Clinical trial results:
A Phase III Open-label, Multicenter Trial of Avelumab (MSB0010718C) as a Third-line Treatment of Unresectable, Recurrent, or Metastatic Gastric or Gastroesophageal Junction Adenocarcinoma

Summary

EudraCT number	2015-003301-42
Trial protocol	DE BE ES CZ FR PL IT
Global end of trial date	13 November 2019

Results information

Result version number	v1 (current)
This version publication date	22 November 2020
First version publication date	22 November 2020

Trial information

Trial identification

Sponsor protocol code	EMR100070-008

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02625623
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Merck KGaA, Darmstadt, Germany
Sponsor organisation address	Frankfurter Strasse 250,, Darmstadt, Germany, 64293
Public contact	Communication Centre, Merck KGaA, Darmstadt, Germany, +49 6151 72 5200, service@merckgroup.com
Scientific contact	Communication Centre, Merck KGaA, Darmstadt, Germany, +49 6151 72 5200, 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	13 November 2019
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	13 November 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective was to demonstrate superiority with regard to Overall Survival (OS) of avelumab plus best supportive care (BSC) versus physician’s choice (chosen from a pre-specified list of therapeutic options) plus BSC.

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	28 December 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	Belgium: 43
Country: Number of subjects enrolled	France: 38
Country: Number of subjects enrolled	Germany: 28
Country: Number of subjects enrolled	Italy: 28
Country: Number of subjects enrolled	Spain: 21
Country: Number of subjects enrolled	Czechia: 8
Country: Number of subjects enrolled	Poland: 12
Country: Number of subjects enrolled	Romania: 19
Country: Number of subjects enrolled	United States: 25
Country: Number of subjects enrolled	Chile: 20
Country: Number of subjects enrolled	Russian Federation: 28
Country: Number of subjects enrolled	Japan: 37
Country: Number of subjects enrolled	Australia: 8
Country: Number of subjects enrolled	Korea, Republic of: 56
Worldwide total number of subjects	371
EEA total number of subjects	197

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)	230
From 65 to 84 years	140
85 years and over	1

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

First subject (informed consent): 28 December 2015 and Last subject last visit: 13 November 2019.

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	Physician choice chemotherapy + Best Supportive Care (BSC)

Arm description:

Subjects received BSC plus physician’s choice chemotherapy. Chemotherapy comprised of one of the following: intravenous (IV) infusion of paclitaxel at a dose of 80 milligrams per meter square (mg/m^2) on Days 1, 8 and 15 of a 4-week treatment cycle until progressive disease or unacceptable toxicity OR irinotecan at a dose of 150 mg/m^2 on Days 1 and 15 of a 4-week treatment cycle until progressive disease or unacceptable toxicity. Subjects who were not deemed eligible to receive paclitaxel or irinotecan at the dose and schedule specified above received BSC alone once every 3 weeks. BSC was defined as treatment administered with the intent to maximize quality of life without a specific antineoplastic regimen and was based on investigator's discretion.

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

Dosage and administration details:

Irinotecan was administered intravenously at a dose of 150 milligrams per square meter (mg/m^2) on Days 1 and 15 of a 4-week treatment cycle until disease progression or unacceptable toxicities along with best supportive care (BSC).

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

Dosage and administration details:

Paclitaxel was administered intravenously at a dose of 80 mg/m^2 on Days 1, 8 and 15 of a 4-week treatment cycle until disease progression or unacceptable toxicities along with BSC.

Arm title	Avelumab + BSC

Arm description:

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 along with BSC. BSC was defined as treatment administered with the intent to maximize quality of life without a specific antineoplastic regimen and was based on investigator's discretion.

Arm type	Active comparator

Investigational medicinal product name	Avelumab
Investigational medicinal product code	
Other name	MSB0010718C Anti PD-L1
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Avelumab was administered as a 1-hour intravenous infusion at 10 milligrams per kilogram (mg/kg) once every 2-week treatment cycle until confirmed progressive disease or unacceptable toxicity along with best supportive care (BSC).

Number of subjects in period 1	Physician choice chemotherapy + Best Supportive Care (BSC)	Avelumab + BSC
Started	186	185
Treated	177	184
Completed	177	184
Not completed	9	1
Subjects randomized not treated	9	1

Baseline characteristics

Reporting groups

Reporting group title	Physician choice chemotherapy + Best Supportive Care (BSC)

Reporting group description:

Subjects received BSC plus physician’s choice chemotherapy. Chemotherapy comprised of one of the following: intravenous (IV) infusion of paclitaxel at a dose of 80 milligrams per meter square (mg/m^2) on Days 1, 8 and 15 of a 4-week treatment cycle until progressive disease or unacceptable toxicity OR irinotecan at a dose of 150 mg/m^2 on Days 1 and 15 of a 4-week treatment cycle until progressive disease or unacceptable toxicity. Subjects who were not deemed eligible to receive paclitaxel or irinotecan at the dose and schedule specified above received BSC alone once every 3 weeks. BSC was defined as treatment administered with the intent to maximize quality of life without a specific antineoplastic regimen and was based on investigator's discretion.

Reporting group title	Avelumab + BSC

Reporting group description:

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 along with BSC. BSC was defined as treatment administered with the intent to maximize quality of life without a specific antineoplastic regimen and was based on investigator's discretion.

Reporting group values	Physician choice chemotherapy + Best Supportive Care (BSC)	Avelumab + BSC	Total
Number of subjects	186	185	371
Age Categorical Units:			
Age Continuous Units: years			
arithmetic mean	60.1	58.8	
standard deviation	± 12.93	± 11.66	-
Gender Categorical Units: subjects			
Female	59	45	104
Male	127	140	267

End points

End points reporting groups

Reporting group title	Physician choice chemotherapy + Best Supportive Care (BSC)

Reporting group description:

Subjects received BSC plus physician's choice chemotherapy. Chemotherapy comprised of one of the following: intravenous (IV) infusion of paclitaxel at a dose of 80 milligrams per meter square (mg/m^2) on Days 1, 8 and 15 of a 4-week treatment cycle until progressive disease or unacceptable toxicity OR irinotecan at a dose of 150 mg/m^2 on Days 1 and 15 of a 4-week treatment cycle until progressive disease or unacceptable toxicity. Subjects who were not deemed eligible to receive paclitaxel or irinotecan at the dose and schedule specified above received BSC alone once every 3 weeks. BSC was defined as treatment administered with the intent to maximize quality of life without a specific antineoplastic regimen and was based on investigator's discretion.

Reporting group title	Avelumab + BSC

Reporting group description:

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 along with BSC. BSC was defined as treatment administered with the intent to maximize quality of life without a specific antineoplastic regimen and was based on investigator's discretion.

Primary: Overall Survival (OS)

End point title	Overall Survival (OS)

End point description:

OS was defined as the time from randomization 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 (FAS) included all subjects who were randomized to study treatment.

End point type	Primary

End point timeframe:

From randomization up to 627 days

End point values	Physician choice chemotherapy + Best Supportive Care (BSC)	Avelumab + BSC		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	186	185		
Units: months				
median (confidence interval 95%)	5.0 (4.5 to 6.3)	4.6 (3.6 to 5.7)		

Statistical analyses

Statistical analysis title	Treatment Comparison
Comparison groups	Physician choice chemotherapy + Best Supportive Care (BSC) v Avelumab + BSC

Number of subjects included in analysis	371
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8078 [1]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.11
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.88
upper limit	1.41

Notes:

[1] - The treatment arms were compared using a stratified, 1-sided, log rank Test. The stratification factor was region (Asia versus non Asia).

Secondary: Progression Free Survival (PFS)

End point title	Progression Free Survival (PFS)

End point description:

The PFS time was defined as the time from date of randomization 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). 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. FAS included all subjects who were randomized to study treatment.

End point type	Secondary

End point timeframe:

From randomization up to 627 days

End point values	Physician choice chemotherapy + Best Supportive Care (BSC)	Avelumab + BSC		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	186	185		
Units: months				
median (confidence interval 95%)	2.7 (1.81 to 2.83)	1.4 (1.38 to 1.45)		

Statistical analyses

Statistical analysis title	Treatment Comparison
Comparison groups	Physician choice chemotherapy + Best Supportive Care (BSC) v Avelumab + BSC

Number of subjects included in analysis	371
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 1 [2]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.73
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.36
upper limit	2.21

Notes:

[2] - The treatment arms were compared using a stratified, 1-sided, log rank Test. The stratification factor was region (Asia versus non Asia).

Secondary: Best Overall Response (BOR)

End point title	Best Overall Response (BOR)

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 randomization until disease progression or 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=progression <=2 weeks after date of randomization (and not qualifying for CR, PR or SD). FAS was used.

End point type	Secondary

End point timeframe:

From randomization up to 627 days

End point values	Physician choice chemotherapy + Best Supportive Care (BSC)	Avelumab + BSC		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	186	185		
Units: subjects				
Complete Response	1	1		
Partial response	7	3		
Stable disease	62	30		
Non-complete response/ Non-progressive disease	12	7		
Progressive disease	59	94		
Non-evaluable	45	50		

Statistical analyses

No statistical analyses for this end point

Secondary: Objective Response Rate (ORR)

End point title	Objective Response Rate (ORR)

End point description:

The ORR defined as the percentage of all randomized subjects with a confirmed best overall response (BOR) of partial response (PR),or complete response (CR) according to RECIST v1.1 and as adjudicated by the Independent Review Committee (IRC). 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. FAS included all subjects who were randomized to study treatment.

End point type	Secondary

End point timeframe:

From randomization up to 627 days

End point values	Physician choice chemotherapy + Best Supportive Care (BSC)	Avelumab + BSC		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	186	185		
Units: percentage of subjects				
number (confidence interval 95%)	4.3 (1.9 to 8.3)	2.2 (0.6 to 5.4)		

Statistical analyses

Statistical analysis title	Treatment Comparison
Comparison groups	Physician choice chemotherapy + Best Supportive Care (BSC) v Avelumab + BSC
Number of subjects included in analysis	371
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8764 [3]
Method	Cochran-Mantel-Haenszel

Notes:

[3] - The treatment arms were compared by 1-sided CMH test. The stratification factor was region (Asia versus non Asia).

Secondary: Change From Baseline in European Quality of Life 5-dimensions (EQ-5D-5L) Health Outcome Questionnaire Through Composite Index Score at End Of Treatment (EOT)

End point title	Change From Baseline in European Quality of Life 5-dimensions (EQ-5D-5L) Health Outcome Questionnaire Through Composite Index Score at End Of Treatment (EOT)

End point description:

EQ-5D-5L was 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 were 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 a subset of the FAS and included FAS subjects who met the following criteria: had 1 Baseline HRQoL assessment, had at least 1 post-Baseline HRQoL questionnaire completed. Here, "Number of Subjects Analyzed" signifies those subjects who were evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Baseline, EOT (up to Week 66)

End point values	Physician choice chemotherapy + Best Supportive Care (BSC)	Avelumab + BSC		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	92	74		
Units: units on a scale				
arithmetic mean (standard deviation)	-0.103 (± 0.2113)	-0.144 (± 0.2088)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in European Quality of Life 5-dimensions (EQ-5D-5L) Health Outcome Questionnaire Through Visual Analogue Scale (VAS) at End Of Treatment (EOT)

End point title	Change From Baseline in European Quality of Life 5-dimensions (EQ-5D-5L) Health Outcome Questionnaire Through Visual Analogue Scale (VAS) at End Of Treatment (EOT)

End point description:

EQ-5D-5L was 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 were 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 a subset of the FAS and included FAS subjects who met the following criteria: had 1 Baseline HRQoL assessment, had at least 1 post-Baseline HRQoL questionnaire completed. Here, "Number of Subjects Analyzed" signifies those subjects who were evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Baseline, EOT (up to Week 66)

End point values	Physician choice chemotherapy + Best Supportive Care (BSC)	Avelumab + BSC		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	92	74		
Units: millimeter (mm)				
arithmetic mean (standard deviation)	-12.3 (± 19.22)	-13.6 (± 19.76)		

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 at End Of Treatment (EOT)

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 at End Of Treatment (EOT)

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 a subset of the FAS and included FAS subjects who met the following criteria: had 1 Baseline HRQoL assessment and had at least 1 post-Baseline HRQoL questionnaire completed. Here, "Number of Subjects Analyzed" signifies those subjects who were evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Baseline, EOT (up to Week 66)

End point values	Physician choice chemotherapy + Best Supportive Care (BSC)	Avelumab + BSC		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	92	74		
Units: units on a scale				
arithmetic mean (standard deviation)	-10.14 (± 19.914)	-15.77 (± 19.437)		

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 at End Of Treatment (EOT)

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 at End Of Treatment (EOT)

End point description:

The 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 a subset of the FAS and included FAS subjects who met the following criteria: had 1 Baseline HRQoL assessment and had at least 1 post-Baseline HRQoL questionnaire completed. "Number of Subjects Analyzed" signifies those subjects who were evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Baseline, EOT (up to Week 66)

End point values	Physician choice chemotherapy + Best Supportive Care (BSC)	Avelumab + BSC		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	92	74		
Units: units on a scale				
arithmetic mean (standard deviation)				
Dysphagia	7.25 (± 28.551)	15.32 (± 29.120)		
Pain	8.88 (± 22.402)	9.23 (± 21.527)		
Reflux	4.59 (± 20.184)	7.96 (± 18.347)		
Eating Restrictions	9.24 (± 22.661)	13.29 (± 21.276)		
Anxiety	7.49 (± 21.860)	6.61 (± 19.456)		
Dry Mouth	15.94 (± 27.725)	9.01 (± 28.827)		
Tasting	9.42 (± 25.832)	2.25 (± 35.897)		
Body Image	5.07 (± 28.787)	4.05 (± 27.561)		
Hair Loss	4.71 (± 33.546)	-13.96 (± 26.029)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From randomization up to 627 days

Adverse event reporting additional description:

All subjects who received at least 1 dose of study drug (that is, treated subjects) were included in safety population.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	20.0

Reporting groups

Reporting group title	Physician choice chemotherapy + Best Supportive Care (BSC)

Reporting group description:

Subjects received BSC plus physician’s choice chemotherapy. Chemotherapy comprised of one of the following: intravenous (IV) infusion of paclitaxel at a dose of 80 milligrams per meter square (mg/m^2) on Days 1, 8 and 15 of a 4-week treatment cycle until progressive disease or unacceptable toxicity OR irinotecan at a dose of 150 mg/m^2 on Days 1 and 15 of a 4-week treatment cycle until progressive disease or unacceptable toxicity. Subjects who were not deemed eligible to receive paclitaxel or irinotecan at the dose and schedule specified above received BSC alone once every 3 weeks. BSC was defined as treatment administered with the intent to maximize quality of life without a specific antineoplastic regimen and was based on investigator's discretion.

Reporting group title	Avelumab + BSC

Reporting group description:

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 along with BSC. BSC was defined as treatment administered with the intent to maximize quality of life without a specific antineoplastic regimen and was based on investigator's discretion.

Serious adverse events	Physician choice chemotherapy + Best Supportive Care (BSC)	Avelumab + BSC	
Total subjects affected by serious adverse events			
subjects affected / exposed	81 / 177 (45.76%)	90 / 184 (48.91%)	
number of deaths (all causes)	131	142	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Lymphangiosis carcinomatosa			
subjects affected / exposed	0 / 177 (0.00%)	1 / 184 (0.54%)	
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 / 177 (0.00%)	1 / 184 (0.54%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malignant neoplasm progression			
subjects affected / exposed	0 / 177 (0.00%)	1 / 184 (0.54%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Metastases to central nervous system			
subjects affected / exposed	0 / 177 (0.00%)	1 / 184 (0.54%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastases to spine			
subjects affected / exposed	0 / 177 (0.00%)	1 / 184 (0.54%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neoplasm swelling			
subjects affected / exposed	0 / 177 (0.00%)	1 / 184 (0.54%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pericarditis malignant			
subjects affected / exposed	0 / 177 (0.00%)	1 / 184 (0.54%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tumour associated fever			
subjects affected / exposed	0 / 177 (0.00%)	1 / 184 (0.54%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tumour pain			
subjects affected / exposed	2 / 177 (1.13%)	1 / 184 (0.54%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neoplasm progression			

subjects affected / exposed	1 / 177 (0.56%)	0 / 184 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	1 / 177 (0.56%)	0 / 184 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Shock symptom			
subjects affected / exposed	1 / 177 (0.56%)	0 / 184 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Disease progression			
subjects affected / exposed	30 / 177 (16.95%)	39 / 184 (21.20%)	
occurrences causally related to treatment / all	0 / 30	1 / 39	
deaths causally related to treatment / all	0 / 24	0 / 35	
General physical health deterioration			
subjects affected / exposed	3 / 177 (1.69%)	11 / 184 (5.98%)	
occurrences causally related to treatment / all	0 / 3	0 / 11	
deaths causally related to treatment / all	0 / 0	0 / 5	
Asthenia			
subjects affected / exposed	2 / 177 (1.13%)	3 / 184 (1.63%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain			
subjects affected / exposed	0 / 177 (0.00%)	1 / 184 (0.54%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	1 / 177 (0.56%)	1 / 184 (0.54%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Chills			
subjects affected / exposed	1 / 177 (0.56%)	0 / 184 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Condition aggravated			
subjects affected / exposed	1 / 177 (0.56%)	0 / 184 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fatigue			
subjects affected / exposed	1 / 177 (0.56%)	0 / 184 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Multiple organ dysfunction syndrome			
subjects affected / exposed	1 / 177 (0.56%)	0 / 184 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Oedema peripheral			
subjects affected / exposed	2 / 177 (1.13%)	0 / 184 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sudden death			
subjects affected / exposed	1 / 177 (0.56%)	0 / 184 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	4 / 177 (2.26%)	2 / 184 (1.09%)	
occurrences causally related to treatment / all	0 / 4	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pneumonia aspiration			
subjects affected / exposed	1 / 177 (0.56%)	2 / 184 (1.09%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	

Pulmonary oedema			
subjects affected / exposed	0 / 177 (0.00%)	1 / 184 (0.54%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory failure			
subjects affected / exposed	1 / 177 (0.56%)	1 / 184 (0.54%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
Pleural effusion			
subjects affected / exposed	1 / 177 (0.56%)	0 / 184 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	2 / 177 (1.13%)	0 / 184 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory distress			
subjects affected / exposed	1 / 177 (0.56%)	0 / 184 (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	0 / 177 (0.00%)	1 / 184 (0.54%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	1 / 177 (0.56%)	1 / 184 (0.54%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aspartate aminotransferase increased			
subjects affected / exposed	1 / 177 (0.56%)	1 / 184 (0.54%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Liver function test increased			
subjects affected / exposed	1 / 177 (0.56%)	1 / 184 (0.54%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Platelet count decreased			
subjects affected / exposed	0 / 177 (0.00%)	1 / 184 (0.54%)	
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			
Hip fracture			
subjects affected / exposed	0 / 177 (0.00%)	1 / 184 (0.54%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infusion related reaction			
subjects affected / exposed	0 / 177 (0.00%)	1 / 184 (0.54%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anastomotic stenosis			
subjects affected / exposed	1 / 177 (0.56%)	0 / 184 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Cardio-respiratory arrest			
subjects affected / exposed	0 / 177 (0.00%)	1 / 184 (0.54%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pericardial effusion			
subjects affected / exposed	0 / 177 (0.00%)	1 / 184 (0.54%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac arrest			
subjects affected / exposed	1 / 177 (0.56%)	0 / 184 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	

Tachycardia			
subjects affected / exposed	1 / 177 (0.56%)	0 / 184 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Dizziness			
subjects affected / exposed	0 / 177 (0.00%)	2 / 184 (1.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	3 / 177 (1.69%)	5 / 184 (2.72%)	
occurrences causally related to treatment / all	1 / 3	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile neutropenia			
subjects affected / exposed	3 / 177 (1.69%)	0 / 184 (0.00%)	
occurrences causally related to treatment / all	3 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Disseminated intravascular coagulation			
subjects affected / exposed	0 / 177 (0.00%)	1 / 184 (0.54%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Lymphadenopathy mediastinal			
subjects affected / exposed	0 / 177 (0.00%)	1 / 184 (0.54%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 177 (0.56%)	6 / 184 (3.26%)	
occurrences causally related to treatment / all	0 / 1	1 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			

subjects affected / exposed	1 / 177 (0.56%)	5 / 184 (2.72%)	
occurrences causally related to treatment / all	0 / 1	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal obstruction			
subjects affected / exposed	1 / 177 (0.56%)	4 / 184 (2.17%)	
occurrences causally related to treatment / all	0 / 1	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 1	
Ascites			
subjects affected / exposed	1 / 177 (0.56%)	3 / 184 (1.63%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dysphagia			
subjects affected / exposed	1 / 177 (0.56%)	3 / 184 (1.63%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 1	
Ileus			
subjects affected / exposed	4 / 177 (2.26%)	2 / 184 (1.09%)	
occurrences causally related to treatment / all	0 / 4	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subileus			
subjects affected / exposed	3 / 177 (1.69%)	1 / 184 (0.54%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	3 / 177 (1.69%)	0 / 184 (0.00%)	
occurrences causally related to treatment / all	3 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain upper			
subjects affected / exposed	0 / 177 (0.00%)	2 / 184 (1.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis			

subjects affected / exposed	0 / 177 (0.00%)	1 / 184 (0.54%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Constipation			
subjects affected / exposed	1 / 177 (0.56%)	1 / 184 (0.54%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Duodenal obstruction			
subjects affected / exposed	0 / 177 (0.00%)	1 / 184 (0.54%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal perforation			
subjects affected / exposed	0 / 177 (0.00%)	1 / 184 (0.54%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Nausea			
subjects affected / exposed	2 / 177 (1.13%)	1 / 184 (0.54%)	
occurrences causally related to treatment / all	2 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small intestinal obstruction			
subjects affected / exposed	1 / 177 (0.56%)	1 / 184 (0.54%)	
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	1 / 177 (0.56%)	0 / 184 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematemesis			
subjects affected / exposed	1 / 177 (0.56%)	0 / 184 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhagic ascites			

subjects affected / exposed	1 / 177 (0.56%)	0 / 184 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Melaena			
subjects affected / exposed	1 / 177 (0.56%)	0 / 184 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Autoimmune hepatitis			
subjects affected / exposed	0 / 177 (0.00%)	1 / 184 (0.54%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bile duct obstruction			
subjects affected / exposed	0 / 177 (0.00%)	1 / 184 (0.54%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bile duct stone			
subjects affected / exposed	0 / 177 (0.00%)	1 / 184 (0.54%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Biliary dilatation			
subjects affected / exposed	0 / 177 (0.00%)	1 / 184 (0.54%)	
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	2 / 177 (1.13%)	1 / 184 (0.54%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Hepatic function abnormal			
subjects affected / exposed	0 / 177 (0.00%)	1 / 184 (0.54%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Jaundice cholestatic			

subjects affected / exposed	1 / 177 (0.56%)	1 / 184 (0.54%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholangitis			
subjects affected / exposed	1 / 177 (0.56%)	0 / 184 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis			
subjects affected / exposed	1 / 177 (0.56%)	0 / 184 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dilatation intrahepatic duct acquired			
subjects affected / exposed	1 / 177 (0.56%)	0 / 184 (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	0 / 177 (0.00%)	1 / 184 (0.54%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute kidney injury			
subjects affected / exposed	1 / 177 (0.56%)	0 / 184 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure			
subjects affected / exposed	1 / 177 (0.56%)	0 / 184 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Endocrine disorders			
Autoimmune hypothyroidism			
subjects affected / exposed	0 / 177 (0.00%)	1 / 184 (0.54%)	
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			
Back pain			
subjects affected / exposed	0 / 177 (0.00%)	2 / 184 (1.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Exostosis			
subjects affected / exposed	0 / 177 (0.00%)	1 / 184 (0.54%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteonecrosis			
subjects affected / exposed	1 / 177 (0.56%)	0 / 184 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Soft tissue disorder			
subjects affected / exposed	1 / 177 (0.56%)	0 / 184 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Pneumonia			
subjects affected / exposed	2 / 177 (1.13%)	5 / 184 (2.72%)	
occurrences causally related to treatment / all	0 / 2	0 / 5	
deaths causally related to treatment / all	0 / 2	0 / 1	
Sepsis			
subjects affected / exposed	2 / 177 (1.13%)	3 / 184 (1.63%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 1	0 / 1	
Device related infection			
subjects affected / exposed	1 / 177 (0.56%)	2 / 184 (1.09%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticulitis			
subjects affected / exposed	0 / 177 (0.00%)	1 / 184 (0.54%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Urinary tract infection			
subjects affected / exposed	0 / 177 (0.00%)	1 / 184 (0.54%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal infection			
subjects affected / exposed	1 / 177 (0.56%)	0 / 184 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device related sepsis			
subjects affected / exposed	1 / 177 (0.56%)	0 / 184 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Empyema			
subjects affected / exposed	1 / 177 (0.56%)	0 / 184 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Herpes zoster			
subjects affected / exposed	2 / 177 (1.13%)	0 / 184 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung infection			
subjects affected / exposed	1 / 177 (0.56%)	0 / 184 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary sepsis			
subjects affected / exposed	1 / 177 (0.56%)	0 / 184 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory tract infection bacterial			
subjects affected / exposed	1 / 177 (0.56%)	0 / 184 (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 / 177 (0.56%)	0 / 184 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	4 / 177 (2.26%)	1 / 184 (0.54%)	
occurrences causally related to treatment / all	3 / 4	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dehydration			
subjects affected / exposed	3 / 177 (1.69%)	1 / 184 (0.54%)	
occurrences causally related to treatment / all	1 / 3	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Hyponatraemia			
subjects affected / exposed	0 / 177 (0.00%)	2 / 184 (1.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malnutrition			
subjects affected / exposed	1 / 177 (0.56%)	1 / 184 (0.54%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Hyperuricaemia			
subjects affected / exposed	1 / 177 (0.56%)	0 / 184 (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	Physician choice chemotherapy + Best Supportive Care (BSC)	Avelumab + BSC	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	150 / 177 (84.75%)	146 / 184 (79.35%)	
Investigations			
Aspartate aminotransferase increased			

subjects affected / exposed	13 / 177 (7.34%)	16 / 184 (8.70%)	
occurrences (all)	13	16	
Weight decreased			
subjects affected / exposed	12 / 177 (6.78%)	16 / 184 (8.70%)	
occurrences (all)	12	16	
Gamma-glutamyltransferase increased			
subjects affected / exposed	13 / 177 (7.34%)	15 / 184 (8.15%)	
occurrences (all)	13	15	
Blood alkaline phosphatase increased			
subjects affected / exposed	10 / 177 (5.65%)	14 / 184 (7.61%)	
occurrences (all)	10	14	
Alanine aminotransferase increased			
subjects affected / exposed	13 / 177 (7.34%)	11 / 184 (5.98%)	
occurrences (all)	13	11	
Neutrophil count decreased			
subjects affected / exposed	16 / 177 (9.04%)	0 / 184 (0.00%)	
occurrences (all)	16	0	
White blood cell count decreased			
subjects affected / exposed	14 / 177 (7.91%)	0 / 184 (0.00%)	
occurrences (all)	14	0	
Injury, poisoning and procedural complications			
Infusion related reaction			
subjects affected / exposed	3 / 177 (1.69%)	18 / 184 (9.78%)	
occurrences (all)	3	18	
Nervous system disorders			
Peripheral sensory neuropathy			
subjects affected / exposed	14 / 177 (7.91%)	1 / 184 (0.54%)	
occurrences (all)	14	1	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	28 / 177 (15.82%)	28 / 184 (15.22%)	
occurrences (all)	28	28	
Asthenia			
subjects affected / exposed	35 / 177 (19.77%)	26 / 184 (14.13%)	
occurrences (all)	35	26	

Pyrexia			
subjects affected / exposed	30 / 177 (16.95%)	21 / 184 (11.41%)	
occurrences (all)	30	21	
Chills			
subjects affected / exposed	3 / 177 (1.69%)	19 / 184 (10.33%)	
occurrences (all)	3	19	
Oedema peripheral			
subjects affected / exposed	16 / 177 (9.04%)	5 / 184 (2.72%)	
occurrences (all)	16	5	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	48 / 177 (27.12%)	30 / 184 (16.30%)	
occurrences (all)	48	30	
Neutropenia			
subjects affected / exposed	25 / 177 (14.12%)	0 / 184 (0.00%)	
occurrences (all)	25	0	
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	61 / 177 (34.46%)	34 / 184 (18.48%)	
occurrences (all)	61	34	
Vomiting			
subjects affected / exposed	32 / 177 (18.08%)	33 / 184 (17.93%)	
occurrences (all)	32	33	
Abdominal pain			
subjects affected / exposed	31 / 177 (17.51%)	25 / 184 (13.59%)	
occurrences (all)	31	25	
Diarrhoea			
subjects affected / exposed	54 / 177 (30.51%)	24 / 184 (13.04%)	
occurrences (all)	54	24	
Constipation			
subjects affected / exposed	27 / 177 (15.25%)	18 / 184 (9.78%)	
occurrences (all)	27	18	
Dysphagia			
subjects affected / exposed	2 / 177 (1.13%)	10 / 184 (5.43%)	
occurrences (all)	2	10	
Abdominal pain upper			

subjects affected / exposed	18 / 177 (10.17%)	7 / 184 (3.80%)	
occurrences (all)	18	7	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	10 / 177 (5.65%)	8 / 184 (4.35%)	
occurrences (all)	10	8	
Dyspnoea			
subjects affected / exposed	15 / 177 (8.47%)	7 / 184 (3.80%)	
occurrences (all)	15	7	
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	25 / 177 (14.12%)	0 / 184 (0.00%)	
occurrences (all)	25	0	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	6 / 177 (3.39%)	18 / 184 (9.78%)	
occurrences (all)	6	18	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	37 / 177 (20.90%)	29 / 184 (15.76%)	
occurrences (all)	37	29	
Dehydration			
subjects affected / exposed	3 / 177 (1.69%)	10 / 184 (5.43%)	
occurrences (all)	3	10	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
22 October 2015	Included blood draws for clinical assessments.
06 January 2016	To update the Investigation New Drug (IND) number. To change the medical responsible for the trial. To modify exclusion criteria for persisting toxicity related to prior therapy according to the National Cancer Institute-Common Terminology Criteria for Adverse Event (NCI-CTCAE) v4.03 criteria. To make minor changes to clarify the schedule of assessments and text for evaluation of radiographic scans. To clarify the role of the Independent Review Committee (IRC) and independent radiologist. To revise the protocol to include epirubicin as an acceptable regimen for the first-line treatment of metastatic, recurrent, or unresectable gastric cancer. To clarify that all prior adjuvant and neo-adjuvant treatments are allowed. To exclude subjects with active tuberculosis from the study. To modify contraceptive measures to include Clinical Trials Facilitation Group (CTFG) recommendations related to contraception and pregnancy testing in clinical trials. To correct a minor typographical error.
29 April 2016	To amend the trial schedule to have an End of Treatment Visit within 7 days of the decision to discontinue, a Safety Follow-up Visit 30 days after last treatment (±5 days), a Safety Follow-up Phone Call 90 days after last treatment (±1 week), and the Long-Term Follow-up every 12 weeks after last treatment (±2 weeks). The reporting of AEs and concomitant medications/procedures was also updated in line with the new schedule. To reduce the frequency of pregnancy testing to every 4 weeks prior to Week 13. To remove the measurement of antinuclear antibody (ANA), antineutrophil cytoplasmic antibodies (ANCA), rheumatoid factor (RF) and adrenocorticotropic hormone (ACTH) from laboratory sampling. To remove the collection of blood samples for PK determination at 2 to 8 hours post-infusion, and at the end of the infusion for both Week 13 and every 12 weeks until progression. To remove the collection of blood samples for soluble factors at 2 to 8 hours post-infusion. To remove the collection of blood samples at the End of Treatment Visit for HAHA (immunogenicity) analysis. To reduce the frequency of tumor evaluation/staging by Computed Tomography (CT) scan/Magnetic Resonance Imaging (MRI)/other established methods to every 12 weeks after the first 12 months. To add the collection of samples for soluble factors, gene expression profiling and biomarkers at Week 1 for the comparator treatment arms. To collect core serum chemistry samples rather than full serum chemistry samples during the treatment phase, and collect additional parameters for core serum chemistry (amylase, lipase, lactate dehydrogenase and creatine kinase).
28 December 2016	To add management guidelines for cardiac irAEs. To update the sponsor’s medical responsible and global program lead. To clarify the monitoring of SAEs that are ongoing at the 30-day Safety Follow-up visit. To provide the clinical trial registry number. To correct a typographical error in the Schedule of Assessments and to replace the terminology of human anti-human antibody (HAHA) with ADA. To make minor editorial corrections to abbreviations and the use of “patient” and “subject.”

30 May 2017	Revise the time point of the primary analysis to occur after a minimum of 6 months follow-up since the last subject randomized. Correct a discrepancy between sections in the acceptable regimens for first-line treatment. Clarify the definition of second-line therapy with the respect to another line of a platinum-based treatment or FOLFIRI. Update the requirements for premedication and mandatory discontinuation. Clarify that Pharmacokinetics (PK) and Anti-drug Antibody (ADA) samples collected at the same time point can be used interchangeably. Clarify the definition and censoring rules for duration of response. Update the background information for avelumab. Clarify the treatment of subjects who continue avelumab plus Best Supportive Care (BSC) beyond progression. Update the guidelines for management of Immune-related Adverse Event (irAEs). Update the Sponsor's medical responsible. Clarify the monitoring of Serious Adverse Events (SAEs) that are ongoing at the 30-day Safety Follow-up visit. Update the contact information for the senior expert statistician.
27 March 2018	To change the follow-up time such that subjects who discontinue treatment will no longer be followed for disease progression of survival. Provided subjects additional treatment options.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported