Clinical trial results:
A Phase III Open-label, Multicenter Trial of Maintenance Therapy With Avelumab (MSB0010718C) Versus Continuation of First-line Chemotherapy in Subjects With Unresectable, Locally Advanced or Metastatic, Adenocarcinoma of the Stomach, or of the Gastro-esophageal Junction

Summary

EudraCT number	2015-003300-23
Trial protocol	GB HU RO DE ES FR IT
Global end of trial date	03 June 2021

Results information

Result version number	v1 (current)
This version publication date	27 May 2022
First version publication date	27 May 2022

Trial information

Trial identification

Sponsor protocol code	EMR100070-007

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02625610
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Merck Healthcare KGaA, Darmstadt Germany
Sponsor organisation address	Frankfurter Strasse 250, Darmstadt, Germany, 64293
Public contact	Communication Centre, Merck Healthcare KGaA, Darmstadt Germany, +49 6151725200, service@merckgroup.com
Scientific contact	Communication Centre, Merck Healthcare 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	03 June 2021
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	03 June 2021
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 of treatment with avelumab versus continuation of first-line chemotherapy.

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	24 December 2015
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
Long term follow-up duration	5 Years
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United States: 50
Country: Number of subjects enrolled	Brazil: 22
Country: Number of subjects enrolled	Canada: 7
Country: Number of subjects enrolled	France: 32
Country: Number of subjects enrolled	Germany: 11
Country: Number of subjects enrolled	Italy: 41
Country: Number of subjects enrolled	Spain: 30
Country: Number of subjects enrolled	United Kingdom: 22
Country: Number of subjects enrolled	Hungary: 19
Country: Number of subjects enrolled	Romania: 20
Country: Number of subjects enrolled	Russian Federation: 58
Country: Number of subjects enrolled	Australia: 35
Country: Number of subjects enrolled	Japan: 40
Country: Number of subjects enrolled	Korea, Democratic People's Republic of: 55
Country: Number of subjects enrolled	Taiwan: 15
Country: Number of subjects enrolled	Thailand: 4
Country: Number of subjects enrolled	Turkey: 38

Worldwide total number of subjects	499
EEA total number of subjects	153

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)	287
From 65 to 84 years	211
85 years and over	1

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Overall, 1284 subjects were screened for this study. Of which 799 subjects received at least 1 dose in the Induction Phase, 499 subjects were randomized into maintenance phase of the study.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Chemotherapy + Best Supportive Care (BSC)

Arm description:

Subjects received 85mg/m^2 of Oxaliplatin intravenous (IV) infusion on Day 1 along with (200/400)mg/m^2 of leucovorin on Day 1 followed by 2600mg/m^2 of 5-Fluorouracil IV infusion on Day 1/400mg/m^2 IV push on Day 1 & 2400mg/m^2 IV infusion every 2 weeks up to 12weeks/Oxaliplatin at 130mg/m^2 IV on Day 1 along with 1000mg/m^2 of capecitabine twice daily for 2weeks followed by 1week rest period given every3weeks up to 12weeks in Induction phase. In Maintenance Phase, subjects continued same regimen of oxaliplatin-fluoropyrimidine doublet chemotherapy as they received during Induction Phase until disease progression, significant clinical deterioration, unacceptable toxicity/discontinuation. Subjects who were not deemed eligible to receive chemotherapy at dose & schedule specified above received BSC alone once every3weeks. BSC: treatment administered with intent to maximize quality of life without a specific antineoplastic regimen & was based on Investigator's discretion.

Arm type	Experimental
Investigational medicinal product name	Oxaliplatin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Oxaliplatin was administered at a dose of 85 mg/m^2 IV infusion in combination with 5FU/LV and 130 mg/m^2 with capecitabine on Day 1 in Induction phase. In Maintenance Phase, same dose of Oxaliplatin was administered until disease progression, significant clinical deterioration, unacceptable toxicity, or discontinuation.

Investigational medicinal product name	Capecitabine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Capecitabine was administered at a dose of 1000 mg/m^2 twice daily for 2 weeks followed by a 1-week rest period given every 3 weeks for up to 12 weeks in Induction phase. in Induction Phase. In Maintenance Phase, same dose of Capecitabine was administered until disease progression, significant clinical deterioration, unacceptable toxicity, or discontinuation.

Investigational medicinal product name	5-Fluorouracil
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

5-Fluorouracil at a dose of 2600 mg/m^2 IV continuous infusion over 24 hours on Day or at 400 mg/m^2 IV push on Day 1 and 2400 mg/m^2 IV continuous infusion over 46-48 hours (Day 1 and 2) every 2 weeks up to 12 weeks in Induction Phase. In Maintenance Phase, same dose of 5-Fluorouracil was administered until disease progression, significant clinical deterioration, unacceptable toxicity, or discontinuation.

Investigational medicinal product name	Leucovorin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Leucovorin was administered at a dose of 200 mg/m^2 or 400 mg/m^2 on Day 1 every 2 weeks up to 12 weeks in Induction Phase. In Maintenance Phase, same dose of Leucovorin was administered until disease progression, significant clinical deterioration, unacceptable toxicity, or discontinuation.

Arm title	Avelumab

Arm description:

Oxaliplatin was administered at a dose of 85 mg/m^2 as a continuous intravenous (IV) infusion on Day 1 along with leucovorin at a dose of 200 mg/m^2 or 400 mg/m^2 on Day 1 followed by 5-Fluorouracil at a dose of 2600 mg/m^2 IV continuous infusion over 24 hours on Day 1 or at 400 mg/m^2 IV push on Day 1 and 2400 mg/m^2 IV continuous infusion over 46-48 hours (Day 1 and 2) every 2 weeks up to 12 weeks (or) Oxaliplatin at 130 mg/m^2 IV on Day 1 along with capecitabine at a dose of 1000 mg/m^2 twice daily for 2 weeks followed by a 1-week rest period given every 3 weeks for up to 12 weeks in Induction phase. In Maintenance phase, subjects received avelumab as a 1-hour intravenous (IV) infusion at 10 milligrams per kilogram (mg/kg) once every 2-week treatment cycle until progressive disease or unacceptable toxicity or discontinuation.

Arm type	Experimental
Investigational medicinal product name	Avelumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Avelumab was administered as a 1-hour IV infusion at 10 mg/kg every 2-week treatment cycle until progressive disease or unacceptable toxicity or discontinuation.

Number of subjects in period 1	Chemotherapy + Best Supportive Care (BSC)	Avelumab
Started	250	249
Completed	250	249

Baseline characteristics

Reporting groups	
Reporting group title	Chemotherapy + Best Supportive Care (BSC)
Reporting group description:	
Subjects received 85mg/m^2 of Oxaliplatin intravenous (IV) infusion on Day 1 along with (200/400)mg/m^2 of leucovorin on Day 1 followed by 2600mg/m^2 of 5-Fluorouracil IV infusion on Day 1/400mg/m^2 IV push on Day 1 & 2400mg/m^2 IV infusion every 2 weeks up to 12weeks/Oxaliplatin at 130mg/m^2 IV on Day 1 along with 1000mg/m^2 of capecitabine twice daily for 2weeks followed by 1week rest period given every3weeks up to 12weeks in Induction phase. In Maintenance Phase, subjects continued same regimen of oxaliplatin-fluoropyrimidine doublet chemotherapy as they received during Induction Phase until disease progression, significant clinical deterioration, unacceptable toxicity/discontinuation. Subjects who were not deemed eligible to receive chemotherapy at dose & schedule specified above received BSC alone once every3weeks. BSC: treatment administered with intent to maximize quality of life without a specific antineoplastic regimen & was based on Investigator's discretion.	
Reporting group title	Avelumab
Reporting group description:	
Oxaliplatin was administered at a dose of 85 mg/m^2 as a continuous intravenous (IV) infusion on Day 1 along with leucovorin at a dose of 200 mg/m^2 or 400 mg/m^2 on Day 1 followed by 5-Fluorouracil at a dose of 2600 mg/m^2 IV continuous infusion over 24 hours on Day 1 or at 400 mg/m^2 IV push on Day 1 and 2400 mg/m^2 IV continuous infusion over 46-48 hours (Day 1 and 2) every 2 weeks up to 12 weeks (or) Oxaliplatin at 130 mg/m^2 IV on Day 1 along with capecitabine at a dose of 1000 mg/m^2 twice daily for 2 weeks followed by a 1-week rest period given every 3 weeks for up to 12 weeks in Induction phase. In Maintenance phase, subjects received avelumab as a 1-hour intravenous (IV) infusion at 10 milligrams per kilogram (mg/kg) once every 2-week treatment cycle until progressive disease or unacceptable toxicity or discontinuation.	

Reporting group values	Chemotherapy + Best Supportive Care (BSC)	Avelumab	Total
Number of subjects	250	249	499
Age categorical Units:			
Age Continuous Units: Years			
arithmetic mean	60.6	60.7	
standard deviation	± 11.70	± 11.03	-
Sex: Female, Male Units: subjects			
Female	83	85	168
Male	167	164	331
Race/Ethnicity, Customized Units: Subjects			
White	161	171	332
Black or African American	2	2	4
Asian	59	61	120
American Indian or Alaska Native	2	0	2
Native Hawaiian or other Pacific Islander	0	0	0
Not collected at this site	22	12	34
Other	3	3	6
Missing	1	0	1
Ethnicity (NIH/OMB)			

Units: Subjects			
Hispanic or Latino	15	19	34
Not Hispanic or Latino	213	220	433
Unknown or Not Reported	22	10	32

End points

End points reporting groups

Reporting group title	Chemotherapy + Best Supportive Care (BSC)

Reporting group description:

Subjects received 85mg/m^2 of Oxaliplatin intravenous (IV) infusion on Day 1 along with (200/400)mg/m^2 of leucovorin on Day 1 followed by 2600mg/m^2 of 5-Fluorouracil IV infusion on Day 1/400mg/m^2 IV push on Day 1 & 2400mg/m^2 IV infusion every 2 weeks up to 12weeks/Oxaliplatin at 130mg/m^2 IV on Day 1 along with 1000mg/m^2 of capecitabine twice daily for 2weeks followed by 1week rest period given every3weeks up to 12weeks in Induction phase. In Maintenance Phase, subjects continued same regimen of oxaliplatin-fluoropyrimidine doublet chemotherapy as they received during Induction Phase until disease progression, significant clinical deterioration, unacceptable toxicity/discontinuation. Subjects who were not deemed eligible to receive chemotherapy at dose & schedule specified above received BSC alone once every3weeks. BSC: treatment administered with intent to maximize quality of life without a specific antineoplastic regimen & was based on Investigator's discretion.

Reporting group title	Avelumab

Reporting group description:

Oxaliplatin was administered at a dose of 85 mg/m^2 as a continuous intravenous (IV) infusion on Day 1 along with leucovorin at a dose of 200 mg/m^2 or 400 mg/m^2 on Day 1 followed by 5-Fluorouracil at a dose of 2600 mg/m^2 IV continuous infusion over 24 hours on Day 1 or at 400 mg/m^2 IV push on Day 1 and 2400 mg/m^2 IV continuous infusion over 46-48 hours (Day 1 and 2) every 2 weeks up to 12 weeks (or) Oxaliplatin at 130 mg/m^2 IV on Day 1 along with capecitabine at a dose of 1000 mg/m^2 twice daily for 2 weeks followed by a 1-week rest period given every 3 weeks for up to 12 weeks in Induction phase. In Maintenance phase, subjects received avelumab as a 1-hour intravenous (IV) infusion at 10 milligrams per kilogram (mg/kg) once every 2-week treatment cycle until progressive disease or unacceptable toxicity or discontinuation.

Primary: Overall Survival (OS)

End point title	Overall Survival (OS)

End point description:

Overall Survival was defined as the time from randomisation to the date of death due to any cause. For subjects who were still alive at the time of data analysis or who were lost to follow-up, OS time was censored at the date of last contact. OS was measured using Kaplan-Meier (KM) estimates. Full analysis set included all randomized subjects included in treatment arm to which they were randomized.

End point type	Primary

End point timeframe:

From randomization into maintenance phase up to 1276 days

End point values	Chemotherapy + Best Supportive Care (BSC)	Avelumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	250	249		
Units: months				
median (confidence interval 95%)	10.9 (9.6 to 12.4)	10.4 (9.1 to 12.0)		

Statistical analyses

Statistical analysis title	Chemotherapy + BSC vs Avelumab
Comparison groups	Chemotherapy + Best Supportive Care (BSC) v Avelumab
Number of subjects included in analysis	499
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1779
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.91
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.74
upper limit	1.11

Secondary: Progression Free Survival (PFS) by Independent Review Committee (IRC)

End point title	Progression Free Survival (PFS) by Independent Review Committee (IRC)

End point description:

The PFS time was defined as the time from date of randomisation until date of the first documentation of progressive disease (PD) or death due to any cause (whichever occurs first). PFS was assessed as per Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1) as per IRC. PD was defined as at least a 20 percent (%) increase in the sum of 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. Full analysis set included all randomized subjects included in treatment arm to which they were randomised.

End point type	Secondary

End point timeframe:

From randomization into maintenance phase up to 1276 days

End point values	Chemotherapy + Best Supportive Care (BSC)	Avelumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	250	249		
Units: months				
median (confidence interval 95%)	4.4 (4.0 to 5.5)	3.2 (2.8 to 4.1)		

Statistical analyses

Statistical analysis title	Chemotherapy + BSC vs Avelumab
Comparison groups	Chemotherapy + Best Supportive Care (BSC) v Avelumab

Number of subjects included in analysis	499
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Hazard ratio (HR)
Point estimate	1.04
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.85
upper limit	1.28

Secondary: Best Overall Response (BOR) by Investigator Assessment

End point title	Best Overall Response (BOR) by Investigator Assessment

End point description:

BOR was determined by RECIST v1.1 and defined as best-confirmed response of any of following: complete response (CR), partial response (PR), stable disease (SD) and PD recorded from date of randomisation until disease progression/recurrence. CR: Disappearance of all evidence of target and non-target lesions. PR: At least 30% reduction from baseline in SLD of all lesions. SD: Neither sufficient increase to qualify for PD nor sufficient shrinkage to qualify for PR. PD is defined as at least a 20% increase in the SLD, taking as reference the smallest SLD recorded from baseline or appearance of 1 or more new lesions. PR or CR confirmed at a subsequent tumor assessment, not sooner than 5 weeks after initial documentation or at an assessment later than the next assessment after the initial documentation of PR or CR. SD confirmed at least 6 weeks after randomization. Confirmed PD equal to progression less than or equal to [<=]2 weeks after date of randomization. Full analysis set was used.

End point type	Secondary

End point timeframe:

From randomization into maintenance phase up to 1276 days

End point values	Chemotherapy + Best Supportive Care (BSC)	Avelumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	250	249		
Units: subjects				
Complete response	5	8		
Partial response	31	25		
Stable disease	117	92		
Noncomplete response/non progressive disease	11	10		
Progressive disease	58	85		
Non evaluable	28	29		

Statistical analyses

No statistical analyses for this end point

Secondary: Objective Response Rate (ORR) by Investigator Assessment

End point title	Objective Response Rate (ORR) by Investigator Assessment

End point description:

The ORR defined as the percentage of all randomised subjects with a confirmed best overall response (BOR) of partial response (PR), or complete response (CR) according to RECIST v1.1 and as per Investigator assessment. CR: Disappearance of all evidence of target and non-target lesions. PR: At least 30 percent (%) reduction from baseline in sum of longest diameter (SLD) of all lesions. Full analysis set included all randomised subjects included in treatment arm to which they were randomised.

End point type	Secondary

End point timeframe:

From randomization into maintenance phase up to 1276 days

End point values	Chemotherapy + Best Supportive Care (BSC)	Avelumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	250	249		
Units: percentage of subjects				
number (confidence interval 95%)	14.4 (10.3 to 19.4)	13.3 (9.3 to 18.1)		

Statistical analyses

Statistical analysis title	Chemotherapy + BSC vs Avelumab
Comparison groups	Chemotherapy + Best Supportive Care (BSC) v Avelumab
Number of subjects included in analysis	499
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Odds ratio (OR)
Point estimate	0.91
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.55
upper limit	1.51

Secondary: Change From Baseline in European Quality of Life 5-dimensions (EQ-5D-5L) Health Outcome Questionnaire Through Composite Index Score up to Safety Follow-up (Up to 152.3 Weeks)

End point title	Change From Baseline in European Quality of Life 5-dimensions (EQ-5D-5L) Health Outcome Questionnaire Through Composite Index Score up to Safety Follow-up (Up to 152.3 Weeks)

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 composite health state index score, with scores ranging from -0.594 to 1. A higher score

indicates better health state. Health-related quality of life (HRQoL) analysis set included randomised subjects who had 1 Maintenance Phase Baseline HRQoL assessment and had at least 1 post-Maintenance Phase Baseline HRQoL questionnaire completed. Here, " Number of Subjects Analysed" signifies those subjects who were evaluable for this endpoint and "n" signified those subjects who were evaluable for the specified category at given time points.

End point type	Secondary

End point timeframe:

Baseline, Week 3/4, Week 7, Week 13, Week 19, Week 25, Week 31, Week 37, Week 43, Week 49, Week 55, Week 61, Week 67, End of Treatment (EOT up to 148 weeks) and Safety Follow-up (Up to 152.3 Weeks)

End point values	Chemotherapy + Best Supportive Care (BSC)	Avelumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	159	186		
Units: units on scale				
arithmetic mean (standard deviation)				
Week 3/4: n = 159, 186	-0.002 (± 0.1242)	0.004 (± 0.1610)		
Week 7: n = 145, 157	-0.032 (± 0.1644)	-0.009 (± 0.1588)		
Week 13: n = 89, 103	-0.053 (± 0.1733)	-0.017 (± 0.1599)		
Week 19: n = 56, 67	-0.039 (± 0.1934)	-0.011 (± 0.1556)		
Week 25: n = 31, 61	-0.049 (± 0.1797)	0.014 (± 0.1518)		
Week 31: n = 26, 45	-0.023 (± 0.1619)	0.013 (± 0.1665)		
Week 37: n = 18, 33	-0.035 (± 0.1505)	0.013 (± 0.2234)		
Week 43: n = 14, 30	-0.046 (± 0.1360)	0.058 (± 0.1990)		
Week 49: n = 11, 27	-0.100 (± 0.1796)	0.026 (± 0.1936)		
Week 55: n = 5, 25	-0.164 (± 0.2056)	0.028 (± 0.2067)		
Week 61: n = 5, 21	-0.091 (± 0.2229)	0.031 (± 0.1364)		
Week 67: n = 6, 17	-0.076 (± 0.2347)	0.039 (± 0.1954)		
End of Treatment: n = 134, 135	-0.125 (± 0.2432)	-0.138 (± 0.2461)		
Safety Follow-Up: n = 70, 69	-0.062 (± 0.2391)	-0.099 (± 0.1942)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in European Quality of Life 5-dimensions Health Outcome Questionnaire Through Visual Analogue Scale up to Safety Follow-up (Up

to 152.3 Weeks)

End point title	Change From Baseline in European Quality of Life 5-dimensions Health Outcome Questionnaire Through Visual Analogue Scale up to Safety Follow-up (Up to 152.3 Weeks)

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. HRQoL analysis set included randomised subjects who had 1 Maintenance Phase Baseline HRQoL assessment and had at least 1 post-Maintenance Phase Baseline HRQoL questionnaire completed. Here, " Number of Subjects Analysed" signifies those subjects who were evaluable for this endpoint and "n" signified those subjects who were evaluable for the specified category at given time points.

End point type	Secondary

End point timeframe:

Baseline, Week 3/4, Week 7, Week 13, Week 19, Week 25, Week 31, Week 37, Week 43, Week 49, Week 55, Week 61, Week 67, End of Treatment (EOT up to 148 weeks) and Safety Follow-up (Up to 152.3 Weeks)

End point values	Chemotherapy + Best Supportive Care (BSC)	Avelumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	159	186		
Units: millimeter				
arithmetic mean (standard deviation)				
Week 3/4: n = 159, 186	0.9 (± 13.94)	0.6 (± 13.11)		
Week 7: n = 145, 157	-0.5 (± 13.59)	-2.1 (± 14.09)		
Week 13: n = 89, 103	-3.2 (± 12.83)	-0.7 (± 13.41)		
Week 19: n = 56, 67	-3.5 (± 16.39)	-0.1 (± 14.93)		
Week 25: n = 31, 61	-4.5 (± 15.66)	-1.4 (± 15.76)		
Week 31: n = 26, 45	-2.3 (± 13.14)	1.4 (± 17.61)		
Week 37: n = 18, 33	-1.7 (± 11.78)	0.9 (± 20.39)		
Week 43: n = 14, 30	-4.4 (± 11.92)	3.2 (± 15.34)		
Week 49: n = 11, 27	-2.9 (± 8.95)	2.1 (± 13.04)		
Week 55: n = 5, 25	-9.4 (± 16.32)	3.4 (± 16.52)		
Week 61: n = 5, 21	-6.4 (± 18.09)	3.5 (± 16.15)		
Week 67: n = 6, 17	-7.3 (± 17.10)	4.9 (± 17.31)		
End of Treatment: n = 135, 135	-12.2 (± 22.39)	-10.3 (± 20.84)		
Safety Follow-Up: n = 70, 69	-8.0 (± 19.24)	-9.6 (± 20.30)		

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 (EORTC QLQ-C30) Global Health Status Scale Score up to Safety Follow-up (Up to 152.3 Weeks)

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 Scale Score up to Safety Follow-up (Up to 152.3 Weeks)

End point description:

EORTC QLQ-C30 is 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, dyspnoea, sleep disturbance, appetite loss, constipation, diarrhea, financial impact. The EORTC QLQ-C30 GHS/QoL score ranges from 0 to 100; High score indicates better GHS/QoL. Score 0 represents: very poor physical condition and QoL. Score 100 represents: excellent overall physical condition and QoL. HRQoL analysis set included randomised subjects who had 1 Maintenance Phase Baseline HRQoL assessment and had at least 1 post-Maintenance Phase Baseline HRQoL questionnaire completed. Here, " Number of Subjects Analysed" signifies those subjects who were evaluable for this endpoint and "n" signified those subjects who were evaluable for the specified category at given time points.

End point type	Secondary

End point timeframe:

Baseline, Week 3/4, Week 7, Week 13, Week 19, Week 25, Week 31, Week 37, Week 43, Week 49, Week 55, Week 61, Week 67, End of Treatment (EOT up to 148 weeks) and Safety Follow-up (Up to 152.3 Weeks)

End point values	Chemotherapy + Best Supportive Care (BSC)	Avelumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	160	186		
Units: units on a scale				
arithmetic mean (standard deviation)				
Week 3/4: n = 160, 186	1.30 (± 15.486)	0.85 (± 15.021)		
Week 7: n = 145, 157	-1.44 (± 14.905)	-1.01 (± 16.967)		
Week 13: n = 90, 103	-2.50 (± 15.424)	0.24 (± 17.637)		
Week 19: n = 57, 67	-5.85 (± 18.363)	1.37 (± 18.611)		
Week 25: n = 32, 61	-4.43 (± 15.407)	0.41 (± 16.204)		
Week 31: n = 27, 45	-3.09 (± 19.902)	1.85 (± 16.938)		
Week 37: n = 18, 33	-1.39 (± 22.186)	1.77 (± 19.293)		
Week 43: n = 14, 30	-1.19 (± 12.167)	3.33 (± 18.518)		
Week 49: n = 11, 27	1.52 (± 9.731)	4.01 (± 15.907)		
Week 55: n = 5, 25	0.00 (± 11.785)	4.00 (± 15.426)		
Week 61: n = 5, 21	-5.00 (± 13.944)	2.38 (± 15.622)		
Week 67: n = 6, 17	0.00 (± 9.129)	4.90 (± 18.413)		
End of Treatment: n = 135, 135	-11.54 (± 23.460)	-11.67 (± 21.409)		
Safety Follow-Up: n = 71, 70	-7.51 (± 19.475)	-9.29 (± 24.881)		

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-Stomach Cancer Specific (EORTC QLQ-STO22) Questionnaire Scores up to Safety Follow-up (Up to 152.3 Weeks)

End point title	Change From Baseline in European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire-Stomach Cancer Specific (EORTC QLQ-STO22) Questionnaire Scores up to Safety Follow-up (Up to 152.3 Weeks)

End point description:

EORTC QLQ-STO22 supplements the EORTC QLQ-C30 to assess symptoms and treatment-related side effects commonly reported in subjects. There are 22 questions which comprise 5 scales (dysphagia, pain, reflux symptom, dietary restrictions, and anxiety) and 4 single items (dry mouth, hair loss, taste, body image). Most questions use 4-point scale (1 'Not at all' to 4 'Very much'; 1 question was a yes or no answer). A linear transformation was used to standardize all scores and single-items to a scale of 0 to 100; higher score=better level of functioning or greater degree of symptoms. HRQoL analysis set included randomised subjects who had 1 Maintenance Phase Baseline HRQoL assessment and had at least 1 post-Maintenance Phase Baseline HRQoL questionnaire completed. Here, " Number of Subjects Analysed" signifies those subjects who were evaluable for this endpoint and "n" signified those subjects who were evaluable for the specified category at given time points.

End point type	Secondary

End point timeframe:

Baseline, Week 3/4, Week 7, Week 13, Week 19, Week 25, Week 31, Week 37, Week 43, Week 49, Week 55, Week 61, Week 67, End of Treatment (EOT up to 148 weeks) and Safety Follow-up (Up to 152.3 Weeks)

End point values	Chemotherapy + Best Supportive Care (BSC)	Avelumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	160	186		
Units: units on a scale				
arithmetic mean (standard deviation)				
Dysphagia: Week 3/4: n = 160, 186	0.76 (± 13.371)	0.60 (± 15.227)		
Dysphagia: Week 7: n = 145, 157	2.84 (± 15.258)	1.34 (± 13.453)		
Dysphagia: Week 13: n = 90, 102	1.60 (± 14.090)	0.65 (± 12.781)		
Dysphagia: Week 19: n = 57, 66	-0.58 (± 15.772)	1.52 (± 14.307)		
Dysphagia: Week 25: n = 32, 59	-1.39 (± 10.465)	1.69 (± 14.852)		
Dysphagia: Week 31: n = 21, 43	0.82 (± 14.755)	4.39 (± 20.877)		

Dysphagia: Week 37: n = 17, 33	-7.19 (± 17.977)	-0.67 (± 14.683)		
Dysphagia: Week 43: n = 14, 30	-4.76 (± 14.265)	-2.59 (± 13.270)		
Dysphagia: Week 49: n = 11, 27	-3.03 (± 8.736)	1.23 (± 13.195)		
Dysphagia: Week 55: n = 5, 25	0.00 (± 13.608)	0.89 (± 13.194)		
Dysphagia: Week 61: n = 5, 21	0.00 (± 15.713)	1.06 (± 12.123)		
Dysphagia: Week 67: n = 6, 17	-1.85 (± 10.924)	1.31 (± 17.516)		
Dysphagia: End of Treatment: n = 136, 134	7.27 (± 25.134)	8.21 (± 22.633)		
Dysphagia: Safety Follow-Up: n = 71, 69	9.39 (± 21.467)	7.25 (± 19.417)		
Pain: Week 3/4: n = 160, 186	1.51 (± 13.013)	-0.04 (± 13.465)		
Pain: Week 7: n = 145, 157	2.53 (± 15.351)	2.60 (± 15.210)		
Pain: Week 13: n = 90, 102	2.96 (± 14.585)	0.16 (± 13.523)		
Pain: Week 19: n = 57, 66	3.22 (± 14.152)	-0.51 (± 14.088)		
Pain: Week 25: n = 32, 59	-1.56 (± 13.789)	-1.55 (± 17.540)		
Pain: Week 31: n = 27, 43	4.01 (± 19.111)	0.97 (± 18.564)		
Pain: Week 37: n = 17, 33	-4.90 (± 19.777)	-1.26 (± 12.346)		
Pain: Week 43: n = 14, 30	1.79 (± 18.251)	-1.94 (± 14.129)		
Pain: Week 49: n = 11, 27	1.52 (± 5.025)	-0.62 (± 12.853)		
Pain: Week 55: n = 5, 25	0.00 (± 19.543)	-1.00 (± 10.012)		
Pain: Week 61: n = 5, 21	3.33 (± 9.501)	-1.59 (± 13.596)		
Pain: Week 67: n = 6, 17	0.00 (± 12.910)	-0.49 (± 15.721)		
Pain: End of Treatment: n = 136, 134	9.25 (± 20.853)	9.45 (± 22.960)		
Pain: Safety Follow-Up: n = 71, 69	8.22 (± 18.011)	10.99 (± 20.931)		
Reflux: Week 3/4: n = 160, 186	1.04 (± 14.197)	0.12 (± 13.571)		
Reflux: Week 7: n = 145, 157	0.31 (± 14.695)	0.50 (± 17.807)		
Reflux: Week 13: n = 90, 102	0.99 (± 14.098)	-1.09 (± 15.753)		
Reflux: Week 19: n = 57, 66	1.75 (± 17.032)	-1.68 (± 15.377)		
Reflux: Week 25: n = 32, 59	0.69 (± 14.648)	1.69 (± 19.770)		
Reflux: Week 31: n = 21, 43	-2.06 (± 14.791)	-1.29 (± 18.339)		
Reflux: Week 37: n = 17, 37	-6.54 (± 18.864)	-4.38 (± 17.773)		
Reflux: Week 43: n = 14, 30	-3.17 (± 15.364)	-5.56 (± 16.699)		
Reflux: Week 49: n = 11, 27	1.01 (± 9.236)	-2.06 (± 16.317)		

Reflux: Week 55: n = 5, 25	2.22 (± 4.969)	-3.56 (± 19.699)		
Reflux: Week 61: n = 5, 21	6.67 (± 9.938)	-6.35 (± 12.944)		
Reflux: Week 67: n = 6, 17	7.41 (± 13.456)	0.00 (± 19.245)		
Reflux: End of Treatment: n = 136, 134	3.43 (± 19.529)	4.73 (± 20.455)		
Reflux: Safety Follow-up: n = 71, 69	1.56 (± 20.254)	2.90 (± 19.212)		
Eating Restrictions: Week 3/4: n = 160, 186	0.73 (± 16.279)	0.13 (± 15.438)		
Eating Restrictions: Week 7: n = 145, 157	0.98 (± 16.123)	-0.27 (± 15.516)		
Eating Restrictions: Week 13: n = 90, 102	1.02 (± 14.234)	0.00 (± 14.023)		
Eating Restrictions: Week 19: n = 57, 66	-2.34 (± 16.648)	-0.63 (± 11.993)		
Eating Restrictions: Week 25: n = 32, 59	-2.08 (± 18.208)	-1.55 (± 15.434)		
Eating Restrictions: Week 31: n = 27, 43	-2.47 (± 15.814)	0.39 (± 14.880)		
Eating Restrictions: Week 37: n = 17, 33	-8.82 (± 21.943)	-3.28 (± 15.014)		
Eating Restrictions: Week 43: n = 14, 30	-4.76 (± 18.115)	-3.89 (± 13.443)		
Eating Restrictions: Week 49: n = 11, 27	0.76 (± 11.459)	-5.25 (± 12.043)		
Eating Restrictions: Week 55: n = 5, 25	3.33 (± 15.138)	-6.00 (± 12.620)		
Eating Restrictions: Week 61: n = 5, 21	0.00 (± 15.590)	-5.56 (± 12.999)		
Eating Restrictions: Week 67: n = 6, 17	1.39 (± 13.351)	-2.45 (± 19.712)		
Eating Restrictions: EOT: n = 136, 134	8.27 (± 20.898)	10.01 (± 22.055)		
Eating Restrictions: Safety Follow-up: n = 71, 69	7.04 (± 24.055)	11.59 (± 25.050)		
Anxiety: Week 3/4: n = 160, 186	-0.28 (± 16.150)	-4.06 (± 18.030)		
Anxiety: Week 7: n = 145, 157	-1.30 (± 16.947)	-1.20 (± 20.580)		
Anxiety: Week 13: n = 90, 102	-0.86 (± 20.685)	-2.83 (± 16.300)		
Anxiety: Week 19: n = 57, 66	-1.56 (± 21.561)	-1.68 (± 19.220)		
Anxiety: Week 25: n = 32, 59	-2.78 (± 23.780)	-1.69 (± 14.562)		
Anxiety: Week 31: n = 27, 43	4.12 (± 23.700)	-0.52 (± 24.119)		
Anxiety: Week 37: n = 17, 33	-3.92 (± 20.765)	-1.01 (± 27.409)		
Anxiety: Week 43: n = 14, 30	-3.97 (± 22.480)	-1.11 (± 24.474)		
Anxiety: Week 49: n = 5, 25	0.00 (± 12.172)	-6.17 (± 17.792)		
Anxiety: Week 55: n = 5, 25	2.22 (± 9.296)	-4.00 (± 20.000)		
Anxiety: Week 61: n = 5, 21	-4.44 (± 12.669)	-4.76 (± 24.488)		
Anxiety: Week 67: n = 6, 17	9.26 (± 16.355)	-1.96 (± 24.918)		

Anxiety: End of Treatment: n = 136, 134	4.58 (± 21.868)	5.89 (± 23.939)		
Anxiety: Safety Follow-Up: n = 71, 69	5.48 (± 24.116)	4.99 (± 26.234)		

Statistical analyses

No statistical analyses for this end point

Secondary: Maintenance Phase: Number of Subjects With Treatment-Emergent Adverse Events (TEAEs) and Serious TEAEs According to National Cancer Institute-Common Terminology Criteria for Adverse Events Version 4.03 (NCI-CTCAE v4.03)

End point title	Maintenance Phase: Number of Subjects With Treatment-Emergent Adverse Events (TEAEs) and Serious TEAEs According to National Cancer Institute-Common Terminology Criteria for Adverse Events Version 4.03 (NCI-CTCAE v4.03)

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. The term TEAE is defined as AEs starting or worsening after the first intake of the study drug. TEAEs included both serious TEAEs and non-serious TEAEs. Number of subjects with TEAEs and serious TEAEs were reported. Safety-Maintenance Analysis Set included all subjects who were administered any dose of the maintenance phase study medication or subjects randomised to the chemotherapy arm who are designated to receive BSC only. Subjects included in the treatment arm according to study treatment actually received.

End point type	Secondary

End point timeframe:

From randomization into maintenance phase up to 1276 days

End point values	Chemotherapy + Best Supportive Care (BSC)	Avelumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	238	243		
Units: subjects				
Any TEAEs	214	223		
Any Serious TEAE	75	89		

Statistical analyses

No statistical analyses for this end point

Secondary: Maintenance Phase: Number of Subjects With Grade Change From Baseline to Worst On-Treatment Grade 4 Hematology Values

End point title	Maintenance Phase: Number of Subjects With Grade Change From Baseline to Worst On-Treatment Grade 4 Hematology Values

End point description:

Blood samples were collected for the analysis of following hematology parameters: lymphocyte count, neutrophil count, white blood cells, platelet count, lipase, serum amylase, creatinine phosphokinase and creatinine. The hematology parameters were graded according to National Cancer Institute - Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 4.03. Grade 1: mild; Grade 2: moderate; Grade 3: severe or medically significant; Grade 4: life-threatening consequences. An increase is defined as an increase in CTCAE grade relative to Baseline grade. Data for worst-case (Grade 4) post Baseline is presented. Only those subjects with increase to grade 4 have been presented. Safety-Maintenance Analysis Set included all subjects who were administered any dose of the maintenance phase study medication or subjects randomised to the chemotherapy arm who are designated to receive BSC only. Subjects included in the treatment arm according to study treatment actually received.

End point type	Secondary

End point timeframe:

From baseline up to 1276 days

End point values	Chemotherapy + Best Supportive Care (BSC)	Avelumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	238	243		
Units: subjects				
lymphocyte count decreased	0	1		
neutrophil count decreased	6	1		
white blood cells decreased	2	0		
platelet count decreased	1	0		
lipase increased	6	8		
serum amylase increased	3	2		
creatinine phosphokinase increased	0	2		
creatinine increased	0	1		

Statistical analyses

No statistical analyses for this end point

Secondary: Maintenance Phase: Number of Subjects With Potentially Clinically Significant Abnormalities in Vital Signs

End point title	Maintenance Phase: Number of Subjects With Potentially Clinically Significant Abnormalities in Vital Signs

End point description:

Vital signs assessment included Systolic blood pressure (SBP), Diastolic blood pressure (DBP) and Pulse Rate (PR). Number of subjects with any potentially clinically significant abnormalities in vital signs were reported. Clinical significance was determined by the investigator. Safety-Maintenance Analysis Set included all subjects who were administered any dose of the maintenance phase study medication or subjects randomised to the chemotherapy arm who are designated to receive BSC only. Subjects included in the treatment arm according to study treatment actually received.

End point type	Secondary

End point timeframe:

From randomization into maintenance phase up to 1276 days

End point values	Chemotherapy + Best Supportive Care (BSC)	Avelumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	238	243		
Units: subjects				
Increased in Systolic blood pressure	57	62		
Decreased in Systolic blood pressure	43	69		
Increased in Diastolic blood pressure	14	24		
Decreased in Diastolic blood pressure	21	26		
Increased in pulse rate	46	48		
Decreased in pulse rate	32	30		

Statistical analyses

No statistical analyses for this end point

Secondary: Maintenance Phase: Number of Subjects With Potentially Clinically Significant Electrocardiogram (ECG) Abnormalities

End point title	Maintenance Phase: Number of Subjects With Potentially Clinically Significant Electrocardiogram (ECG) Abnormalities

End point description:

ECG parameters included heart rate, pulse rate intervals, QRS interval, QT interval corrected based on Fridericia's formula (QTcF) intervals and QTcB intervals. Clinical significance was determined by the investigator. Number of subjects with potentially clinically significant ECG abnormalities were reported. Safety-Maintenance Analysis Set included all subjects who were administered any dose of the maintenance phase study medication or subjects randomised to the chemotherapy arm who are designated to receive BSC only. Subjects included in the treatment arm according to study treatment actually received.

End point type	Secondary

End point timeframe:

From randomization into maintenance phase up to 1276 days

End point values	Chemotherapy + Best Supportive Care (BSC)	Avelumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	238	243		
Units: subjects				
Decreased heart rate	0	1		
Increased heart rate	2	2		
Increased Pulse Rate interval	1	3		
Increased QRS interval	5	8		
QTcF interval >450 ms <=480ms	9	9		

QTcF interval: > 480 ms <= 500 ms	2	3		
QTcF interval: > 500 ms	3	1		
QTcB Interval: > 450 msec <= 480 msec	19	18		
QTcB Interval: > 480 msec <= 500 msec	2	2		
QTcB Interval: > 500 msec	5	3		

Statistical analyses

No statistical analyses for this end point

Secondary: Maintenance Phase: Number of Subjects With Shift in Eastern Cooperative Oncology Group (ECOG) Performance Status Score to 1 or Higher Than 1

End point title	Maintenance Phase: Number of Subjects With Shift in Eastern Cooperative Oncology Group (ECOG) Performance Status Score to 1 or Higher Than 1

End point description:

ECOG PS score is widely used by doctors and researchers to assess how a subject's disease is progressing and is used to assess how the disease affects the daily living abilities of the subject and determine appropriate treatment and prognosis. The score ranges from Grade 0 to Grade 5, where Grade 0 = Fully active, able to carry on all pre-disease performance without restriction, Grade 1 = Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature (like light house work, office work), Grade 2 = Ambulatory and capable of all self-care but unable to carry out any work activities, Grade 3 = Capable of only limited self-care, confined to bed or chair more than 50% of waking hours and Grade 4 = Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair, Grade 5 = Death. Number of subjects with shift in ECOG PS Score to 1 or Higher Than 1 were reported. Safety-Maintenance Analysis Set was used.

End point type	Secondary

End point timeframe:

From randomization into maintenance phase up to 1276 days

End point values	Chemotherapy + Best Supportive Care (BSC)	Avelumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	238	243		
Units: subjects	140	144		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From randomisation into maintenance phase up to 1276 days

Adverse event reporting additional description:

Safety-Maintenance Analysis Set included all subjects who were administered any dose of the maintenance phase study medication or subjects randomised to the chemotherapy arm who are designated to receive BSC only. Subjects included in the treatment arm according to study treatment actually received.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	22.0

Reporting groups

Reporting group title	Chemotherapy + Best Supportive Care (BSC)

Reporting group description:

Subjects received 85mg/m^2 of Oxaliplatin IV infusion on Day 1 along with (200/400)mg/m^2 of leucovorin on Day 1 followed by 2600mg/m^2 of 5-Fluorouracil IV infusion on Day 1/400mg/m^2 IV push on Day 1 & 2400mg/m^2 IV infusion every 2 weeks up to 12weeks/Oxaliplatin at 130mg/m^2 IV on Day 1 along with 1000mg/m^2 of capecitabine twice daily for 2weeks followed by 1week rest period given every3weeks up to 12weeks in Induction phase. In Maintenance Phase, subjects continued same regimen of oxaliplatin-fluoropyrimidine doublet chemotherapy as they received during Induction Phase until disease progression, significant clinical deterioration, unacceptable toxicity/discontinuation. Subjects who were not deemed eligible to receive chemotherapy at dose & schedule specified above received BSC alone once every3weeks. BSC: treatment administered with intent to maximize quality of life without a specific antineoplastic regimen & was based on Investigator's discretion.

Reporting group title	Avelumab

Reporting group description:

Oxaliplatin was administered at a dose of 85 mg/m^2 as a continuous intravenous (IV) infusion on Day 1 along with leucovorin at a dose of 200 mg/m^2 or 400 mg/m^2 on Day 1 followed by 5-Fluorouracil at a dose of 2600 mg/m^2 IV continuous infusion over 24 hours on Day 1 or at 400 mg/m^2 IV push on Day 1 and 2400 mg/m^2 IV continuous infusion over 46-48 hours (Day 1 and 2) every 2 weeks up to 12 weeks (or) Oxaliplatin at 130 mg/m^2 IV on Day 1 along with capecitabine at a dose of 1000 mg/m^2 twice daily for 2 weeks followed by a 1-week rest period given every 3 weeks for up to 12 weeks in Induction phase. In Maintenance phase, subjects received avelumab as a 1-hour intravenous (IV) infusion at 10 milligrams per kilogram (mg/kg) once every 2-week treatment cycle until progressive disease or unacceptable toxicity or discontinuation.

Serious adverse events	Chemotherapy + Best Supportive Care (BSC)	Avelumab	
Total subjects affected by serious adverse events			
subjects affected / exposed	75 / 238 (31.51%)	89 / 243 (36.63%)	
number of deaths (all causes)	13	16	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Metastases to meninges			

subjects affected / exposed	1 / 238 (0.42%)	2 / 243 (0.82%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 2	
Tumour haemorrhage			
subjects affected / exposed	0 / 238 (0.00%)	1 / 243 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malignant ascites			
subjects affected / exposed	0 / 238 (0.00%)	1 / 243 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastases to liver			
subjects affected / exposed	1 / 238 (0.42%)	0 / 243 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophageal carcinoma recurrent			
subjects affected / exposed	0 / 238 (0.00%)	1 / 243 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	0 / 238 (0.00%)	1 / 243 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Embolism			
subjects affected / exposed	1 / 238 (0.42%)	2 / 243 (0.82%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypotension			
subjects affected / exposed	1 / 238 (0.42%)	0 / 243 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			

Nephrostomy			
subjects affected / exposed	0 / 238 (0.00%)	1 / 243 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Disease progression			
subjects affected / exposed	6 / 238 (2.52%)	14 / 243 (5.76%)	
occurrences causally related to treatment / all	0 / 6	0 / 14	
deaths causally related to treatment / all	0 / 3	0 / 9	
Pyrexia			
subjects affected / exposed	2 / 238 (0.84%)	4 / 243 (1.65%)	
occurrences causally related to treatment / all	1 / 2	1 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Asthenia			
subjects affected / exposed	0 / 238 (0.00%)	1 / 243 (0.41%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malaise			
subjects affected / exposed	0 / 238 (0.00%)	1 / 243 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General physical health deterioration			
subjects affected / exposed	1 / 238 (0.42%)	1 / 243 (0.41%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Immune system disorders			
Drug hypersensitivity			
subjects affected / exposed	3 / 238 (1.26%)	1 / 243 (0.41%)	
occurrences causally related to treatment / all	3 / 3	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Contrast media reaction			
subjects affected / exposed	0 / 238 (0.00%)	1 / 243 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Respiratory, thoracic and mediastinal disorders			
Pneumonitis			
subjects affected / exposed	1 / 238 (0.42%)	4 / 243 (1.65%)	
occurrences causally related to treatment / all	1 / 1	4 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Asphyxia			
subjects affected / exposed	0 / 238 (0.00%)	2 / 243 (0.82%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia aspiration			
subjects affected / exposed	0 / 238 (0.00%)	1 / 243 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	1 / 238 (0.42%)	2 / 243 (0.82%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	1 / 238 (0.42%)	1 / 243 (0.41%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
Acute respiratory failure			
subjects affected / exposed	1 / 238 (0.42%)	0 / 243 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung disorder			
subjects affected / exposed	1 / 238 (0.42%)	0 / 243 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			
subjects affected / exposed	3 / 238 (1.26%)	0 / 243 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Respiratory failure			
subjects affected / exposed	1 / 238 (0.42%)	0 / 243 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Product issues			
Device occlusion			
subjects affected / exposed	1 / 238 (0.42%)	0 / 243 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Lipase increased			
subjects affected / exposed	1 / 238 (0.42%)	0 / 243 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood bilirubin increased			
subjects affected / exposed	0 / 238 (0.00%)	1 / 243 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Anastomotic ulcer haemorrhage			
subjects affected / exposed	0 / 238 (0.00%)	1 / 243 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anastomotic stenosis			
subjects affected / exposed	0 / 238 (0.00%)	1 / 243 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Overdose			
subjects affected / exposed	1 / 238 (0.42%)	1 / 243 (0.41%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chemical burn of respiratory tract			

subjects affected / exposed	1 / 238 (0.42%)	0 / 243 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal stoma complication			
subjects affected / exposed	1 / 238 (0.42%)	0 / 243 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrostomy tube site complication			
subjects affected / exposed	1 / 238 (0.42%)	0 / 243 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infusion related reaction			
subjects affected / exposed	3 / 238 (1.26%)	0 / 243 (0.00%)	
occurrences causally related to treatment / all	3 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Limb injury			
subjects affected / exposed	1 / 238 (0.42%)	0 / 243 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Myocardial infarction			
subjects affected / exposed	0 / 238 (0.00%)	1 / 243 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocarditis			
subjects affected / exposed	0 / 238 (0.00%)	1 / 243 (0.41%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pericarditis			
subjects affected / exposed	0 / 238 (0.00%)	1 / 243 (0.41%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prinzmetal angina			

subjects affected / exposed	0 / 238 (0.00%)	1 / 243 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute coronary syndrome			
subjects affected / exposed	1 / 238 (0.42%)	0 / 243 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Acute myocardial infarction			
subjects affected / exposed	1 / 238 (0.42%)	0 / 243 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary artery disease			
subjects affected / exposed	1 / 238 (0.42%)	0 / 243 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrioventricular block complete			
subjects affected / exposed	1 / 238 (0.42%)	0 / 243 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pericardial effusion			
subjects affected / exposed	2 / 238 (0.84%)	0 / 243 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Headache			
subjects affected / exposed	0 / 238 (0.00%)	1 / 243 (0.41%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Seizure			
subjects affected / exposed	0 / 238 (0.00%)	1 / 243 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral infarction			

subjects affected / exposed	2 / 238 (0.84%)	0 / 243 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cerebrovascular accident			
subjects affected / exposed	1 / 238 (0.42%)	0 / 243 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Dizziness			
subjects affected / exposed	1 / 238 (0.42%)	0 / 243 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhage intracranial			
subjects affected / exposed	1 / 238 (0.42%)	0 / 243 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	3 / 238 (1.26%)	2 / 243 (0.82%)	
occurrences causally related to treatment / all	1 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Neutropenia			
subjects affected / exposed	3 / 238 (1.26%)	1 / 243 (0.41%)	
occurrences causally related to treatment / all	3 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile neutropenia			
subjects affected / exposed	1 / 238 (0.42%)	0 / 243 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemolytic anaemia			
subjects affected / exposed	1 / 238 (0.42%)	0 / 243 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombotic microangiopathy			

subjects affected / exposed	1 / 238 (0.42%)	0 / 243 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Eye disorders			
Cataract			
subjects affected / exposed	1 / 238 (0.42%)	0 / 243 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diplopia			
subjects affected / exposed	0 / 238 (0.00%)	1 / 243 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Vomiting			
subjects affected / exposed	4 / 238 (1.68%)	4 / 243 (1.65%)	
occurrences causally related to treatment / all	3 / 4	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dysphagia			
subjects affected / exposed	2 / 238 (0.84%)	6 / 243 (2.47%)	
occurrences causally related to treatment / all	0 / 2	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain			
subjects affected / exposed	2 / 238 (0.84%)	4 / 243 (1.65%)	
occurrences causally related to treatment / all	0 / 2	1 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileus			
subjects affected / exposed	0 / 238 (0.00%)	3 / 243 (1.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis			
subjects affected / exposed	0 / 238 (0.00%)	3 / 243 (1.23%)	
occurrences causally related to treatment / all	0 / 0	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ascites			

subjects affected / exposed	3 / 238 (1.26%)	3 / 243 (1.23%)	
occurrences causally related to treatment / all	0 / 3	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Obstruction gastric			
subjects affected / exposed	4 / 238 (1.68%)	3 / 243 (1.23%)	
occurrences causally related to treatment / all	0 / 4	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	0 / 238 (0.00%)	2 / 243 (0.82%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal obstruction			
subjects affected / exposed	0 / 238 (0.00%)	2 / 243 (0.82%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Constipation			
subjects affected / exposed	1 / 238 (0.42%)	1 / 243 (0.41%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric stenosis			
subjects affected / exposed	2 / 238 (0.84%)	1 / 243 (0.41%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal haemorrhage			
subjects affected / exposed	1 / 238 (0.42%)	1 / 243 (0.41%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Large intestine perforation			
subjects affected / exposed	0 / 238 (0.00%)	1 / 243 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophageal stenosis			

subjects affected / exposed	0 / 238 (0.00%)	1 / 243 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small intestinal obstruction			
subjects affected / exposed	0 / 238 (0.00%)	1 / 243 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis acute			
subjects affected / exposed	0 / 238 (0.00%)	1 / 243 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis			
subjects affected / exposed	0 / 238 (0.00%)	1 / 243 (0.41%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper gastrointestinal haemorrhage			
subjects affected / exposed	2 / 238 (0.84%)	1 / 243 (0.41%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subileus			
subjects affected / exposed	1 / 238 (0.42%)	1 / 243 (0.41%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal hernia			
subjects affected / exposed	1 / 238 (0.42%)	0 / 243 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspepsia			
subjects affected / exposed	1 / 238 (0.42%)	0 / 243 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain upper			

subjects affected / exposed	1 / 238 (0.42%)	0 / 243 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastritis			
subjects affected / exposed	0 / 238 (0.00%)	1 / 243 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric haemorrhage			
subjects affected / exposed	4 / 238 (1.68%)	0 / 243 (0.00%)	
occurrences causally related to treatment / all	1 / 4	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Large intestinal obstruction			
subjects affected / exposed	1 / 238 (0.42%)	0 / 243 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal ischaemia			
subjects affected / exposed	1 / 238 (0.42%)	0 / 243 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric ulcer			
subjects affected / exposed	1 / 238 (0.42%)	0 / 243 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Melaena			
subjects affected / exposed	1 / 238 (0.42%)	0 / 243 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	2 / 238 (0.84%)	0 / 243 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Jaundice cholestatic			

subjects affected / exposed	1 / 238 (0.42%)	2 / 243 (0.82%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bile duct stenosis			
subjects affected / exposed	0 / 238 (0.00%)	1 / 243 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bile duct obstruction			
subjects affected / exposed	1 / 238 (0.42%)	1 / 243 (0.41%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis acute			
subjects affected / exposed	0 / 238 (0.00%)	1 / 243 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic failure			
subjects affected / exposed	1 / 238 (0.42%)	1 / 243 (0.41%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
Cholangitis			
subjects affected / exposed	1 / 238 (0.42%)	0 / 243 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatitis			
subjects affected / exposed	1 / 238 (0.42%)	0 / 243 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Jaundice			
subjects affected / exposed	1 / 238 (0.42%)	0 / 243 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Hydronephrosis			

subjects affected / exposed	1 / 238 (0.42%)	1 / 243 (0.41%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tubulointerstitial nephritis			
subjects affected / exposed	0 / 238 (0.00%)	1 / 243 (0.41%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematuria			
subjects affected / exposed	1 / 238 (0.42%)	0 / 243 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal tubular necrosis			
subjects affected / exposed	1 / 238 (0.42%)	0 / 243 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract obstruction			
subjects affected / exposed	1 / 238 (0.42%)	0 / 243 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
Adrenal insufficiency			
subjects affected / exposed	0 / 238 (0.00%)	1 / 243 (0.41%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperthyroidism			
subjects affected / exposed	0 / 238 (0.00%)	1 / 243 (0.41%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypophysitis			
subjects affected / exposed	0 / 238 (0.00%)	1 / 243 (0.41%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			

Arthralgia			
subjects affected / exposed	0 / 238 (0.00%)	2 / 243 (0.82%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Back pain			
subjects affected / exposed	1 / 238 (0.42%)	2 / 243 (0.82%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Groin pain			
subjects affected / exposed	0 / 238 (0.00%)	1 / 243 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal pain			
subjects affected / exposed	1 / 238 (0.42%)	0 / 243 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myositis			
subjects affected / exposed	0 / 238 (0.00%)	1 / 243 (0.41%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Device related infection			
subjects affected / exposed	0 / 238 (0.00%)	2 / 243 (0.82%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	2 / 238 (0.84%)	2 / 243 (0.82%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza			
subjects affected / exposed	1 / 238 (0.42%)	1 / 243 (0.41%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			

subjects affected / exposed	2 / 238 (0.84%)	2 / 243 (0.82%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower respiratory tract infection			
subjects affected / exposed	1 / 238 (0.42%)	1 / 243 (0.41%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory tract infection			
subjects affected / exposed	0 / 238 (0.00%)	1 / 243 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung infection			
subjects affected / exposed	0 / 238 (0.00%)	1 / 243 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enteritis infectious			
subjects affected / exposed	1 / 238 (0.42%)	0 / 243 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Septic shock			
subjects affected / exposed	1 / 238 (0.42%)	0 / 243 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	1 / 238 (0.42%)	0 / 243 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound infection			
subjects affected / exposed	1 / 238 (0.42%)	0 / 243 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Decreased appetite			

subjects affected / exposed	4 / 238 (1.68%)	4 / 243 (1.65%)	
occurrences causally related to treatment / all	2 / 4	1 / 4	
deaths causally related to treatment / all	0 / 0	0 / 1	
Dehydration			
subjects affected / exposed	1 / 238 (0.42%)	1 / 243 (0.41%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Failure to thrive			
subjects affected / exposed	0 / 238 (0.00%)	1 / 243 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia			
subjects affected / exposed	2 / 238 (0.84%)	0 / 243 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypokalaemia			
subjects affected / exposed	1 / 238 (0.42%)	0 / 243 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypophagia			
subjects affected / exposed	1 / 238 (0.42%)	0 / 243 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Chemotherapy + Best Supportive Care (BSC)	Avelumab	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	203 / 238 (85.29%)	191 / 243 (78.60%)	
Investigations			
Blood alkaline phosphatase increased			
subjects affected / exposed	16 / 238 (6.72%)	17 / 243 (7.00%)	
occurrences (all)	16	17	

Aspartate aminotransferase increased			
subjects affected / exposed	17 / 238 (7.14%)	17 / 243 (7.00%)	
occurrences (all)	17	17	
Gamma-glutamyltransferase increased			
subjects affected / exposed	15 / 238 (6.30%)	18 / 243 (7.41%)	
occurrences (all)	15	18	
Blood creatine phosphokinase increased			
subjects affected / exposed	6 / 238 (2.52%)	19 / 243 (7.82%)	
occurrences (all)	6	19	
Blood cholesterol increased			
subjects affected / exposed	10 / 238 (4.20%)	15 / 243 (6.17%)	
occurrences (all)	10	15	
Weight decreased			
subjects affected / exposed	19 / 238 (7.98%)	12 / 243 (4.94%)	
occurrences (all)	19	12	
Alanine aminotransferase increased			
subjects affected / exposed	12 / 238 (5.04%)	13 / 243 (5.35%)	
occurrences (all)	12	13	
Amylase increased			
subjects affected / exposed	13 / 238 (5.46%)	14 / 243 (5.76%)	
occurrences (all)	13	14	
Lipase increased			
subjects affected / exposed	22 / 238 (9.24%)	15 / 243 (6.17%)	
occurrences (all)	22	15	
Blood bilirubin increased			
subjects affected / exposed	13 / 238 (5.46%)	9 / 243 (3.70%)	
occurrences (all)	13	9	
Platelet count decreased			
subjects affected / exposed	34 / 238 (14.29%)	6 / 243 (2.47%)	
occurrences (all)	34	6	
Neutrophil count decreased			
subjects affected / exposed	35 / 238 (14.71%)	4 / 243 (1.65%)	
occurrences (all)	35	4	
Injury, poisoning and procedural complications			

Infusion related reaction			
subjects affected / exposed	7 / 238 (2.94%)	18 / 243 (7.41%)	
occurrences (all)	7	18	
Vascular disorders			
Hypertension			
subjects affected / exposed	6 / 238 (2.52%)	14 / 243 (5.76%)	
occurrences (all)	6	14	
Nervous system disorders			
Dizziness			
subjects affected / exposed	8 / 238 (3.36%)	13 / 243 (5.35%)	
occurrences (all)	8	13	
Peripheral sensory neuropathy			
subjects affected / exposed	42 / 238 (17.65%)	14 / 243 (5.76%)	
occurrences (all)	42	14	
Headache			
subjects affected / exposed	6 / 238 (2.52%)	17 / 243 (7.00%)	
occurrences (all)	6	17	
Neuropathy peripheral			
subjects affected / exposed	32 / 238 (13.45%)	7 / 243 (2.88%)	
occurrences (all)	32	7	
Paraesthesia			
subjects affected / exposed	22 / 238 (9.24%)	11 / 243 (4.53%)	
occurrences (all)	22	11	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	29 / 238 (12.18%)	35 / 243 (14.40%)	
occurrences (all)	29	35	
Asthenia			
subjects affected / exposed	24 / 238 (10.08%)	30 / 243 (12.35%)	
occurrences (all)	24	30	
Pyrexia			
subjects affected / exposed	28 / 238 (11.76%)	28 / 243 (11.52%)	
occurrences (all)	28	28	
Chills			
subjects affected / exposed	4 / 238 (1.68%)	19 / 243 (7.82%)	
occurrences (all)	4	19	

Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	48 / 238 (20.17%)	35 / 243 (14.40%)	
occurrences (all)	48	35	
Neutropenia			
subjects affected / exposed	36 / 238 (15.13%)	12 / 243 (4.94%)	
occurrences (all)	36	12	
Leukopenia			
subjects affected / exposed	17 / 238 (7.14%)	9 / 243 (3.70%)	
occurrences (all)	17	9	
Thrombocytopenia			
subjects affected / exposed	34 / 238 (14.29%)	8 / 243 (3.29%)	
occurrences (all)	34	8	
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	52 / 238 (21.85%)	41 / 243 (16.87%)	
occurrences (all)	52	41	
Abdominal Pain			
subjects affected / exposed	24 / 238 (10.08%)	34 / 243 (13.99%)	
occurrences (all)	24	34	
Vomiting			
subjects affected / exposed	27 / 238 (11.34%)	30 / 243 (12.35%)	
occurrences (all)	27	30	
Constipation			
subjects affected / exposed	18 / 238 (7.56%)	28 / 243 (11.52%)	
occurrences (all)	18	28	
Diarrhoea			
subjects affected / exposed	39 / 238 (16.39%)	27 / 243 (11.11%)	
occurrences (all)	39	27	
Abdominal pain upper			
subjects affected / exposed	5 / 238 (2.10%)	22 / 243 (9.05%)	
occurrences (all)	5	22	
Dyspepsia			
subjects affected / exposed	15 / 238 (6.30%)	11 / 243 (4.53%)	
occurrences (all)	15	11	
Skin and subcutaneous tissue disorders			

Pruritus			
subjects affected / exposed	2 / 238 (0.84%)	17 / 243 (7.00%)	
occurrences (all)	2	17	
Rash			
subjects affected / exposed	5 / 238 (2.10%)	15 / 243 (6.17%)	
occurrences (all)	5	15	
Palmar-plantar erythrodysaesthesia syndrome			
subjects affected / exposed	19 / 238 (7.98%)	1 / 243 (0.41%)	
occurrences (all)	19	1	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	9 / 238 (3.78%)	16 / 243 (6.58%)	
occurrences (all)	9	16	
Musculoskeletal and connective tissue disorders			
Back Pain			
subjects affected / exposed	7 / 238 (2.94%)	17 / 243 (7.00%)	
occurrences (all)	7	17	
Arthralgia			
subjects affected / exposed	4 / 238 (1.68%)	16 / 243 (6.58%)	
occurrences (all)	4	16	
Infections and infestations			
Upper respiratory tract infection			
subjects affected / exposed	12 / 238 (5.04%)	11 / 243 (4.53%)	
occurrences (all)	12	11	
Metabolism and nutrition disorders			
Hyperglycaemia			
subjects affected / exposed	9 / 238 (3.78%)	14 / 243 (5.76%)	
occurrences (all)	9	14	
Decreased appetite			
subjects affected / exposed	42 / 238 (17.65%)	26 / 243 (10.70%)	
occurrences (all)	42	26	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
17 July 2019	• To change the primary objective to include OS in PD-L1+ subjects. In addition to OS in all randomised subjects, where PD-L1 status was defined based on a 1% cut-off for tumor cells. • As per the results of the PD-L1 scoring with validated assay available in June 2019, the number of previously projected events (Protocol Version 6) in the PD-L1+ subjects was not be reached. Thus, the condition of meeting the pre-specified number of PD-L1+ events for the Final Analysis data cut-off has been removed as a trigger for the Final Analysis. The Final Analysis was triggered by the events in the ITT population as well as a minimum follow-up time of 18 months for primary analysis which was expected to ensure sufficiently mature data for OS in PDL1+ subjects. The primary analysis of OS in PD-L1+ subjects was conducted at the same time as OS in all randomized subjects with substantially reduced power. • The sampling for Pharmacokinetic (PK) and Antidrug Antibody Analysis (ADA) was limited to 2 years from randomization, as further sampling would not add value to pharmacokinetic and immunogenicity evaluation. Therefore, the last sampling point was at Week 109 to avoid unnecessary burden to the subjects.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported