Clinical trial results:
A Randomized, Open-Label, Phase 2 Study of Nivolumab in Combination with Ipilimumab or Nivolumab Monotherapy in Participants with Advanced or Metastatic Solid Tumors of High Tumor Mutational Burden (TMB-H)
(CheckMate 848: CHECKpoint pathway and nivoluMAb clinical Trial Evaluation 848)

Summary

EudraCT number	2016-002898-35
Trial protocol	DE FR DK GB ES NL PL BE Outside EU/EEA IT RO
Global end of trial date	02 August 2023

Results information

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

Trial information

Trial identification

Sponsor protocol code	CA209-848

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Bristol-Myers Squibb
Sponsor organisation address	Chaussée de la Hulpe 185, Brussels, Belgium, 1170
Public contact	EU Study Start-Up Unit, Bristol-Myers Squibb International Corporation, Clinical.Trials@bms.com
Scientific contact	Bristol-Myers Squibb Study Director, Bristol-Myers Squibb, Clinical.Trials@bms.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	20 September 2023
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	02 August 2023
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To estimate BICR-assessed objective response rate (ORR) in participants of either tTMB-H or bTMBH treated with nivolumab combined with ipilimumab.

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 Conference on Harmonization Good Clinical Practice Guidelines. All the local regulatory requirements pertinent to safety of trial participants were followed.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	31 October 2018
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Canada: 5
Country: Number of subjects enrolled	United States: 6
Country: Number of subjects enrolled	Belgium: 12
Country: Number of subjects enrolled	Denmark: 4
Country: Number of subjects enrolled	France: 23
Country: Number of subjects enrolled	Germany: 12
Country: Number of subjects enrolled	Italy: 28
Country: Number of subjects enrolled	Netherlands: 11
Country: Number of subjects enrolled	Poland: 9
Country: Number of subjects enrolled	Romania: 31
Country: Number of subjects enrolled	Spain: 7
Country: Number of subjects enrolled	United Kingdom: 3
Country: Number of subjects enrolled	Singapore: 8
Country: Number of subjects enrolled	Argentina: 27
Country: Number of subjects enrolled	Australia: 9
Country: Number of subjects enrolled	Chile: 17
Worldwide total number of subjects	212
EEA total number of subjects	137

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)	132
From 65 to 84 years	80
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Participants with refractory metastatic or unresectable solid malignant tumors with high Tumor Mutational Burden (TMB-H) who are refractory to standard therapies or have no standard treatment options were included as salvage setting. Those randomized to Nivolumab monotherapy arm could switch to the Nivolumab-Ipilimumab arm upon progression.

Period 1

Period 1 title	Pre-treatment
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Arm A: Nivolumab+Ipilimumab

Arm description:

Nivolumab 240 mg every 2 weeks (Q2W) + Ipilimumab 1 mg/kg every 6 weeks (Q6W) up to 24 months

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

Dosage and administration details:

1 mg/kg Q6W (every 6 weeks)

Investigational medicinal product name	Nivolumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

240 mg Q2W (every 2 weeks)

Arm title	Arm B: Nivolumab

Arm description:

Nivolumab Monotherapy 480 mg every 4 weeks (Q4W) up to 24 months

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

Dosage and administration details:

480 mg Q4W (every 4 weeks)

Number of subjects in period 1	Arm A: Nivolumab+Ipilimumab	Arm B: Nivolumab
Started	136	76
bTMB-H Started	80 [1]	45 [2]
tTMB-H Started	88 [3]	47 [4]
Completed	135	76
Not completed	1	0
Disease Progression	1	-

Notes:

[1] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: tTMB-H Started

[2] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: tTMB-H Started

[3] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: bTMB-H Started

[4] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: bTMB-H Started

Period 2

Period 2 title	Treatment
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Arm A: Nivolumab+Ipilimumab

Arm description:

Nivolumab 240 mg every 2 weeks (Q2W) + Ipilimumab 1 mg/kg every 6 weeks (Q6W) up to 24 months

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

Dosage and administration details:

1 mg/kg Q6W (every 6 weeks)

Investigational medicinal product name	Nivolumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

240 mg Q2W (every 2 weeks)

Arm title	Arm B: Nivolumab

Arm description:

Nivolumab Monotherapy 480 mg every 4 weeks (Q4W) up to 24 months

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

Dosage and administration details:

480 mg Q4W (every 4 weeks)

Number of subjects in period 2	Arm A: Nivolumab+Ipilimumab	Arm B: Nivolumab
Started	135	76
bTMB-H Started	83	47
tTMB-H Started	94	50
Arm B Rollover	0	22
Completed	0	0
Not completed	135	76
Adverse event, serious fatal	3	-
Consent withdrawn by subject	1	1
Study drug toxicity	19	1
Adverse Event unrelated to Study drug	4	3
Maximum Clinical Benefit	-	1
Participants completed treatment	27	11
Other reasons	2	1
Disease Progression	76	57
Participant request to discontinue study treatment	3	1

Baseline characteristics

Reporting groups	
Reporting group title	Arm A: Nivolumab+Ipilimumab
Reporting group description:	
Nivolumab 240 mg every 2 weeks (Q2W) + Ipilimumab 1 mg/kg every 6 weeks (Q6W) up to 24 months	
Reporting group title	Arm B: Nivolumab
Reporting group description:	
Nivolumab Monotherapy 480 mg every 4 weeks (Q4W) up to 24 months	

Reporting group values	Arm A: Nivolumab+Ipilimumab	Arm B: Nivolumab	Total
Number of subjects	136	76	212
Age categorical Units:			
Age Continuous Units: years			
arithmetic mean	60.0	57.6	
standard deviation	± 11.7	± 12.1	-
Sex: Female, Male Units: Participants			
Female	71	44	115
Male	65	32	97
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	6	3	9
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	1	1	2
White	124	60	184
More than one race	0	0	0
Unknown or Not Reported	5	12	17
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	13	5	18
Not Hispanic or Latino	45	20	65
Unknown or Not Reported	78	51	129

End points

End points reporting groups

Reporting group title	Arm A: Nivolumab+Ipilimumab
Reporting group description: Nivolumab 240 mg every 2 weeks (Q2W) + Ipilimumab 1 mg/kg every 6 weeks (Q6W) up to 24 months	
Reporting group title	Arm B: Nivolumab
Reporting group description: Nivolumab Monotherapy 480 mg every 4 weeks (Q4W) up to 24 months	
Reporting group title	Arm A: Nivolumab+Ipilimumab
Reporting group description: Nivolumab 240 mg every 2 weeks (Q2W) + Ipilimumab 1 mg/kg every 6 weeks (Q6W) up to 24 months	
Reporting group title	Arm B: Nivolumab
Reporting group description: Nivolumab Monotherapy 480 mg every 4 weeks (Q4W) up to 24 months	

Primary: Objective Response Rate (ORR) per Blinded Independent Central Review (BICR) - Arm A

End point title	Objective Response Rate (ORR) per Blinded Independent Central Review (BICR) - Arm A[1][2]

End point description:

ORR was defined as the percentage of participants with a best overall response of confirmed complete response (CR) or partial response (PR) based on Blinded Independent Central Review (BICR) assessment.
RECIST Criteria:
CR= Disappearance of all target lesions. Any pathological lymph nodes must have reduction in short axis to < 10 mm.
PR= ≥ 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.
RANO Criteria:
CR= Disappearance of all enhancing measurable and nonmeasurable disease; stable or improved nonenhancing T2/FLAIR lesions; off corticosteroids; and stable or improved clinically
PR= ≥ 50% decrease compared with baseline in the sum of products of perpendicular diameters of all measurable enhancing lesions; no progression of nonmeasureable disease; no new lesions; stable or improved nonenhancing (T2/FLAIR) lesions on same or lower dose of corticosteroids compared with baseline scan; and stable or improved clinically.

End point type	Primary

End point timeframe:

From date of randomization up to 42 months

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: only pre-specified arms reported

[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: only pre-specified arms reported

End point values	Arm A: Nivolumab+Ipilimumab			
Subject group type	Reporting group			
Number of subjects analysed	88			
Units: Precentage of participants				
number (confidence interval 95%)				

Blood TMB-H (bTMB-H)	22.5 (13.9 to 33.2)			
Tissue TMB-H (tTMB-H)	38.6 (28.4 to 49.6)			

Statistical analyses

No statistical analyses for this end point

Secondary: Objective Response Rate (ORR) per Blinded Independent Central Review (BICR) - Arm B

End point title	Objective Response Rate (ORR) per Blinded Independent Central Review (BICR) - Arm B[3]

End point description:

ORR was defined as the percentage of participants with a best overall response of confirmed complete response (CR) or partial response (PR) based on Blinded Independent Central Review (BICR) assessment.
RECIST Criteria:
CR= Disappearance of all target lesions. Any pathological lymph nodes must have reduction in short axis to < 10 mm.
PR= ≥ 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.
RANO Criteria:
CR= Disappearance of all enhancing measurable and nonmeasurable disease; stable or improved nonenhancing T2/FLAIR lesions; off corticosteroids; and stable or improved clinically
PR= ≥ 50% decrease compared with baseline in the sum of products of perpendicular diameters of all measurable enhancing lesions; no progression of nonmeasureable disease; no new lesions; stable or improved nonenhancing (T2/FLAIR) lesions on same or lower dose of corticosteroids compared with baseline scan; and stable or improved clinically.

End point type	Secondary

End point timeframe:

From date of randomization up to 57 months

Notes:

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

End point values	Arm B: Nivolumab			
Subject group type	Reporting group			
Number of subjects analysed	47			
Units: Percentage of participants				
number (confidence interval 95%)				
Blood TMB-H (bTMB-H)	15.6 (6.5 to 29.5)			
Tissue TMB-H (tTMB-H)	29.8 (17.3 to 44.9)			

Statistical analyses

No statistical analyses for this end point

Secondary: Objective Response Rate (ORR) per Investigator

End point title	Objective Response Rate (ORR) per Investigator

End point description:

ORR was defined as the percentage of participants with a best overall response of confirmed complete response (CR) or partial response (PR) based on investigator assessment. Calculated using Clopper-Pearson method.
RECIST Criteria:
CR= Disappearance of all target lesions. Any pathological lymph nodes must have reduction in short axis to < 10 mm.
PR= ≥ 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.
RANO Criteria:
CR= Disappearance of all enhancing measurable and nonmeasurable disease; stable or improved nonenhancing T2/FLAIR lesions; off corticosteroids; and stable or improved clinically
PR= ≥ 50% decrease compared with baseline in the sum of products of perpendicular diameters of all measurable enhancing lesions; no progression of nonmeasureable disease; no new lesions; stable or improved nonenhancing (T2/FLAIR) lesions on same or lower dose of corticosteroids compared with baseline scan; and stable or improved clinically.

End point type	Secondary

End point timeframe:

From date of randomization up to 57 months

End point values	Arm A: Nivolumab+Ipilimumab	Arm B: Nivolumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	88	47		
Units: Percentage of participants				
number (confidence interval 95%)				
Blood TMB-H (bTMB-H)	25.0 (16.0 to 35.9)	13.3 (5.1 to 26.8)		
Tissue TMB-H (tTMB-H)	44.3 (33.7 to 55.3)	23.4 (12.3 to 38.0)		

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Response (DoR) per Investigator

End point title	Duration of Response (DoR) per Investigator

End point description:

DoR was defined as the time from first confirmed complete or partial response to the date of the first documented tumor progression, or death due to any cause, whichever occurs first. Calculated using KM method.
RECIST Criteria:
CR= Disappearance of all target lesions.
PR= ≥ 30% decrease in the sum of diameters of target lesions.
PD= ≥ 20% increase in the sum of diameters of target lesions.
RANO Criteria:
CR= Disappearance of all enhancing measurable and nonmeasurable disease; stable/improved T2/FLAIR; off corticosteroids; stable/improved clinically
PR= ≥ 50% decrease in the sum of diameters of all measurable enhancing lesions; no progression of nonmeasurable disease; no new lesions; stable/improved T2/FLAIR; stable/improved clinically.
PD= ≥ 25% increase in sum of diameters of enhancing lesions, on stable/increasing doses of corticosteroids; significant increase in T2/FLAIR; any new lesion; clear clinical deterioration or clear progression of nonmeasurable disease.

99999=NA

End point type	Secondary

End point timeframe:

From date of randomization to date of first documented tumor progression, or date of death, whichever occurs first (Up to 57 months)

End point values	Arm A: Nivolumab+Ipilimumab	Arm B: Nivolumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	39	11		
Units: Months				
median (confidence interval 95%)				
Blood TMB-H (bTMB-H)	27.96 (11.20 to 99999)	99999 (11.24 to 99999)		
Tissue TMB-H (tTMB-H)	99999 (27.96 to 99999)	99999 (8.05 to 99999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Response (DoR) per Blinded Independent Central Review (BICR)

End point title	Duration of Response (DoR) per Blinded Independent Central Review (BICR)

End point description:

DoR was defined as the time from first confirmed complete or partial response to the date of the first documented tumor progression, or death due to any cause, whichever occurs first. Calculated using KM method.
RECIST Criteria:
CR= Disappearance of all target lesions.
PR= ≥ 30% decrease in the sum of diameters of target lesions.
PD= ≥ 20% increase in the sum of diameters of target lesions.
RANO Criteria:
CR= Disappearance of all enhancing measurable and nonmeasurable disease; stable/improved T2/FLAIR; off corticosteroids; stable/improved clinically
PR= ≥ 50% decrease in the sum of diameters of all measurable enhancing lesions; no progression of nonmeasurable disease; no new lesions; stable/improved T2/FLAIR; stable/improved clinically.
PD= ≥ 25% increase in sum of diameters of enhancing lesions, on stable/increasing doses of corticosteroids; significant increase in T2/FLAIR; any new lesion; clear clinical deterioration or clear progression of nonmeasurable disease.
99999=NA

End point type	Secondary

End point timeframe:

From date of randomization to date of first documented tumor progression, or date of death, whichever occurs first (Up to 57 months)

End point values	Arm A: Nivolumab+Ipilimumab	Arm B: Nivolumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	34	14		
Units: Months				
median (confidence interval 95%)				
Blood TMB-H (bTMB-H)	99999 (10.15 to 99999)	99999 (5.52 to 99999)		
Tissue TMB-H (tTMB-H)	99999 (33.51 to 99999)	99999 (8.31 to 99999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Objective Response (TTR) per Investigator

End point title	Time to Objective Response (TTR) per Investigator

End point description:

TTR is defined as the time from randomization date to the date of the first confirmed response (complete response (CR) or partial response (PR)), based on investigator assessment.
RECIST Criteria:
CR= Disappearance of all target lesions. Any pathological lymph nodes must have reduction in short axis to < 10 mm.
PR= ≥ 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.
RANO Criteria:
CR= Disappearance of all enhancing measurable and nonmeasurable disease; stable or improved nonenhancing T2/FLAIR lesions; off corticosteroids; and stable or improved clinically
PR= ≥ 50% decrease compared with baseline in the sum of products of perpendicular diameters of all measurable enhancing lesions; no progression of nonmeasureable disease; no new lesions; stable or improved nonenhancing (T2/FLAIR) lesions on same or lower dose of corticosteroids compared with baseline scan; and stable or improved clinically.

End point type	Secondary

End point timeframe:

From date of randomization to date of first confirmed response (CR or PR) (Up to 57 months)

End point values	Arm A: Nivolumab+Ipilimumab	Arm B: Nivolumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	39	11		
Units: Months				
arithmetic mean (standard deviation)				
Blood TMB-H (bTMB-H)	3.48 (± 1.17)	4.08 (± 3.40)		
Tissue TMB-H (tTMB-H)	3.56 (± 1.74)	3.75 (± 2.50)		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Objective Response (TTR) per Blinded Independent Central Review (BICR)

End point title	Time to Objective Response (TTR) per Blinded Independent Central Review (BICR)

End point description:

TTR is defined as the time from randomization date to the date of the first confirmed response (complete response (CR) or partial response (PR)), based on Blinded Independent Central Review (BICR) assessment.
RECIST Criteria:
CR= Disappearance of all target lesions. Any pathological lymph nodes must have reduction in short axis to < 10 mm.
PR= ≥ 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.
RANO Criteria:
CR= Disappearance of all enhancing measurable and nonmeasurable disease; stable or improved nonenhancing T2/FLAIR lesions; off corticosteroids; and stable or improved clinically
PR= ≥ 50% decrease compared with baseline in the sum of products of perpendicular diameters of all measurable enhancing lesions; no progression of nonmeasureable disease; no new lesions; stable or improved nonenhancing (T2/FLAIR) lesions on same or lower dose of corticosteroids compared with baseline scan; and stable or improved clinically.

End point type	Secondary

End point timeframe:

From date of randomization to date of first confirmed response (CR or PR) (Up to 57 months)

End point values	Arm A: Nivolumab+Ipilimumab	Arm B: Nivolumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	34	14		
Units: Months				
arithmetic mean (standard deviation)				
Blood TMB-H (bTMB-H)	3.59 (± 1.65)	4.33 (± 2.93)		
Tissue TMB-H (tTMB-H)	4.37 (± 5.10)	3.98 (± 2.47)		

Statistical analyses

No statistical analyses for this end point

Secondary: Clinical Benefit Rate (CBR) per Investigator

End point title	Clinical Benefit Rate (CBR) per Investigator

End point description:

CBR is defined as the percentage of participants with a best overall response of confirmed complete response (CR) or partial response (PR) or stable disease (SD) based on investigator assessment.
RECIST Criteria:
CR= Disappearance of all target lesions. Any pathological lymph nodes must have reduction in short axis to < 10 mm
PR= ≥ 30% decrease in the sum of diameters of target lesions
SD= Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD
RANO Criteria:
CR= Disappearance of all enhancing disease; stable or improved nonenhancing T2/FLAIR lesions; off corticosteroids; and stable or improved clinically

PR= ≥ 50% decrease in the sum of products of perpendicular diameters of all measurable enhancing lesions; no progression of nonmeasureable disease; no new lesions; stable or improved nonenhancing (T2/FLAIR) lesions; stable or improved clinically
SD= does not qualify for CR, PR, or progression; stable nonenhancing T2/FLAIR lesions

End point type	Secondary

End point timeframe:

From date of randomization up to 57 months

End point values	Arm A: Nivolumab+Ipilimumab	Arm B: Nivolumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	88	47		
Units: Percentage of participants				
number (confidence interval 95%)				
Blood TMB-H (bTMB-H)	42.5 (31.5 to 54.1)	40.0 (25.7 to 55.7)		
Tissue TMB-H (tTMB-H)	63.6 (52.7 to 73.6)	46.8 (32.1 to 61.9)		

Statistical analyses

No statistical analyses for this end point

Secondary: Clinical Benefit Rate (CBR) per Blinded Independent Central Review (BICR)

End point title	Clinical Benefit Rate (CBR) per Blinded Independent Central Review (BICR)

End point description:

CBR is defined as the percentage of participants with a best overall response of confirmed complete response (CR) or partial response (PR) or stable disease (SD) per Blinded Independent Central Review (BICR) assessment.
RECIST Criteria:
CR= Disappearance of all target lesions. Any pathological lymph nodes must have reduction in short axis to < 10 mm
PR= ≥ 30% decrease in the sum of diameters of target lesions
SD= does not qualify for PR or progressive disease
RANO Criteria:
CR= Disappearance of all enhancing disease; stable or improved nonenhancing T2/FLAIR lesions; off corticosteroids; and stable or improved clinically
PR= ≥ 50% decrease in the sum of products of perpendicular diameters of all measurable enhancing lesions; no progression of nonmeasureable disease; no new lesions; stable or improved nonenhancing (T2/FLAIR) lesions; stable or improved clinically
SD= does not qualify for CR, PR, or progression; stable nonenhancing T2/FLAIR lesions

End point type	Secondary

End point timeframe:

From date of randomization up to 57 months

End point values	Arm A: Nivolumab+Ipilimumab	Arm B: Nivolumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	88	47		
Units: Percentage of participants				
number (confidence interval 95%)				
Blood TMB-H (bTMB-H)	32.5 (22.4 to 43.9)	28.9 (16.4 to 44.3)		
Tissue TMB-H (tTMB-H)	53.4 (42.5 to 64.1)	38.3 (24.5 to 53.6)		

Statistical analyses

No statistical analyses for this end point

Secondary: Progression Free Survival (PFS) per Investigator

End point title	Progression Free Survival (PFS) per Investigator

End point description:

PFS is defined as the time from randomization date to the date of the first documented tumor progression, determined by investigator assessment, or death due to any cause, whichever occurs first. Calculated using KM method.
RECIST Criteria:
Progressive Disease (PD)= ≥ 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study. In addition, the sum must also demonstrate an absolute increase of ≥ 5 mm.
RANO Criteria:
PD= ≥ 25% increase in sum of the products of perpendicular diameters of enhancing lesions compared with the smallest tumor measurement obtained either at baseline or best response, on stable or increasing doses of corticosteroids; significant increase in T2/FLAIR nonenhancing lesions on stable or increasing doses of corticosteroids compared with baseline scan or best response after initiation of therapy; any new lesion; clear clinical deterioration or clear progression of nonmeasurable disease.

End point type	Secondary

End point timeframe:

From date of randomization to date of first documented tumor progression, or date of death, whichever occurs first (Up to 57 months)

End point values	Arm A: Nivolumab+Ipilimumab	Arm B: Nivolumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	88	47		
Units: Months				
median (confidence interval 95%)				
Blood TMB-H (bTMB-H)	2.99 (2.66 to 4.34)	3.04 (2.79 to 5.36)		
Tissue TMB-H (tTMB-H)	8.15 (4.83 to 12.94)	3.06 (2.79 to 10.91)		

Statistical analyses

No statistical analyses for this end point

Secondary: Progression Free Survival (PFS) per Blinded Independent Central Review (BICR)

End point title	Progression Free Survival (PFS) per Blinded Independent Central Review (BICR)

End point description:

PFS is defined as the time from randomization date to the date of the first documented tumor progression, determined by Blinded Independent Central Review (BICR) assessment, or death due to any cause, whichever occurs first. Calculated using KM method.
RECIST Criteria:
Progressive Disease (PD)= ≥ 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study. In addition, the sum must also demonstrate an absolute increase of ≥ 5 mm.
RANO Criteria:
PD= ≥ 25% increase in sum of the products of perpendicular diameters of enhancing lesions compared with the smallest tumor measurement obtained either at baseline or best response, on stable or increasing doses of corticosteroids; significant increase in T2/FLAIR nonenhancing lesions on stable or increasing doses of corticosteroids compared with baseline scan or best response after initiation of therapy; any new lesion; clear clinical deterioration or clear progression of nonmeasurable disease.

End point type	Secondary

End point timeframe:

From date of randomization to date of first documented tumor progression, or date of death, whichever occurs first (Up to 57 months)

End point values	Arm A: Nivolumab+Ipilimumab	Arm B: Nivolumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	88	47		
Units: Months				
median (confidence interval 95%)				
Blood TMB-H (bTMB-H)	2.83 (2.33 to 2.99)	2.83 (2.60 to 3.25)		
Tissue TMB-H (tTMB-H)	5.68 (3.19 to 11.60)	2.83 (2.69 to 5.72)		

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival (OS)

End point title	Overall Survival (OS)

End point description:

OS is defined as the time between the date of randomization and the date of death due to any cause. Participants who did not have a date of death were censored on the last date for which a participant was known to be alive. Calculated using KM method.

End point type	Secondary

End point timeframe:

From date of randomization to date of death (Up to 57 months)

End point values	Arm A: Nivolumab+Ipilimumab	Arm B: Nivolumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	88	47		
Units: Months				
median (confidence interval 95%)				
Blood TMB-H (bTMB-H)	8.07 (5.82 to 10.45)	11.24 (5.26 to 18.99)		
Tissue TMB-H (tTMB-H)	16.48 (10.18 to 30.52)	14.59 (7.69 to 18.23)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants with Adverse Events (AEs) and Serious Adverse Events (SAEs)

End point title	Number of Participants with Adverse Events (AEs) and Serious Adverse Events (SAEs)

End point description:

Number of participants with any grade adverse events (AEs), serious adverse events (SAEs), drug-related AEs, and drug-related SAEs by Tumor Mutational Burden- High (TMB-H) status using worst grade per national cancer institute (NCI) common terminology criteria for adverse events (CTCAE) v5 criteria. An AE is defined as any new untoward medical occurrence or worsening of a preexisting medical condition in a clinical investigation participant administered study treatment and that does not necessarily have a causal relationship with this treatment.
TMB-H = ≥ 10 mutations per megabase
bTMB-H and tTMB-H are not mutually exclusive

End point type	Secondary

End point timeframe:

From first dose to 30 days post last dose (Up to 25 months)

End point values	Arm A: Nivolumab+Ipilimumab	Arm B: Nivolumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	94	50		
Units: Participants				
Blood TMB-H (bTMB-H) AEs	82	46		
Tissue TMB-H (tTMB-H) AEs	93	50		
bTMB-H SAEs	51	17		
tTMB-H SAEs	46	16		
bTMB-H drug-related AEs	64	29		
tTMB-H drug-related AEs	78	27		
bTMB-H drug-related SAEs	17	1		
tTMB-H drug-related SAEs	16	2		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants with On-Treatment Laboratory Parameters

End point title	Number of Participants with On-Treatment Laboratory Parameters

End point description:

Number of participants with grade 3-4 on-treatment laboratory parameters. Parameters include hematology, chemistry, liver function, and renal function using worst grade per national cancer institute (NCI) common terminology criteria for adverse events (CTCAE) v5 criteria.
Grade 3=Severe event
Grade 4=Life threatening event
TMB-H = ≥ 10 mutations per megabase
bTMB-H and tTMB-H are not mutually exclusive

End point type	Secondary

End point timeframe:

From first dose to 30 days post last dose (Up to 25 months)

End point values	Arm A: Nivolumab+Ipilimumab	Arm B: Nivolumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	91	45		
Units: Participants				
Blood TMB-H (bTMB-H) Hemoglobin grade 3	6	3		
Tissue TMB-H (tTMB-H) Hemoglobin grade 3	8	7		
Blood TMB-H (bTMB-H) Platelet Count grade 3-4	1	0		
Tissue TMB-H (tTMB-H) Platelet Count grade 3-4	0	1		
Blood TMB-H (bTMB-H) Leukocytes grade 3- 4	1	0		
Tissue TMB-H (tTMB-H) Leukocytes grade 3- 4	0	0		
bTMB-H Leukocytes Absolute grade 3- 4	2	1		
tTMB-H Leukocytes Absolute grade 3- 4	5	3		
bTMB-H Absolute Neutrophil grade 3- 4	1	1		
tTMB-H Absolute Neutrophil grade 3- 4	0	0		
bTMB-H Alkaline Phosphatase grade 3-4	2	1		
tTMB-H Alkaline Phosphatase grade 3-4	2	0		
bTMB-H Aspartate Aminotransferase grade 3-4	2	3		
tTMB-H Aspartate Aminotransferase grade 3-4	4	1		

bTMB-H Alanine Aminotransferase grade 3-4	5	2		
tTMB-H Alanine Aminotransferase grade 3-4	3	1		
bTMB-H Bilirubin grade 3-4	3	2		
tTMB-H Bilirubin grade 3-4	3	1		
bTMB-H Creatinine grade 3-4	3	1		
tTMB-H Creatinine grade 3-4	3	0		
bTMB-H Hypernatremia grade 3-4	0	0		
tTMB-H Hypernatremia grade 3-4	0	0		
bTMB-H Hyponatremia grade 3-4	4	1		
tTMB-H Hyponatremia grade 3-4	3	1		
bTMB-H Hyperkalemia grade 3-4	2	0		
tTMB-H Hyperkalemia grade 3-4	2	0		
bTMB-H Hypokalemia grade 3-4	4	0		
tTMB-H Hypokalemia grade 3-4	3	1		
bTMB-H Hypercalcemia grade 3-4	0	1		
tTMB-H Hypercalcemia grade 3-4	2	0		
bTMB-H Hypocalcemia grade 3-4	2	0		
tTMB-H Hypocalcemia grade 3-4	0	1		
bTMB-H Hyperglycemia grade 3-4	0	0		
tTMB-H Hyperglycemia grade 3-4	0	0		
bTMB-H Hypoglycemia grade 3-4	0	0		
tTMB-H Hypoglycemia grade 3-4	0	0		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

SAEs and NSAEs are assessed from first dose to 100 days post last dose (Up to 27 months). Participants were assessed for deaths (all-cause) from their first dose to study completion (Up to 57 months).

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	26.0

Reporting groups

Reporting group title	Arm A: Nivolumab+Ipilimumab

Reporting group description:

Nivolumab 240 mg every 2 weeks (Q2W) + Ipilimumab 1 mg/kg every 6 weeks (Q6W) up to 24 months

Reporting group title	Arm B: Nivolumab+Ipilimumab (Rollover)

Reporting group description:

Nivolumab 240 mg every 2 weeks (Q2W) + Ipilimumab 1 mg/kg every 6 weeks (Q6W)

Reporting group title	Arm B: Nivolumab

Reporting group description:

Nivolumab Monotherapy 480 mg every 4 weeks (Q4W) up to 24 months

Serious adverse events	Arm A: Nivolumab+Ipilimumab	Arm B: Nivolumab+Ipilimumab (Rollover)	Arm B: Nivolumab
Total subjects affected by serious adverse events			
subjects affected / exposed	90 / 135 (66.67%)	11 / 22 (50.00%)	39 / 76 (51.32%)
number of deaths (all causes)	97	20	42
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Meningioma			
subjects affected / exposed	1 / 135 (0.74%)	0 / 22 (0.00%)	0 / 76 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Basal cell carcinoma			
subjects affected / exposed	1 / 135 (0.74%)	0 / 22 (0.00%)	0 / 76 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Malignant neoplasm progression			

subjects affected / exposed	43 / 135 (31.85%)	7 / 22 (31.82%)	25 / 76 (32.89%)
occurrences causally related to treatment / all	0 / 44	0 / 7	0 / 26
deaths causally related to treatment / all	0 / 40	0 / 7	0 / 23
Tumour pain			
subjects affected / exposed	1 / 135 (0.74%)	0 / 22 (0.00%)	0 / 76 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Pelvic venous thrombosis			
subjects affected / exposed	1 / 135 (0.74%)	0 / 22 (0.00%)	0 / 76 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Jugular vein thrombosis			
subjects affected / exposed	0 / 135 (0.00%)	0 / 22 (0.00%)	1 / 76 (1.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemorrhage			
subjects affected / exposed	1 / 135 (0.74%)	0 / 22 (0.00%)	0 / 76 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Superior vena cava syndrome			
subjects affected / exposed	0 / 135 (0.00%)	0 / 22 (0.00%)	2 / 76 (2.63%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Deep vein thrombosis			
subjects affected / exposed	1 / 135 (0.74%)	0 / 22 (0.00%)	0 / 76 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Hyperpyrexia			
subjects affected / exposed	0 / 135 (0.00%)	0 / 22 (0.00%)	1 / 76 (1.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

General physical health deterioration			
subjects affected / exposed	2 / 135 (1.48%)	0 / 22 (0.00%)	0 / 76 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Fatigue			
subjects affected / exposed	3 / 135 (2.22%)	0 / 22 (0.00%)	1 / 76 (1.32%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Death			
subjects affected / exposed	3 / 135 (2.22%)	0 / 22 (0.00%)	0 / 76 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 3	0 / 0	0 / 0
Malaise			
subjects affected / exposed	0 / 135 (0.00%)	1 / 22 (4.55%)	0 / 76 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pain			
subjects affected / exposed	1 / 135 (0.74%)	0 / 22 (0.00%)	0 / 76 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sudden death			
subjects affected / exposed	1 / 135 (0.74%)	0 / 22 (0.00%)	0 / 76 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Pyrexia			
subjects affected / exposed	5 / 135 (3.70%)	1 / 22 (4.55%)	0 / 76 (0.00%)
occurrences causally related to treatment / all	4 / 7	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
Uterine fistula			
subjects affected / exposed	1 / 135 (0.74%)	0 / 22 (0.00%)	0 / 76 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Female genital tract fistula			
subjects affected / exposed	1 / 135 (0.74%)	0 / 22 (0.00%)	0 / 76 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	2 / 135 (1.48%)	1 / 22 (4.55%)	1 / 76 (1.32%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory failure			
subjects affected / exposed	0 / 135 (0.00%)	0 / 22 (0.00%)	1 / 76 (1.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary oedema			
subjects affected / exposed	1 / 135 (0.74%)	0 / 22 (0.00%)	0 / 76 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pleural effusion			
subjects affected / exposed	0 / 135 (0.00%)	0 / 22 (0.00%)	2 / 76 (2.63%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Confusional state			
subjects affected / exposed	0 / 135 (0.00%)	1 / 22 (4.55%)	0 / 76 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Product issues			
Device occlusion			
subjects affected / exposed	1 / 135 (0.74%)	0 / 22 (0.00%)	0 / 76 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Blood creatinine increased			

subjects affected / exposed	2 / 135 (1.48%)	0 / 22 (0.00%)	0 / 76 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gamma-glutamyltransferase increased			
subjects affected / exposed	1 / 135 (0.74%)	0 / 22 (0.00%)	0 / 76 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urine output decreased			
subjects affected / exposed	0 / 135 (0.00%)	1 / 22 (4.55%)	0 / 76 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Femoral neck fracture			
subjects affected / exposed	1 / 135 (0.74%)	0 / 22 (0.00%)	0 / 76 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract injury			
subjects affected / exposed	1 / 135 (0.74%)	0 / 22 (0.00%)	0 / 76 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Myocarditis			
subjects affected / exposed	1 / 135 (0.74%)	0 / 22 (0.00%)	0 / 76 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myocardial infarction			
subjects affected / exposed	0 / 135 (0.00%)	0 / 22 (0.00%)	1 / 76 (1.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Cardiac failure			
subjects affected / exposed	0 / 135 (0.00%)	0 / 22 (0.00%)	1 / 76 (1.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Angina pectoris			
subjects affected / exposed	1 / 135 (0.74%)	0 / 22 (0.00%)	0 / 76 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pericarditis malignant			
subjects affected / exposed	1 / 135 (0.74%)	0 / 22 (0.00%)	0 / 76 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Intracranial pressure increased			
subjects affected / exposed	0 / 135 (0.00%)	0 / 22 (0.00%)	1 / 76 (1.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Encephalopathy			
subjects affected / exposed	2 / 135 (1.48%)	0 / 22 (0.00%)	0 / 76 (0.00%)
occurrences causally related to treatment / all	1 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Dysarthria			
subjects affected / exposed	1 / 135 (0.74%)	0 / 22 (0.00%)	0 / 76 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cognitive disorder			
subjects affected / exposed	1 / 135 (0.74%)	0 / 22 (0.00%)	0 / 76 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Brain oedema			
subjects affected / exposed	1 / 135 (0.74%)	0 / 22 (0.00%)	0 / 76 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Transient ischaemic attack			
subjects affected / exposed	1 / 135 (0.74%)	0 / 22 (0.00%)	0 / 76 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			

Leukopenia			
subjects affected / exposed	1 / 135 (0.74%)	0 / 22 (0.00%)	0 / 76 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anaemia			
subjects affected / exposed	1 / 135 (0.74%)	0 / 22 (0.00%)	2 / 76 (2.63%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal adhesions			
subjects affected / exposed	1 / 135 (0.74%)	0 / 22 (0.00%)	0 / 76 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal pain			
subjects affected / exposed	2 / 135 (1.48%)	0 / 22 (0.00%)	1 / 76 (1.32%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ascites			
subjects affected / exposed	1 / 135 (0.74%)	0 / 22 (0.00%)	0 / 76 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colitis			
subjects affected / exposed	4 / 135 (2.96%)	1 / 22 (4.55%)	0 / 76 (0.00%)
occurrences causally related to treatment / all	5 / 5	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea			
subjects affected / exposed	3 / 135 (2.22%)	0 / 22 (0.00%)	1 / 76 (1.32%)
occurrences causally related to treatment / all	1 / 4	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Large intestinal stenosis			
subjects affected / exposed	1 / 135 (0.74%)	0 / 22 (0.00%)	0 / 76 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intestinal obstruction			

subjects affected / exposed	3 / 135 (2.22%)	0 / 22 (0.00%)	0 / 76 (0.00%)
occurrences causally related to treatment / all	0 / 4	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastritis			
subjects affected / exposed	2 / 135 (1.48%)	0 / 22 (0.00%)	0 / 76 (0.00%)
occurrences causally related to treatment / all	4 / 6	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastric perforation			
subjects affected / exposed	1 / 135 (0.74%)	1 / 22 (4.55%)	0 / 76 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Enteritis			
subjects affected / exposed	1 / 135 (0.74%)	0 / 22 (0.00%)	0 / 76 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Large intestine perforation			
subjects affected / exposed	1 / 135 (0.74%)	0 / 22 (0.00%)	0 / 76 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			
subjects affected / exposed	3 / 135 (2.22%)	0 / 22 (0.00%)	0 / 76 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper gastrointestinal haemorrhage			
subjects affected / exposed	1 / 135 (0.74%)	0 / 22 (0.00%)	0 / 76 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Small intestinal obstruction			
subjects affected / exposed	1 / 135 (0.74%)	0 / 22 (0.00%)	0 / 76 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rectal haemorrhage			

subjects affected / exposed	1 / 135 (0.74%)	0 / 22 (0.00%)	0 / 76 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatitis chronic			
subjects affected / exposed	1 / 135 (0.74%)	0 / 22 (0.00%)	0 / 76 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatitis			
subjects affected / exposed	1 / 135 (0.74%)	0 / 22 (0.00%)	0 / 76 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nausea			
subjects affected / exposed	1 / 135 (0.74%)	1 / 22 (4.55%)	0 / 76 (0.00%)
occurrences causally related to treatment / all	0 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Hypertransaminasaemia			
subjects affected / exposed	0 / 135 (0.00%)	0 / 22 (0.00%)	1 / 76 (1.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatitis			
subjects affected / exposed	1 / 135 (0.74%)	1 / 22 (4.55%)	0 / 76 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholangitis			
subjects affected / exposed	1 / 135 (0.74%)	0 / 22 (0.00%)	1 / 76 (1.32%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Biliary obstruction			
subjects affected / exposed	1 / 135 (0.74%)	0 / 22 (0.00%)	0 / 76 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Jaundice			

subjects affected / exposed	1 / 135 (0.74%)	0 / 22 (0.00%)	0 / 76 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Pruritus			
subjects affected / exposed	1 / 135 (0.74%)	0 / 22 (0.00%)	0 / 76 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Ureteric obstruction			
subjects affected / exposed	1 / 135 (0.74%)	0 / 22 (0.00%)	0 / 76 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tubulointerstitial nephritis			
subjects affected / exposed	1 / 135 (0.74%)	0 / 22 (0.00%)	0 / 76 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Obstructive nephropathy			
subjects affected / exposed	1 / 135 (0.74%)	0 / 22 (0.00%)	0 / 76 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute kidney injury			
subjects affected / exposed	1 / 135 (0.74%)	0 / 22 (0.00%)	0 / 76 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endocrine disorders			
Hypopituitarism			
subjects affected / exposed	1 / 135 (0.74%)	0 / 22 (0.00%)	0 / 76 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypophysitis			
subjects affected / exposed	2 / 135 (1.48%)	0 / 22 (0.00%)	0 / 76 (0.00%)
occurrences causally related to treatment / all	2 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Adrenocorticotropic hormone deficiency			
subjects affected / exposed	1 / 135 (0.74%)	0 / 22 (0.00%)	0 / 76 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Adrenocortical insufficiency acute			
subjects affected / exposed	0 / 135 (0.00%)	0 / 22 (0.00%)	1 / 76 (1.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Adrenal insufficiency			
subjects affected / exposed	2 / 135 (1.48%)	0 / 22 (0.00%)	0 / 76 (0.00%)
occurrences causally related to treatment / all	2 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypothyroidism			
subjects affected / exposed	1 / 135 (0.74%)	0 / 22 (0.00%)	1 / 76 (1.32%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thyroiditis			
subjects affected / exposed	1 / 135 (0.74%)	0 / 22 (0.00%)	0 / 76 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Secondary adrenocortical insufficiency			
subjects affected / exposed	1 / 135 (0.74%)	0 / 22 (0.00%)	0 / 76 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Myositis			
subjects affected / exposed	1 / 135 (0.74%)	0 / 22 (0.00%)	0 / 76 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bone pain			

subjects affected / exposed	1 / 135 (0.74%)	0 / 22 (0.00%)	0 / 76 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Back pain			
subjects affected / exposed	1 / 135 (0.74%)	0 / 22 (0.00%)	1 / 76 (1.32%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteonecrosis			
subjects affected / exposed	1 / 135 (0.74%)	0 / 22 (0.00%)	0 / 76 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pain in extremity			
subjects affected / exposed	0 / 135 (0.00%)	0 / 22 (0.00%)	2 / 76 (2.63%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pathological fracture			
subjects affected / exposed	1 / 135 (0.74%)	0 / 22 (0.00%)	1 / 76 (1.32%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
COVID-19			
subjects affected / exposed	1 / 135 (0.74%)	0 / 22 (0.00%)	0 / 76 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchopulmonary aspergillosis			
subjects affected / exposed	1 / 135 (0.74%)	0 / 22 (0.00%)	0 / 76 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anal abscess			
subjects affected / exposed	1 / 135 (0.74%)	0 / 22 (0.00%)	0 / 76 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal abscess			

subjects affected / exposed	1 / 135 (0.74%)	0 / 22 (0.00%)	0 / 76 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infection			
subjects affected / exposed	1 / 135 (0.74%)	0 / 22 (0.00%)	1 / 76 (1.32%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lymph gland infection			
subjects affected / exposed	0 / 135 (0.00%)	0 / 22 (0.00%)	1 / 76 (1.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pelvic inflammatory disease			
subjects affected / exposed	1 / 135 (0.74%)	0 / 22 (0.00%)	0 / 76 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peritonitis			
subjects affected / exposed	1 / 135 (0.74%)	0 / 22 (0.00%)	0 / 76 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	2 / 135 (1.48%)	0 / 22 (0.00%)	3 / 76 (3.95%)
occurrences causally related to treatment / all	0 / 2	0 / 0	1 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Prostate infection			
subjects affected / exposed	0 / 135 (0.00%)	1 / 22 (4.55%)	0 / 76 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory tract infection			
subjects affected / exposed	0 / 135 (0.00%)	0 / 22 (0.00%)	1 / 76 (1.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin infection			

subjects affected / exposed	1 / 135 (0.74%)	0 / 22 (0.00%)	0 / 76 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			
subjects affected / exposed	3 / 135 (2.22%)	1 / 22 (4.55%)	1 / 76 (1.32%)
occurrences causally related to treatment / all	0 / 3	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urosepsis			
subjects affected / exposed	2 / 135 (1.48%)	2 / 22 (9.09%)	0 / 76 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Metabolism and nutrition disorders			
Hypokalaemia			
subjects affected / exposed	1 / 135 (0.74%)	0 / 22 (0.00%)	0 / 76 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperglycaemia			
subjects affected / exposed	1 / 135 (0.74%)	0 / 22 (0.00%)	0 / 76 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
Hypercalcaemia			
subjects affected / exposed	2 / 135 (1.48%)	0 / 22 (0.00%)	1 / 76 (1.32%)
occurrences causally related to treatment / all	0 / 2	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	Arm A: Nivolumab+Ipilimumab	Arm B: Nivolumab+Ipilimumab (Rollover)	Arm B: Nivolumab
Total subjects affected by non-serious adverse events			
subjects affected / exposed	121 / 135 (89.63%)	13 / 22 (59.09%)	64 / 76 (84.21%)
Vascular disorders			
Hypotension			

subjects affected / exposed	7 / 135 (5.19%)	1 / 22 (4.55%)	0 / 76 (0.00%)
occurrences (all)	8	2	0
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	21 / 135 (15.56%)	2 / 22 (9.09%)	10 / 76 (13.16%)
occurrences (all)	35	2	13
Oedema peripheral			
subjects affected / exposed	22 / 135 (16.30%)	0 / 22 (0.00%)	5 / 76 (6.58%)
occurrences (all)	32	0	6
Fatigue			
subjects affected / exposed	41 / 135 (30.37%)	2 / 22 (9.09%)	17 / 76 (22.37%)
occurrences (all)	50	2	24
Asthenia			
subjects affected / exposed	16 / 135 (11.85%)	1 / 22 (4.55%)	10 / 76 (13.16%)
occurrences (all)	25	3	12
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	20 / 135 (14.81%)	1 / 22 (4.55%)	5 / 76 (6.58%)
occurrences (all)	20	2	6
Cough			
subjects affected / exposed	16 / 135 (11.85%)	0 / 22 (0.00%)	6 / 76 (7.89%)
occurrences (all)	21	0	13
Psychiatric disorders			
Insomnia			
subjects affected / exposed	13 / 135 (9.63%)	1 / 22 (4.55%)	4 / 76 (5.26%)
occurrences (all)	13	1	4
Investigations			
Aspartate aminotransferase increased			
subjects affected / exposed	20 / 135 (14.81%)	1 / 22 (4.55%)	12 / 76 (15.79%)
occurrences (all)	26	1	12
Amylase increased			
subjects affected / exposed	7 / 135 (5.19%)	0 / 22 (0.00%)	4 / 76 (5.26%)
occurrences (all)	17	0	5
Alanine aminotransferase increased			

subjects affected / exposed	19 / 135 (14.07%)	2 / 22 (9.09%)	8 / 76 (10.53%)
occurrences (all)	33	3	8
Blood alkaline phosphatase increased			
subjects affected / exposed	13 / 135 (9.63%)	1 / 22 (4.55%)	8 / 76 (10.53%)
occurrences (all)	24	1	10
Blood bilirubin increased			
subjects affected / exposed	10 / 135 (7.41%)	0 / 22 (0.00%)	7 / 76 (9.21%)
occurrences (all)	13	0	9
Blood creatinine increased			
subjects affected / exposed	11 / 135 (8.15%)	2 / 22 (9.09%)	7 / 76 (9.21%)
occurrences (all)	27	3	9
Blood glucose increased			
subjects affected / exposed	7 / 135 (5.19%)	0 / 22 (0.00%)	3 / 76 (3.95%)
occurrences (all)	10	0	7
Weight decreased			
subjects affected / exposed	4 / 135 (2.96%)	0 / 22 (0.00%)	6 / 76 (7.89%)
occurrences (all)	4	0	7
Injury, poisoning and procedural complications			
Infusion related reaction			
subjects affected / exposed	6 / 135 (4.44%)	0 / 22 (0.00%)	4 / 76 (5.26%)
occurrences (all)	6	0	6
Nervous system disorders			
Neuropathy peripheral			
subjects affected / exposed	2 / 135 (1.48%)	0 / 22 (0.00%)	4 / 76 (5.26%)
occurrences (all)	2	0	7
Headache			
subjects affected / exposed	11 / 135 (8.15%)	2 / 22 (9.09%)	4 / 76 (5.26%)
occurrences (all)	16	2	8
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	32 / 135 (23.70%)	3 / 22 (13.64%)	16 / 76 (21.05%)
occurrences (all)	62	3	19
Thrombocytopenia			
subjects affected / exposed	6 / 135 (4.44%)	0 / 22 (0.00%)	5 / 76 (6.58%)
occurrences (all)	7	0	8
Gastrointestinal disorders			

Dry mouth			
subjects affected / exposed	6 / 135 (4.44%)	0 / 22 (0.00%)	6 / 76 (7.89%)
occurrences (all)	6	0	9
Diarrhoea			
subjects affected / exposed	50 / 135 (37.04%)	3 / 22 (13.64%)	14 / 76 (18.42%)
occurrences (all)	84	12	40
Constipation			
subjects affected / exposed	23 / 135 (17.04%)	1 / 22 (4.55%)	10 / 76 (13.16%)
occurrences (all)	28	1	11
Abdominal pain upper			
subjects affected / exposed	7 / 135 (5.19%)	2 / 22 (9.09%)	4 / 76 (5.26%)
occurrences (all)	10	3	4
Abdominal pain			
subjects affected / exposed	23 / 135 (17.04%)	1 / 22 (4.55%)	6 / 76 (7.89%)
occurrences (all)	24	1	7
Nausea			
subjects affected / exposed	19 / 135 (14.07%)	4 / 22 (18.18%)	15 / 76 (19.74%)
occurrences (all)	26	4	19
Colitis			
subjects affected / exposed	1 / 135 (0.74%)	2 / 22 (9.09%)	0 / 76 (0.00%)
occurrences (all)	1	2	0
Vomiting			
subjects affected / exposed	19 / 135 (14.07%)	3 / 22 (13.64%)	7 / 76 (9.21%)
occurrences (all)	31	3	12
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	25 / 135 (18.52%)	1 / 22 (4.55%)	7 / 76 (9.21%)
occurrences (all)	30	1	14
Pruritus			
subjects affected / exposed	36 / 135 (26.67%)	8 / 22 (36.36%)	15 / 76 (19.74%)
occurrences (all)	65	10	25
Dry skin			
subjects affected / exposed	6 / 135 (4.44%)	2 / 22 (9.09%)	2 / 76 (2.63%)
occurrences (all)	8	2	2
Endocrine disorders			

Hypothyroidism			
subjects affected / exposed	18 / 135 (13.33%)	0 / 22 (0.00%)	11 / 76 (14.47%)
occurrences (all)	20	0	11
Hyperthyroidism			
subjects affected / exposed	15 / 135 (11.11%)	1 / 22 (4.55%)	3 / 76 (3.95%)
occurrences (all)	15	1	3
Musculoskeletal and connective tissue disorders			
Pain in extremity			
subjects affected / exposed	7 / 135 (5.19%)	0 / 22 (0.00%)	2 / 76 (2.63%)
occurrences (all)	9	0	2
Neck pain			
subjects affected / exposed	1 / 135 (0.74%)	0 / 22 (0.00%)	4 / 76 (5.26%)
occurrences (all)	1	0	5
Arthralgia			
subjects affected / exposed	22 / 135 (16.30%)	0 / 22 (0.00%)	7 / 76 (9.21%)
occurrences (all)	29	0	10
Back pain			
subjects affected / exposed	18 / 135 (13.33%)	1 / 22 (4.55%)	5 / 76 (6.58%)
occurrences (all)	18	1	7
Myalgia			
subjects affected / exposed	11 / 135 (8.15%)	1 / 22 (4.55%)	8 / 76 (10.53%)
occurrences (all)	11	1	10
Infections and infestations			
Urinary tract infection			
subjects affected / exposed	12 / 135 (8.89%)	4 / 22 (18.18%)	2 / 76 (2.63%)
occurrences (all)	17	6	2
Pharyngitis			
subjects affected / exposed	1 / 135 (0.74%)	2 / 22 (9.09%)	0 / 76 (0.00%)
occurrences (all)	1	2	0
COVID-19			
subjects affected / exposed	10 / 135 (7.41%)	1 / 22 (4.55%)	2 / 76 (2.63%)
occurrences (all)	10	1	2
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	28 / 135 (20.74%)	2 / 22 (9.09%)	6 / 76 (7.89%)
occurrences (all)	30	2	6

Hyperglycaemia			
subjects affected / exposed	8 / 135 (5.93%)	1 / 22 (4.55%)	3 / 76 (3.95%)
occurrences (all)	8	2	4
Hypoalbuminaemia			
subjects affected / exposed	7 / 135 (5.19%)	1 / 22 (4.55%)	3 / 76 (3.95%)
occurrences (all)	10	1	3
Hypocalcaemia			
subjects affected / exposed	8 / 135 (5.93%)	0 / 22 (0.00%)	1 / 76 (1.32%)
occurrences (all)	11	0	1
Hypokalaemia			
subjects affected / exposed	12 / 135 (8.89%)	1 / 22 (4.55%)	1 / 76 (1.32%)
occurrences (all)	15	1	1
Hyponatraemia			
subjects affected / exposed	11 / 135 (8.15%)	1 / 22 (4.55%)	3 / 76 (3.95%)
occurrences (all)	11	1	3
Hypophosphataemia			
subjects affected / exposed	5 / 135 (3.70%)	2 / 22 (9.09%)	1 / 76 (1.32%)
occurrences (all)	7	2	1

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
11 December 2018	Study design update
14 August 2019	pre-screening and enrollment requirements update
04 May 2021	Statisical analysis population clarification

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported