Clinical trial results:
A Phase II, Open-Label, Multicenter Trial to Investigate the Clinical Activity and Safety of Avelumab (MSB0010718C) in Subjects With Merkel Cell Carcinoma

Summary

EudraCT number	2014-000445-79
Trial protocol	IT DE AT ES
Global end of trial date	03 May 2023

Results information

Result version number	v1 (current)
This version publication date	06 March 2024
First version publication date	06 March 2024

Trial information

Trial identification

Sponsor protocol code	EMR100070-003

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02155647
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Merck Healthcare KGaA, Darmstadt Germany
Sponsor organisation address	Frankfurter Strasse 250, Darmstadt, Germany, 64293
Public contact	Communication Centre, Merck Healthcare KGaA, Darmstadt Germany, +49 6151725200, service@merckgroup.com
Scientific contact	Communication Centre, Merck Healthcare KGaA, Darmstadt Germany, +49 6151725200, service@merckgroup.com

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	03 May 2023
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	03 May 2023
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main purpose of this trial was to evaluate the efficacy and safety of avelumab in subjects with metastatic Merkel cell carcinoma (MCC).

Protection of trial subjects:

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

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	03 July 2014
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Australia: 14
Country: Number of subjects enrolled	Switzerland: 1
Country: Number of subjects enrolled	Germany: 25
Country: Number of subjects enrolled	Spain: 3
Country: Number of subjects enrolled	France: 46
Country: Number of subjects enrolled	Italy: 29
Country: Number of subjects enrolled	Japan: 6
Country: Number of subjects enrolled	United States: 80
Worldwide total number of subjects	204
EEA total number of subjects	103

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)	44
From 65 to 84 years	143
85 years and over	17

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

A total of 88 subjects were enrolled in Part A of the study and a total of 116 subjects were enrolled in Part B of the study. Subjects enrolled in Part A were not eligible for enrollment in Part B.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Part A: Avelumab

Arm description:

Subjects with metastatic Merkel cell carcinoma (MCC) after failing first-line chemotherapy received Avelumab at a dose of 10 milligram per kilogram (mg/kg) as 1-hour intravenous infusion once every 2 weeks until therapeutic failure, significant clinical deterioration, unacceptable toxicity, or any criterion for withdrawal from the trial or investigational medicinal product occurs.

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

Dosage and administration details:

Subjects with MCC after failing first-line chemotherapy received Avelumab at a dose of 10 mg/kg as 1-hour intravenous infusion once every 2 weeks until therapeutic failure, significant clinical deterioration, unacceptable toxicity, or any criterion for withdrawal from the trial or investigational medicinal product occurs.

Arm title	Part B: Avelumab

Arm description:

Subjects received Avelumab as first-line treatment for metastatic or distally recurrent MCC at a dose of 10 mg/kg as 1-hour intravenous infusion once every 2 weeks until therapeutic failure, significant clinical deterioration, unacceptable toxicity, or any criterion for withdrawal from the trial or investigational medicinal product occurs.

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

Dosage and administration details:

Subjects received Avelumab as first-line treatment for metastatic or distally recurrent MCC at a dose of 10 mg/kg as 1-hour intravenous infusion once every 2 weeks until therapeutic failure, significant clinical deterioration, unacceptable toxicity, or any criterion for withdrawal from the trial or investigational medicinal product occurs.

Number of subjects in period 1	Part A: Avelumab	Part B: Avelumab
Started	88	116
Completed	88	116

Baseline characteristics

Reporting groups	
Reporting group title	Part A: Avelumab
Reporting group description:	
Subjects with metastatic Merkel cell carcinoma (MCC) after failing first-line chemotherapy received Avelumab at a dose of 10 milligram per kilogram (mg/kg) as 1-hour intravenous infusion once every 2 weeks until therapeutic failure, significant clinical deterioration, unacceptable toxicity, or any criterion for withdrawal from the trial or investigational medicinal product occurs.	
Reporting group title	Part B: Avelumab
Reporting group description:	
Subjects received Avelumab as first-line treatment for metastatic or distally recurrent MCC at a dose of 10 mg/kg as 1-hour intravenous infusion once every 2 weeks until therapeutic failure, significant clinical deterioration, unacceptable toxicity, or any criterion for withdrawal from the trial or investigational medicinal product occurs.	

Reporting group values	Part A: Avelumab	Part B: Avelumab	Total
Number of subjects	88	116	204
Age Categorical Units: Subjects			
<=18 years	0	0	0
Between 18 and 65 years	22	22	44
>=65 years	66	94	160
Sex: Female, Male Units: Subjects			
Female	23	35	58
Male	65	81	146
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	3	3	6
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	0	2	2
White	81	75	156
More than one race	0	0	0
Unknown or Not Reported	4	36	40
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	4	29	33
Not Hispanic or Latino	58	75	133
Unknown or Not Reported	26	12	38

End points

End points reporting groups

Reporting group title	Part A: Avelumab

Reporting group description:

Subjects with metastatic Merkel cell carcinoma (MCC) after failing first-line chemotherapy received Avelumab at a dose of 10 milligram per kilogram (mg/kg) as 1-hour intravenous infusion once every 2 weeks until therapeutic failure, significant clinical deterioration, unacceptable toxicity, or any criterion for withdrawal from the trial or investigational medicinal product occurs.

Reporting group title	Part B: Avelumab

Reporting group description:

Subjects received Avelumab as first-line treatment for metastatic or distally recurrent MCC at a dose of 10 mg/kg as 1-hour intravenous infusion once every 2 weeks until therapeutic failure, significant clinical deterioration, unacceptable toxicity, or any criterion for withdrawal from the trial or investigational medicinal product occurs.

Primary: Part A: Number of Subjects with Confirmed Best Overall Response (BOR) as per Response Evaluation Criteria in Solid Tumors version (RECIST) 1.1

End point title	Part A: Number of Subjects with Confirmed Best Overall Response (BOR) as per Response Evaluation Criteria in Solid Tumors version (RECIST) 1.1[1][2]

End point description:

Confirmed BOR was determined according to RECIST 1.1 and as adjudicated by an Independent Endpoint Review Committee (IERC) and defined as best response of any of complete response (CR), partial response (PR), stable disease (SD) and progressive disease (PD) recorded from date of randomization until disease progression/recurrence (taking smallest measurement recorded since start of treatment as reference). CR:Disappearance of all evidence of target/non-target lesions. PR:At least 30%reduction from baseline in sum of longest diameter (SLD) of all lesions. SD:Neither sufficient increase to qualify for PD nor sufficient shrinkage to qualify for PR. PD:at least 20% increase in SLD, taking as reference smallest SLD recorded from baseline/appearance of 1or more new lesions and unequivocal progression of non-target lesions. Intent-to-Treat analysis set included all subject who received at least 1 dose of study treatment.

End point type	Primary

End point timeframe:

Up to 113 weeks

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: This endpoint was planned to be reported for Part A only.

[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: This endpoint was planned to be reported for Part A only.

End point values	Part A: Avelumab			
Subject group type	Reporting group			
Number of subjects analysed	88			
Units: Subjects				
Complete Response	10			
Partial Response	19			
Stable Disease	9			
Non-complete Response/ Non-progressive Disease	0			
Progressive Disease	32			
Not evaluable	18			

Statistical analyses

No statistical analyses for this end point

Primary: Part B: Durable Response Rate (DRR)

End point title	Part B: Durable Response Rate (DRR)[3][4]

End point description:

Durable response is defined as an objective response (confirmed complete response [CR] or confirmed Partial response [PR]) according to Response Evaluation Criteria in Solid Tumors version (RECIST) 1.1, determined by the Independent Endpoint Review Committee (IERC), with a duration of at least 6 months. The DRR was determined as the percentage of participants with an objective response in terms of CR or PR according to RECIST 1.1, as determined by the IERC, with a duration of at least 6 months. CR: Disappearance of all evidence of target and non-target lesions. PR: At least 30% reduction from baseline in the sum of the longest diameter (SLD) of all lesions. Full analysis set (FAS) included all subjects who received at least 1 dose of study treatment.

End point type	Primary

End point timeframe:

Up to 161 weeks

Notes:

[3] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only descriptive summary statistics was planned to be reported for this endpoint.

[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: This endpoint was planned to be reported for Part B only.

End point values	Part B: Avelumab			
Subject group type	Reporting group			
Number of subjects analysed	116			
Units: Percentage of subjects				
number (confidence interval 95%)	30.2 (22.0 to 39.4)			

Statistical analyses

No statistical analyses for this end point

Secondary: Part A: Duration of Response According to Response Evaluation Criteria in Solid Tumors version (RECIST) 1.1

End point title	Part A: Duration of Response According to Response Evaluation Criteria in Solid Tumors version (RECIST) 1.1[5]

End point description:

The duration of response as determined from IERC tumor assessment was calculated for each subject with a confirmed response (CR or PR) as the time from first observation of response until first observation of documented disease progression or death when death occurs within 12 weeks of the last tumor assessment, whichever occurs first. CR: Disappearance of all evidence of target and non-target lesions. PR: At least 30% reduction from baseline in the sum of the longest diameter (SLD) of all

lesions. Results were calculated based on Kaplan-Meier estimates. Intent-to-Treat analysis set included all subjects who received at least 1 dose of study treatment. Here "Number of subjects analyzed" signifies those subjects who were evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Up to 325 weeks

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: This endpoint was planned to reported for Part A only.

End point values	Part A: Avelumab			
Subject group type	Reporting group			
Number of subjects analysed	29			
Units: Months				
median (full range (min-max))	40.5 (2.8 to 41.5)			

Statistical analyses

No statistical analyses for this end point

Secondary: Part A: Number of Subjects with Treatment-Related (TR) Treatment-Emergent Adverse Events (TEAEs), Treatment-Related Serious TEAEs and Treatment-Related TEAEs leading to Death

End point title	Part A: Number of Subjects with Treatment-Related (TR) Treatment-Emergent Adverse Events (TEAEs), Treatment-Related Serious TEAEs and Treatment-Related TEAEs leading to Death[6]

End point description:

Related Adverse events (AE) were defined according to National Cancer Institute Common Terminology Criteria for Adverse Events Version 4.0 (NCI-CTCAE) as adverse events with relationship to study treatment reported by the investigator. A serious adverse event (SAE) was an AE that resulted in any of the following outcomes: death; life threatening; persistent/significant disability/incapacity; initial or prolonged inpatient hospitalization; congenital anomaly/birth defect or was otherwise considered medically important. Treatment-emergent are events between first dose of study drug that were absent before treatment or that worsened relative to pre-treatment state up to 30 days after last administration. TEAEs included both Serious TEAEs and non-serious TEAEs. Related TEAEs are defined as events with a relationship of missing, unknown, or yes. Safety analysis set included all subjects who received at least 1 dose of study treatment.

End point type	Secondary

End point timeframe:

Up to 325 weeks

Notes:

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

End point values	Part A: Avelumab			
Subject group type	Reporting group			
Number of subjects analysed	88			
Units: Subjects				
Participants with TR-TEAEs	68			
Participants with TR-Serious-TEAEs	9			
Participants with TR-TEAEs leading to Death	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Part A: Progression-Free Survival (PFS) Time According to Response Evaluation Criteria in Solid Tumors version (RECIST) 1.1

End point title	Part A: Progression-Free Survival (PFS) Time According to Response Evaluation Criteria in Solid Tumors version (RECIST) 1.1[7]

End point description:

The PFS time (based on IERC tumor assessments), according to the RECIST 1.1, was defined as the time from first administration of study treatment until first observation of PD or death when death occurred within 12 weeks of the last tumor assessment or first administration of study treatment (whichever was later). PFS time (in months) was defined as: (date of PD or death – date of the first dose of study treatment + 1)/30.4375 (months). PD was defined as at least a 20% increase in the SLD, taking as reference the smallest SLD recorded from baseline or the appearance
of 1 or more new lesions and unequivocal progression of non-target lesions Intent-to-Treat analysis set included all subjects who received at least 1 dose of study treatment.

End point type	Secondary

End point timeframe:

Up to 325 weeks

Notes:

[7] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint was planned to reported for Part A only.

End point values	Part A: Avelumab			
Subject group type	Reporting group			
Number of subjects analysed	88			
Units: Months				
median (full range (min-max))	2.7 (0.03 to 45.6)			

Statistical analyses

No statistical analyses for this end point

Secondary: Part A: Number of Subjects with Clinically Significant Abnormalities in Laboratory Values Reported as Treatment Emergent Adverse Events (TEAEs)

End point title	Part A: Number of Subjects with Clinically Significant

	Abnormalities in Laboratory Values Reported as Treatment Emergent Adverse Events (TEAEs)[8]

End point description:

The laboratory measurements included hematology, liver function and blood chemistry. Number of subjects with clinically significant abnormalities with Grade greater than or equals to (>=) 3 in laboratory values reported as TEAEs were reported. Clinically Significance was decided by investigator. Safety analysis set included all subjects who received at least 1 dose of study treatment.

End point type	Secondary

End point timeframe:

Up to 325 weeks

Notes:

[8] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: This endpoint was planned to be reported for Part A only.

End point values	Part A: Avelumab			
Subject group type	Reporting group			
Number of subjects analysed	88			
Units: Subjects				
Anemia	9			
Lymphocyte count decreased	18			
Neutrophil count decreased	1			
Platelet count decreased	1			
White blood cell count decreased	1			
Hypoalbuminemia	2			
Alkaline phosphatase increased	1			
Alanine aminotransferase increased	3			
Serum amylase increased	1			
Aspartate aminotransferase increased	1			
Blood bilirubin increased	1			
Cholesterol high	1			
Creatine phosphokinase increased	1			
Creatinine increased	2			
Chronic kidney disease	3			
Gamma-glutamyltransferase increased	6			
Hyperglycemia	7			
Hypoglycemia	1			
Hyperkalemia	1			
Hypokalemia	2			
Lipase increased	4			
Hypermagnesemia	1			
Hypophosphatemia	3			
Hyponatremia	11			
Hypertriglyceridemia	1			

Statistical analyses

No statistical analyses for this end point

Secondary: Part A: Number of Subjects with Clinically Significant Abnormalities in

Vital Signs Reported as Treatment Emergent Adverse Events (TEAEs)

End point title	Part A: Number of Subjects with Clinically Significant Abnormalities in Vital Signs Reported as Treatment Emergent Adverse Events (TEAEs)[9]

End point description:

Vital signs including body temperature, body weight, respiratory rate, heart rate (after 5-minute rest), and arterial blood pressure (after 5-minute rest) were evaluated. Number of subjects with clinically significant abnormalities in Vital Signs reported as TEAEs. Clinically Significance was decided by investigator. Safety analysis set included all subjects who received at least 1 dose of study treatment.

End point type	Secondary

End point timeframe:

Up to 325 weeks

Notes:

[9] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint was planned to be reported for Part A only.

End point values	Part A: Avelumab			
Subject group type	Reporting group			
Number of subjects analysed	88			
Units: Subjects				
Body temperature Increased	0			
Weight Increased	57			
Weight Decreased	54			
Increased Heart Rate	83			
Decreased Heart Rate	84			
Increased Systolic Blood Pressure	84			
Decreased Systolic Blood Pressure	84			
Increased Diastolic Blood Pressure	84			
Decreased Diastolic Blood Pressure	84			
Increased Respiratory Rate	81			
Decreased Respiratory Rate	81			

Statistical analyses

No statistical analyses for this end point

Secondary: Part A: Number of Subjects with Clinically Significant Abnormalities in Electrocardiogram (ECG)

End point title	Part A: Number of Subjects with Clinically Significant Abnormalities in Electrocardiogram (ECG)[10]

End point description:

A 12-lead ECG was recorded after the subject has been in a supine position breathing quietly for 5 minutes. The ECG results was used to evaluate the heart rate, atrial ventricular conduction, PR interval, QRS, QTcF and QTcB. Number of subjects with clinical significant abnormalities in ECG parameter reported here. Clinically Significance was decided by investigator. Safety analysis set included all subjects who received at least 1 dose of study treatment. Here "Number of subjects analyzed" signifies those who were evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Up to 325 weeks

Notes:

[10] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint was planned to be reported for Part A only.

End point values	Part A: Avelumab			
Subject group type	Reporting group			
Number of subjects analysed	81			
Units: Subjects				
PR interval >= 220 ms	16			
QRS >= 120 ms	12			
QTcF > 30 ms and <= 60 ms	20			
QTcF > 60 ms	1			
QTcB > 30 ms and <= 60 ms	25			
QTcB > 60 ms	2			
Heart rate <= 50 bpm	3			
Heart rate >= 120 bpm	2			

Statistical analyses

No statistical analyses for this end point

Secondary: Part A: Interim Analysis: Overall Survival (OS) Time

End point title	Part A: Interim Analysis: Overall Survival (OS) Time[11]

End point description:

The OS time was defined as the time from first administration of trial treatment until death. The OS time was analyzed using the Kaplan-Meier method. Intent-to-Treat analysis set included all subjects who received at least 1 dose of study treatment.

End point type	Secondary

End point timeframe:

Up to 87 weeks (Data reported are per pre-specified interim analysis with a data cut-off date of 3 Mar 2016)

Notes:

[11] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint was planned to reported for Part A only.

End point values	Part A: Avelumab			
Subject group type	Reporting group			
Number of subjects analysed	88			
Units: Months				
median (confidence interval 95%)	11.3 (7.5 to 14.0)			

Statistical analyses

No statistical analyses for this end point

Secondary: Part A: Final Analysis: Overall Survival (OS) Time

End point title	Part A: Final Analysis: Overall Survival (OS) Time[12]

End point description:

The OS time was defined as the time from first administration of trial treatment until death. The OS time was analyzed using the Kaplan-Meier method. Intent-to-Treat analysis set included all subjects who received at least 1 dose of study treatment.

End point type	Secondary

End point timeframe:

Time from first administration of trial treatment until death (Up to 325 weeks)

Notes:

[12] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint was planned to reported for Part A only.

End point values	Part A: Avelumab			
Subject group type	Reporting group			
Number of subjects analysed	88			
Units: months				
median (full range (min-max))	12.6 (0.4 to 71.9)			

Statistical analyses

No statistical analyses for this end point

Secondary: Part A: Subject's Response Status According to Response Evaluation Criteria in Solid Tumors version (RECIST) 1.1 at 6 and 12 months

End point title	Part A: Subject's Response Status According to Response Evaluation Criteria in Solid Tumors version (RECIST) 1.1 at 6 and 12 months[13]

End point description:

The response status at 6 and 12 months after start of trial treatment according to RECIST 1.1 (as determined by the IERC) was determined. A subject was considered to be in response at the given timepoint (6 or 12 months after the start of the subject's treatment) if the subject had a documented response (PR or CR) prior to that timepoint, and neither died nor experienced disease progression according to the RECIST 1.1 nor was lost to follow-up up to the given timepoint. CR: Disappearance of all evidence of target and non-target lesions. PR: At least 30% reduction from baseline in the sum of the longest diameter (SLD) of all lesions. Percentage of subjects in response and not in response according to RECIST1.1 at 6 and 12 months were reported. Intent-to-Treat analysis set included all subjects who received at least 1 dose of study treatment.

End point type	Secondary

End point timeframe:

At Month 6 and 12

Notes:

[13] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint was planned to be reported for Part A only.

End point values	Part A: Avelumab			
Subject group type	Reporting group			
Number of subjects analysed	88			
Units: Percentage of subjects				
number (not applicable)				
In-response at Month 6	30.7			
In-response at Month 12	20.7			
Not in-response at Month 6	69.3			
Not In-response at Month 12	79.3			

Statistical analyses

No statistical analyses for this end point

Secondary: Part A: Number of Subjects with Positive Treatment Emergent Anti-Avelumab Antibodies

End point title	Part A: Number of Subjects with Positive Treatment Emergent Anti-Avelumab Antibodies[14]

End point description:

Serum samples were analyzed by a validated electrochemiluminesce immunoassay to detect the presence of anti-avelumab antibodies. Samples that screened positive were subsequently tested in a confirmatory assay. Those confirmed positive were titered for a quasi-quantitative result. Number of subjects with positive treatment emergent anti-Avelumab antibodies were reported. Subjects not positive prior to treatment with avelumab and with at least one positive result in the human-Antihuman Antibodies assay were characterized as treatment-emergent. Safety analysis set included all participants who received at least 1 dose of study treatment. Here "Number of subjects analyzed" signifies those who were evaluable for this outcome measure.

End point type	Secondary

End point timeframe:

Up to 80 weeks

Notes:

[14] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint was planned to be reported for Part A only.

End point values	Part A: Avelumab			
Subject group type	Reporting group			
Number of subjects analysed	82			
Units: Subjects	3			

Statistical analyses

No statistical analyses for this end point

Secondary: Part A: Serum Concentration at End of Infusion (CEOI) of Avelumab

End point title	Part A: Serum Concentration at End of Infusion (CEOI) of Avelumab[15]

End point description:

Serum concentration at end of infusion (CEOI) of Avelumab is reported. Pharmacokinetic analysis set consists of all subjects who received at least 1 dose of avelumab, and provide at least 1 measurable post-dose concentration. Here "n" signifies those subjects who were evaluable at specified timepoints.

End point type	Secondary

End point timeframe:

Day 1, 43, 85, 169, 253, 337 and 421

Notes:

[15] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint was planned to be reported for Part A only.

End point values	Part A: Avelumab			
Subject group type	Reporting group			
Number of subjects analysed	88			
Units: Micrograms per milliliter				
arithmetic mean (standard deviation)				
Day 1: n = 59	252 (± 129)			
Day 43: n = 48	266 (± 74.2)			
Day 85: n = 30	274 (± 57.7)			
Day 169: n = 23	315 (± 65.0)			
Day 253: n = 15	318 (± 70.1)			
Day 337: n = 6	373 (± 48.3)			
Day 421: n = 4	453 (± 71.5)			

Statistical analyses

No statistical analyses for this end point

Secondary: Part A: Minimum Serum Post-dose (Ctrough) Concentration of Aveluamb

End point title	Part A: Minimum Serum Post-dose (Ctrough) Concentration of Aveluamb[16]

End point description:

Minimum serum post-dose (Ctrough) concentration of avelumab was reported. Pharmacokinetic analysis set consists of all subjects who received at least 1 dose of avelumab, and provide at least 1 measurable post-dose concentration. Here "n" signifies those subjects who were evaluable at specified timepoints and "9999" signifies that standard deviation was not calculable for n = 1.

End point type	Secondary

End point timeframe:

Day 15, 29, 43, 57, 71, 85, 99, 169, 211, 253, 337 and 421

Notes:

[16] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint was planned to be reported for Part A only.

End point values	Part A: Avelumab			
Subject group type	Reporting group			
Number of subjects analysed	88			
Units: Micrograms per milliliter				
arithmetic mean (standard deviation)				
Day 15: n = 77	23.8 (± 28.4)			
Day 29: n = 69	26.4 (± 13.7)			
Day 43: n = 69	32.3 (± 35.8)			
Day 57: n = 56	32.7 (± 18.8)			
Day 71: n = 52	33.5 (± 21.1)			
Day 85: n = 42	45.5 (± 53.6)			
Day 99: n = 37	40.3 (± 24.0)			
Day 169: n = 24	43.6 (± 19.6)			
Day 211: n = 1	57.2 (± 9999)			
Day 253: n = 11	38.4 (± 15.7)			
Day 337: n = 4	43.9 (± 23.7)			
Day 421: n = 2	61.4 (± 7.79)			

Statistical analyses

No statistical analyses for this end point

Secondary: Part B: Interim Analysis: Overall Survival (OS) Time

End point title	Part B: Interim Analysis: Overall Survival (OS) Time[17]

End point description:

The OS time was defined as the time from first administration of study treatment until the date of death. OS was calculated using following formula = (date of death – date of the first dose of study treatment + 1)/30.4375 (months). Full Analysis Set included all subjects who received at least 1 dose of study treatment.

End point type	Secondary

End point timeframe:

Up to 161 weeks (Data reported are per pre-specified interim analysis with a data cut-off date of 2 May 2019)

Notes:

[17] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint was planned to be reported for Part B only.

End point values	Part B: Avelumab			
Subject group type	Reporting group			
Number of subjects analysed	116			
Units: Months				
median (full range (min-max))	20.3 (0.5 to 34.9)			

Statistical analyses

No statistical analyses for this end point

Secondary: Part B: Final Analysis: Overall Survival (OS) Time

End point title	Part B: Final Analysis: Overall Survival (OS) Time[18]

End point description:

The OS time was defined as the time from first administration of study treatment until the date of death. OS was calculated using following formula = (date of death – date of the first dose of study treatment + 1)/30.4375 (months). Full Analysis Set included all subjects who received at least 1 dose of study treatment.

End point type	Secondary

End point timeframe:

Time from first administration of trial treatment until death (Up to 396 weeks)

Notes:

[18] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint was planned to be reported for Part B only.

End point values	Part B: Avelumab			
Subject group type	Reporting group			
Number of subjects analysed	116			
Units: months				
median (full range (min-max))	20.3 (0.5 to 65.8)			

Statistical analyses

No statistical analyses for this end point

Secondary: Part B: Number of Subjects with Confirmed Best Overall Response (BOR) as per Response Evaluation Criteria in Solid Tumors version (RECIST) 1.1

End point title	Part B: Number of Subjects with Confirmed Best Overall Response (BOR) as per Response Evaluation Criteria in Solid Tumors version (RECIST) 1.1[19]

End point description:

Confirmed BOR was determined according to RECIST 1.1 and as adjudicated by an Independent Endpoint Review Committee (IERC) and defined as best response of any of complete response (CR), partial response (PR), stable disease (SD) and progressive disease (PD) recorded from date of randomization until disease progression/recurrence (taking smallest measurement recorded since start of treatment as reference). CR:Disappearance of all evidence of target/non-target lesions. PR:At least 30%reduction from baseline in sum of longest diameter (SLD) of all lesions. SD:Neither sufficient increase to qualify for PD nor sufficient shrinkage to qualify for PR. PD:at least 20% increase in SLD, taking as reference smallest SLD recorded from baseline/appearance of 1or more new lesions and unequivocal progression of non-target lesions. Full Analysis Set included all subjects who received at least 1 dose of study treatment.

End point type	Secondary

End point timeframe:

Up to 396 weeks

Notes:

[19] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint was planned to reported for Part B only.

End point values	Part B: Avelumab			
Subject group type	Reporting group			
Number of subjects analysed	116			
Units: Subjects				
Complete Response	19			
Partial Response	27			
Stable Disease	12			
Non-complete Response/ Non-progressive Disease	1			
Progressive Disease	48			
Not evaluable	9			

Statistical analyses

No statistical analyses for this end point

Secondary: Part B: Duration of Response According to Response Evaluation Criteria in Solid Tumors version (RECIST) 1.1

End point title	Part B: Duration of Response According to Response Evaluation Criteria in Solid Tumors version (RECIST) 1.1[20]

End point description:

The duration of response as determined from IERC tumor assessment was calculated for each subject with a confirmed response (CR or PR) as the time from first observation of response until first observation of documented disease progression or death when death occurs within 12 weeks of the last tumor assessment, whichever occurs first. CR: Disappearance of all evidence of target and non-target lesions. PR: At least 30% reduction from baseline in the sum of the longest diameter (SLD) of all lesions. Full Analysis Set included all subjects who received at least 1 dose of study treatment. Here "Number of subjects analyzed" signifies those subjects who were evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Up to 396 weeks

Notes:

[20] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint was planned to be reported for Part B only.

End point values	Part B: Avelumab			
Subject group type	Reporting group			
Number of subjects analysed	46			
Units: Months				
median (full range (min-max))	18.2 (1.2 to 28.3)			

Statistical analyses

No statistical analyses for this end point

Secondary: Part B: Progression-Free Survival (PFS) Time According to Response

Evaluation Criteria in Solid Tumors version (RECIST) 1.1

End point title	Part B: Progression-Free Survival (PFS) Time According to Response Evaluation Criteria in Solid Tumors version (RECIST) 1.1[21]

End point description:

The PFS time (based on IERC tumor assessments), according to the RECIST 1.1, was defined as the time from first administration of study treatment until first observation of PD or death when death occurred within 12 weeks of the last tumor assessment or first administration of study treatment (whichever was later). PFS time (in months) was defined as: (date of PD or death – date of the first dose of study treatment + 1)/30.4375 (months). PD was defined as at least a 20% increase in the SLD, taking as reference the smallest SLD recorded from baseline or the appearance of 1 or more new lesions and unequivocal progression of non-target lesions. Full Analysis Set included all subjects who received at least 1 dose of study treatment.

End point type	Secondary

End point timeframe:

Up to 396 weeks

Notes:

[21] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint was planned to be reported for Part B only.

End point values	Part B: Avelumab			
Subject group type	Reporting group			
Number of subjects analysed	116			
Units: Months				
median (full range (min-max))	4.1 (0.03 to 29.6)			

Statistical analyses

No statistical analyses for this end point

Secondary: Part B: Number of Subjects with Treatment-Related (TR) Treatment-Emergent Adverse Events (TEAEs), Treatment-Related Serious TEAEs and Treatment-Related TEAEs leading to Death

End point title	Part B: Number of Subjects with Treatment-Related (TR) Treatment-Emergent Adverse Events (TEAEs), Treatment-Related Serious TEAEs and Treatment-Related TEAEs leading to Death[22]

End point description:

Related Adverse events (AE) were defined according to National Cancer Institute Common Terminology Criteria for Adverse Events Version 4.0 (NCI-CTCAE) as adverse events with relationship to study treatment reported by the investigator. A serious adverse event (SAE) was an AE that resulted in any of the following outcomes: death; life threatening; persistent/significant disability/incapacity; initial or prolonged inpatient hospitalization; congenital anomaly/birth defect or was otherwise considered medically important. Treatment-emergent are events between first dose of study drug that were absent before treatment or that worsened relative to pre-treatment state up to 30 days after last administration. TEAEs included both Serious TEAEs and non-serious TEAEs. Related TEAEs are defined as events with a relationship of missing, unknown, or yes. Full Analysis Set included all subjects who received at least 1 dose of study treatment.

End point type	Secondary

End point timeframe:

Up to 396 weeks

Notes:

[22] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint was planned to be reported for Part B only.

End point values	Part B: Avelumab			
Subject group type	Reporting group			
Number of subjects analysed	116			
Units: Subjects				
Participants with TR-TEAEs	94			
Participants with TR-Serious-TEAEs	17			
Participants with TR-TEAEs leading to Death	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Part B: Subject's Response Status According to RECIST 1.1 at 6 and 12 months

End point title	Part B: Subject's Response Status According to RECIST 1.1 at 6 and 12 months[23]

End point description:

The response status at 6 and 12 months after start of trial treatment according to RECIST 1.1 (as determined by the IERC) was determined. A subject was considered to be in response at the given timepoint (6 or 12 months after the start of the subject's treatment) if the subject had a documented response (PR or CR) prior to that timepoint, and neither died nor experienced disease progression according to the RECIST 1.1 nor was lost to follow-up up to the given timepoint. CR: Disappearance of all evidence of target and non-target lesions. PR: At least 30% reduction from baseline in the sum of the longest diameter (SLD) of all lesions. Percentage of subjects in response and not in response according to RECIST1.1 at 6 and 12 months were reported. Full Analysis Set included all subjects who received at least 1 dose of study treatment.

End point type	Secondary

End point timeframe:

At Month 6 and 12

Notes:

[23] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint was planned to be reported for Part B only.

End point values	Part B: Avelumab			
Subject group type	Reporting group			
Number of subjects analysed	116			
Units: Percentage of subjects				
number (not applicable)				
In-response at Month 6	33.6			
In-response at Month 12	26.7			
Not in-response at Month 6	66.4			
Not in-response at Month 12	73.3			

Statistical analyses

No statistical analyses for this end point

Secondary: Part B: Number of Subjects with Positive Treatment Emergent Anti-Avelumab Antibodies

End point title	Part B: Number of Subjects with Positive Treatment Emergent Anti-Avelumab Antibodies[24]

End point description:

Serum samples were analyzed by a validated electrochemiluminescence immunoassay to detect the presence of antidrug antibodies (ADA). Samples that screened positive were subsequently tested in a confirmatory assay. Those that confirmed positive were titered for a quasi-quantitative result. Number of subjects with positive treatment emergent anti-Avelumab antibodies were reported. Subjects not positive prior to treatment with avelumab and with at least one positive result in the human-Antihuman Antibodies assay were characterized as treatment-emergent. Full Analysis Set included all subjects who received at least 1 dose of study treatment. Here "Number of subjects analyzed" signifies those participants who were evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Up to 161 weeks

Notes:

[24] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint was planned to be reported for Part B only.

End point values	Part B: Avelumab			
Subject group type	Reporting group			
Number of subjects analysed	110			
Units: Subjects	8			

Statistical analyses

No statistical analyses for this end point

Secondary: Part B: Serum Concentration at End of Infusion (CEOI) of Avelumab

End point title	Part B: Serum Concentration at End of Infusion (CEOI) of Avelumab[25]

End point description:

Serum concentration at end of infusion (CEOI) of Avelumab is reported. PK Analysis Set included all subjects who received at least 1 dose of avelumab, and provided at least 1 measurable post-dose concentration. Here "n" signifies those subjects who were evaluable at specified time-point for this endpoint.

End point type	Secondary

End point timeframe:

At Day 1, 43 and 169

Notes:

[25] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint was planned to be reported for Part B only.

End point values	Part B: Avelumab			
Subject group type	Reporting group			
Number of subjects analysed	116			
Units: Microgram per milliliter				
geometric mean (geometric coefficient of variation)				
Day 1: n = 104	237 (± 31.1)			
Day 43: n = 78	244 (± 32.1)			
Day 169: n = 41	255 (± 27.7)			

Statistical analyses

No statistical analyses for this end point

Secondary: Part B: Minimum Serum Post-dose (Ctrough) Concentration of Aveluamb

End point title	Part B: Minimum Serum Post-dose (Ctrough) Concentration of Aveluamb[26]

End point description:

Minimum serum post-dose (Ctrough) concentration of avelumab was reported. PK Analysis Set included all subjects who received at least 1 dose of avelumab, and provided at least 1 measurable post-dose concentration. Here "n" signifies those subjects who were evaluable at specified time-point for this endpoint.

End point type	Secondary

End point timeframe:

Day 15, Day 29, Day 43, Day 85, Day 127, Day 169, Day 253, Day 337, Day 421, Day 505, Day 589, Day 673

Notes:

[26] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint was planned to be reported for Part B only.

End point values	Part B: Avelumab			
Subject group type	Reporting group			
Number of subjects analysed	116			
Units: Microgram per milliliter				
geometric mean (geometric coefficient of variation)				
Day 15: n =100	22.2 (± 57.5)			
Day 29: n = 86	27.8 (± 80.2)			
Day 43: n = 76	27.5 (± 89.4)			
Day 85: n = 61	29.4 (± 130.4)			
Day 127: n = 54	37.0 (± 65.6)			
Day 169: n = 45	45.6 (± 60.3)			
Day 253: n = 47	39.9 (± 53.0)			

Day 337: n = 36	39.5 (± 37.3)			
Day 421: n = 24	43.6 (± 30.3)			
Day 505: n = 14	41.8 (± 30.4)			
Day 589: n = 4	57.5 (± 24.1)			
Day 673: n = 5	44.9 (± 21.4)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Part A: Up to 325 weeks; Part B: Up to 396 weeks

Adverse event reporting additional description:

Adverse events were reported as per MedDRA v21.1 for Part A arm and MedDRA v22.0 for Part B.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	21.122.0

Reporting groups

Reporting group title	Part B: Avelumab

Reporting group description:

Participants received Avelumab as first-line treatment for metastatic or distally recurrent MCC at a dose of 10 mg/kg as 1-hour intravenous infusion once every 2 weeks until therapeutic failure, significant clinical deterioration, unacceptable toxicity, or any criterion for withdrawal from the trial or investigational medicinal product occurs.

Reporting group title	Part A: Avelumab

Reporting group description:

Participants with metastatic Merkel cell carcinoma (MCC) after failing first-line chemotherapy received Avelumab at a dose of 10 milligram per kilogram (mg/kg) as 1-hour intravenous infusion once every 2 weeks until therapeutic failure, significant clinical deterioration, unacceptable toxicity, or any criterion for withdrawal from the trial or investigational medicinal product occurs.

Serious adverse events	Part B: Avelumab	Part A: Avelumab	
Total subjects affected by serious adverse events			
subjects affected / exposed	58 / 116 (50.00%)	48 / 88 (54.55%)	
number of deaths (all causes)	72	63	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Malignant neoplasm progression			
subjects affected / exposed	2 / 116 (1.72%)	1 / 88 (1.14%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Metastases to meninges			
subjects affected / exposed	0 / 116 (0.00%)	1 / 88 (1.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Neoplasm progression			

subjects affected / exposed	0 / 116 (0.00%)	1 / 88 (1.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pericardial effusion malignant			
subjects affected / exposed	0 / 116 (0.00%)	1 / 88 (1.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Squamous cell carcinoma			
subjects affected / exposed	0 / 116 (0.00%)	1 / 88 (1.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Squamous cell carcinoma of skin			
subjects affected / exposed	0 / 116 (0.00%)	1 / 88 (1.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastases to central nervous system			
subjects affected / exposed	2 / 116 (1.72%)	0 / 88 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Lung adenocarcinoma			
subjects affected / exposed	1 / 116 (0.86%)	0 / 88 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tumour compression			
subjects affected / exposed	1 / 116 (0.86%)	0 / 88 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prostate cancer			
subjects affected / exposed	1 / 116 (0.86%)	0 / 88 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Paraneoplastic syndrome			

subjects affected / exposed	1 / 116 (0.86%)	0 / 88 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastasis			
subjects affected / exposed	1 / 116 (0.86%)	0 / 88 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Basal cell carcinoma			
subjects affected / exposed	1 / 116 (0.86%)	0 / 88 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bowen's disease			
subjects affected / exposed	1 / 116 (0.86%)	0 / 88 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Superior vena cava syndrome			
subjects affected / exposed	0 / 116 (0.00%)	1 / 88 (1.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Deep vein thrombosis			
subjects affected / exposed	0 / 116 (0.00%)	1 / 88 (1.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypotension			
subjects affected / exposed	1 / 116 (0.86%)	0 / 88 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lymphoedema			
subjects affected / exposed	2 / 116 (1.72%)	0 / 88 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Shock haemorrhagic			

subjects affected / exposed	1 / 116 (0.86%)	0 / 88 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Surgical and medical procedures			
Knee arthroplasty			
subjects affected / exposed	1 / 116 (0.86%)	0 / 88 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	1 / 116 (0.86%)	1 / 88 (1.14%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Asthenia			
subjects affected / exposed	2 / 116 (1.72%)	1 / 88 (1.14%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain			
subjects affected / exposed	0 / 116 (0.00%)	1 / 88 (1.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Non-cardiac chest pain			
subjects affected / exposed	0 / 116 (0.00%)	1 / 88 (1.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General physical health deterioration			
subjects affected / exposed	6 / 116 (5.17%)	2 / 88 (2.27%)	
occurrences causally related to treatment / all	0 / 6	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fatigue			
subjects affected / exposed	0 / 116 (0.00%)	1 / 88 (1.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Disease progression			
subjects affected / exposed	10 / 116 (8.62%)	9 / 88 (10.23%)	
occurrences causally related to treatment / all	0 / 10	0 / 9	
deaths causally related to treatment / all	0 / 7	0 / 7	
Pyrexia			
subjects affected / exposed	1 / 116 (0.86%)	0 / 88 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Multiple organ dysfunction syndrome			
subjects affected / exposed	1 / 116 (0.86%)	0 / 88 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Influenza like illness			
subjects affected / exposed	1 / 116 (0.86%)	0 / 88 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gait disturbance			
subjects affected / exposed	1 / 116 (0.86%)	0 / 88 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Autoimmune disorder			
subjects affected / exposed	0 / 116 (0.00%)	1 / 88 (1.14%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Epiglottic cyst			
subjects affected / exposed	1 / 116 (0.86%)	0 / 88 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			
subjects affected / exposed	0 / 116 (0.00%)	1 / 88 (1.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Dyspnoea exertional			
subjects affected / exposed	0 / 116 (0.00%)	1 / 88 (1.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	1 / 116 (0.86%)	1 / 88 (1.14%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoxia			
subjects affected / exposed	1 / 116 (0.86%)	0 / 88 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory failure			
subjects affected / exposed	1 / 116 (0.86%)	0 / 88 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	2 / 116 (1.72%)	1 / 88 (1.14%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Productive cough			
subjects affected / exposed	1 / 116 (0.86%)	0 / 88 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonitis			
subjects affected / exposed	1 / 116 (0.86%)	0 / 88 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural thickening			
subjects affected / exposed	1 / 116 (0.86%)	0 / 88 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic obstructive pulmonary disease			

subjects affected / exposed	0 / 116 (0.00%)	1 / 88 (1.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Psychiatric disorders			
Delirium			
subjects affected / exposed	1 / 116 (0.86%)	1 / 88 (1.14%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Confusional state			
subjects affected / exposed	1 / 116 (0.86%)	1 / 88 (1.14%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anxiety			
subjects affected / exposed	1 / 116 (0.86%)	1 / 88 (1.14%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Transaminases increased			
subjects affected / exposed	0 / 116 (0.00%)	1 / 88 (1.14%)	
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 / 116 (0.86%)	0 / 88 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Weight decreased			
subjects affected / exposed	1 / 116 (0.86%)	0 / 88 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intraocular pressure increased			
subjects affected / exposed	0 / 116 (0.00%)	1 / 88 (1.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural			

complications			
Infusion related reaction			
subjects affected / exposed	3 / 116 (2.59%)	1 / 88 (1.14%)	
occurrences causally related to treatment / all	3 / 3	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hip fracture			
subjects affected / exposed	1 / 116 (0.86%)	0 / 88 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Radiation mucositis			
subjects affected / exposed	1 / 116 (0.86%)	0 / 88 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Radiation skin injury			
subjects affected / exposed	1 / 116 (0.86%)	0 / 88 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tendon rupture			
subjects affected / exposed	1 / 116 (0.86%)	0 / 88 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femoral neck fracture			
subjects affected / exposed	0 / 116 (0.00%)	1 / 88 (1.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Atrial flutter			
subjects affected / exposed	0 / 116 (0.00%)	1 / 88 (1.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pericardial effusion			
subjects affected / exposed	0 / 116 (0.00%)	1 / 88 (1.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Tachycardia			
subjects affected / exposed	0 / 116 (0.00%)	1 / 88 (1.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocarditis			
subjects affected / exposed	1 / 116 (0.86%)	0 / 88 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bundle branch block right			
subjects affected / exposed	1 / 116 (0.86%)	0 / 88 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac tamponade			
subjects affected / exposed	0 / 116 (0.00%)	1 / 88 (1.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Nervous system disorders			
Dizziness			
subjects affected / exposed	1 / 116 (0.86%)	0 / 88 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebrovascular accident			
subjects affected / exposed	1 / 116 (0.86%)	0 / 88 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Autoimmune neuropathy			
subjects affected / exposed	1 / 116 (0.86%)	0 / 88 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post herpetic neuralgia			
subjects affected / exposed	0 / 116 (0.00%)	1 / 88 (1.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Encephalopathy			

subjects affected / exposed	1 / 116 (0.86%)	1 / 88 (1.14%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient ischaemic attack			
subjects affected / exposed	1 / 116 (0.86%)	0 / 88 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Polyneuropathy in malignant disease			
subjects affected / exposed	1 / 116 (0.86%)	0 / 88 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Polyneuropathy			
subjects affected / exposed	1 / 116 (0.86%)	0 / 88 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Paraneoplastic encephalomyelitis			
subjects affected / exposed	1 / 116 (0.86%)	0 / 88 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dysarthria			
subjects affected / exposed	1 / 116 (0.86%)	0 / 88 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 116 (0.86%)	4 / 88 (4.55%)	
occurrences causally related to treatment / all	0 / 1	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Leukocytosis			
subjects affected / exposed	0 / 116 (0.00%)	1 / 88 (1.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Microcytic anaemia			

subjects affected / exposed	0 / 116 (0.00%)	1 / 88 (1.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Normochromic normocytic anaemia			
subjects affected / exposed	0 / 116 (0.00%)	1 / 88 (1.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia			
subjects affected / exposed	0 / 116 (0.00%)	1 / 88 (1.14%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Eyelid function disorder			
subjects affected / exposed	0 / 116 (0.00%)	1 / 88 (1.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Glaucoma			
subjects affected / exposed	0 / 116 (0.00%)	1 / 88 (1.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Retinal artery occlusion			
subjects affected / exposed	0 / 116 (0.00%)	1 / 88 (1.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ulcerative keratitis			
subjects affected / exposed	0 / 116 (0.00%)	1 / 88 (1.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diplopia			
subjects affected / exposed	1 / 116 (0.86%)	0 / 88 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			

Oesophageal spasm			
subjects affected / exposed	0 / 116 (0.00%)	1 / 88 (1.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileus			
subjects affected / exposed	1 / 116 (0.86%)	2 / 88 (2.27%)	
occurrences causally related to treatment / all	0 / 1	1 / 2	
deaths causally related to treatment / all	0 / 1	0 / 1	
Gastrointestinal haemorrhage			
subjects affected / exposed	0 / 116 (0.00%)	1 / 88 (1.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Faecaloma			
subjects affected / exposed	0 / 116 (0.00%)	1 / 88 (1.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain			
subjects affected / exposed	2 / 116 (1.72%)	3 / 88 (3.41%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterocolitis			
subjects affected / exposed	0 / 116 (0.00%)	1 / 88 (1.14%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric haemorrhage			
subjects affected / exposed	0 / 116 (0.00%)	1 / 88 (1.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain upper			
subjects affected / exposed	1 / 116 (0.86%)	0 / 88 (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	2 / 116 (1.72%)	0 / 88 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Upper gastrointestinal haemorrhage			
subjects affected / exposed	1 / 116 (0.86%)	0 / 88 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Large intestine perforation			
subjects affected / exposed	1 / 116 (0.86%)	0 / 88 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Faeces discoloured			
subjects affected / exposed	1 / 116 (0.86%)	0 / 88 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dysphagia			
subjects affected / exposed	2 / 116 (1.72%)	0 / 88 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticulum			
subjects affected / exposed	1 / 116 (0.86%)	0 / 88 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis			
subjects affected / exposed	1 / 116 (0.86%)	0 / 88 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Autoimmune colitis			
subjects affected / exposed	0 / 116 (0.00%)	1 / 88 (1.14%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal hernia			

subjects affected / exposed	0 / 116 (0.00%)	1 / 88 (1.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Liver injury			
subjects affected / exposed	0 / 116 (0.00%)	1 / 88 (1.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic failure			
subjects affected / exposed	0 / 116 (0.00%)	1 / 88 (1.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Skin and subcutaneous tissue disorders			
Vascular purpura			
subjects affected / exposed	1 / 116 (0.86%)	0 / 88 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetic foot			
subjects affected / exposed	0 / 116 (0.00%)	1 / 88 (1.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Hydronephrosis			
subjects affected / exposed	3 / 116 (2.59%)	0 / 88 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tubulointerstitial nephritis			
subjects affected / exposed	0 / 116 (0.00%)	1 / 88 (1.14%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute kidney injury			
subjects affected / exposed	1 / 116 (0.86%)	4 / 88 (4.55%)	
occurrences causally related to treatment / all	0 / 1	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	

Renal impairment			
subjects affected / exposed	1 / 116 (0.86%)	0 / 88 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematuria			
subjects affected / exposed	0 / 116 (0.00%)	1 / 88 (1.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
Hypothyroidism			
subjects affected / exposed	0 / 116 (0.00%)	1 / 88 (1.14%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetes insipidus			
subjects affected / exposed	0 / 116 (0.00%)	1 / 88 (1.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Bone pain			
subjects affected / exposed	0 / 116 (0.00%)	1 / 88 (1.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Synovitis			
subjects affected / exposed	1 / 116 (0.86%)	1 / 88 (1.14%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal pain			
subjects affected / exposed	0 / 116 (0.00%)	1 / 88 (1.14%)	
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 / 116 (0.00%)	1 / 88 (1.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Chondrocalcinosis			
subjects affected / exposed	0 / 116 (0.00%)	1 / 88 (1.14%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arthritis			
subjects affected / exposed	1 / 116 (0.86%)	0 / 88 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myopathy			
subjects affected / exposed	1 / 116 (0.86%)	0 / 88 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myositis			
subjects affected / exposed	1 / 116 (0.86%)	0 / 88 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spondylitis			
subjects affected / exposed	1 / 116 (0.86%)	0 / 88 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Muscle spasms			
subjects affected / exposed	0 / 116 (0.00%)	1 / 88 (1.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Lung infection			
subjects affected / exposed	1 / 116 (0.86%)	2 / 88 (2.27%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Klebsiella sepsis			
subjects affected / exposed	1 / 116 (0.86%)	1 / 88 (1.14%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Erysipelas			

subjects affected / exposed	0 / 116 (0.00%)	1 / 88 (1.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetic foot infection			
subjects affected / exposed	0 / 116 (0.00%)	1 / 88 (1.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	0 / 116 (0.00%)	2 / 88 (2.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	1 / 116 (0.86%)	1 / 88 (1.14%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Urinary tract infection			
subjects affected / exposed	1 / 116 (0.86%)	1 / 88 (1.14%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Streptococcal sepsis			
subjects affected / exposed	0 / 116 (0.00%)	1 / 88 (1.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocarditis			
subjects affected / exposed	1 / 116 (0.86%)	0 / 88 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Streptococcal infection			
subjects affected / exposed	1 / 116 (0.86%)	0 / 88 (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	4 / 116 (3.45%)	0 / 88 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peritonitis			
subjects affected / exposed	1 / 116 (0.86%)	0 / 88 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infective exacerbation of bronchiectasis			
subjects affected / exposed	1 / 116 (0.86%)	0 / 88 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infection			
subjects affected / exposed	1 / 116 (0.86%)	0 / 88 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematoma infection			
subjects affected / exposed	0 / 116 (0.00%)	1 / 88 (1.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye infection			
subjects affected / exposed	0 / 116 (0.00%)	1 / 88 (1.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal cord infection			
subjects affected / exposed	0 / 116 (0.00%)	1 / 88 (1.14%)	
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 / 116 (0.00%)	1 / 88 (1.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Hyponatraemia			

subjects affected / exposed	3 / 116 (2.59%)	1 / 88 (1.14%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetes mellitus			
subjects affected / exposed	2 / 116 (1.72%)	1 / 88 (1.14%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Decreased appetite			
subjects affected / exposed	1 / 116 (0.86%)	0 / 88 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dehydration			
subjects affected / exposed	2 / 116 (1.72%)	0 / 88 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tumour lysis syndrome			
subjects affected / exposed	1 / 116 (0.86%)	0 / 88 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypernatraemia			
subjects affected / exposed	0 / 116 (0.00%)	1 / 88 (1.14%)	
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	Part B: Avelumab	Part A: Avelumab	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	114 / 116 (98.28%)	86 / 88 (97.73%)	
Vascular disorders			
Lymphoedema			
subjects affected / exposed	0 / 116 (0.00%)	6 / 88 (6.82%)	
occurrences (all)	0	6	
Hypotension			

subjects affected / exposed	0 / 116 (0.00%)	5 / 88 (5.68%)	
occurrences (all)	0	5	
Hypertension			
subjects affected / exposed	11 / 116 (9.48%)	11 / 88 (12.50%)	
occurrences (all)	11	11	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	24 / 116 (20.69%)	10 / 88 (11.36%)	
occurrences (all)	24	10	
Chills			
subjects affected / exposed	14 / 116 (12.07%)	10 / 88 (11.36%)	
occurrences (all)	14	10	
Fatigue			
subjects affected / exposed	27 / 116 (23.28%)	34 / 88 (38.64%)	
occurrences (all)	27	34	
Oedema peripheral			
subjects affected / exposed	15 / 116 (12.93%)	19 / 88 (21.59%)	
occurrences (all)	15	19	
Pyrexia			
subjects affected / exposed	13 / 116 (11.21%)	9 / 88 (10.23%)	
occurrences (all)	13	9	
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	16 / 116 (13.79%)	9 / 88 (10.23%)	
occurrences (all)	16	9	
Cough			
subjects affected / exposed	28 / 116 (24.14%)	16 / 88 (18.18%)	
occurrences (all)	28	16	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	0 / 116 (0.00%)	6 / 88 (6.82%)	
occurrences (all)	0	6	
Anxiety			
subjects affected / exposed	0 / 116 (0.00%)	7 / 88 (7.95%)	
occurrences (all)	0	7	
Investigations			

Lipase increased			
subjects affected / exposed	10 / 116 (8.62%)	5 / 88 (5.68%)	
occurrences (all)	10	5	
Blood creatine phosphokinase increased			
subjects affected / exposed	7 / 116 (6.03%)	7 / 88 (7.95%)	
occurrences (all)	7	7	
Blood creatinine increased			
subjects affected / exposed	10 / 116 (8.62%)	6 / 88 (6.82%)	
occurrences (all)	10	6	
Blood bilirubin increased			
subjects affected / exposed	6 / 116 (5.17%)	0 / 88 (0.00%)	
occurrences (all)	6	0	
Aspartate aminotransferase increased			
subjects affected / exposed	6 / 116 (5.17%)	7 / 88 (7.95%)	
occurrences (all)	6	7	
Alanine aminotransferase increased			
subjects affected / exposed	9 / 116 (7.76%)	7 / 88 (7.95%)	
occurrences (all)	9	7	
Weight decreased			
subjects affected / exposed	18 / 116 (15.52%)	14 / 88 (15.91%)	
occurrences (all)	18	14	
Weight increased			
subjects affected / exposed	0 / 116 (0.00%)	5 / 88 (5.68%)	
occurrences (all)	0	5	
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	9 / 116 (7.76%)	0 / 88 (0.00%)	
occurrences (all)	9	0	
Infusion related reaction			
subjects affected / exposed	10 / 116 (8.62%)	12 / 88 (13.64%)	
occurrences (all)	10	12	
Nervous system disorders			
Headache			
subjects affected / exposed	0 / 116 (0.00%)	10 / 88 (11.36%)	
occurrences (all)	0	10	

Dizziness			
subjects affected / exposed	0 / 116 (0.00%)	12 / 88 (13.64%)	
occurrences (all)	0	12	
Blood and lymphatic system disorders			
Eosinophilia			
subjects affected / exposed	6 / 116 (5.17%)	0 / 88 (0.00%)	
occurrences (all)	6	0	
Lymphopenia			
subjects affected / exposed	9 / 116 (7.76%)	7 / 88 (7.95%)	
occurrences (all)	9	7	
Anaemia			
subjects affected / exposed	19 / 116 (16.38%)	14 / 88 (15.91%)	
occurrences (all)	19	14	
Eye disorders			
Vision blurred			
subjects affected / exposed	0 / 116 (0.00%)	5 / 88 (5.68%)	
occurrences (all)	0	5	
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	22 / 116 (18.97%)	24 / 88 (27.27%)	
occurrences (all)	22	24	
Vomiting			
subjects affected / exposed	10 / 116 (8.62%)	13 / 88 (14.77%)	
occurrences (all)	10	13	
Abdominal pain			
subjects affected / exposed	11 / 116 (9.48%)	11 / 88 (12.50%)	
occurrences (all)	11	11	
Diarrhoea			
subjects affected / exposed	18 / 116 (15.52%)	23 / 88 (26.14%)	
occurrences (all)	18	23	
Constipation			
subjects affected / exposed	29 / 116 (25.00%)	16 / 88 (18.18%)	
occurrences (all)	29	16	
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	11 / 116 (9.48%)	13 / 88 (14.77%)	
occurrences (all)	11	13	

Pruritus			
subjects affected / exposed	18 / 116 (15.52%)	12 / 88 (13.64%)	
occurrences (all)	18	12	
Erythema			
subjects affected / exposed	7 / 116 (6.03%)	5 / 88 (5.68%)	
occurrences (all)	7	5	
Dry skin			
subjects affected / exposed	9 / 116 (7.76%)	5 / 88 (5.68%)	
occurrences (all)	9	5	
Actinic keratosis			
subjects affected / exposed	9 / 116 (7.76%)	0 / 88 (0.00%)	
occurrences (all)	9	0	
Rash maculo-papular			
subjects affected / exposed	7 / 116 (6.03%)	5 / 88 (5.68%)	
occurrences (all)	7	5	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	6 / 116 (5.17%)	0 / 88 (0.00%)	
occurrences (all)	6	0	
Endocrine disorders			
Hypothyroidism			
subjects affected / exposed	0 / 116 (0.00%)	6 / 88 (6.82%)	
occurrences (all)	0	6	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	10 / 116 (8.62%)	16 / 88 (18.18%)	
occurrences (all)	10	16	
Pain in extremity			
subjects affected / exposed	0 / 116 (0.00%)	17 / 88 (19.32%)	
occurrences (all)	0	17	
Muscle spasms			
subjects affected / exposed	0 / 116 (0.00%)	7 / 88 (7.95%)	
occurrences (all)	0	7	
Back pain			
subjects affected / exposed	13 / 116 (11.21%)	13 / 88 (14.77%)	
occurrences (all)	13	13	

Flank pain			
subjects affected / exposed	0 / 116 (0.00%)	5 / 88 (5.68%)	
occurrences (all)	0	5	
Myalgia			
subjects affected / exposed	0 / 116 (0.00%)	6 / 88 (6.82%)	
occurrences (all)	0	6	
Arthritis			
subjects affected / exposed	0 / 116 (0.00%)	6 / 88 (6.82%)	
occurrences (all)	0	6	
Muscular weakness			
subjects affected / exposed	0 / 116 (0.00%)	7 / 88 (7.95%)	
occurrences (all)	0	7	
Infections and infestations			
Bronchitis			
subjects affected / exposed	7 / 116 (6.03%)	5 / 88 (5.68%)	
occurrences (all)	7	5	
Upper respiratory tract infection			
subjects affected / exposed	8 / 116 (6.90%)	6 / 88 (6.82%)	
occurrences (all)	8	6	
Nasopharyngitis			
subjects affected / exposed	8 / 116 (6.90%)	8 / 88 (9.09%)	
occurrences (all)	8	8	
Sinusitis			
subjects affected / exposed	0 / 116 (0.00%)	5 / 88 (5.68%)	
occurrences (all)	0	5	
Cellulitis			
subjects affected / exposed	0 / 116 (0.00%)	5 / 88 (5.68%)	
occurrences (all)	0	5	
Metabolism and nutrition disorders			
Hyponatraemia			
subjects affected / exposed	11 / 116 (9.48%)	0 / 88 (0.00%)	
occurrences (all)	11	0	
Hypomagnesaemia			
subjects affected / exposed	7 / 116 (6.03%)	0 / 88 (0.00%)	
occurrences (all)	7	0	
Hyperkalaemia			

subjects affected / exposed	9 / 116 (7.76%)	0 / 88 (0.00%)	
occurrences (all)	9	0	
Decreased appetite			
subjects affected / exposed	16 / 116 (13.79%)	21 / 88 (23.86%)	
occurrences (all)	16	21	
Dehydration			
subjects affected / exposed	0 / 116 (0.00%)	6 / 88 (6.82%)	
occurrences (all)	0	6	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
10 April 2014	• Changed the frequency of electrocardiogram monitoring in the study. • Clarified that contraceptive use (Inclusion Criterion #9) is required for 30 days prior to first study drug administration through 60 days after the stopping study participation if the risk of conception exists (ie, females subjects of childbearing potential and male subjects). • Revised the Exclusion Criterion #4 so that radiotherapy administered to superficial lesions is not allowed if such lesions are considered target lesions in efficacy evaluation or may influence efficacy evaluation of the investigational agent. • Clarified required premedication and allow for flexibility based on local treatment standards and guideline.
06 June 2014	• Added response status at 6 and 12 months as a secondary objective. • Changed from the characterization of PK profile (exploratory objective) to the characterization of population PK (secondary objective). • Updated PK sampling to provide additional post infusion samples for characterization of population PK. • Clarified the wording of the exploratory objective regarding the immunogenicity of MSB0010718C and change to a secondary objective. • Added additional immunogenicity sampling in the follow-up period. • Added a comparison of the TTP on last prior anticancer therapy to PFS time on treatment with MSB0010718C as an exploratory objective. • Added a further exploratory analysis repeating the analysis of secondary and exploratory objectives that will be conducted 12 months after the accrual of the last subject. • Added health-related quality of life questionnaires (the EuroQol EQ-5D and Functional Assessment of Cancer Therapy – Melanoma questionnaires) used for a new exploratory objective "To explore the benefits of MSB0010718C as perceived by subjects with metastatic MCC". • Aligned the study endpoints with the amended objectives. • Updated the study procedures and assessments and Schedule of Assessments to align with the added PK sampling and patient reported outcome assessments. • Clarified discontinuation criteria for therapeutic failure.
05 September 2014	• Added optional subject interviews to the health-related quality of life assessments and added new exploratory endpoint regarding the subjects experience with their disease and treatment as reported in the optional subject interviews. • Modified language in Inclusion Criterion 3 (histologically proven MCC); • Added new Inclusion Criterion 4 and allowed for archival biopsy at Screening if fresh or recent biopsy was not feasible; • Added updated results in the Background Information from previous studies. • Modified language regarding the collection and storage of tissue samples. • Modified language regarding pharmacogenetic samples and identity protection. • Added clarifying language regarding unplanned interim analysis.
17 November 2014	• Added language stipulating that subjects with confirmed CR should stay on treatment for a minimum of 6 months and maximum of 12 months. • Deleted the 1-year time restriction for re-initiation of treatment for subjects who had confirmed CR and relapse after treatment discontinuation. • Added an algorithm for the treatment of immune-related AEs. • Added language stipulating that Grade 3 and 4 diagnostic tests (for example, ECGs, laboratory findings) must be reported as an AE by the Investigator to the Sponsor.

22 December 2014	• Added new safety visits at Week 2, 4, and 6 for blood draws for the analysis of liver enzymes for subjects with liver metastases. • Modified Inclusion Criterion 7 regarding hepatic function so that all subjects were to have Alanine aminotransferase (ALT) and Aspartate aminotransferase (AST) <= 2.5 × Upper limit of normal (ULN). • Added new Inclusion criterion of estimated life expectancy of 12 weeks.
26 February 2015	• Changed in IMP name from MSB0010718C to avelumab. • Added tumor shrinkage as exploratory objective and added to endpoints. • Changed timing of interim analysis. • Updated safety results. • Deleted MCV cellular responses from Schedule of Assessments.
08 January 2016	• Designated a "Part A" and "Part B" of the study. • Designated all subjects who had enrolled in the study prior to Amendment 7 as subjects participating in Part A of the study and updated all sections accordingly – Note, apart from this designation, no changes were made to the language for subjects participating in Part A. • Added a new cohort of subjects who had not received any prior systemic treatment for metastatic MCC. These subjects were designated as participating in Part B of the study. • Updated all sections as necessary for the Part A and Part B designations.
23 May 2017	• To allow for 5-year survival follow-up • For consistency between Part A and Part B and to ensure complete data collection to evaluate the duration of response in subjects with response regardless of whether they discontinued study drug or not. • Regular review of safety data by the SMC no longer deemed necessary due to the now well characterized avelumab safety profile. • Changed the mandatory observation based on the latest avelumab safety information. • To ensure clarity for Investigators, country reviewers and IRB/IEC reviewers of importance of completion of the trial, even with health authority approvals.
25 May 2018	• Clarified that survival follow-up for 5 years is for both Parts A and B. • Added new language regarding continued treatment past initial determination of PD. • Modified mandatory 2-hour post infusion observation to be based on based upon clinical judgment and presence/severity of prior infusion reactions.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported