverse event reporting additional description:

Only subjects who received study medication were included in the analysis of adverse events. All randomized subjects were included in the analysis of all-cause mortality.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	24.0

Reporting groups

Reporting group title	Avelumab Biweekly

Reporting group description:

Subjects received Avelumab at a dose of 10 milligrams per kilogram (mg/kg) as a 1-hour (-10/+20 minutes) intravenous (IV) infusion once every 2 weeks until disease progression or unacceptable toxicities.

Reporting group title	Chemotherapy

Reporting group description:

Subjects with tumor of nonsquamous histology received Pemetrexed in combination with Cisplatin (75 mg/m^2) administered on Day 1 of each cycle or pemetrexed (500 mg/m^2) in combination with carboplatin AUC 6 milligrams per milliliter minutes administered on Day 1 of each cycle. Subjects who were assigned pemetrexed could continue to receive pemetrexed as a maintenance therapy after 4 cycles of platinum-based chemotherapy if their disease had not progressed.Subjects with tumor of squamous histology received Paclitaxel (200 mg/m^2) plus carboplatin (AUC 6 mg/mL * min administered on Day 1 of each cycle) or Gemcitabine (1250 mg/m^2 administered on Day 1 and Day 8 of each cycle) plus cisplatin (75 mg/m^2) or Gemcitabine (1000 mg/m^2 administered on Day 1 and Day 8 of each cycle) plus carboplatin (AUC 5 mg/mL * min) in 3-week cycles up to a maximum of 6 cycles of IV injection or until disease progression or unacceptable toxicities.

Reporting group title	Avelumab Weekly

Reporting group description:

Subjects received Avelumab at a dose of 10 mg/kg as a 1-hour (-10/+20 minutes) IV infusion every week for 12 consecutive weeks, followed by Avelumab at a dose of 10 mg/kg once every 2 weeks until disease progression or unacceptable toxicities.

Serious adverse events	Avelumab Biweekly	Chemotherapy	Avelumab Weekly
Total subjects affected by serious adverse events			
subjects affected / exposed	181 / 361 (50.14%)	195 / 500 (39.00%)	143 / 318 (44.97%)
number of deaths (all causes)	279	405	237
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Lymphangiosis carcinomatosa			
subjects affected / exposed	1 / 361 (0.28%)	0 / 500 (0.00%)	0 / 318 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Laryngeal cancer			

subjects affected / exposed	1 / 361 (0.28%)	0 / 500 (0.00%)	0 / 318 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metastases to central nervous system			
subjects affected / exposed	2 / 361 (0.55%)	2 / 500 (0.40%)	2 / 318 (0.63%)
occurrences causally related to treatment / all	0 / 2	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 1	0 / 1	0 / 1
Cancer pain			
subjects affected / exposed	3 / 361 (0.83%)	3 / 500 (0.60%)	1 / 318 (0.31%)
occurrences causally related to treatment / all	0 / 3	0 / 3	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Malignant pleural effusion			
subjects affected / exposed	1 / 361 (0.28%)	0 / 500 (0.00%)	1 / 318 (0.31%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Metastases to bone			
subjects affected / exposed	1 / 361 (0.28%)	1 / 500 (0.20%)	0 / 318 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Squamous cell carcinoma of the oral cavity			
subjects affected / exposed	1 / 361 (0.28%)	0 / 500 (0.00%)	0 / 318 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Adenocarcinoma of colon			
subjects affected / exposed	0 / 361 (0.00%)	0 / 500 (0.00%)	2 / 318 (0.63%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tumor compression			
subjects affected / exposed	0 / 361 (0.00%)	0 / 500 (0.00%)	1 / 318 (0.31%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Seborrhoeic keratosis			

subjects affected / exposed	0 / 361 (0.00%)	1 / 500 (0.20%)	0 / 318 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metastases to meninges			
subjects affected / exposed	0 / 361 (0.00%)	1 / 500 (0.20%)	0 / 318 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metastases to lymph nodes			
subjects affected / exposed	0 / 361 (0.00%)	0 / 500 (0.00%)	1 / 318 (0.31%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Malignant ascites			
subjects affected / exposed	0 / 361 (0.00%)	1 / 500 (0.20%)	0 / 318 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Duodenal neoplasm			
subjects affected / exposed	0 / 361 (0.00%)	0 / 500 (0.00%)	1 / 318 (0.31%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Tumor hemorrhage			
subjects affected / exposed	0 / 361 (0.00%)	0 / 500 (0.00%)	1 / 318 (0.31%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Tumor pain			
subjects affected / exposed	0 / 361 (0.00%)	0 / 500 (0.00%)	1 / 318 (0.31%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Superior vena cava syndrome			
subjects affected / exposed	3 / 361 (0.83%)	0 / 500 (0.00%)	0 / 318 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Aortic stenosis			

subjects affected / exposed	1 / 361 (0.28%)	0 / 500 (0.00%)	0 / 318 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Shock hemorrhagic			
subjects affected / exposed	1 / 361 (0.28%)	1 / 500 (0.20%)	1 / 318 (0.31%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 1	0 / 1
Peripheral ischemia			
subjects affected / exposed	1 / 361 (0.28%)	0 / 500 (0.00%)	1 / 318 (0.31%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peripheral arterial occlusive disease			
subjects affected / exposed	1 / 361 (0.28%)	1 / 500 (0.20%)	0 / 318 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypotension			
subjects affected / exposed	1 / 361 (0.28%)	1 / 500 (0.20%)	2 / 318 (0.63%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thrombosis			
subjects affected / exposed	1 / 361 (0.28%)	0 / 500 (0.00%)	0 / 318 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Inferior vena caval occlusion			
subjects affected / exposed	0 / 361 (0.00%)	0 / 500 (0.00%)	1 / 318 (0.31%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Deep vein thrombosis			
subjects affected / exposed	0 / 361 (0.00%)	1 / 500 (0.20%)	0 / 318 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Arterial thrombosis			

subjects affected / exposed	0 / 361 (0.00%)	1 / 500 (0.20%)	0 / 318 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Venous thrombosis limb			
subjects affected / exposed	1 / 361 (0.28%)	0 / 500 (0.00%)	0 / 318 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Orthostatic hypotension			
subjects affected / exposed	0 / 361 (0.00%)	1 / 500 (0.20%)	0 / 318 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peripheral artery stenosis			
subjects affected / exposed	0 / 361 (0.00%)	0 / 500 (0.00%)	1 / 318 (0.31%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peripheral artery thrombosis			
subjects affected / exposed	0 / 361 (0.00%)	0 / 500 (0.00%)	1 / 318 (0.31%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	1 / 361 (0.28%)	8 / 500 (1.60%)	3 / 318 (0.94%)
occurrences causally related to treatment / all	1 / 1	3 / 8	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Disease progression			
subjects affected / exposed	33 / 361 (9.14%)	22 / 500 (4.40%)	18 / 318 (5.66%)
occurrences causally related to treatment / all	0 / 33	0 / 22	1 / 18
deaths causally related to treatment / all	0 / 26	0 / 21	0 / 17
Fatigue			
subjects affected / exposed	4 / 361 (1.11%)	1 / 500 (0.20%)	0 / 318 (0.00%)
occurrences causally related to treatment / all	1 / 4	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Asthenia			

subjects affected / exposed	2 / 361 (0.55%)	5 / 500 (1.00%)	1 / 318 (0.31%)
occurrences causally related to treatment / all	1 / 2	3 / 5	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chest pain			
subjects affected / exposed	1 / 361 (0.28%)	1 / 500 (0.20%)	0 / 318 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Death			
subjects affected / exposed	2 / 361 (0.55%)	2 / 500 (0.40%)	2 / 318 (0.63%)
occurrences causally related to treatment / all	0 / 2	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 2	0 / 2	0 / 2
Sudden death			
subjects affected / exposed	1 / 361 (0.28%)	1 / 500 (0.20%)	3 / 318 (0.94%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 3
deaths causally related to treatment / all	0 / 1	0 / 1	0 / 3
General physical health deterioration			
subjects affected / exposed	0 / 361 (0.00%)	0 / 500 (0.00%)	3 / 318 (0.94%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 2
Mucosal inflammation			
subjects affected / exposed	0 / 361 (0.00%)	1 / 500 (0.20%)	0 / 318 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Multiple organ dysfunction syndrome			
subjects affected / exposed	0 / 361 (0.00%)	2 / 500 (0.40%)	0 / 318 (0.00%)
occurrences causally related to treatment / all	0 / 0	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 2	0 / 0
Sudden cardiac death			
subjects affected / exposed	0 / 361 (0.00%)	1 / 500 (0.20%)	1 / 318 (0.31%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 1
Systemic inflammatory response syndrome			

subjects affected / exposed	0 / 361 (0.00%)	1 / 500 (0.20%)	0 / 318 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peripheral swelling			
subjects affected / exposed	0 / 361 (0.00%)	1 / 500 (0.20%)	0 / 318 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune system disorders			
Cytokine release syndrome			
subjects affected / exposed	3 / 361 (0.83%)	0 / 500 (0.00%)	0 / 318 (0.00%)
occurrences causally related to treatment / all	3 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
Anaphylactic shock			
subjects affected / exposed	0 / 361 (0.00%)	1 / 500 (0.20%)	0 / 318 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anaphylactic reaction			
subjects affected / exposed	1 / 361 (0.28%)	1 / 500 (0.20%)	0 / 318 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Contrast media allergy			
subjects affected / exposed	0 / 361 (0.00%)	0 / 500 (0.00%)	1 / 318 (0.31%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypersensitivity			
subjects affected / exposed	0 / 361 (0.00%)	0 / 500 (0.00%)	3 / 318 (0.94%)
occurrences causally related to treatment / all	0 / 0	0 / 0	3 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Pleural effusion			
subjects affected / exposed	11 / 361 (3.05%)	7 / 500 (1.40%)	3 / 318 (0.94%)
occurrences causally related to treatment / all	0 / 11	0 / 7	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Dyspnea			
subjects affected / exposed	9 / 361 (2.49%)	8 / 500 (1.60%)	5 / 318 (1.57%)
occurrences causally related to treatment / all	0 / 9	1 / 8	1 / 5
deaths causally related to treatment / all	0 / 2	0 / 1	1 / 1
Chronic obstructive pulmonary disease			
subjects affected / exposed	5 / 361 (1.39%)	3 / 500 (0.60%)	6 / 318 (1.89%)
occurrences causally related to treatment / all	0 / 5	0 / 3	0 / 6
deaths causally related to treatment / all	0 / 2	0 / 2	0 / 1
Pulmonary embolism			
subjects affected / exposed	6 / 361 (1.66%)	6 / 500 (1.20%)	5 / 318 (1.57%)
occurrences causally related to treatment / all	0 / 6	0 / 6	0 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonitis			
subjects affected / exposed	8 / 361 (2.22%)	0 / 500 (0.00%)	5 / 318 (1.57%)
occurrences causally related to treatment / all	8 / 8	0 / 0	3 / 5
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
Respiratory failure			
subjects affected / exposed	5 / 361 (1.39%)	4 / 500 (0.80%)	2 / 318 (0.63%)
occurrences causally related to treatment / all	0 / 5	0 / 4	0 / 2
deaths causally related to treatment / all	0 / 4	0 / 3	0 / 2
Pulmonary haemorrhage			
subjects affected / exposed	2 / 361 (0.55%)	2 / 500 (0.40%)	4 / 318 (1.26%)
occurrences causally related to treatment / all	0 / 2	0 / 2	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 2
Haemoptysis			
subjects affected / exposed	3 / 361 (0.83%)	3 / 500 (0.60%)	4 / 318 (1.26%)
occurrences causally related to treatment / all	0 / 3	0 / 3	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia aspiration			
subjects affected / exposed	2 / 361 (0.55%)	1 / 500 (0.20%)	0 / 318 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Stridor			

subjects affected / exposed	1 / 361 (0.28%)	0 / 500 (0.00%)	0 / 318 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Idiopathic pulmonary fibrosis			
subjects affected / exposed	1 / 361 (0.28%)	0 / 500 (0.00%)	0 / 318 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pleurisy			
subjects affected / exposed	1 / 361 (0.28%)	0 / 500 (0.00%)	0 / 318 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumothorax			
subjects affected / exposed	1 / 361 (0.28%)	1 / 500 (0.20%)	2 / 318 (0.63%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 1	0 / 1	0 / 2
Pulmonary congestion			
subjects affected / exposed	1 / 361 (0.28%)	0 / 500 (0.00%)	0 / 318 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dysphonia			
subjects affected / exposed	1 / 361 (0.28%)	0 / 500 (0.00%)	0 / 318 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute pulmonary oedema			
subjects affected / exposed	0 / 361 (0.00%)	0 / 500 (0.00%)	1 / 318 (0.31%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aspiration			
subjects affected / exposed	0 / 361 (0.00%)	1 / 500 (0.20%)	0 / 318 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Bronchospasm			

subjects affected / exposed	0 / 361 (0.00%)	1 / 500 (0.20%)	0 / 318 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyspnoea exertional			
subjects affected / exposed	0 / 361 (0.00%)	0 / 500 (0.00%)	1 / 318 (0.31%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary oedema			
subjects affected / exposed	0 / 361 (0.00%)	1 / 500 (0.20%)	0 / 318 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemothorax			
subjects affected / exposed	0 / 361 (0.00%)	1 / 500 (0.20%)	0 / 318 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypoxia			
subjects affected / exposed	0 / 361 (0.00%)	2 / 500 (0.40%)	2 / 318 (0.63%)
occurrences causally related to treatment / all	0 / 0	1 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Interstitial lung disease			
subjects affected / exposed	0 / 361 (0.00%)	0 / 500 (0.00%)	2 / 318 (0.63%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 2
Epistaxis			
subjects affected / exposed	0 / 361 (0.00%)	1 / 500 (0.20%)	0 / 318 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory depression			
subjects affected / exposed	0 / 361 (0.00%)	1 / 500 (0.20%)	0 / 318 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Confusional state			

subjects affected / exposed	2 / 361 (0.55%)	0 / 500 (0.00%)	1 / 318 (0.31%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Agitation			
subjects affected / exposed	1 / 361 (0.28%)	0 / 500 (0.00%)	0 / 318 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anxiety			
subjects affected / exposed	0 / 361 (0.00%)	1 / 500 (0.20%)	0 / 318 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Breath holding			
subjects affected / exposed	0 / 361 (0.00%)	0 / 500 (0.00%)	1 / 318 (0.31%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Suicide attempt			
subjects affected / exposed	0 / 361 (0.00%)	1 / 500 (0.20%)	0 / 318 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Platelet count decreased			
subjects affected / exposed	0 / 361 (0.00%)	7 / 500 (1.40%)	0 / 318 (0.00%)
occurrences causally related to treatment / all	0 / 0	7 / 7	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Alanine aminotransferase increased			
subjects affected / exposed	3 / 361 (0.83%)	0 / 500 (0.00%)	2 / 318 (0.63%)
occurrences causally related to treatment / all	2 / 3	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood sodium decreased			
subjects affected / exposed	2 / 361 (0.55%)	0 / 500 (0.00%)	0 / 318 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aspartate aminotransferase increased			

subjects affected / exposed	1 / 361 (0.28%)	0 / 500 (0.00%)	1 / 318 (0.31%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood bilirubin increased			
subjects affected / exposed	1 / 361 (0.28%)	0 / 500 (0.00%)	0 / 318 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatic enzyme increased			
subjects affected / exposed	0 / 361 (0.00%)	0 / 500 (0.00%)	1 / 318 (0.31%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ejection fraction decreased			
subjects affected / exposed	0 / 361 (0.00%)	1 / 500 (0.20%)	0 / 318 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
White blood cell count decreased			
subjects affected / exposed	0 / 361 (0.00%)	1 / 500 (0.20%)	0 / 318 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Weight decreased			
subjects affected / exposed	0 / 361 (0.00%)	0 / 500 (0.00%)	1 / 318 (0.31%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neutrophil count decreased			
subjects affected / exposed	0 / 361 (0.00%)	2 / 500 (0.40%)	0 / 318 (0.00%)
occurrences causally related to treatment / all	0 / 0	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gamma-glutamyltransferase increased			
subjects affected / exposed	1 / 361 (0.28%)	0 / 500 (0.00%)	0 / 318 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Transaminases increased			

subjects affected / exposed	1 / 361 (0.28%)	0 / 500 (0.00%)	0 / 318 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Troponin T increased			
subjects affected / exposed	1 / 361 (0.28%)	0 / 500 (0.00%)	0 / 318 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood creatine phosphokinase increased			
subjects affected / exposed	0 / 361 (0.00%)	0 / 500 (0.00%)	1 / 318 (0.31%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood creatinine increased			
subjects affected / exposed	0 / 361 (0.00%)	1 / 500 (0.20%)	0 / 318 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Infusion related reaction			
subjects affected / exposed	11 / 361 (3.05%)	0 / 500 (0.00%)	7 / 318 (2.20%)
occurrences causally related to treatment / all	11 / 11	0 / 0	7 / 7
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Femur fracture			
subjects affected / exposed	1 / 361 (0.28%)	0 / 500 (0.00%)	2 / 318 (0.63%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fracture			
subjects affected / exposed	2 / 361 (0.55%)	0 / 500 (0.00%)	0 / 318 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cervical vertebral fracture			
subjects affected / exposed	1 / 361 (0.28%)	1 / 500 (0.20%)	0 / 318 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Post procedural discomfort			

subjects affected / exposed	1 / 361 (0.28%)	0 / 500 (0.00%)	0 / 318 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rib fracture			
subjects affected / exposed	1 / 361 (0.28%)	1 / 500 (0.20%)	0 / 318 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin laceration			
subjects affected / exposed	1 / 361 (0.28%)	0 / 500 (0.00%)	1 / 318 (0.31%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal cord injury			
subjects affected / exposed	1 / 361 (0.28%)	0 / 500 (0.00%)	0 / 318 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Toxicity to various agents			
subjects affected / exposed	1 / 361 (0.28%)	0 / 500 (0.00%)	0 / 318 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Wrist fracture			
subjects affected / exposed	1 / 361 (0.28%)	0 / 500 (0.00%)	0 / 318 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Femoral neck fracture			
subjects affected / exposed	0 / 361 (0.00%)	1 / 500 (0.20%)	0 / 318 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fibula fracture			
subjects affected / exposed	0 / 361 (0.00%)	0 / 500 (0.00%)	1 / 318 (0.31%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Head injury			

subjects affected / exposed	0 / 361 (0.00%)	0 / 500 (0.00%)	1 / 318 (0.31%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Radiation necrosis			
subjects affected / exposed	0 / 361 (0.00%)	1 / 500 (0.20%)	1 / 318 (0.31%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal fracture			
subjects affected / exposed	0 / 361 (0.00%)	0 / 500 (0.00%)	1 / 318 (0.31%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal compression fracture			
subjects affected / exposed	0 / 361 (0.00%)	1 / 500 (0.20%)	1 / 318 (0.31%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Soft tissue injury			
subjects affected / exposed	0 / 361 (0.00%)	1 / 500 (0.20%)	0 / 318 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Congenital, familial and genetic disorders			
Aplasia			
subjects affected / exposed	0 / 361 (0.00%)	1 / 500 (0.20%)	0 / 318 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Cardiac arrest			
subjects affected / exposed	2 / 361 (0.55%)	3 / 500 (0.60%)	1 / 318 (0.31%)
occurrences causally related to treatment / all	0 / 2	0 / 3	0 / 1
deaths causally related to treatment / all	0 / 2	0 / 3	0 / 1
Cardiac failure			
subjects affected / exposed	2 / 361 (0.55%)	4 / 500 (0.80%)	0 / 318 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 4	0 / 0
deaths causally related to treatment / all	0 / 2	0 / 2	0 / 0

Sinus node dysfunction			
subjects affected / exposed	1 / 361 (0.28%)	0 / 500 (0.00%)	0 / 318 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myocarditis			
subjects affected / exposed	1 / 361 (0.28%)	0 / 500 (0.00%)	1 / 318 (0.31%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardio-respiratory arrest			
subjects affected / exposed	1 / 361 (0.28%)	1 / 500 (0.20%)	1 / 318 (0.31%)
occurrences causally related to treatment / all	0 / 1	1 / 1	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 1
Cardiac tamponade			
subjects affected / exposed	1 / 361 (0.28%)	1 / 500 (0.20%)	1 / 318 (0.31%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 1	0 / 0
Atrioventricular block complete			
subjects affected / exposed	1 / 361 (0.28%)	0 / 500 (0.00%)	0 / 318 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial flutter			
subjects affected / exposed	1 / 361 (0.28%)	0 / 500 (0.00%)	0 / 318 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pericardial effusion			
subjects affected / exposed	2 / 361 (0.55%)	1 / 500 (0.20%)	3 / 318 (0.94%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute coronary syndrome			
subjects affected / exposed	1 / 361 (0.28%)	1 / 500 (0.20%)	0 / 318 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Acute myocardial infarction			

subjects affected / exposed	1 / 361 (0.28%)	1 / 500 (0.20%)	1 / 318 (0.31%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ventricle rupture			
subjects affected / exposed	1 / 361 (0.28%)	0 / 500 (0.00%)	0 / 318 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Angina pectoris			
subjects affected / exposed	0 / 361 (0.00%)	1 / 500 (0.20%)	0 / 318 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial fibrillation			
subjects affected / exposed	0 / 361 (0.00%)	4 / 500 (0.80%)	1 / 318 (0.31%)
occurrences causally related to treatment / all	0 / 0	0 / 4	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bradycardia			
subjects affected / exposed	0 / 361 (0.00%)	1 / 500 (0.20%)	0 / 318 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac failure congestive			
subjects affected / exposed	0 / 361 (0.00%)	0 / 500 (0.00%)	1 / 318 (0.31%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Cardiac hypertrophy			
subjects affected / exposed	0 / 361 (0.00%)	0 / 500 (0.00%)	1 / 318 (0.31%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Cardiopulmonary failure			
subjects affected / exposed	0 / 361 (0.00%)	0 / 500 (0.00%)	1 / 318 (0.31%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Myocardial infarction			

subjects affected / exposed	0 / 361 (0.00%)	2 / 500 (0.40%)	1 / 318 (0.31%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 1
Pericarditis			
subjects affected / exposed	0 / 361 (0.00%)	1 / 500 (0.20%)	0 / 318 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Right ventricular failure			
subjects affected / exposed	0 / 361 (0.00%)	1 / 500 (0.20%)	0 / 318 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Supraventricular tachycardia			
subjects affected / exposed	0 / 361 (0.00%)	1 / 500 (0.20%)	0 / 318 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tachycardia			
subjects affected / exposed	0 / 361 (0.00%)	1 / 500 (0.20%)	0 / 318 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Toxic cardiomyopathy			
subjects affected / exposed	0 / 361 (0.00%)	1 / 500 (0.20%)	0 / 318 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ventricular extrasystoles			
subjects affected / exposed	0 / 361 (0.00%)	1 / 500 (0.20%)	0 / 318 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Cerebral infarction			
subjects affected / exposed	4 / 361 (1.11%)	1 / 500 (0.20%)	3 / 318 (0.94%)
occurrences causally related to treatment / all	0 / 4	0 / 1	0 / 3
deaths causally related to treatment / all	0 / 2	0 / 0	0 / 1
Epilepsy			

subjects affected / exposed	1 / 361 (0.28%)	0 / 500 (0.00%)	0 / 318 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Brain oedema			
subjects affected / exposed	1 / 361 (0.28%)	1 / 500 (0.20%)	1 / 318 (0.31%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebrovascular accident			
subjects affected / exposed	1 / 361 (0.28%)	1 / 500 (0.20%)	0 / 318 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Coma			
subjects affected / exposed	1 / 361 (0.28%)	0 / 500 (0.00%)	0 / 318 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dysarthria			
subjects affected / exposed	1 / 361 (0.28%)	0 / 500 (0.00%)	0 / 318 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Brachial plexopathy			
subjects affected / exposed	1 / 361 (0.28%)	0 / 500 (0.00%)	0 / 318 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorder			
subjects affected / exposed	1 / 361 (0.28%)	0 / 500 (0.00%)	0 / 318 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ischaemic stroke			
subjects affected / exposed	1 / 361 (0.28%)	2 / 500 (0.40%)	1 / 318 (0.31%)
occurrences causally related to treatment / all	0 / 1	1 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Hydrocephalus			

subjects affected / exposed	1 / 361 (0.28%)	0 / 500 (0.00%)	0 / 318 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hemiparesis			
subjects affected / exposed	1 / 361 (0.28%)	0 / 500 (0.00%)	0 / 318 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cognitive disorder			
subjects affected / exposed	0 / 361 (0.00%)	1 / 500 (0.20%)	0 / 318 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Radiculopathy			
subjects affected / exposed	1 / 361 (0.28%)	0 / 500 (0.00%)	0 / 318 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal cord compression			
subjects affected / exposed	1 / 361 (0.28%)	0 / 500 (0.00%)	0 / 318 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Carotid artery stenosis			
subjects affected / exposed	0 / 361 (0.00%)	0 / 500 (0.00%)	1 / 318 (0.31%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Facial paralysis			
subjects affected / exposed	1 / 361 (0.28%)	0 / 500 (0.00%)	0 / 318 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Seizure			
subjects affected / exposed	0 / 361 (0.00%)	0 / 500 (0.00%)	1 / 318 (0.31%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Partial seizures			

subjects affected / exposed	0 / 361 (0.00%)	1 / 500 (0.20%)	0 / 318 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myasthenic syndrome			
subjects affected / exposed	0 / 361 (0.00%)	0 / 500 (0.00%)	1 / 318 (0.31%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Lethargy			
subjects affected / exposed	0 / 361 (0.00%)	0 / 500 (0.00%)	1 / 318 (0.31%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Headache			
subjects affected / exposed	0 / 361 (0.00%)	0 / 500 (0.00%)	1 / 318 (0.31%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Transient ischaemic attack			
subjects affected / exposed	0 / 361 (0.00%)	1 / 500 (0.20%)	0 / 318 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Febrile neutropenia			
subjects affected / exposed	0 / 361 (0.00%)	13 / 500 (2.60%)	0 / 318 (0.00%)
occurrences causally related to treatment / all	0 / 0	12 / 13	0 / 0
deaths causally related to treatment / all	0 / 0	2 / 2	0 / 0
Anaemia			
subjects affected / exposed	4 / 361 (1.11%)	19 / 500 (3.80%)	2 / 318 (0.63%)
occurrences causally related to treatment / all	1 / 4	19 / 19	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neutropenia			
subjects affected / exposed	0 / 361 (0.00%)	6 / 500 (1.20%)	0 / 318 (0.00%)
occurrences causally related to treatment / all	0 / 0	6 / 6	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancytopenia			

subjects affected / exposed	0 / 361 (0.00%)	7 / 500 (1.40%)	0 / 318 (0.00%)
occurrences causally related to treatment / all	0 / 0	7 / 7	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thrombocytopenia			
subjects affected / exposed	0 / 361 (0.00%)	5 / 500 (1.00%)	1 / 318 (0.31%)
occurrences causally related to treatment / all	0 / 0	5 / 5	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lymphopenia			
subjects affected / exposed	0 / 361 (0.00%)	1 / 500 (0.20%)	0 / 318 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haematotoxicity			
subjects affected / exposed	0 / 361 (0.00%)	1 / 500 (0.20%)	0 / 318 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myelosuppression			
subjects affected / exposed	0 / 361 (0.00%)	2 / 500 (0.40%)	0 / 318 (0.00%)
occurrences causally related to treatment / all	0 / 0	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	2 / 361 (0.55%)	0 / 500 (0.00%)	1 / 318 (0.31%)
occurrences causally related to treatment / all	0 / 2	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
Macular fibrosis			
subjects affected / exposed	1 / 361 (0.28%)	0 / 500 (0.00%)	0 / 318 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Swelling of eyelid			
subjects affected / exposed	0 / 361 (0.00%)	1 / 500 (0.20%)	0 / 318 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cataract			

subjects affected / exposed	1 / 361 (0.28%)	0 / 500 (0.00%)	0 / 318 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal pain upper			
subjects affected / exposed	4 / 361 (1.11%)	0 / 500 (0.00%)	0 / 318 (0.00%)
occurrences causally related to treatment / all	0 / 4	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea			
subjects affected / exposed	4 / 361 (1.11%)	3 / 500 (0.60%)	4 / 318 (1.26%)
occurrences causally related to treatment / all	3 / 4	1 / 3	4 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			
subjects affected / exposed	2 / 361 (0.55%)	9 / 500 (1.80%)	0 / 318 (0.00%)
occurrences causally related to treatment / all	2 / 2	2 / 9	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haematochezia			
subjects affected / exposed	1 / 361 (0.28%)	0 / 500 (0.00%)	0 / 318 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal inflammation			
subjects affected / exposed	1 / 361 (0.28%)	0 / 500 (0.00%)	0 / 318 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dysphagia			
subjects affected / exposed	1 / 361 (0.28%)	0 / 500 (0.00%)	1 / 318 (0.31%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nausea			
subjects affected / exposed	2 / 361 (0.55%)	2 / 500 (0.40%)	2 / 318 (0.63%)
occurrences causally related to treatment / all	2 / 2	2 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colitis			

subjects affected / exposed	1 / 361 (0.28%)	2 / 500 (0.40%)	1 / 318 (0.31%)
occurrences causally related to treatment / all	1 / 1	2 / 2	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Incarcerated inguinal hernia			
subjects affected / exposed	0 / 361 (0.00%)	1 / 500 (0.20%)	0 / 318 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal haemorrhage			
subjects affected / exposed	0 / 361 (0.00%)	3 / 500 (0.60%)	0 / 318 (0.00%)
occurrences causally related to treatment / all	0 / 0	2 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	1 / 1	0 / 0
Gastric ulcer			
subjects affected / exposed	0 / 361 (0.00%)	1 / 500 (0.20%)	0 / 318 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	1 / 1	0 / 0
Gastric haemorrhage			
subjects affected / exposed	0 / 361 (0.00%)	1 / 500 (0.20%)	0 / 318 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Constipation			
subjects affected / exposed	0 / 361 (0.00%)	2 / 500 (0.40%)	0 / 318 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Autoimmune colitis			
subjects affected / exposed	0 / 361 (0.00%)	0 / 500 (0.00%)	1 / 318 (0.31%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal pain			
subjects affected / exposed	0 / 361 (0.00%)	1 / 500 (0.20%)	0 / 318 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mechanical ileus			

subjects affected / exposed	1 / 361 (0.28%)	0 / 500 (0.00%)	0 / 318 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Large intestinal ulcer			
subjects affected / exposed	1 / 361 (0.28%)	0 / 500 (0.00%)	0 / 318 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ileus			
subjects affected / exposed	1 / 361 (0.28%)	0 / 500 (0.00%)	1 / 318 (0.31%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Inflammatory bowel disease			
subjects affected / exposed	0 / 361 (0.00%)	0 / 500 (0.00%)	1 / 318 (0.31%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper gastrointestinal haemorrhage			
subjects affected / exposed	0 / 361 (0.00%)	1 / 500 (0.20%)	0 / 318 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Stomatitis			
subjects affected / exposed	0 / 361 (0.00%)	0 / 500 (0.00%)	1 / 318 (0.31%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intestinal obstruction			
subjects affected / exposed	0 / 361 (0.00%)	2 / 500 (0.40%)	0 / 318 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatitis			
subjects affected / exposed	0 / 361 (0.00%)	1 / 500 (0.20%)	0 / 318 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Large intestine polyp			

subjects affected / exposed	0 / 361 (0.00%)	0 / 500 (0.00%)	1 / 318 (0.31%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intussusception			
subjects affected / exposed	0 / 361 (0.00%)	1 / 500 (0.20%)	0 / 318 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Small intestinal obstruction			
subjects affected / exposed	0 / 361 (0.00%)	0 / 500 (0.00%)	1 / 318 (0.31%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	3 / 361 (0.83%)	1 / 500 (0.20%)	0 / 318 (0.00%)
occurrences causally related to treatment / all	1 / 3	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Biliary obstruction			
subjects affected / exposed	0 / 361 (0.00%)	1 / 500 (0.20%)	0 / 318 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholecystitis acute			
subjects affected / exposed	0 / 361 (0.00%)	1 / 500 (0.20%)	0 / 318 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune-mediated hepatitis			
subjects affected / exposed	0 / 361 (0.00%)	0 / 500 (0.00%)	1 / 318 (0.31%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatic failure			
subjects affected / exposed	0 / 361 (0.00%)	0 / 500 (0.00%)	1 / 318 (0.31%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatic function abnormal			

subjects affected / exposed	0 / 361 (0.00%)	1 / 500 (0.20%)	0 / 318 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatitis			
subjects affected / exposed	0 / 361 (0.00%)	0 / 500 (0.00%)	1 / 318 (0.31%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatitis toxic			
subjects affected / exposed	0 / 361 (0.00%)	1 / 500 (0.20%)	0 / 318 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatic cytolysis			
subjects affected / exposed	0 / 361 (0.00%)	1 / 500 (0.20%)	0 / 318 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	1 / 1	0 / 0
Jaundice			
subjects affected / exposed	0 / 361 (0.00%)	0 / 500 (0.00%)	1 / 318 (0.31%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	2 / 361 (0.55%)	0 / 500 (0.00%)	0 / 318 (0.00%)
occurrences causally related to treatment / all	2 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urticaria			
subjects affected / exposed	0 / 361 (0.00%)	2 / 500 (0.40%)	0 / 318 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Angioedema			
subjects affected / exposed	0 / 361 (0.00%)	1 / 500 (0.20%)	0 / 318 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rash maculo-papular			

subjects affected / exposed	1 / 361 (0.28%)	0 / 500 (0.00%)	0 / 318 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rash macular			
subjects affected / exposed	1 / 361 (0.28%)	0 / 500 (0.00%)	0 / 318 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dermatitis exfoliative generalized			
subjects affected / exposed	1 / 361 (0.28%)	0 / 500 (0.00%)	0 / 318 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lichenoid keratosis			
subjects affected / exposed	0 / 361 (0.00%)	0 / 500 (0.00%)	1 / 318 (0.31%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Renal failure			
subjects affected / exposed	0 / 361 (0.00%)	2 / 500 (0.40%)	0 / 318 (0.00%)
occurrences causally related to treatment / all	0 / 0	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	1 / 1	0 / 0
Nephropathy			
subjects affected / exposed	0 / 361 (0.00%)	1 / 500 (0.20%)	0 / 318 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nephritis			
subjects affected / exposed	1 / 361 (0.28%)	0 / 500 (0.00%)	0 / 318 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute kidney injury			
subjects affected / exposed	2 / 361 (0.55%)	0 / 500 (0.00%)	1 / 318 (0.31%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endocrine disorders			

Hypopituitarism			
subjects affected / exposed	0 / 361 (0.00%)	0 / 500 (0.00%)	1 / 318 (0.31%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Adrenal insufficiency			
subjects affected / exposed	0 / 361 (0.00%)	1 / 500 (0.20%)	0 / 318 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thyroiditis			
subjects affected / exposed	1 / 361 (0.28%)	0 / 500 (0.00%)	0 / 318 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune-mediated hypothyroidism			
subjects affected / exposed	1 / 361 (0.28%)	0 / 500 (0.00%)	0 / 318 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperthyroidism			
subjects affected / exposed	1 / 361 (0.28%)	0 / 500 (0.00%)	0 / 318 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Goiter			
subjects affected / exposed	1 / 361 (0.28%)	0 / 500 (0.00%)	0 / 318 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypothyroidism			
subjects affected / exposed	2 / 361 (0.55%)	1 / 500 (0.20%)	0 / 318 (0.00%)
occurrences causally related to treatment / all	2 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Flank pain			
subjects affected / exposed	1 / 361 (0.28%)	0 / 500 (0.00%)	0 / 318 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Groin pain			
subjects affected / exposed	1 / 361 (0.28%)	0 / 500 (0.00%)	0 / 318 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Back pain			
subjects affected / exposed	1 / 361 (0.28%)	2 / 500 (0.40%)	1 / 318 (0.31%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bone pain			
subjects affected / exposed	1 / 361 (0.28%)	0 / 500 (0.00%)	2 / 318 (0.63%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Crystal arthropathy			
subjects affected / exposed	1 / 361 (0.28%)	0 / 500 (0.00%)	0 / 318 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Arthralgia			
subjects affected / exposed	1 / 361 (0.28%)	1 / 500 (0.20%)	1 / 318 (0.31%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pathological fracture			
subjects affected / exposed	1 / 361 (0.28%)	0 / 500 (0.00%)	1 / 318 (0.31%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal pain			
subjects affected / exposed	0 / 361 (0.00%)	0 / 500 (0.00%)	1 / 318 (0.31%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Muscle twitching			
subjects affected / exposed	0 / 361 (0.00%)	1 / 500 (0.20%)	0 / 318 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal chest pain			

subjects affected / exposed	1 / 361 (0.28%)	1 / 500 (0.20%)	0 / 318 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pain in extremity			
subjects affected / exposed	1 / 361 (0.28%)	0 / 500 (0.00%)	1 / 318 (0.31%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Pneumonia			
subjects affected / exposed	28 / 361 (7.76%)	28 / 500 (5.60%)	13 / 318 (4.09%)
occurrences causally related to treatment / all	2 / 28	8 / 28	0 / 13
deaths causally related to treatment / all	1 / 7	1 / 6	0 / 1
Respiratory tract infection			
subjects affected / exposed	4 / 361 (1.11%)	3 / 500 (0.60%)	1 / 318 (0.31%)
occurrences causally related to treatment / all	1 / 4	2 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			
subjects affected / exposed	4 / 361 (1.11%)	4 / 500 (0.80%)	1 / 318 (0.31%)
occurrences causally related to treatment / all	0 / 4	3 / 4	0 / 1
deaths causally related to treatment / all	0 / 2	0 / 0	0 / 0
Bronchitis			
subjects affected / exposed	2 / 361 (0.55%)	1 / 500 (0.20%)	5 / 318 (1.57%)
occurrences causally related to treatment / all	0 / 2	1 / 1	0 / 5
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Septic shock			
subjects affected / exposed	0 / 361 (0.00%)	6 / 500 (1.20%)	0 / 318 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 6	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 5	0 / 0
Lower respiratory tract infection			
subjects affected / exposed	3 / 361 (0.83%)	2 / 500 (0.40%)	0 / 318 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infective exacerbation of chronic obstructive airways disease			

subjects affected / exposed	2 / 361 (0.55%)	0 / 500 (0.00%)	0 / 318 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Amoebiasis			
subjects affected / exposed	1 / 361 (0.28%)	0 / 500 (0.00%)	0 / 318 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oral candidiasis			
subjects affected / exposed	1 / 361 (0.28%)	1 / 500 (0.20%)	0 / 318 (0.00%)
occurrences causally related to treatment / all	0 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Device related infection			
subjects affected / exposed	1 / 361 (0.28%)	0 / 500 (0.00%)	0 / 318 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Herpes zoster			
subjects affected / exposed	1 / 361 (0.28%)	0 / 500 (0.00%)	1 / 318 (0.31%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Influenza			
subjects affected / exposed	1 / 361 (0.28%)	2 / 500 (0.40%)	2 / 318 (0.63%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung abscess			
subjects affected / exposed	1 / 361 (0.28%)	0 / 500 (0.00%)	0 / 318 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
COVID-19			
subjects affected / exposed	1 / 361 (0.28%)	0 / 500 (0.00%)	2 / 318 (0.63%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia pneumococcal			

subjects affected / exposed	1 / 361 (0.28%)	1 / 500 (0.20%)	0 / 318 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sinusitis			
subjects affected / exposed	1 / 361 (0.28%)	0 / 500 (0.00%)	0 / 318 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			
subjects affected / exposed	1 / 361 (0.28%)	1 / 500 (0.20%)	1 / 318 (0.31%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anal abscess			
subjects affected / exposed	0 / 361 (0.00%)	1 / 500 (0.20%)	0 / 318 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Device related sepsis			
subjects affected / exposed	0 / 361 (0.00%)	1 / 500 (0.20%)	0 / 318 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bacterial sepsis			
subjects affected / exposed	0 / 361 (0.00%)	0 / 500 (0.00%)	1 / 318 (0.31%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cellulitis			
subjects affected / exposed	0 / 361 (0.00%)	3 / 500 (0.60%)	0 / 318 (0.00%)
occurrences causally related to treatment / all	0 / 0	2 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Clostridium difficile colitis			
subjects affected / exposed	0 / 361 (0.00%)	1 / 500 (0.20%)	0 / 318 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
COVID-19 pneumonia			

subjects affected / exposed	0 / 361 (0.00%)	0 / 500 (0.00%)	1 / 318 (0.31%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Bacteraemia			
subjects affected / exposed	0 / 361 (0.00%)	0 / 500 (0.00%)	1 / 318 (0.31%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Large intestine infection			
subjects affected / exposed	0 / 361 (0.00%)	1 / 500 (0.20%)	0 / 318 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nosocomial infection			
subjects affected / exposed	0 / 361 (0.00%)	1 / 500 (0.20%)	0 / 318 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oral fungal infection			
subjects affected / exposed	0 / 361 (0.00%)	0 / 500 (0.00%)	1 / 318 (0.31%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Perirectal abscess			
subjects affected / exposed	0 / 361 (0.00%)	1 / 500 (0.20%)	0 / 318 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infection			
subjects affected / exposed	0 / 361 (0.00%)	1 / 500 (0.20%)	0 / 318 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diverticulitis			
subjects affected / exposed	0 / 361 (0.00%)	1 / 500 (0.20%)	0 / 318 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Enterobacter infection			

subjects affected / exposed	0 / 361 (0.00%)	1 / 500 (0.20%)	0 / 318 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Erysipelas			
subjects affected / exposed	0 / 361 (0.00%)	1 / 500 (0.20%)	0 / 318 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peritonitis			
subjects affected / exposed	0 / 361 (0.00%)	0 / 500 (0.00%)	1 / 318 (0.31%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Pseudomembranous colitis			
subjects affected / exposed	0 / 361 (0.00%)	1 / 500 (0.20%)	0 / 318 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Pseudomonal sepsis			
subjects affected / exposed	0 / 361 (0.00%)	1 / 500 (0.20%)	0 / 318 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary sepsis			
subjects affected / exposed	0 / 361 (0.00%)	2 / 500 (0.40%)	0 / 318 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Respiratory syncytial virus infection			
subjects affected / exposed	0 / 361 (0.00%)	0 / 500 (0.00%)	1 / 318 (0.31%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Systemic candida			
subjects affected / exposed	0 / 361 (0.00%)	1 / 500 (0.20%)	0 / 318 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tuberculosis			

subjects affected / exposed	0 / 361 (0.00%)	1 / 500 (0.20%)	0 / 318 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper respiratory tract infection			
subjects affected / exposed	0 / 361 (0.00%)	1 / 500 (0.20%)	1 / 318 (0.31%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis syndrome			
subjects affected / exposed	0 / 361 (0.00%)	1 / 500 (0.20%)	0 / 318 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	2 / 361 (0.55%)	2 / 500 (0.40%)	6 / 318 (1.89%)
occurrences causally related to treatment / all	0 / 2	2 / 2	2 / 6
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypokalaemia			
subjects affected / exposed	1 / 361 (0.28%)	1 / 500 (0.20%)	2 / 318 (0.63%)
occurrences causally related to treatment / all	1 / 1	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diabetes mellitus inadequate control			
subjects affected / exposed	1 / 361 (0.28%)	0 / 500 (0.00%)	0 / 318 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyponatraemia			
subjects affected / exposed	2 / 361 (0.55%)	0 / 500 (0.00%)	0 / 318 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypercalcaemia			
subjects affected / exposed	2 / 361 (0.55%)	0 / 500 (0.00%)	3 / 318 (0.94%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dehydration			

subjects affected / exposed	2 / 361 (0.55%)	1 / 500 (0.20%)	0 / 318 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypocalcaemia			
subjects affected / exposed	0 / 361 (0.00%)	2 / 500 (0.40%)	1 / 318 (0.31%)
occurrences causally related to treatment / all	0 / 0	1 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperglycaemia			
subjects affected / exposed	0 / 361 (0.00%)	1 / 500 (0.20%)	0 / 318 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fluid overload			
subjects affected / exposed	0 / 361 (0.00%)	1 / 500 (0.20%)	0 / 318 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Malnutrition			
subjects affected / exposed	1 / 361 (0.28%)	0 / 500 (0.00%)	1 / 318 (0.31%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypoglycaemia			
subjects affected / exposed	0 / 361 (0.00%)	2 / 500 (0.40%)	0 / 318 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypomagnesaemia			
subjects affected / exposed	0 / 361 (0.00%)	2 / 500 (0.40%)	0 / 318 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Avelumab Biweekly	Chemotherapy	Avelumab Weekly
Total subjects affected by non-serious adverse events			
subjects affected / exposed	331 / 361 (91.69%)	474 / 500 (94.80%)	298 / 318 (93.71%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Tumor pain			
subjects affected / exposed	2 / 361 (0.55%)	0 / 500 (0.00%)	5 / 318 (1.57%)
occurrences (all)	2	0	5
Vascular disorders			
Hot flush			
subjects affected / exposed	1 / 361 (0.28%)	2 / 500 (0.40%)	1 / 318 (0.31%)
occurrences (all)	1	2	1
Hypotension			
subjects affected / exposed	11 / 361 (3.05%)	8 / 500 (1.60%)	1 / 318 (0.31%)
occurrences (all)	11	8	1
Hypertension			
subjects affected / exposed	22 / 361 (6.09%)	20 / 500 (4.00%)	13 / 318 (4.09%)
occurrences (all)	22	20	13
General disorders and administration site conditions			
Non-cardiac chest pain			
subjects affected / exposed	15 / 361 (4.16%)	16 / 500 (3.20%)	12 / 318 (3.77%)
occurrences (all)	15	16	12
Fatigue			
subjects affected / exposed	58 / 361 (16.07%)	99 / 500 (19.80%)	56 / 318 (17.61%)
occurrences (all)	58	99	56
Pyrexia			
subjects affected / exposed	51 / 361 (14.13%)	32 / 500 (6.40%)	50 / 318 (15.72%)
occurrences (all)	51	32	50
Chills			
subjects affected / exposed	28 / 361 (7.76%)	2 / 500 (0.40%)	20 / 318 (6.29%)
occurrences (all)	28	2	20
Asthenia			
subjects affected / exposed	58 / 361 (16.07%)	74 / 500 (14.80%)	54 / 318 (16.98%)
occurrences (all)	58	74	54
Oedema peripheral			
subjects affected / exposed	14 / 361 (3.88%)	48 / 500 (9.60%)	9 / 318 (2.83%)
occurrences (all)	14	48	9

Chest pain			
subjects affected / exposed	13 / 361 (3.60%)	10 / 500 (2.00%)	15 / 318 (4.72%)
occurrences (all)	13	10	15
Influenza like illness			
subjects affected / exposed	10 / 361 (2.77%)	5 / 500 (1.00%)	1 / 318 (0.31%)
occurrences (all)	10	5	1
Immune system disorders			
Contrast media allergy			
subjects affected / exposed	1 / 361 (0.28%)	0 / 500 (0.00%)	0 / 318 (0.00%)
occurrences (all)	1	0	0
Respiratory, thoracic and mediastinal disorders			
Dyspnea			
subjects affected / exposed	50 / 361 (13.85%)	49 / 500 (9.80%)	50 / 318 (15.72%)
occurrences (all)	50	49	50
Hypoxia			
subjects affected / exposed	1 / 361 (0.28%)	1 / 500 (0.20%)	2 / 318 (0.63%)
occurrences (all)	1	1	2
Rhinitis allergic			
subjects affected / exposed	2 / 361 (0.55%)	5 / 500 (1.00%)	1 / 318 (0.31%)
occurrences (all)	2	5	1
Pleural effusion			
subjects affected / exposed	7 / 361 (1.94%)	11 / 500 (2.20%)	6 / 318 (1.89%)
occurrences (all)	7	11	6
Productive cough			
subjects affected / exposed	14 / 361 (3.88%)	14 / 500 (2.80%)	8 / 318 (2.52%)
occurrences (all)	14	14	8
Haemoptysis			
subjects affected / exposed	25 / 361 (6.93%)	23 / 500 (4.60%)	23 / 318 (7.23%)
occurrences (all)	25	23	23
Cough			
subjects affected / exposed	48 / 361 (13.30%)	45 / 500 (9.00%)	41 / 318 (12.89%)
occurrences (all)	48	45	41
Psychiatric disorders			
Depression			
subjects affected / exposed	6 / 361 (1.66%)	8 / 500 (1.60%)	2 / 318 (0.63%)
occurrences (all)	6	8	2

Insomnia			
subjects affected / exposed	29 / 361 (8.03%)	33 / 500 (6.60%)	13 / 318 (4.09%)
occurrences (all)	29	33	13
Confusional state			
subjects affected / exposed	2 / 361 (0.55%)	2 / 500 (0.40%)	2 / 318 (0.63%)
occurrences (all)	2	2	2
Investigations			
Aspartate aminotransferase increased			
subjects affected / exposed	24 / 361 (6.65%)	30 / 500 (6.00%)	22 / 318 (6.92%)
occurrences (all)	24	30	22
Alanine aminotransferase increased			
subjects affected / exposed	31 / 361 (8.59%)	37 / 500 (7.40%)	37 / 318 (11.64%)
occurrences (all)	31	37	37
Weight decreased			
subjects affected / exposed	37 / 361 (10.25%)	41 / 500 (8.20%)	32 / 318 (10.06%)
occurrences (all)	37	41	32
Lipase increased			
subjects affected / exposed	20 / 361 (5.54%)	11 / 500 (2.20%)	17 / 318 (5.35%)
occurrences (all)	20	11	17
Weight increased			
subjects affected / exposed	15 / 361 (4.16%)	8 / 500 (1.60%)	12 / 318 (3.77%)
occurrences (all)	15	8	12
Amylase increased			
subjects affected / exposed	15 / 361 (4.16%)	17 / 500 (3.40%)	17 / 318 (5.35%)
occurrences (all)	15	17	17
Blood creatinine increased			
subjects affected / exposed	16 / 361 (4.43%)	30 / 500 (6.00%)	12 / 318 (3.77%)
occurrences (all)	16	30	12
Gamma-glutamyltransferase increased			
subjects affected / exposed	19 / 361 (5.26%)	22 / 500 (4.40%)	20 / 318 (6.29%)
occurrences (all)	19	22	20
Blood creatine phosphokinase increased			
subjects affected / exposed	8 / 361 (2.22%)	4 / 500 (0.80%)	10 / 318 (3.14%)
occurrences (all)	8	1	10
Blood lactate dehydrogenase			

increased			
subjects affected / exposed	5 / 361 (1.39%)	4 / 500 (0.80%)	3 / 318 (0.94%)
occurrences (all)	5	4	3
Neutrophil count decreased			
subjects affected / exposed	2 / 361 (0.55%)	62 / 500 (12.40%)	2 / 318 (0.63%)
occurrences (all)	2	62	2
Blood calcium decreased			
subjects affected / exposed	1 / 361 (0.28%)	1 / 500 (0.20%)	0 / 318 (0.00%)
occurrences (all)	1	1	0
C-reactive protein increased			
subjects affected / exposed	1 / 361 (0.28%)	4 / 500 (0.80%)	6 / 318 (1.89%)
occurrences (all)	1	4	6
White blood cell count decreased			
subjects affected / exposed	1 / 361 (0.28%)	39 / 500 (7.80%)	1 / 318 (0.31%)
occurrences (all)	1	39	1
White blood cell count increased			
subjects affected / exposed	1 / 361 (0.28%)	1 / 500 (0.20%)	2 / 318 (0.63%)
occurrences (all)	1	1	2
Platelet count decreased			
subjects affected / exposed	6 / 361 (1.66%)	43 / 500 (8.60%)	2 / 318 (0.63%)
occurrences (all)	6	43	2
Injury, poisoning and procedural complications			
Infusion related reaction			
subjects affected / exposed	52 / 361 (14.40%)	2 / 500 (0.40%)	28 / 318 (8.81%)
occurrences (all)	52	2	28
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	10 / 361 (2.77%)	3 / 500 (0.60%)	4 / 318 (1.26%)
occurrences (all)	10	3	4
Tachycardia			
subjects affected / exposed	5 / 361 (1.39%)	7 / 500 (1.40%)	9 / 318 (2.83%)
occurrences (all)	5	7	9
Nervous system disorders			
Headache			
subjects affected / exposed	24 / 361 (6.65%)	24 / 500 (4.80%)	21 / 318 (6.60%)
occurrences (all)	24	24	21

Paraesthesia			
subjects affected / exposed	5 / 361 (1.39%)	14 / 500 (2.80%)	5 / 318 (1.57%)
occurrences (all)	5	14	5
Hypoaesthesia			
subjects affected / exposed	5 / 361 (1.39%)	5 / 500 (1.00%)	2 / 318 (0.63%)
occurrences (all)	5	5	2
Dizziness			
subjects affected / exposed	20 / 361 (5.54%)	29 / 500 (5.80%)	12 / 318 (3.77%)
occurrences (all)	20	29	12
Taste disorder			
subjects affected / exposed	0 / 361 (0.00%)	3 / 500 (0.60%)	0 / 318 (0.00%)
occurrences (all)	0	1	0
Blood and lymphatic system disorders			
Leukocytosis			
subjects affected / exposed	1 / 361 (0.28%)	0 / 500 (0.00%)	3 / 318 (0.94%)
occurrences (all)	1	0	3
Thrombocytopenia			
subjects affected / exposed	5 / 361 (1.39%)	60 / 500 (12.00%)	8 / 318 (2.52%)
occurrences (all)	5	60	8
Anaemia			
subjects affected / exposed	37 / 361 (10.25%)	232 / 500 (46.40%)	57 / 318 (17.92%)
occurrences (all)	37	232	57
Leukopenia			
subjects affected / exposed	6 / 361 (1.66%)	42 / 500 (8.40%)	2 / 318 (0.63%)
occurrences (all)	6	42	2
Neutropenia			
subjects affected / exposed	6 / 361 (1.66%)	113 / 500 (22.60%)	3 / 318 (0.94%)
occurrences (all)	6	113	3
Eye disorders			
Vitreous floaters			
subjects affected / exposed	1 / 361 (0.28%)	0 / 500 (0.00%)	0 / 318 (0.00%)
occurrences (all)	1	0	0
Vision blurred			
subjects affected / exposed	3 / 361 (0.83%)	2 / 500 (0.40%)	0 / 318 (0.00%)
occurrences (all)	3	2	0
Gastrointestinal disorders			

Gastrooesophageal reflux disease			
subjects affected / exposed	4 / 361 (1.11%)	7 / 500 (1.40%)	1 / 318 (0.31%)
occurrences (all)	4	7	1
Constipation			
subjects affected / exposed	59 / 361 (16.34%)	87 / 500 (17.40%)	21 / 318 (6.60%)
occurrences (all)	59	87	21
Nausea			
subjects affected / exposed	41 / 361 (11.36%)	164 / 500 (32.80%)	33 / 318 (10.38%)
occurrences (all)	41	164	33
Dysphagia			
subjects affected / exposed	5 / 361 (1.39%)	4 / 500 (0.80%)	6 / 318 (1.89%)
occurrences (all)	5	4	6
Dyspepsia			
subjects affected / exposed	12 / 361 (3.32%)	16 / 500 (3.20%)	2 / 318 (0.63%)
occurrences (all)	12	16	2
Vomiting			
subjects affected / exposed	19 / 361 (5.26%)	73 / 500 (14.60%)	24 / 318 (7.55%)
occurrences (all)	19	73	24
Diarrhoea			
subjects affected / exposed	37 / 361 (10.25%)	47 / 500 (9.40%)	39 / 318 (12.26%)
occurrences (all)	37	47	39
Haemorrhoids			
subjects affected / exposed	2 / 361 (0.55%)	4 / 500 (0.80%)	3 / 318 (0.94%)
occurrences (all)	2	4	3
Odynophagia			
subjects affected / exposed	1 / 361 (0.28%)	1 / 500 (0.20%)	3 / 318 (0.94%)
occurrences (all)	1	1	3
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	30 / 361 (8.31%)	36 / 500 (7.20%)	27 / 318 (8.49%)
occurrences (all)	30	36	27
Pruritus			
subjects affected / exposed	26 / 361 (7.20%)	15 / 500 (3.00%)	28 / 318 (8.81%)
occurrences (all)	26	15	28
Dry skin			

subjects affected / exposed	19 / 361 (5.26%)	4 / 500 (0.80%)	12 / 318 (3.77%)
occurrences (all)	19	4	12
Alopecia			
subjects affected / exposed	4 / 361 (1.11%)	30 / 500 (6.00%)	3 / 318 (0.94%)
occurrences (all)	4	30	3
Rash maculo-papular			
subjects affected / exposed	4 / 361 (1.11%)	1 / 500 (0.20%)	3 / 318 (0.94%)
occurrences (all)	4	1	3
Night sweats			
subjects affected / exposed	1 / 361 (0.28%)	1 / 500 (0.20%)	0 / 318 (0.00%)
occurrences (all)	1	1	0
Photosensitivity reaction			
subjects affected / exposed	0 / 361 (0.00%)	3 / 500 (0.60%)	0 / 318 (0.00%)
occurrences (all)	0	3	0
Endocrine disorders			
Hypothyroidism			
subjects affected / exposed	24 / 361 (6.65%)	8 / 500 (1.60%)	21 / 318 (6.60%)
occurrences (all)	24	8	21
Musculoskeletal and connective tissue disorders			
Myalgia			
subjects affected / exposed	15 / 361 (4.16%)	11 / 500 (2.20%)	15 / 318 (4.72%)
occurrences (all)	15	11	15
Arthralgia			
subjects affected / exposed	50 / 361 (13.85%)	31 / 500 (6.20%)	31 / 318 (9.75%)
occurrences (all)	50	31	31
Pain in extremity			
subjects affected / exposed	15 / 361 (4.16%)	20 / 500 (4.00%)	12 / 318 (3.77%)
occurrences (all)	15	20	12
Musculoskeletal chest pain			
subjects affected / exposed	14 / 361 (3.88%)	15 / 500 (3.00%)	12 / 318 (3.77%)
occurrences (all)	14	15	12
Bone pain			
subjects affected / exposed	10 / 361 (2.77%)	9 / 500 (1.80%)	6 / 318 (1.89%)
occurrences (all)	10	9	6
Flank pain			

subjects affected / exposed	6 / 361 (1.66%)	0 / 500 (0.00%)	0 / 318 (0.00%)
occurrences (all)	6	0	0
Neck pain			
subjects affected / exposed	4 / 361 (1.11%)	12 / 500 (2.40%)	5 / 318 (1.57%)
occurrences (all)	4	12	5
Back pain			
subjects affected / exposed	39 / 361 (10.80%)	34 / 500 (6.80%)	29 / 318 (9.12%)
occurrences (all)	39	34	29
Infections and infestations			
Upper respiratory tract infection			
subjects affected / exposed	25 / 361 (6.93%)	21 / 500 (4.20%)	21 / 318 (6.60%)
occurrences (all)	25	21	21
Nasopharyngitis			
subjects affected / exposed	23 / 361 (6.37%)	16 / 500 (3.20%)	11 / 318 (3.46%)
occurrences (all)	23	16	11
Pneumonia			
subjects affected / exposed	23 / 361 (6.37%)	28 / 500 (5.60%)	24 / 318 (7.55%)
occurrences (all)	23	28	24
Respiratory tract infection			
subjects affected / exposed	13 / 361 (3.60%)	12 / 500 (2.40%)	6 / 318 (1.89%)
occurrences (all)	13	12	6
Bronchitis			
subjects affected / exposed	12 / 361 (3.32%)	12 / 500 (2.40%)	9 / 318 (2.83%)
occurrences (all)	12	12	9
Urinary tract infection			
subjects affected / exposed	12 / 361 (3.32%)	17 / 500 (3.40%)	14 / 318 (4.40%)
occurrences (all)	12	17	14
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	65 / 361 (18.01%)	90 / 500 (18.00%)	61 / 318 (19.18%)
occurrences (all)	65	90	61
Hypoalbuminaemia			
subjects affected / exposed	14 / 361 (3.88%)	12 / 500 (2.40%)	20 / 318 (6.29%)
occurrences (all)	14	12	20
Hyponatraemia			

subjects affected / exposed	12 / 361 (3.32%)	15 / 500 (3.00%)	16 / 318 (5.03%)
occurrences (all)	12	15	16
Hyperglycaemia			
subjects affected / exposed	9 / 361 (2.49%)	21 / 500 (4.20%)	10 / 318 (3.14%)
occurrences (all)	9	21	10
Hypomagnesaemia			
subjects affected / exposed	5 / 361 (1.39%)	26 / 500 (5.20%)	5 / 318 (1.57%)
occurrences (all)	5	26	5

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
03 January 2019	Assumptions on PFS drop-out rate were revised.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported