Clinical trial results:
A Phase 3, Multicenter, Multinational, Randomized, Open-label, Parallel-arm Study of Avelumab (MSB0010718C) Plus Best Supportive Care Versus Best Supportive Care Alone As a Maintenance Treatment in Patients With Locally Advanced or Metastatic Urothelial Cancer Whose Disease Did Not Progress After Completion of First-Line Platinum-Containing Chemotherapy

Summary

EudraCT number	2015-003262-86
Trial protocol	NL GB SE BE CZ PT DK ES IT FR GR
Global end of trial date	28 March 2023

Results information

Result version number	v1 (current)
This version publication date	16 March 2024
First version publication date	16 March 2024

Trial information

Trial identification

Sponsor protocol code	B9991001

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02603432
WHO universal trial number (UTN)	-
Other trial identifiers	JAVELIN BLADDER 100: Other Study ID

Notes:

Sponsors

Sponsor organisation name	Pfizer Inc.
Sponsor organisation address	235 E 42nd Street, New York, United States, NY 10017
Public contact	Pfizer ClinicalTrials.gov Call Center, Pfizer Inc., 001 8007181021, ClinicalTrials.gov_Inquiries@pfizer.com
Scientific contact	Pfizer ClinicalTrials.gov Call Center, Pfizer Inc., 001 8007181021, ClinicalTrials.gov_Inquiries@pfizer.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	04 May 2023
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	28 March 2023
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To demonstrate the benefit of maintenance treatment with avelumab plus BSC vs. BSC alone in prolonging overall survival (OS) in subjects with unresectable locally advanced or metastatic UC whose disease did not progress on or following completion of first-line platinum-containing chemotherapy in each co-primary UC subject population: 1) subjects determined to have Programmed Death-Ligand 1 (PD-L1) positive tumors (including infiltrating immune cells) by a verified Good Manufacturing Practice (GMP) PD-L1 Immunohistochemistry (IHC) test , and 2) all randomized subjects.

Protection of trial subjects:

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

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	25 April 2016
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy
Long term follow-up duration	70 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Argentina: 4
Country: Number of subjects enrolled	Australia: 59
Country: Number of subjects enrolled	Belgium: 24
Country: Number of subjects enrolled	Brazil: 13
Country: Number of subjects enrolled	Canada: 15
Country: Number of subjects enrolled	Czechia: 1
Country: Number of subjects enrolled	Denmark: 23
Country: Number of subjects enrolled	France: 85
Country: Number of subjects enrolled	Greece: 25
Country: Number of subjects enrolled	Hong Kong: 2
Country: Number of subjects enrolled	Hungary: 1
Country: Number of subjects enrolled	India: 6
Country: Number of subjects enrolled	Israel: 7
Country: Number of subjects enrolled	Italy: 62
Country: Number of subjects enrolled	Japan: 73

Country: Number of subjects enrolled	Korea, Republic of: 45
Country: Number of subjects enrolled	Mexico: 7
Country: Number of subjects enrolled	Netherlands: 15
Country: Number of subjects enrolled	New Zealand: 12
Country: Number of subjects enrolled	Norway: 7
Country: Number of subjects enrolled	Poland: 5
Country: Number of subjects enrolled	Portugal: 6
Country: Number of subjects enrolled	Russian Federation: 17
Country: Number of subjects enrolled	Serbia: 10
Country: Number of subjects enrolled	Spain: 110
Country: Number of subjects enrolled	Sweden: 7
Country: Number of subjects enrolled	Taiwan: 21
Country: Number of subjects enrolled	United Kingdom: 19
Country: Number of subjects enrolled	United States: 19
Worldwide total number of subjects	700
EEA total number of subjects	371

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)	236
From 65 to 84 years	457
85 years and over	7

Subject disposition

Recruitment

Recruitment details:

This study included only those subjects who did not show evidence of disease progression after completion of at least 4 and not more than 6 cycles of first-line platinum-containing chemotherapy (prior to this study).

Pre-assignment

Screening details:

A total of 1005 subjects were screened, out of which 305 subjects discontinued during the screening phase and 700 subjects were enrolled into 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	Avelumab + Best Supportive Care (BSC)

Arm description:

Subjects received an intravenous (IV) infusion of 10 milligrams per kilograms (mg/kg) of Avelumab along with BSC, on Day 1 and 15 of each 28 days treatment cycle, until confirmed disease progression, subject refusal, lost to follow up, unacceptable toxicity, or study termination by the sponsor, whichever occurred first. BSC was administered as per the treating physician. Subjects were followed up until death, end of the study or withdrawal of consent, whichever comes first, regardless of initiation of new anti-cancer therapy.

Arm type	Experimental
Investigational medicinal product name	Avelumab 10 mg/kg
Investigational medicinal product code	MSB0010718C
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Subjects received avelumab 10 mg/kg intravenously on day 1 and day 15 of each 4-week treatment cycle.

Arm title	Best Supportive Care

Arm description:

As prescribed by the treating physician, subjects received BSC which included treatment with antibiotics, nutritional support, correction of metabolic disorders, optimal symptom control and pain management, until confirmed disease progression, subject refusal, lost to follow up, unacceptable toxicity, or study termination by the sponsor, whichever occurred first. Subjects were followed up until death, end of the study or withdrawal of consent, whichever comes first, regardless of initiation of new anti-cancer therapy.

Arm type	No intervention

No investigational medicinal product assigned in this arm

Number of subjects in period 1	Avelumab + Best Supportive Care (BSC)	Best Supportive Care
Started	350	350
Completed	16	1
Not completed	334	349
Adverse event, serious fatal	221	242
Consent withdrawn by subject	12	18
Adverse event, non-fatal	1	-
Progressive Disease	7	5
Study terminated by sponsor	74	75
Unspecified	13	-
Lost to follow-up	3	9
No Longer Meets Eligibility Criteria	3	-

Baseline characteristics

Reporting groups	
Reporting group title	Avelumab + Best Supportive Care (BSC)
Reporting group description:	
Subjects received an intravenous (IV) infusion of 10 milligrams per kilograms (mg/kg) of Avelumab along with BSC, on Day 1 and 15 of each 28 days treatment cycle, until confirmed disease progression, subject refusal, lost to follow up, unacceptable toxicity, or study termination by the sponsor, whichever occurred first. BSC was administered as per the treating physician. Subjects were followed up until death, end of the study or withdrawal of consent, whichever comes first, regardless of initiation of new anti-cancer therapy.	
Reporting group title	Best Supportive Care
Reporting group description:	
As prescribed by the treating physician, subjects received BSC which included treatment with antibiotics, nutritional support, correction of metabolic disorders, optimal symptom control and pain management, until confirmed disease progression, subject refusal, lost to follow up, unacceptable toxicity, or study termination by the sponsor, whichever occurred first. Subjects were followed up until death, end of the study or withdrawal of consent, whichever comes first, regardless of initiation of new anti-cancer therapy.	

Reporting group values	Avelumab + Best Supportive Care (BSC)	Best Supportive Care	Total
Number of subjects	350	350	700
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	129	107	236
From 65-84 years	216	241	457
85 years and over	5	2	7
Age Continuous Units: Years			
arithmetic mean	67.2	67.7	
standard deviation	± 9.52	± 9.20	-
Sex: Female, Male Units: Subjects			
Female	84	75	159
Male	266	275	541
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	75	81	156
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	2	0	2
White	232	238	470
More than one race	0	0	0

Unknown or Not Reported	41	31	72
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	18	12	30
Not Hispanic or Latino	286	298	584
Unknown or Not Reported	46	40	86

End points

End points reporting groups

Reporting group title	Avelumab + Best Supportive Care (BSC)

Reporting group description:

Subjects received an intravenous (IV) infusion of 10 milligrams per kilograms (mg/kg) of Avelumab along with BSC, on Day 1 and 15 of each 28 days treatment cycle, until confirmed disease progression, subject refusal, lost to follow up, unacceptable toxicity, or study termination by the sponsor, whichever occurred first. BSC was administered as per the treating physician. Subjects were followed up until death, end of the study or withdrawal of consent, whichever comes first, regardless of initiation of new anti-cancer therapy.

Reporting group title	Best Supportive Care

Reporting group description:

As prescribed by the treating physician, subjects received BSC which included treatment with antibiotics, nutritional support, correction of metabolic disorders, optimal symptom control and pain management, until confirmed disease progression, subject refusal, lost to follow up, unacceptable toxicity, or study termination by the sponsor, whichever occurred first. Subjects were followed up until death, end of the study or withdrawal of consent, whichever comes first, regardless of initiation of new anti-cancer therapy.

Primary: Overall Survival (OS)

End point title	Overall Survival (OS)

End point description:

Overall survival was defined as the time (in months) from the date of randomization to the date of death due to any cause. Subjects last known to be alive were censored at date of last contact. Analysis was performed using Kaplan-Meier method. The Full Analysis Set (FAS) included all randomized subjects.

End point type	Primary

End point timeframe:

From randomization to discontinuation from the study, death or date of censoring, whichever occurred first (for a maximum duration of 41 months)

End point values	Avelumab + Best Supportive Care (BSC)	Best Supportive Care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	350	350		
Units: Months				
median (confidence interval 95%)	21.4 (18.9 to 26.1)	14.3 (12.9 to 17.9)		

Statistical analyses

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

Number of subjects included in analysis	700
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0005 [1]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.69
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.556
upper limit	0.863

Notes:

[1] - One-sided log-rank test was used.

Secondary: Progression-Free Survival (PFS) as Assessed by Blinded Independent Central Review (BICR)

End point title	Progression-Free Survival (PFS) as Assessed by Blinded Independent Central Review (BICR)

End point description:

BICR assessed PFS: PD as per Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 was defined for target disease as at least a 20% increase in sum of diameters of target lesions, taking as reference smallest sum on study (included baseline sum if that was smallest on study). In addition to relative increase of 20%, sum must have also demonstrated an absolute increase of at least 5 millimeters. For non-target disease: PD: unequivocal progression of pre-existing lesions and if overall tumor burden increased sufficiently to merit discontinuation of therapy. Appearance of any new unequivocal malignant lesion was also considered PD. Analysis was performed using Kaplan-Meier. PFS data was censored on date of last adequate tumor assessment for subjects with no event (PD or death), who started new anti-cancer therapy prior to an event or with an event after 2 or more missing tumor assessments. Full analysis set was analysed.

End point type	Secondary

End point timeframe:

From randomization to date of progression of disease, discontinuation from the study, death or date of censoring, whichever occurred first (for a maximum duration of 41 months)

End point values	Avelumab + Best Supportive Care (BSC)	Best Supportive Care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	350	350		
Units: Months				
median (confidence interval 95%)	3.7 (3.5 to 5.5)	2.0 (1.9 to 2.7)		

Statistical analyses

No statistical analyses for this end point

Secondary: Progression-Free Survival (PFS) as Assessed by Investigator

End point title	Progression-Free Survival (PFS) as Assessed by Investigator

End point description:

Investigator assessed PFS: PD as per Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 was defined for target disease as at least a 20% increase in sum of diameters of target lesions, taking as reference smallest sum on study (included baseline sum if that was smallest on study). In addition to relative increase of 20%, sum must have also demonstrated an absolute increase of at least 5 millimeters. For non-target disease: PD: unequivocal progression of pre-existing lesions and if overall tumor burden increased sufficiently to merit discontinuation of therapy. Appearance of any new unequivocal malignant lesion was also considered PD. Analysis was performed using Kaplan-Meier. PFS data was censored on date of last adequate tumor assessment for subjects with no event (PD or death), who started new anti-cancer therapy prior to an event or with an event after 2 or more missing tumor assessments. Full analysis set was analysed.

End point type	Secondary

End point timeframe:

From randomization to date of progression of disease, discontinuation from the study, death or date of censoring, whichever occurred first (for a maximum duration of 41 months)

End point values	Avelumab + Best Supportive Care (BSC)	Best Supportive Care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	350	350		
Units: Months				
median (confidence interval 95%)	5.5 (4.2 to 7.2)	2.1 (1.9 to 3.0)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With OR as Assessed by Investigator

End point title	Percentage of Subjects With OR as Assessed by Investigator

End point description:

Investigator assessed objective response according to RECIST version 1.1, was defined as subjects with confirmed best overall response of CR or PR. CR was defined as complete disappearance of all target and non-target lesions, with the exception of nodal disease and sustained for at least 4 weeks. A CR also required normalization of tumor marker levels and any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm. PR was defined as at least 30% decrease in the sum of the longest dimensions of target lesions taking as reference the baseline sum longest dimensions. The full analysis set included all randomized subjects.

End point type	Secondary

End point timeframe:

From randomization to progression of disease, start of new anti-cancer therapy or discontinuation from study or death, whichever occurred first (for a maximum duration of 41 months)

End point values	Avelumab + Best Supportive Care (BSC)	Best Supportive Care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	350	350		
Units: Percentage of subjects				
number (confidence interval 95%)	12.3 (9.0 to 16.2)	3.4 (1.8 to 5.9)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With OR as Assessed by BICR

End point title	Percentage of Subjects With OR as Assessed by BICR

End point description:

BICR assessed objective response according to RECIST version 1.1, was defined as subjects with confirmed best overall response of complete response (CR) or partial response (PR). CR was defined as complete disappearance of all target and non-target lesions, with the exception of nodal disease and sustained for at least 4 weeks. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to less than (<) 10 mm. PR was defined as at least 30% decrease in the sum of the longest dimensions of target lesions taking as reference the baseline sum longest dimensions. The full analysis set included all randomized subjects.

End point type	Secondary

End point timeframe:

From randomization to progression of disease, start of new anti-cancer therapy or discontinuation from study or death, whichever occurred first (for a maximum duration of 41 months)

End point values	Avelumab + Best Supportive Care (BSC)	Best Supportive Care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	350	350		
Units: Percentage of subjects				
number (confidence interval 95%)	9.7 (6.8 to 13.3)	1.4 (0.5 to 3.3)		

Statistical analyses

No statistical analyses for this end point

Secondary: TTR as Assessed by Investigator

End point title	TTR as Assessed by Investigator

End point description:

TTR was defined, for subjects with an objective response as the time from 'start date' to the first documentation of objective tumor response (CR or PR). CR was defined as complete disappearance of all target and non-target lesions, with the exception of nodal disease and sustained for at least 4 weeks. A

CR also required normalization of tumor marker levels and any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm. PR was defined as at least 30% decrease in the sum of the longest dimensions of target lesions taking as reference the baseline sum longest dimensions. The full analysis set included all randomized subjects. Here, 'Overall Number of subjects analyzed' signifies subjects who were evaluable for this outcome measure.

End point type	Secondary

End point timeframe:

From the date of randomization to the first documentation of objective response (CR or PR) (for a maximum duration of 41 months)

End point values	Avelumab + Best Supportive Care (BSC)	Best Supportive Care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	43	12		
Units: Months				
median (full range (min-max))	2.0 (1.8 to 22.2)	1.9 (1.1 to 10.9)		

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Response (DOR) as Assessed by Blinded Independent Central Review (BICR)

End point title	Duration of Response (DOR) as Assessed by Blinded Independent Central Review (BICR)

End point description:

BICR assessed DOR: time from first documentation of OR(confirmed CR/PR) to date of first PD/death due to any cause. Per RECISTv1.1,CR:complete disappearance of all target(T)&non-target(NT)lesions,with exception of nodal disease sustained 4 weeks. Additionally, normalization of tumor marker level&pathological lymph nodes reduced short axis<10mm. PR:at least 30%decrease in sum of longest dimensions of T lesions taking as reference baseline sum longest dimensions. PD for T: at least 20% increase(inc) in sum of diameters of T lesions,taking as reference smallest sum on study and relative inc of 20%,sum also demonstrated absolute inc of at least 5mm. PD for NT: unequivocal progression of pre-existing lesions and if overall tumor burden inc sufficiently to merit discontinuation of therapy.Appearance of any new unequivocal malignant lesion was also considered PD. 99999=data not estimated due to limited number of events. Analysis=subset of randomized subjects who had OR, as assessed by BICR.

End point type	Secondary

End point timeframe:

First response subsequently confirmed to progression of disease or start of new anti-cancer therapy or discontinuation from the study or death, whichever occurred first (for a maximum duration of 41 months)

End point values	Avelumab + Best Supportive Care (BSC)	Best Supportive Care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	34	5		
Units: Months				
median (confidence interval 95%)	99999 (15.6 to 99999)	99999 (99999 to 99999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Tumor Response (TTR) as Assessed by BICR

End point title	Time to Tumor Response (TTR) as Assessed by BICR

End point description:

TTR was defined, for subjects with an objective response as the time from 'start date' to the first documentation of objective tumor response (CR or PR), which was confirmed subsequently. CR was defined as complete disappearance of all target and non-target lesions, with the exception of nodal disease and sustained for at least 4 weeks. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm. PR was defined as at least 30% decrease in the sum of the longest dimensions of target lesions taking as reference the baseline sum longest dimensions. The full analysis set included all randomized subjects. Here, 'Overall Number of subjects analyzed (N)' signifies subjects who were evaluable for this outcome measure (OM).

End point type	Secondary

End point timeframe:

From the date of randomization to the first documentation of objective response (CR or PR) (for a maximum duration of 41 months)

End point values	Avelumab + Best Supportive Care (BSC)	Best Supportive Care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	34	5		
Units: Months				
median (full range (min-max))	2.0 (1.7 to 16.4)	2.0 (1.8 to 7.0)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With Disease Control (DC) as Assessed by BICR

End point title	Percentage of Subjects With Disease Control (DC) as Assessed by BICR

End point description:

DC was defined as a best overall response of CR, PR, non-CR/non-PD or stable disease (SD) as assessed

by BICR. CR was defined as complete disappearance of all target and non-target lesions, with the exception of nodal disease and sustained for at least 4 weeks. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm. PR was defined as at least 30% decrease in the sum of the longest dimensions of target lesions taking as reference the baseline sum longest dimensions. Non-CR/Non-PD was defined as persistence of any non-target lesions and/or tumor marker level above the normal limits. SD was defined as not to qualify for CR, PR or PD for target lesions and followed PR only if the sum increased by less than 20% from the nadir, but enough that a previously documented 30% decrease no longer holds. The full analysis set included all randomized subjects.

End point type	Secondary

End point timeframe:

From randomization to PD, death or start of new anti-cancer therapy (for a maximum duration of 41 months)

End point values	Avelumab + Best Supportive Care (BSC)	Best Supportive Care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	350	350		
Units: Percentage of subjects				
number (confidence interval 95%)	41.1 (35.9 to 46.5)	27.4 (22.8 to 32.4)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With DC as Assessed by Investigator

End point title	Percentage of Subjects With DC as Assessed by Investigator

End point description:

DC was defined as a best overall response of CR, PR, non-CR/non-PD or SD as assessed by Investigator. CR was defined as complete disappearance of all target and non-target lesions, with the exception of nodal disease and sustained for at least 4 weeks. Additionally, normalization of tumor marker levels and any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm. PR was defined as at least 30% decrease in the sum of the longest dimensions of target lesions taking as reference the baseline sum longest dimensions. Non-CR/Non-PD was defined as persistence of any non-target lesions and/or tumor marker level above the normal limits. SD was defined as not to qualify for CR, PR or PD for target lesions and followed PR only if the sum increased by less than 20% from the nadir, but enough that a previously documented 30% decrease no longer holds. The full analysis set included all randomized subjects.

End point type	Secondary

End point timeframe:

From randomization to PD, death or start of new anti-cancer therapy (for a maximum duration of 41 months)

End point values	Avelumab + Best Supportive Care (BSC)	Best Supportive Care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	350	350		
Units: Percentage of subjects				
number (confidence interval 95%)	50.9 (45.5 to 56.2)	34.0 (29.0 to 39.2)		

Statistical analyses

No statistical analyses for this end point

Secondary: DOR as Assessed by Investigator

End point title	DOR as Assessed by Investigator

End point description:

Investigator assessed DOR: time from first documentation of OR(confirmed CR/PR) to date of first PD/death due to any cause. Per RECISTv1.1,CR:complete disappearance of all target(T)&non-target(NT)lesions,with exception of nodal disease sustained 4 weeks. Additionally, normalization of tumor marker level&pathological lymph nodes reduced short axis<10mm. PR:at least 30%decrease in sum of longest dimensions of T lesions taking as reference baseline sum longest dimensions. PD for T: at least 20%inc in sum of diameters of T lesions,taking as reference smallest sum on study and relative inc of 20%,sum also demonstrated absolute inc of at least 5mm. PD for NT: unequivocal progression of pre-existing lesions and if overall tumor burden inc sufficiently to merit discontinuation of therapy.Appearance of any new unequivocal malignant lesion was considered PD. 99999=data not estimated due to limited number of events. Analysis=subset of randomized subjects who had OR, as

End point type	Secondary

End point timeframe:

First response subsequently confirmed to progression of disease or start of new anti-cancer therapy or discontinuation from the study or death, whichever occurred first (for a maximum duration of 41 months)

End point values	Avelumab + Best Supportive Care (BSC)	Best Supportive Care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	43	12		
Units: Months				
median (confidence interval 95%)	25.6 (12.0 to 99999)	99999 (3.6 to 99999)		

Statistical analyses

No statistical analyses for this end point

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

End point title	Number of Subjects With Treatment-Emergent Adverse Events (AEs) Graded Based on National Cancer Institute Common Terminology Criteria (NCI-CTCAE), Version 4.03

End point description:

An AE was any untoward medical occurrence in subject who received study drug without regard to possibility of causal relationship. Per NCI CTCAEv4.03,Grade(G)1:asymptomatic/mild symptoms,clinical/diagnostic observations,intervention not indicated; G2:moderate,minimal, local/noninvasive intervention indicated, limiting age-appropriate instrumental activities of daily life(ADL); G3:severe/medically significant but not immediately life-threatening,hospitalization/prolongation of existing indicated,disabling,limiting self-care ADL;G4:life-threatening consequence,urgent intervention indicated;G5:death related to AE.Treatment-emergent AEs are events between first dose&up to90 days after last dose of study drug/end of treatment visit, that were absent before treatment/worsened relative to pretreatment.Safety analysis set=subjects who had received at least one dose of study drug on arm'Avelumab+BSC'/completed Cycle1Day1(C1D1) on arm

End point type	Secondary

End point timeframe:

For "Avelumab + Best Supportive Care (BSC)'' group: Day 1 up to 90 days after last dose of study drug; for BSC group: Day 1 up to 90 days after EOT visit (for a maximum duration of up to approximately 70 months)

End point values	Avelumab + Best Supportive Care (BSC)	Best Supportive Care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	344	345		
Units: Subjects				
Grade 1	37	76		
Grade 2	113	104		
Grade 3	163	58		
Grade 4	18	8		
Grade 5	7	24		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Laboratory Abnormalities Greater Than or Equal to (>=) Grade 3 (G3), Based on NCI-CTCAE, V4.03

End point title	Number of Subjects With Laboratory Abnormalities Greater Than or Equal to (>=) Grade 3 (G3), Based on NCI-CTCAE, V4.03

End point description:

Hematology:(Anemia G3:hemoglobin<8.0 g/dL,<4.9 mmol/L,<80 g/L, transfusion indicated,Grade[G]4: life-threatening consequence, urgent intervention indicated,G5:death; platelet count decreased[dec]-G3:<50.0-25.0*10^9/L, G4: <25.0*10^9/L; lymphocyte count dec-G3:<0.5-0.2*10^9/L, G4:<0.2*10^9/L; neutrophil count dec-G3:<1.0-0.5*10^9 /L, G4:<0.5*10^9/L). Chemistry:(creatinine increased[inc]-G3:>3.0-6.0*upper limit of normal [ULN], G4:>6.0*ULN; serum amylase inc, lipase inc-G3:>2.0-5.0*ULN, G4:>5.0*ULN. Aspartate aminotransferase[AST], alanine aminotransferase[ALT]-G3:>5.0-20.0*ULN, G4:>20.0*ULN].Blood bilirubin inc-[G3:>3.0-10.0*ULN, G4:>10.0*ULN], Creatine phosphokinase inc- [G3:>5.0-10.0*ULN, G4:>10.0*ULN], Hyperglycemia-[G3:>250-500 mg/dL; >13.9-27.8 mmol/L hospitalization indicated,G4:>500 mg/DL;>27.8 mmol/L life-threatening consequence]).Safety analysis set. All subject reported under 'Number of Participants Analyzed'contributed data to table may not have evaluable data for each row.

End point type	Secondary

End point timeframe:

For "Avelumab + Best Supportive Care (BSC)'' group: Day 1 up to 90 days after last dose of study drug; for BSC group: Day 1 up to 90 days after EOT visit (for a maximum duration of up to approximately 70 months)

End point values	Avelumab + Best Supportive Care (BSC)	Best Supportive Care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	344	345		
Units: Subjects				
Anemia (n=344,339)	16	12		
Platelet Count Decreased (n=344,339)	3	1		
Lymphocyte Count Decreased (n=344,339)	20	11		
Neutrophil Count Decreased (n=344,339)	7	0		
Creatinine Increased (n=344,341)	7	5		
Serum Amylase Increased (n=340,329)	25	9		
Lipase Increased (n=343,332)	37	22		
ALT Increased (n=344,341)	11	3		
AST Increased (n=344,340)	6	3		
Blood Bilirubin Increased (n=344,340)	0	3		
CPK Increased (n=339,331)	9	0		
Hyperglycemia (n=344,341)	28	16		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Vital Signs - Blood Pressure at Day 1 of Cycle 2, 3, 4, 5, 6, 7 and End of Treatment (EOT) Visit

End point title	Change From Baseline in Vital Signs - Blood Pressure at Day 1 of Cycle 2, 3, 4, 5, 6, 7 and End of Treatment (EOT) Visit

End point description:

Vital signs included blood pressure and pulse rate. Blood pressure included sitting diastolic blood pressure (DBP) and sitting systolic blood pressure (SBP). Safety set analyzed. All subjects reported under 'Overall Number of subjects Analyzed' contributed data to the table; however, may not have evaluable data for every row. Here, 'Number analyzed' = subjects evaluable for this outcome measure at specified time points.

End point type	Secondary

End point timeframe:

Baseline (D1 of Cycle 1), Day 1 of Cycle 2, 3, 4, 5, 6, 7, EOT visit (for a maximum duration of 41 months) (each cycle=28 days)

End point values	Avelumab + Best Supportive Care (BSC)	Best Supportive Care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	344	345		
Units: millimeters of mercury				
arithmetic mean (standard deviation)				
Baseline (C1D1): Sitting DBP (n=324,329)	75.7 (± 10.81)	77.0 (± 10.48)		
Change at Cycle 2, Day1: Sitting DBP(n=295,287)	-0.9 (± 9.37)	-0.0 (± 9.06)		
Change at Cycle 3, Day 1: Sitting DBP (n=268,228)	-1.7 (± 10.36)	-1.6 (± 9.38)		
Change at Cycle 4, Day 1: Sitting DBP (n=230,153)	-1.7 (± 9.97)	-1.0 (± 9.90)		
Change at Cycle 5, Day 1: Sitting DBP (n=201,119)	-1.1 (± 10.60)	-1.0 (± 10.22)		
Change at Cycle 6, Day 1: Sitting DBP (n=181,107)	-1.2 (± 10.89)	-1.1 (± 10.89)		
Change at Cycle 7, Day 1: Sitting DBP (n=158,81)	-0.7 (± 10.90)	0.2 (± 9.95)		
Change at End of Treatment:SittingDBP(n=190,237)	-0.1 (± 12.09)	-1.7 (± 10.23)		
Baseline (C1D1): Sitting SBP (n=324,329)	131.3 (± 17.34)	130.6 (± 16.32)		
Change at Cycle 2, Day 1: Sitting SBP (n=295,287)	-2.2 (± 14.85)	-0.3 (± 13.79)		
Change at Cycle 3, Day 1: Sitting SBP (n=268,228)	-1.9 (± 16.10)	1.0 (± 14.94)		
Change at Cycle 4, Day 1: Sitting SBP (n=230,153)	-0.6 (± 16.54)	1.3 (± 16.54)		
Change at Cycle 5, Day 1: Sitting SBP (n=201,119)	-1.9 (± 15.49)	1.9 (± 15.85)		
Change at Cycle 6, Day 1: Sitting SBP (n=181,107)	-2.3 (± 15.77)	3.3 (± 16.81)		
Change at Cycle 7, Day 1: Sitting SBP (n=158,81)	-1.8 (± 16.13)	2.7 (± 19.86)		
Change at End of Treatment:Sitting SBP(n=190,237)	-0.9 (± 18.99)	-0.3 (± 16.78)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Vital Signs - Pulse Rate at Day 1 of Cycle 2, 3, 4, 5, 6, 7 and EOT Visit

End point title	Change From Baseline in Vital Signs - Pulse Rate at Day 1 of Cycle 2, 3, 4, 5, 6, 7 and EOT Visit

End point description:

Vital signs included blood pressure and pulse rate. Changes from baseline in sitting pulse rate were summarized. Safety set analyzed. All subjects reported under 'Overall Number of subjects Analyzed' contributed data to the table; however, may not have evaluable data for every row. Here, 'Number analyzed' = subjects evaluable for this outcome measure at specified time points.

End point type	Secondary

End point timeframe:

Baseline (D1 of Cycle 1), Day 1 of Cycle 2, 3, 4, 5, 6, 7, EOT visit (for a maximum duration of 41

End point values	Avelumab + Best Supportive Care (BSC)	Best Supportive Care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	344	345		
Units: beats per minute				
arithmetic mean (standard deviation)				
Baseline (C1D1) (n=324,327)	76.1 (± 12.84)	77.1 (± 12.95)		
Change at Cycle 2, Day 1 (n=295,286)	0.3 (± 11.81)	0.1 (± 9.98)		
Change at Cycle 3, Day 1 (n=268,226)	-0.2 (± 12.10)	-0.4 (± 10.20)		
Change at Cycle 4, Day 1 (n=230,152)	-0.5 (± 12.84)	-0.1 (± 11.26)		
Change at Cycle 5, Day 1 (n=201,118)	0.4 (± 12.32)	-1.0 (± 11.45)		
Change at Cycle 6, Day 1 (n=181,105)	-0.8 (± 11.54)	-2.6 (± 10.52)		
Change at Cycle 7, Day 1 (n=158,80)	-0.6 (± 11.89)	-2.6 (± 11.48)		
Change at End of Treatment (n=190,235)	2.5 (± 12.25)	1.4 (± 12.45)		

Statistical analyses

No statistical analyses for this end point

Secondary: Maximum Plasma Concentration (Cmax) of Avelumab

End point title	Maximum Plasma Concentration (Cmax) of Avelumab[2]

End point description:

The Lower Limit of Quantitation (LLQ) of avelumab was 0.20 micrograms (mcg)/milliliter (mL). Data for this outcome measure was not collected for reporting group "Best Supportive Care", since avelumab was not administered in this arm. Avelumab pharmacokinetic (PK) parameter analysis set: all subjects who received at least one dose of avelumab and who had at least one post-dose concentration measurement above the LLQ for avelumab. All subjects reported under 'Overall Number of Subjects Analyzed' contributed data to the table; however, may not have evaluable data for every row. Here, 'n' signifies subjects evaluable for this OM at specified time points.

End point type	Secondary

End point timeframe:

End of avelumab infusion on Day 1 of Cycle 1, 2, 3, 5, 7, 9, 11, 13 and Day 15 of Cycle 1, 2, 3 (each cycle=28 days)

Notes:

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

End point values	Avelumab + Best Supportive Care (BSC)			
Subject group type	Reporting group			
Number of subjects analysed	344			
Units: microgram per milliliter (mcg/mL)				
geometric mean (geometric coefficient				

of variation)				
Cycle 1, Day 1 (n=295)	192.7 (± 68.4)			
Cycle 1, Day 15 (n=283)	216.2 (± 49.6)			
Cycle 2, Day 1 (n=274)	201.5 (± 54.5)			
Cycle 2, Day 15 (n=262)	208.5 (± 60.2)			
Cycle 3, Day 1 (n=251)	213.1 (± 39.6)			
Cycle 3, Day 15 (n=228)	213.1 (± 52.7)			
Cycle 5, Day 1 (n=179)	197.5 (± 67.7)			
Cycle 7, Day 1 (n=147)	191.9 (± 86.2)			
Cycle 9, Day 1 (n=111)	168.9 (± 84.4)			
Cycle 11, Day 1 (n=86)	203.4 (± 51.6)			
Cycle 13, Day 1 (n=74)	222.8 (± 30.3)			

Statistical analyses

No statistical analyses for this end point

Secondary: Predose Plasma Concentration (Ctrough) of Avelumab

End point title	Predose Plasma Concentration (Ctrough) of Avelumab[3]

End point description:

The LLQ of avelumab was 0.20 mcg/mL. Data for this outcome measure was not collected for reporting group "Best Supportive Care", since avelumab was not administered in this arm. Avelumab pharmacokinetic (PK) parameter analysis set: all subjects who received at least one dose of avelumab and who had at least one post-dose concentration measurement above the LLQ for avelumab. All subjects reported under 'Overall Number of Subjects Analyzed' contributed data to the table; however, may not have evaluable data for every row. Here, 'n' signifies subjects evaluable for this OM at specified time points.

End point type	Secondary

End point timeframe:

Pre-dose (0 hour) on Day 1 of Cycle 1, 2, 3, 5, 7, 9, 11, 13 and Day 15 of Cycle 1, 2, 3 (each cycle=28 days)

Notes:

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

End point values	Avelumab + Best Supportive Care (BSC)			
Subject group type	Reporting group			
Number of subjects analysed	344			
Units: microgram per milliliter (mcg/mL)				
geometric mean (geometric coefficient of variation)				
Cycle 1, Day 1 (n=321)	3.1 (± 247.6)			
Cycle 1, Day 15 (n=296)	22.2 (± 48.6)			
Cycle 2, Day 1 (n=268)	25.2 (± 64.2)			
Cycle 2, Day 15 (n=253)	26.5 (± 65.4)			
Cycle 3, Day 1 (n=240)	26.4 (± 76.2)			
Cycle 3, Day 15 (n=220)	25.7 (± 85.2)			
Cycle 5, Day 1 (n=183)	26.8 (± 67.5)			
Cycle 7, Day 1 (n=146)	29.7 (± 60.2)			

Cycle 9, Day 1 (n=111)	32.4 (± 55.9)			
Cycle 11, Day 1 (n=90)	29.8 (± 68.9)			
Cycle 13, Day 1 (n=75)	32.4 (± 54.9)			

Statistical analyses

No statistical analyses for this end point

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

End point title	Number of Subjects With Anti-Drug Antibodies (ADA) Against Avelumab by Never and Ever Positive Status[4]

End point description:

ADA against avelumab in serum samples was determined and reported separately for ADA never positive and ADA ever positive subjects. Subjects were considered ADA ever-positive if they had at least one positive ADA result at any time point during study and were otherwise considered negative. Data for this outcome measure was not planned to be collected and analyzed for reporting arm "Best Supportive Care", since avelumab was not administered in this arm. The immunogenicity analysis set included all subjects who had received at least one dose of study drug and who had at least one ADA sample collected for avelumab in the avelumab containing arm.

End point type	Secondary

End point timeframe:

From randomization up to the 30-Day Follow-up visit (maximum duration of up to approximately 68 months)

Notes:

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

End point values	Avelumab + Best Supportive Care (BSC)			
Subject group type	Reporting group			
Number of subjects analysed	344			
Units: subjects				
Never-positive	278			
Ever-positive	66			

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

PD-L1 assessment was performed using immunohistochemistry on pre-treatment tumor tissue samples. Subjects were classified as having PD-L1 -positive status if at least one of the following three criteria

were met: at least 25% of tumor cells stained for PD-L1, at least 25% of immune cells stained for PD-L1 if more than 1% of the tumor area contained immune cells, or 100% of immune cells stained for PD-L1 if no more than 1% of the tumor area contained immune cells. The full analysis set included all randomized subjects.

End point type	Secondary

End point timeframe:

Up to 41 months at the time of the analysis

End point values	Avelumab + Best Supportive Care (BSC)	Best Supportive Care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	350	350		
Units: subjects				
Positive	189	169		
Negative	139	131		
Unknown	22	50		

Statistical analyses

No statistical analyses for this end point

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

End point title	Number of Subjects With Neutralizing Antibodies (nAb) Against Avelumab by Never Positive and Ever Positive Status[5]

End point description:

nAb against avelumab in serum samples was determined and reported separately for nAb never positive and nAb ever positive subjects. Subjects were considered nAb ever-positive if they had at least one positive nAb result at any time point during study and were otherwise considered negative. The immunogenicity analysis set included all subjects who had received at least one dose of study drug and who had at least one nAb sample collected for avelumab in the avelumab containing arm.

End point type	Secondary

End point timeframe:

From randomization up to the 30-Day Follow-up visit (maximum duration of up to approximately 68 months)

Notes:

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

End point values	Avelumab + Best Supportive Care (BSC)			
Subject group type	Reporting group			
Number of subjects analysed	344			
Units: subjects				
Never-positive	284			
Ever-positive	60			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of ADA Ever Positive Subjects For Each Serum of ADA Titers for Avelumab

End point title	Number of ADA Ever Positive Subjects For Each Serum of ADA Titers for Avelumab[6]

End point description:

Serum samples were assayed for ADA using a validated analytical method. Number of ADA ever positive subjects for each serum of ADA titer (60, 180, 540, 1620, 4860, 14580, and 131220) are reported. The immunogenicity analysis set included subjects who had received at least one dose of study drug and who had ADA ever-positive results. Here "Overall number of subjects analyzed" signifies subjects who had data available for this outcome measure.

End point type	Secondary

End point timeframe:

From randomization up to the 30-Day Follow-up visit (maximum duration of up to approximately 68 months)

Notes:

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

End point values	Avelumab + Best Supportive Care (BSC)			
Subject group type	Reporting group			
Number of subjects analysed	66			
Units: subjects				
60	4			
180	14			
540	19			
1620	10			
4860	11			
14580	7			
131220	1			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Cluster of differentiation 8 (CD8) T Lymphocytes (Cytotoxic T lymphocytes)

End point title	Number of Subjects With Cluster of differentiation 8 (CD8) T Lymphocytes (Cytotoxic T lymphocytes)

End point description:

Number of subjects with CD8 T Lymphocytes (Cytotoxic T lymphocytes) were presented in this outcome. Biomarker analysis set is a subset of the safety analysis set and included subjects who have at least one baseline biomarker assessment performed. Here, 'Overall Number of subjects analyzed' signifies subjects who were evaluable for this outcome measure.

End point type	Secondary

End point timeframe:

Up to approximately 60 months

End point values	Avelumab + Best Supportive Care (BSC)	Best Supportive Care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	337	326		
Units: Subjects	148	134		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in National Comprehensive Cancer Network-Functional Assessment of Cancer Therapy (NCCN-FACT) Bladder Symptom Index- 18 (FBlSI-18) Score at Day 1 of Cycle 6

End point title	Change From Baseline in National Comprehensive Cancer Network- Functional Assessment of Cancer Therapy (NCCN-FACT) Bladder Symptom Index- 18 (FBlSI-18) Score at Day 1 of Cycle 6

End point description:

NCCN-FACT FBlSI-18 is an 18-item subject completed questionnaire, designed to assess impact of cancer therapy/urothelial cancer-related symptoms and quality of life based on numerical point scoring of symptoms/concerns.Included four subscales: Disease related symptoms(DRS)-physical subscale (9 items), DRS-emotional subscale(2), treatment side effects subscale with (5)&general function/well-being subscale(2). Subjects rated their level of symptoms for each item using 5-point scale ranging from 0=not at all to 4=very much. Items that were negatively framed, and the scores were reversed for analysis so that higher scores= good quality of life. Overall score: total of 18 items, ranging from 0=severely symptomatic to 72=asymptomatic. Higher scores= better functioning or lower symptom burden. Full analysis set. Here N=subjects who had data available for this outcome measure and n=subjects evaluable for this outcome at specified time points.

End point type	Secondary

End point timeframe:

Baseline, Day 1 of Cycle 6

End point values	Avelumab + Best Supportive Care (BSC)	Best Supportive Care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	332	329		
Units: units on a scale				
arithmetic mean (standard deviation)				
Baseline (n=332,329)	53.3 (± 9.59)	52.7 (± 9.31)		
Change at Day 1 of Cycle 6 (n=178,109)	1.0 (± 8.25)	1.6 (± 8.35)		

Statistical analyses

No statistical analyses for this end point

Secondary: TTD Based on NCCN-FACT Bladder Symptom Index- 18 (FBlSI-18) Disease Related Symptoms-Physical subscale (DRS-P) Scores

End point title	TTD Based on NCCN-FACT Bladder Symptom Index- 18 (FBlSI-18) Disease Related Symptoms-Physical subscale (DRS-P) Scores

End point description:

NCCN-FACT FBlSI-18: an 18-item subject completed questionnaire, designed to assess impact of cancer therapy on urothelial cancer-related symptoms and quality of life(QOL) based on numerical point scoring of symptoms/concerns. It included 4 subscales: Disease related symptoms(DRS)-physical subscale (9), DRS-emotional subscale (2), treatment side effects subscale (5), general function/well-being subscale-(2). Subjects rated level of symptoms for each item using 5-point scale ranging: 0=not at all to 4=very much. For items negatively framed, scores were reversed for analysis so higher scores= good QOL. DRS-P score: total 9 items, ranging from 0=severely symptomatic to 36=asymptomatic. Higher scores=better functioning or lower symptom burden. TTD: time from randomization to first time subjects score showed 3 point/greater decrease from baseline in FBlSI-DRS-P subscale for 2 consecutive assessments. 99999=data could not be estimated due to small number of events. Full analysis set.

End point type	Secondary

End point timeframe:

From randomization up to the 90-Day Follow-up Visit (maximum duration of up to 41 months)

End point values	Avelumab + Best Supportive Care (BSC)	Best Supportive Care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	350	350		
Units: months				
median (confidence interval 95%)	99999 (13.9 to 99999)	13.8 (12.9 to 99999)		

Statistical analyses

Statistical analysis title	Avelumab+BSC Versus BSC
Comparison groups	Avelumab + Best Supportive Care (BSC) v Best Supportive Care
Number of subjects included in analysis	700
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.913
Method	Logrank
Parameter estimate	Cox proportional hazard
Point estimate	1.26
Confidence interval	
level	95 %
sides	1-sided
lower limit	0.901

Secondary: Change From Baseline in Levels EQ-5D-5L - Visual Analog Scale (VAS) Score at Cycle 6

End point title	Change From Baseline in Levels EQ-5D-5L - Visual Analog Scale (VAS) Score at Cycle 6

End point description:

The EQ-5D-5L was a 6-item subject-completed questionnaire designed to assess health status in terms of a single utility score. There were 2 components to the EQ-5D-5L, a Health State Profile which had individuals rate their level of problems (none, slight, moderate, severe, extreme/unable) in 5 areas (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression), and a Visual Analogue Scale (VAS) in which subject rated their overall health status from 0 (worst imaginable) to 100 (best imaginable), higher scores indicating a better health state. The full analysis set included all randomized subjects. Here, 'Overall number of subjects analyzed' signifies subjects who had data available for this outcome measure and ‘number analyzed’ signifies subjects evaluable for this outcome measure at specified time points.

End point type	Secondary

End point timeframe:

Baseline, Day 1 of Cycle 6

End point values	Avelumab + Best Supportive Care (BSC)	Best Supportive Care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	335	325		
Units: units on a scale				
arithmetic mean (standard deviation)				
Baseline (n=335,325)	74.9 (± 18.87)	74.9 (± 16.34)		
Change at Day 1 of Cycle 6 (n=183,109)	1.6 (± 17.74)	0.2 (± 14.74)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in European Quality of Life-5 Dimensions-5 Levels (EQ-5D-5L) Overall Health Utility Score at Cycle 6

End point title	Change From Baseline in European Quality of Life-5 Dimensions-5 Levels (EQ-5D-5L) Overall Health Utility Score at Cycle 6

End point description:

EQ-5D-5L was a 6-item subject -completed questionnaire designed to assess health status in terms of a single utility score. There were 2 components to the EQ-5D-5L, a Health State Profile which had individuals rate their level of problems (none, slight, moderate, severe, extreme/unable) in 5 areas (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression), and a Visual Analogue Scale (VAS) in which subject rated their overall health status from 0 (worst imaginable) to 100 (best imaginable). Published UK weights was used to create a single summary utility score. Utility scores range from -0.594 to 1, with low scores representing lower health status. The full analysis set included all randomized subjects. Here, 'Overall number of subjects analyzed' signifies subjects who had data available for this outcome measure and ‘number analyzed’ signifies subjects evaluable for this outcome measure at specified time points.

End point type	Secondary

End point timeframe:

Baseline, Day 1 of Cycle 6

End point values	Avelumab + Best Supportive Care (BSC)	Best Supportive Care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	336	327		
Units: units on a scale				
arithmetic mean (standard deviation)				
Baseline (n=336,327)	0.814 (± 0.1794)	0.792 (± 0.2013)		
Change at Day 1 of Cycle 6 (n=181,111)	-0.029 (± 0.1919)	-0.020 (± 0.1684)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

For ''Avelumab+Best Supportive Care (BSC)'' reporting group: Day1 up to 90 days after last dose of study drug and for ''BSC'' group: Day1 up to 90 days after end of treatment visit, for a maximum duration of up to 70 months at the time of the analysis.

Adverse event reporting additional description:

Same event may appear as both as Non SAE and Serious Adverse Events (SAE). However, what is presented are distinct events. An event may be categorized as serious in one subject and as non-serious in another, or a subject may have experienced both SAE and non-SAE. All-Cause Mortality, SAEs and non-SAEs were assessed in Safety Analysis set.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	26.0

Reporting groups

Reporting group title	Best Supportive Care

Reporting group description:

As prescribed by the treating physician, subjects received BSC which included treatment with antibiotics, nutritional support, correction of metabolic disorders, optimal symptom control and pain management, until confirmed disease progression, subject refusal, lost to follow up, unacceptable toxicity, or study termination by the sponsor, whichever occurred first. Subjects were followed up until death, end of the study or withdrawal of consent, whichever comes first, regardless of initiation of new anti-cancer therapy.

Reporting group title	Avelumab + Best Supportive Care (BSC)

Reporting group description:

Subjects received an intravenous (IV) infusion of 10 milligrams per kilograms (mg/kg) of Avelumab along with BSC, on Day 1 and 15 of each 28 days treatment cycle, until confirmed disease progression, subject refusal, lost to follow up, unacceptable toxicity, or study termination by the sponsor, whichever occurred first. BSC was administered as per the treating physician. Subjects were followed up until death, end of the study or withdrawal of consent, whichever comes first, regardless of initiation of new anti-cancer therapy.

Serious adverse events	Best Supportive Care	Avelumab + Best Supportive Care (BSC)	
Total subjects affected by serious adverse events			
subjects affected / exposed	73 / 345 (21.16%)	111 / 344 (32.27%)	
number of deaths (all causes)	242	225	
number of deaths resulting from adverse events	0	2	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Adenocarcinoma gastric			
subjects affected / exposed	1 / 345 (0.29%)	0 / 344 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Adenocarcinoma of colon			

subjects affected / exposed	1 / 345 (0.29%)	0 / 344 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anogenital warts			
subjects affected / exposed	0 / 345 (0.00%)	1 / 344 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Basal cell carcinoma			
subjects affected / exposed	1 / 345 (0.29%)	1 / 344 (0.29%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bladder cancer			
subjects affected / exposed	1 / 345 (0.29%)	0 / 344 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bladder neoplasm			
subjects affected / exposed	0 / 345 (0.00%)	1 / 344 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malignant melanoma			
subjects affected / exposed	0 / 345 (0.00%)	1 / 344 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malignant melanoma in situ			
subjects affected / exposed	1 / 345 (0.29%)	0 / 344 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malignant neoplasm progression			
subjects affected / exposed	1 / 345 (0.29%)	0 / 344 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastatic carcinoma of the bladder			

subjects affected / exposed	1 / 345 (0.29%)	0 / 344 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neoplasm progression			
subjects affected / exposed	1 / 345 (0.29%)	0 / 344 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophageal squamous cell carcinoma			
subjects affected / exposed	0 / 345 (0.00%)	1 / 344 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Polycythaemia vera			
subjects affected / exposed	1 / 345 (0.29%)	0 / 344 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transitional cell carcinoma			
subjects affected / exposed	0 / 345 (0.00%)	1 / 344 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tumour pain			
subjects affected / exposed	2 / 345 (0.58%)	0 / 344 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	0 / 345 (0.00%)	1 / 344 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Orthostatic hypotension			
subjects affected / exposed	0 / 345 (0.00%)	1 / 344 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypotension			

subjects affected / exposed	0 / 345 (0.00%)	1 / 344 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Hernia			
subjects affected / exposed	0 / 345 (0.00%)	1 / 344 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malaise			
subjects affected / exposed	1 / 345 (0.29%)	1 / 344 (0.29%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mass			
subjects affected / exposed	1 / 345 (0.29%)	0 / 344 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain			
subjects affected / exposed	1 / 345 (0.29%)	4 / 344 (1.16%)	
occurrences causally related to treatment / all	0 / 1	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	1 / 345 (0.29%)	2 / 344 (0.58%)	
occurrences causally related to treatment / all	0 / 1	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Systemic inflammatory response syndrome			
subjects affected / exposed	0 / 345 (0.00%)	1 / 344 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thirst			
subjects affected / exposed	0 / 345 (0.00%)	1 / 344 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Incarcerated hernia			

subjects affected / exposed	1 / 345 (0.29%)	0 / 344 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chest pain			
subjects affected / exposed	1 / 345 (0.29%)	0 / 344 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Disease progression			
subjects affected / exposed	16 / 345 (4.64%)	4 / 344 (1.16%)	
occurrences causally related to treatment / all	0 / 16	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fatigue			
subjects affected / exposed	1 / 345 (0.29%)	0 / 344 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General physical health deterioration			
subjects affected / exposed	1 / 345 (0.29%)	0 / 344 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Anaphylactic reaction			
subjects affected / exposed	1 / 345 (0.29%)	0 / 344 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Pelvic pain			
subjects affected / exposed	1 / 345 (0.29%)	1 / 344 (0.29%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cystocele			
subjects affected / exposed	1 / 345 (0.29%)	0 / 344 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Respiratory, thoracic and mediastinal disorders			
Acute respiratory failure			
subjects affected / exposed	0 / 345 (0.00%)	1 / 344 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute pulmonary oedema			
subjects affected / exposed	0 / 345 (0.00%)	1 / 344 (0.29%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory distress			
subjects affected / exposed	0 / 345 (0.00%)	1 / 344 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	1 / 345 (0.29%)	1 / 344 (0.29%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonitis			
subjects affected / exposed	0 / 345 (0.00%)	1 / 344 (0.29%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	1 / 345 (0.29%)	2 / 344 (0.58%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic obstructive pulmonary disease			
subjects affected / exposed	1 / 345 (0.29%)	2 / 344 (0.58%)	
occurrences causally related to treatment / all	0 / 1	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Interstitial lung disease			
subjects affected / exposed	0 / 345 (0.00%)	1 / 344 (0.29%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Psychiatric disorders			
Anxiety disorder			
subjects affected / exposed	1 / 345 (0.29%)	0 / 344 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Confusional state			
subjects affected / exposed	0 / 345 (0.00%)	1 / 344 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Depression			
subjects affected / exposed	0 / 345 (0.00%)	1 / 344 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Product issues			
Device occlusion			
subjects affected / exposed	0 / 345 (0.00%)	1 / 344 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Troponin T increased			
subjects affected / exposed	0 / 345 (0.00%)	1 / 344 (0.29%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
SARS-CoV-2 test positive			
subjects affected / exposed	0 / 345 (0.00%)	1 / 344 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Platelet count decreased			
subjects affected / exposed	0 / 345 (0.00%)	1 / 344 (0.29%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Liver function test increased			

subjects affected / exposed	1 / 345 (0.29%)	0 / 344 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic enzyme increased			
subjects affected / exposed	1 / 345 (0.29%)	0 / 344 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood creatine phosphokinase increased			
subjects affected / exposed	0 / 345 (0.00%)	2 / 344 (0.58%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Patella fracture			
subjects affected / exposed	0 / 345 (0.00%)	1 / 344 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infusion related reaction			
subjects affected / exposed	0 / 345 (0.00%)	4 / 344 (1.16%)	
occurrences causally related to treatment / all	0 / 0	4 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fractured sacrum			
subjects affected / exposed	0 / 345 (0.00%)	1 / 344 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fall			
subjects affected / exposed	0 / 345 (0.00%)	1 / 344 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Road traffic accident			
subjects affected / exposed	0 / 345 (0.00%)	1 / 344 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Concussion			

subjects affected / exposed	0 / 345 (0.00%)	1 / 344 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chest injury			
subjects affected / exposed	0 / 345 (0.00%)	1 / 344 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cervical vertebral fracture			
subjects affected / exposed	0 / 345 (0.00%)	1 / 344 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Contusion			
subjects affected / exposed	0 / 345 (0.00%)	1 / 344 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stomal hernia			
subjects affected / exposed	0 / 345 (0.00%)	1 / 344 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract stoma complication			
subjects affected / exposed	1 / 345 (0.29%)	1 / 344 (0.29%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subdural haematoma			
subjects affected / exposed	0 / 345 (0.00%)	1 / 344 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Coronary artery disease			
subjects affected / exposed	0 / 345 (0.00%)	1 / 344 (0.29%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiogenic shock			

subjects affected / exposed	1 / 345 (0.29%)	0 / 344 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial infarction			
subjects affected / exposed	0 / 345 (0.00%)	2 / 344 (0.58%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleuropericarditis			
subjects affected / exposed	0 / 345 (0.00%)	1 / 344 (0.29%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinus tachycardia			
subjects affected / exposed	0 / 345 (0.00%)	1 / 344 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Supraventricular tachycardia			
subjects affected / exposed	0 / 345 (0.00%)	1 / 344 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary artery stenosis			
subjects affected / exposed	0 / 345 (0.00%)	1 / 344 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial thrombosis			
subjects affected / exposed	0 / 345 (0.00%)	1 / 344 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation			
subjects affected / exposed	1 / 345 (0.29%)	3 / 344 (0.87%)	
occurrences causally related to treatment / all	0 / 1	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angina pectoris			

subjects affected / exposed	0 / 345 (0.00%)	1 / 344 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute myocardial infarction			
subjects affected / exposed	0 / 345 (0.00%)	1 / 344 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Cerebrovascular accident			
subjects affected / exposed	1 / 345 (0.29%)	1 / 344 (0.29%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cognitive disorder			
subjects affected / exposed	0 / 345 (0.00%)	1 / 344 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Headache			
subjects affected / exposed	1 / 345 (0.29%)	1 / 344 (0.29%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral infarction			
subjects affected / exposed	0 / 345 (0.00%)	1 / 344 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Seizure			
subjects affected / exposed	1 / 345 (0.29%)	1 / 344 (0.29%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	2 / 345 (0.58%)	0 / 344 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient ischaemic attack			

subjects affected / exposed	0 / 345 (0.00%)	1 / 344 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	2 / 345 (0.58%)	1 / 344 (0.29%)	
occurrences causally related to treatment / all	0 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
Vertigo positional			
subjects affected / exposed	0 / 345 (0.00%)	1 / 344 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	3 / 345 (0.87%)	2 / 344 (0.58%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Autoimmune pancreatitis			
subjects affected / exposed	0 / 345 (0.00%)	1 / 344 (0.29%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis			
subjects affected / exposed	0 / 345 (0.00%)	2 / 344 (0.58%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileus			
subjects affected / exposed	1 / 345 (0.29%)	3 / 344 (0.87%)	
occurrences causally related to treatment / all	0 / 1	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal obstruction			
subjects affected / exposed	1 / 345 (0.29%)	0 / 344 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Pancreatitis acute			
subjects affected / exposed	0 / 345 (0.00%)	1 / 344 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis chronic			
subjects affected / exposed	1 / 345 (0.29%)	0 / 344 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Retroperitoneal haemorrhage			
subjects affected / exposed	0 / 345 (0.00%)	1 / 344 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Constipation			
subjects affected / exposed	0 / 345 (0.00%)	2 / 344 (0.58%)	
occurrences causally related to treatment / all	0 / 0	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal haemorrhage			
subjects affected / exposed	1 / 345 (0.29%)	0 / 344 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric ulcer haemorrhage			
subjects affected / exposed	0 / 345 (0.00%)	1 / 344 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric ulcer			
subjects affected / exposed	0 / 345 (0.00%)	1 / 344 (0.29%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enteritis			
subjects affected / exposed	0 / 345 (0.00%)	1 / 344 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			

subjects affected / exposed	1 / 345 (0.29%)	0 / 344 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Umbilical hernia			
subjects affected / exposed	1 / 345 (0.29%)	0 / 344 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	0 / 345 (0.00%)	3 / 344 (0.87%)	
occurrences causally related to treatment / all	0 / 0	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Autoimmune hepatitis			
subjects affected / exposed	0 / 345 (0.00%)	1 / 344 (0.29%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Biliary obstruction			
subjects affected / exposed	1 / 345 (0.29%)	0 / 344 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholangitis acute			
subjects affected / exposed	0 / 345 (0.00%)	1 / 344 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis acute			
subjects affected / exposed	0 / 345 (0.00%)	1 / 344 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatotoxicity			
subjects affected / exposed	0 / 345 (0.00%)	1 / 344 (0.29%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			

Hydronephrosis			
subjects affected / exposed	1 / 345 (0.29%)	4 / 344 (1.16%)	
occurrences causally related to treatment / all	0 / 1	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute kidney injury			
subjects affected / exposed	6 / 345 (1.74%)	6 / 344 (1.74%)	
occurrences causally related to treatment / all	0 / 10	1 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anuria			
subjects affected / exposed	1 / 345 (0.29%)	0 / 344 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bladder perforation			
subjects affected / exposed	1 / 345 (0.29%)	0 / 344 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cystitis haemorrhagic			
subjects affected / exposed	0 / 345 (0.00%)	1 / 344 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematuria			
subjects affected / exposed	2 / 345 (0.58%)	5 / 344 (1.45%)	
occurrences causally related to treatment / all	0 / 2	0 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhage urinary tract			
subjects affected / exposed	0 / 345 (0.00%)	1 / 344 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune-mediated nephritis			
subjects affected / exposed	0 / 345 (0.00%)	1 / 344 (0.29%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	1 / 1	
Nephritis			

subjects affected / exposed	0 / 345 (0.00%)	1 / 344 (0.29%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract obstruction			
subjects affected / exposed	2 / 345 (0.58%)	0 / 344 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary bladder haemorrhage			
subjects affected / exposed	0 / 345 (0.00%)	1 / 344 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ureteric obstruction			
subjects affected / exposed	0 / 345 (0.00%)	1 / 344 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tubulointerstitial nephritis			
subjects affected / exposed	0 / 345 (0.00%)	1 / 344 (0.29%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal impairment			
subjects affected / exposed	1 / 345 (0.29%)	0 / 344 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
Hyperthyroidism			
subjects affected / exposed	0 / 345 (0.00%)	1 / 344 (0.29%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypothyroidism			
subjects affected / exposed	0 / 345 (0.00%)	1 / 344 (0.29%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			

Arthralgia			
subjects affected / exposed	1 / 345 (0.29%)	0 / 344 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Back pain			
subjects affected / exposed	1 / 345 (0.29%)	3 / 344 (0.87%)	
occurrences causally related to treatment / all	0 / 1	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Synovial cyst			
subjects affected / exposed	1 / 345 (0.29%)	0 / 344 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal stenosis			
subjects affected / exposed	0 / 345 (0.00%)	1 / 344 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pathological fracture			
subjects affected / exposed	1 / 345 (0.29%)	0 / 344 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteoarthritis			
subjects affected / exposed	2 / 345 (0.58%)	0 / 344 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myositis			
subjects affected / exposed	0 / 345 (0.00%)	1 / 344 (0.29%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Muscular weakness			
subjects affected / exposed	0 / 345 (0.00%)	1 / 344 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intervertebral disc protrusion			

subjects affected / exposed	0 / 345 (0.00%)	1 / 344 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Flank pain			
subjects affected / exposed	0 / 345 (0.00%)	1 / 344 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bone pain			
subjects affected / exposed	0 / 345 (0.00%)	1 / 344 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain in extremity			
subjects affected / exposed	1 / 345 (0.29%)	2 / 344 (0.58%)	
occurrences causally related to treatment / all	0 / 1	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Bacteraemia			
subjects affected / exposed	1 / 345 (0.29%)	0 / 344 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Biliary sepsis			
subjects affected / exposed	1 / 345 (0.29%)	0 / 344 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
COVID-19			
subjects affected / exposed	0 / 345 (0.00%)	1 / 344 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	1 / 345 (0.29%)	0 / 344 (0.00%)	
occurrences causally related to treatment / all	0 / 5	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis orbital			

subjects affected / exposed	1 / 345 (0.29%)	0 / 344 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device related infection			
subjects affected / exposed	1 / 345 (0.29%)	1 / 344 (0.29%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticulitis			
subjects affected / exposed	1 / 345 (0.29%)	1 / 344 (0.29%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gallbladder abscess			
subjects affected / exposed	1 / 345 (0.29%)	0 / 344 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper respiratory tract infection			
subjects affected / exposed	0 / 345 (0.00%)	1 / 344 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tracheobronchitis			
subjects affected / exposed	1 / 345 (0.29%)	0 / 344 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	1 / 345 (0.29%)	4 / 344 (1.16%)	
occurrences causally related to treatment / all	0 / 1	2 / 5	
deaths causally related to treatment / all	0 / 0	1 / 1	
Pyelonephritis acute			
subjects affected / exposed	1 / 345 (0.29%)	1 / 344 (0.29%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis			

subjects affected / exposed	4 / 345 (1.16%)	4 / 344 (1.16%)	
occurrences causally related to treatment / all	0 / 4	1 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	
Postoperative wound infection			
subjects affected / exposed	0 / 345 (0.00%)	1 / 344 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	0 / 345 (0.00%)	1 / 344 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Kidney infection			
subjects affected / exposed	0 / 345 (0.00%)	1 / 344 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infection			
subjects affected / exposed	0 / 345 (0.00%)	1 / 344 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Herpes zoster			
subjects affected / exposed	0 / 345 (0.00%)	1 / 344 (0.29%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	7 / 345 (2.03%)	17 / 344 (4.94%)	
occurrences causally related to treatment / all	0 / 8	1 / 18	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular device infection			
subjects affected / exposed	0 / 345 (0.00%)	2 / 344 (0.58%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urosepsis			

subjects affected / exposed	2 / 345 (0.58%)	1 / 344 (0.29%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Hyperkalaemia			
subjects affected / exposed	0 / 345 (0.00%)	1 / 344 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperglycaemia			
subjects affected / exposed	0 / 345 (0.00%)	1 / 344 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypercalcaemia			
subjects affected / exposed	0 / 345 (0.00%)	1 / 344 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Best Supportive Care	Avelumab + Best Supportive Care (BSC)	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	214 / 345 (62.03%)	321 / 344 (93.31%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	8 / 345 (2.32%)	22 / 344 (6.40%)	
occurrences (all)	8	25	
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	12 / 345 (3.48%)	56 / 344 (16.28%)	
occurrences (all)	14	69	
Oedema peripheral			
subjects affected / exposed	21 / 345 (6.09%)	24 / 344 (6.98%)	
occurrences (all)	27	37	
Influenza like illness			

subjects affected / exposed	4 / 345 (1.16%)	20 / 344 (5.81%)	
occurrences (all)	4	23	
Fatigue			
subjects affected / exposed	23 / 345 (6.67%)	66 / 344 (19.19%)	
occurrences (all)	24	100	
Asthenia			
subjects affected / exposed	19 / 345 (5.51%)	64 / 344 (18.60%)	
occurrences (all)	22	125	
Chills			
subjects affected / exposed	3 / 345 (0.87%)	29 / 344 (8.43%)	
occurrences (all)	4	33	
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	11 / 345 (3.19%)	26 / 344 (7.56%)	
occurrences (all)	11	36	
Cough			
subjects affected / exposed	18 / 345 (5.22%)	49 / 344 (14.24%)	
occurrences (all)	20	61	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	9 / 345 (2.61%)	24 / 344 (6.98%)	
occurrences (all)	9	26	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	3 / 345 (0.87%)	19 / 344 (5.52%)	
occurrences (all)	4	29	
Amylase increased			
subjects affected / exposed	3 / 345 (0.87%)	24 / 344 (6.98%)	
occurrences (all)	6	40	
Blood creatine phosphokinase increased			
subjects affected / exposed	2 / 345 (0.58%)	18 / 344 (5.23%)	
occurrences (all)	2	48	
Blood creatinine increased			
subjects affected / exposed	6 / 345 (1.74%)	29 / 344 (8.43%)	
occurrences (all)	6	41	
Lipase increased			

subjects affected / exposed	1 / 345 (0.29%)	22 / 344 (6.40%)	
occurrences (all)	1	42	
Injury, poisoning and procedural complications			
Infusion related reaction			
subjects affected / exposed	0 / 345 (0.00%)	30 / 344 (8.72%)	
occurrences (all)	0	38	
Nervous system disorders			
Dizziness			
subjects affected / exposed	12 / 345 (3.48%)	23 / 344 (6.69%)	
occurrences (all)	14	28	
Headache			
subjects affected / exposed	9 / 345 (2.61%)	27 / 344 (7.85%)	
occurrences (all)	12	37	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	22 / 345 (6.38%)	47 / 344 (13.66%)	
occurrences (all)	34	75	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	23 / 345 (6.67%)	34 / 344 (9.88%)	
occurrences (all)	27	44	
Vomiting			
subjects affected / exposed	12 / 345 (3.48%)	45 / 344 (13.08%)	
occurrences (all)	13	61	
Nausea			
subjects affected / exposed	22 / 345 (6.38%)	55 / 344 (15.99%)	
occurrences (all)	24	74	
Diarrhoea			
subjects affected / exposed	17 / 345 (4.93%)	63 / 344 (18.31%)	
occurrences (all)	21	97	
Constipation			
subjects affected / exposed	34 / 345 (9.86%)	60 / 344 (17.44%)	
occurrences (all)	37	73	
Skin and subcutaneous tissue disorders			
Rash			

subjects affected / exposed	5 / 345 (1.45%)	43 / 344 (12.50%)	
occurrences (all)	5	71	
Pruritus			
subjects affected / exposed	6 / 345 (1.74%)	64 / 344 (18.60%)	
occurrences (all)	6	94	
Dry skin			
subjects affected / exposed	3 / 345 (0.87%)	23 / 344 (6.69%)	
occurrences (all)	3	31	
Renal and urinary disorders			
Haematuria			
subjects affected / exposed	35 / 345 (10.14%)	38 / 344 (11.05%)	
occurrences (all)	42	51	
Endocrine disorders			
Hypothyroidism			
subjects affected / exposed	2 / 345 (0.58%)	44 / 344 (12.79%)	
occurrences (all)	2	51	
Hyperthyroidism			
subjects affected / exposed	1 / 345 (0.29%)	21 / 344 (6.10%)	
occurrences (all)	1	22	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	29 / 345 (8.41%)	68 / 344 (19.77%)	
occurrences (all)	38	99	
Back pain			
subjects affected / exposed	34 / 345 (9.86%)	57 / 344 (16.57%)	
occurrences (all)	54	72	
Myalgia			
subjects affected / exposed	10 / 345 (2.90%)	32 / 344 (9.30%)	
occurrences (all)	10	42	
Pain in extremity			
subjects affected / exposed	23 / 345 (6.67%)	20 / 344 (5.81%)	
occurrences (all)	31	22	
Infections and infestations			
Urinary tract infection			
subjects affected / exposed	33 / 345 (9.57%)	53 / 344 (15.41%)	
occurrences (all)	53	72	

Upper respiratory tract infection subjects affected / exposed occurrences (all)	8 / 345 (2.32%) 12	24 / 344 (6.98%) 32	
Nasopharyngitis subjects affected / exposed occurrences (all)	13 / 345 (3.77%) 17	33 / 344 (9.59%) 42	
Influenza subjects affected / exposed occurrences (all)	11 / 345 (3.19%) 12	23 / 344 (6.69%) 25	
Metabolism and nutrition disorders Decreased appetite subjects affected / exposed occurrences (all)	24 / 345 (6.96%) 26	48 / 344 (13.95%) 60	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
17 December 2015	Amendment 1: Per FDA request, implemented clarifications in section 5.4.3.5, table 5 management of Avelumab irAEs: Clarified requirement for delaying or discontinuing avelumab for Grade 3 or 4 dermatological irAEs. Clarified requirement to delay or discontinue avelumab therapy for suspicion of adrenal crisis. Per FDA request, added a requirement in section 5.4.3.5, table 5, to permanently discontinue avelumab therapy for subjects with AST/ALT >3 x ULN with concurrent elevation of total bilirubin >2 x ULN without another obvious cause. Inclusion criterion #11 was revised to allow enrollment of patients with a creatinine clearance (CrCl) ≥30 mL/min (changed from ≥50 mL/min).
24 March 2016	Amendment 2: Added an HIV screening test unless not permitted by local laws and regulations (schedule of activities table and footnote #12; and table 6, section 7.1.3) and exclusion of HIV positive subjects (exclusion criterion #16, Section 4.2). Clarified that exclusion criterion #21 (section 4.2) includes but is not limited to those medical conditions listed, and add 'pulmonary fibrosis' as a listed condition. Clarified in Section 7.1.3 that the requirement to repeat abnormal laboratory test results applies only for clinically significant abnormal results.
19 December 2016	Amendment 3: To mitigate the potential for bias in determining disease progression, an expedited blinded independent central review (BICR) for investigator-assessed disease progression was added. To optimize trial logistics, removed the requirement for central eligibility review of first-line chemotherapy response. Per United States FDA request, to assess the utility of serum troponin measurements in early detection of myocarditis, a rare and potentially fatal risk associated with avelumab and other check-point inhibitors, the following additions were made: Mandatory measurement of cardiac troponin levels at screening and at each clinic visit ending on Cycle 4 Day 1 (ie, for a total of 12 weeks), and as clinically indicated; Management guidelines for myocarditis. Clarified that first-line chemotherapy must have been completed no less than 4 weeks and no more than 10 weeks prior to randomization (inclusion criterion 2a).
28 March 2019	Amendment 4: immune-related Response Criteria (irRECIST) has been removed as an exploratory endpoint and required study assessment. Management of avelumab-related toxicity has been updated to reflect current avelumab program standard recommendations (Section 5.4.3). Premedications to mitigate avelumab infusion-related reactions were revised such that premedication is only required for the first 4 infusions. Contraception requirements have been updated for females and males in accordance with the current Pfizer and avelumab program standards. The contraception check and pregnancy test were removed as required study procedures at the 60 Day Follow-up visit, in accordance with the current avelumab program standard. It has been added that if new cancer therapy is started, reporting of concomitant medications should end at the time the new cancer therapy starts in order to match the AE reporting period, and in accordance with the current avelumab program standard.Survival assessments for long-term follow-up (every 3 months) were clarified to begin after the last study clinic visit, and to allow additional timepoints at a sponsor request in preparation for interim and final analyses in order to update survival information and add uniformity in the time since most recent contact.

13 February 2020	Amendment 5: The purpose of this protocol amendment is to implement the External-Data Monitoring Committee (E-DMC) recommendation at the pre-specified interim analysis (section 9.6) that remaining patients on Arm B who are progression-free are offered crossover to avelumab. Also, added section 17, supplement 1: crossover from BSC alone (arm B) to avelumab plus best supportive care. This supplement provided details for arm B subjects who crossover to receive avelumab plus BSC including required eligibility criteria, general treatment or study plan, and schedule of activities for screening, treatment period, end of treatment or withdrawal and short and long term follow-up.
08 March 2021	Amendment 6: Following a final OS update, the frequency of study procedures was reduced while providing continued treatment for patients actively receiving avelumab and ending study participation for all patients who were not actively receiving avelumab. A new Schedule of Activities (SoA) table and a new required laboratory tests table (Table 7) were added, BICR tumor assessments were no longer performed, arm B subjects who are eligible to crossover to avelumab plus best supportive care (BSC) as per supplement 1 were permitted to do so until 60 days after the final OS update or approval of amendment 6, whichever is later and CRF data collection was reduced to those items relating to study drug exposure and adverse events.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported