Clinical trial results:
A Phase 3 Randomized, Double-Blind Study of Nivolumab Monotherapy or Nivolumab Combined with Ipilimumab vs Placebo in Participants with Localized Renal Cell Carcinoma Who Underwent Radical or Partial Nephrectomy and Who Are at High Risk of Relapse

CheckMate 914: CHECKpoint pathway and nivoluMAb clinical Trial Evaluation 914

Summary

EudraCT number	2016-004502-34
Trial protocol	AT DE BE CZ NL GB FR ES IT RO
Global end of trial date	01 February 2024

Results information

Result version number	v1
This version publication date	10 August 2024
First version publication date	10 August 2024

Trial information

Trial identification

Sponsor protocol code	CA209-914

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03138512
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	28 February 2024
Is this the analysis of the primary completion data?	Yes
Primary completion date	12 September 2023
Global end of trial reached?	Yes
Global end of trial date	01 February 2024
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Part A: To compare disease-free survival (DFS) per Blinded Independent Central Review (BICR) of nivolumab combined with ipilimumab versus placebo infusions in participants with localized RCC, with a predominantly clear cell histology who have undergone a nephrectomy.

Part B: To compare disease-free survival (DFS) per Blinded Independent Central Review (BICR) of nivolumab versus placebo infusions in participants with localized renal cell carcinoma, with a predominantly clear cell histology who have undergone nephrectomy.

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	29 August 2017
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	Argentina: 159
Country: Number of subjects enrolled	Australia: 85
Country: Number of subjects enrolled	Austria: 4
Country: Number of subjects enrolled	Belgium: 23
Country: Number of subjects enrolled	Brazil: 60
Country: Number of subjects enrolled	Canada: 40
Country: Number of subjects enrolled	Chile: 30
Country: Number of subjects enrolled	China: 100
Country: Number of subjects enrolled	Colombia: 11
Country: Number of subjects enrolled	Czechia: 39
Country: Number of subjects enrolled	France: 163
Country: Number of subjects enrolled	Germany: 67
Country: Number of subjects enrolled	Italy: 93
Country: Number of subjects enrolled	Japan: 124
Country: Number of subjects enrolled	Mexico: 132
Country: Number of subjects enrolled	Netherlands: 30
Country: Number of subjects enrolled	Poland: 50

Country: Number of subjects enrolled	Romania: 19
Country: Number of subjects enrolled	Russian Federation: 20
Country: Number of subjects enrolled	Singapore: 6
Country: Number of subjects enrolled	Spain: 49
Country: Number of subjects enrolled	Switzerland: 7
Country: Number of subjects enrolled	Türkiye: 10
Country: Number of subjects enrolled	United Kingdom: 72
Country: Number of subjects enrolled	United States: 248
Worldwide total number of subjects	1641
EEA total number of subjects	537

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)	1142
From 65 to 84 years	498
85 years and over	1

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Part A and B participants are separately randomized and treated.

Period 1

Period 1 title	Randomization
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Carer, Data analyst, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Arm A: Nivo + Ipi

Arm description:

Nivolumab 240 mg every 2 weeks and ipilimumab 1 mg/kg every 6 weeks (or every third nivolumab dose if dosing is delayed).

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

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

Dosage and administration details:

240 mg

Arm title	Arm B: Placebo

Arm description:

Placebo infusions at the same frequency of nivolumab and ipilimumab infusions.

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

Dosage and administration details:

0.9% Sodium Chloride or 5% Dextrose Injection

Investigational medicinal product name	Nivolumab-Placebo
Investigational medicinal product code	
Other name	

Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

0.9% Sodium Chloride or 5% Dextrose Injection

Arm title	Arm C: Nivo

Arm description:

Nivolumab 240 mg every 2 weeks and ipilimumab Placebo every 6 weeks (or every third nivolumab dose if dosing is delayed).

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

Dosage and administration details:

0.9% Sodium Chloride or 5% Dextrose Injection

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

Dosage and administration details:

240 mg

Number of subjects in period 1	Arm A: Nivo + Ipi	Arm B: Placebo	Arm C: Nivo
Started	611	619	411
Randomized to Part A	405 [1]	411 [2]	0 [3]
Randomized to Part B	206 [4]	208 [5]	411
Completed	608	614	408
Not completed	3	5	3
Participant no longer meets study criteria	1	4	3
Other reasons	1	-	-
Participants withdrew consent	1	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: The numbers are correct. The confusion may be due to that CM914 had two Parts (A & B), which were consisted with 2 arms (O+Y versus Placebo) and 3 arms (O+Y, Placebo and Nivo mono).
[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: The numbers are correct. The confusion may be due to that CM914 had two Parts (A & B), which were consisted with 2 arms (O+Y versus Placebo) and 3 arms (O+Y, Placebo and Nivo mono).

[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: The numbers are correct. The confusion may be due to that CM914 had two Parts (A & B), which were consisted with 2 arms (O+Y versus Placebo) and 3 arms (O+Y, Placebo and Nivo mono).
[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: The numbers are correct. The confusion may be due to that CM914 had two Parts (A & B), which were consisted with 2 arms (O+Y versus Placebo) and 3 arms (O+Y, Placebo and Nivo mono).
[5] - 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: The numbers are correct. The confusion may be due to that CM914 had two Parts (A & B), which were consisted with 2 arms (O+Y versus Placebo) and 3 arms (O+Y, Placebo and Nivo mono).

Period 2

Period 2 title	Treatment Part A
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Carer, Assessor

Arms

Are arms mutually exclusive?	No
Arm title	Arm A: Nivo + Ipi

Arm description:

Nivolumab 240 mg every 2 weeks and ipilimumab 1 mg/kg every 6 weeks (or every third nivolumab dose if dosing is delayed).

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

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

Dosage and administration details:

240 mg

Arm title	Arm B: Placebo

Arm description:

Placebo infusions at the same frequency of nivolumab and ipilimumab infusions.

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

Dosage and administration details:

0.9% Sodium Chloride or 5% Dextrose Injection

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

Dosage and administration details:

0.9% Sodium Chloride or 5% Dextrose Injection

Number of subjects in period 2	Arm A: Nivo + Ipi	Arm B: Placebo
Started	404	407
Completed	229	360
Not completed	175	47
Participant request to discontinue treatment	9	4
Disease recurrence	10	20
Participant withdrew consent	2	4
Death	1	-
Pregnancy	-	1
Adverse event unrelated to study drug	9	4
Other reasons	11	8
Study Drug Toxicity	132	5
Lost to follow-up	-	1
Poor/non-compliance	1	-

Period 3

Period 3 title	Treatment Part B
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Carer, Data analyst, Assessor

Arms

Are arms mutually exclusive?	No
Arm title	Arm A: Nivo + Ipi

Arm description:

Nivolumab 240 mg every 2 weeks and ipilimumab 1 mg/kg every 6 weeks (or every third nivolumab dose if dosing is delayed).

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

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

Dosage and administration details:

240 mg

Arm title	Arm B: Placebo

Arm description:

Placebo infusions at the same frequency of nivolumab and ipilimumab infusions.

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

Dosage and administration details:

0.9% Sodium Chloride or 5% Dextrose Injection

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

Dosage and administration details:

0.9% Sodium Chloride or 5% Dextrose Injection

Arm title	Arm C: Nivo

Arm description:

Nivolumab 240 mg every 2 weeks and ipilimumab Placebo every 6 weeks (or every third nivolumab dose if dosing is delayed).

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

Dosage and administration details:

0.9% Sodium Chloride or 5% Dextrose Injection

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

Dosage and administration details:
240 mg

Number of subjects in period 3	Arm A: Nivo + Ipi	Arm B: Placebo	Arm C: Nivo
Started	204	207	408
Completed	118	182	327
Not completed	86	25	81
Disease recurrence	6	12	10
Participant withdrew consent	1	1	2
Death	1	-	-
Request to discontinue study treatment	6	4	6
Adverse event unrelated to study drug	5	2	12
Other reasons	3	1	5
Study Drug Toxicity	63	3	45
Lost to follow-up	-	1	-
Poor/non-compliance	1	1	1

Baseline characteristics

Reporting groups	
Reporting group title	Arm A: Nivo + Ipi
Reporting group description:	
Nivolumab 240 mg every 2 weeks and ipilimumab 1 mg/kg every 6 weeks (or every third nivolumab dose if dosing is delayed).	
Reporting group title	Arm B: Placebo
Reporting group description:	
Placebo infusions at the same frequency of nivolumab and ipilimumab infusions.	
Reporting group title	Arm C: Nivo
Reporting group description:	
Nivolumab 240 mg every 2 weeks and ipilimumab Placebo every 6 weeks (or every third nivolumab dose if dosing is delayed).	

Reporting group values	Arm A: Nivo + Ipi	Arm B: Placebo	Arm C: Nivo
Number of subjects	611	619	411
Age Categorical Units: Participants			
Part A|< 65	293	301	0
Part B|< 65	132	137	279
Part A|>= 65 AND < 75	93	91	0
Part B|>= 65 AND < 75	64	60	108
Part A|>= 75 AND < 85	19	19	0
Part B|>= 75 AND < 85	10	11	23
Part A|>= 85	0	0	0
Part B|>= 85	0	0	1
Age Continuous			
All Randomized Part A Subjects Note: 0.99999 - N/A (No participants randomized to Arm C for Part A)			
Units: years			
arithmetic mean	57.9	57.3	0.99999
standard deviation	± 10.49	± 10.53	± 0.99999
Sex: Female, Male Units: Participants			
Part A|Female	119	117	0
Part B|Female	59	67	106
Part A|Male	286	294	0
Part B|Male	147	141	305
Race (NIH/OMB) Units: Subjects			
Part A|American Indian or Alaska Native	0	3	0
Part B|American Indian or Alaska Native	5	3	14
Part A|Asian	93	65	0
Part B|Asian	20	26	50
Part A|Native Hawaiian or Other Pacific Islander	0	1	0
Part B|Native Hawaiian or Other Pacific Islander	0	0	0

Part A|Black or African American	3	6	0
Part B|Black or African American	0	1	4
Part A|White	303	322	0
Part B|White	173	169	331
Part A|More than one race	0	0	0
Part B|More than one race	0	0	0
Part A|Unknown or Not Reported	6	14	0
Part B|Unknown or Not Reported	8	9	12
Ethnicity (NIH/OMB) Units: Subjects			
Part A|Hispanic or Latino	41	44	0
Part B|Hispanic or Latino	26	34	67
Part A|Not Hispanic or Latino	189	197	0
Part B|Not Hispanic or Latino	93	79	157
Part A|Unknown or Not Reported	175	170	0
Part B|Unknown or Not Reported	87	95	187
Age Continuous			
All Randomized Part B Subjects			
Units: Years			
arithmetic mean	58.6	58.1	58.0
standard deviation	± 10.9	± 11.2	± 11.1

Reporting group values	Total		
Number of subjects	1641		
Age Categorical Units: Participants			
Part A|< 65	594		
Part B|< 65	548		
Part A|>= 65 AND < 75	184		
Part B|>= 65 AND < 75	232		
Part A|>= 75 AND < 85	38		
Part B|>= 75 AND < 85	44		
Part A|>= 85	0		
Part B|>= 85	1		
Age Continuous			
All Randomized Part A Subjects Note: 0.99999 - N/A (No participants randomized to Arm C for Part A)			
Units: years			
arithmetic mean			
standard deviation	-		
Sex: Female, Male Units: Participants			
Part A|Female	236		
Part B|Female	232		
Part A|Male	580		
Part B|Male	593		
Race (NIH/OMB) Units: Subjects			
Part A|American Indian or Alaska Native	3		
Part B|American Indian or Alaska Native	22		

Part A|Asian	158		
Part B|Asian	96		
Part A|Native Hawaiian or Other Pacific Islander	1		
Part B|Native Hawaiian or Other Pacific Islander	0		
Part A|Black or African American	9		
Part B|Black or African American	5		
Part A|White	625		
Part B|White	673		
Part A|More than one race	0		
Part B|More than one race	0		
Part A|Unknown or Not Reported	20		
Part B|Unknown or Not Reported	29		
Ethnicity (NIH/OMB) Units: Subjects			
Part A|Hispanic or Latino	85		
Part B|Hispanic or Latino	127		
Part A|Not Hispanic or Latino	386		
Part B|Not Hispanic or Latino	329		
Part A|Unknown or Not Reported	345		
Part B|Unknown or Not Reported	369		
Age Continuous			
All Randomized Part B Subjects			
Units: Years arithmetic mean standard deviation	- -		

End points

End points reporting groups

Reporting group title	Arm A: Nivo + Ipi
Reporting group description:	
Nivolumab 240 mg every 2 weeks and ipilimumab 1 mg/kg every 6 weeks (or every third nivolumab dose if dosing is delayed).	
Reporting group title	Arm B: Placebo
Reporting group description:	
Placebo infusions at the same frequency of nivolumab and ipilimumab infusions.	
Reporting group title	Arm C: Nivo
Reporting group description:	
Nivolumab 240 mg every 2 weeks and ipilimumab Placebo every 6 weeks (or every third nivolumab dose if dosing is delayed).	
Reporting group title	Arm A: Nivo + Ipi
Reporting group description:	
Nivolumab 240 mg every 2 weeks and ipilimumab 1 mg/kg every 6 weeks (or every third nivolumab dose if dosing is delayed).	
Reporting group title	Arm B: Placebo
Reporting group description:	
Placebo infusions at the same frequency of nivolumab and ipilimumab infusions.	
Reporting group title	Arm A: Nivo + Ipi
Reporting group description:	
Nivolumab 240 mg every 2 weeks and ipilimumab 1 mg/kg every 6 weeks (or every third nivolumab dose if dosing is delayed).	
Reporting group title	Arm B: Placebo
Reporting group description:	
Placebo infusions at the same frequency of nivolumab and ipilimumab infusions.	
Reporting group title	Arm C: Nivo
Reporting group description:	
Nivolumab 240 mg every 2 weeks and ipilimumab Placebo every 6 weeks (or every third nivolumab dose if dosing is delayed).	

Primary: Disease-Free Survival (DFS) by BICR - Part A and B

End point title	Disease-Free Survival (DFS) by BICR - Part A and B
End point description:	
Disease-Free Survival (DFS) is defined as the time from randomization to development of local disease recurrence (ie, recurrence of primary tumor in situ or occurrence of a secondary renal cell carcinoma (RCC) primary cancer), distance metastasis, or death, whichever came first per Blinded Independent Central Review (BICR) based on Kaplan-Meier estimates. Analyzed in all randomized participants in Part A (Arm A and B) and Part B (Arm B and C). Note: 99999 - N/A (Insufficient number of participants with events) Note: 00000 - 0 Participants analyzed. Arm A was prespecified to be excluded from the endpoint objective for Part B.	
End point type	Primary
End point timeframe:	
From randomization to development of local disease recurrence, distance metastasis, or death, whichever came first (up to an average of 72 months)	

End point values	Arm A: Nivo + Ipi	Arm B: Placebo	Arm C: Nivo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	611	619	411	
Units: Months				
median (confidence interval 95%)				
Part A	99999 (99999 to 99999)	99999 (65.58 to 99999)	00000 (00000 to 00000)	
Part B	00000 (00000 to 00000)	99999 (99999 to 99999)	99999 (99999 to 99999)	

Statistical analyses

Statistical analysis title	Arm A vs Arm B in Part A
Comparison groups	Arm A: Nivo + Ipi v Arm B: Placebo
Number of subjects included in analysis	1230
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6676
Method	Logrank
Parameter estimate	Cox proportional hazard
Point estimate	0.95
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.75
upper limit	1.2

Statistical analysis title	Arm A vs Arm B in Part B
Comparison groups	Arm B: Placebo v Arm C: Nivo
Number of subjects included in analysis	1030
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6556
Method	Logrank
Parameter estimate	Cox proportional hazard
Point estimate	0.93
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.67
upper limit	1.28

Secondary: Overall Survival (OS) - Part A and B	
End point title	Overall Survival (OS) - Part A and B

End point description:

Overall Survival (OS) is defined as the time between the date of randomization and the date of death. For participants without documentation of death, OS will be censored on the last date the participants was known to be alive. Based on Kaplan-Meier estimates. Analyzed in all randomized participants in Part A (Arm A and B) and Part B (Arm B and C).

Note: 99999 - N/A (Insufficient number of participants with events)
Note: 00000 - 0 Participants analyzed. Arm A was prespecified to be excluded from the endpoint objective for Part B.

End point type	Secondary

End point timeframe:

From randomization to the date of death (up to an average of 72 months)

End point values	Arm A: Nivo + Ipi	Arm B: Placebo	Arm C: Nivo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	611	619	411	
Units: Months				
median (confidence interval 95%)				
Part A	99999 (99999 to 99999)	99999 (99999 to 99999)	00000 (00000 to 00000)	
Part B	00000 (00000 to 00000)	99999 (99999 to 99999)	99999 (99999 to 99999)	

Statistical analyses

Statistical analysis title	Arm B vs Arm C in Part B

Statistical analysis description:

Part B

Comparison groups	Arm B: Placebo v Arm C: Nivo
Number of subjects included in analysis	1030
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.45
Method	Logrank
Parameter estimate	Cox proportional hazard
Point estimate	1.36
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.61
upper limit	3.07

Statistical analysis title	Arm A vs Arm B in Part A

Statistical analysis description:

Part A

Comparison groups	Arm A: Nivo + Ipi v Arm B: Placebo

Number of subjects included in analysis	1230
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2436
Method	Logrank
Parameter estimate	Cox proportional hazard
Point estimate	1.26
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.85
upper limit	1.85

Secondary: Overall Survival (OS) Rate (5 years) - Part A and B

End point title	Overall Survival (OS) Rate (5 years) - Part A and B

End point description:

Overall survival rate at 5 years is defined as the percentage of participants who are alive at 5 years. Analyzed in all randomized participants in Part A (Arm A and B) and Part B (Arm B and C).

End point type	Secondary

End point timeframe:

At 5 years

End point values	Arm A: Nivo + Ipi	Arm B: Placebo	Arm C: Nivo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	0[1]	0[2]	0[3]	
Units: Months				
median (confidence interval 95%)				
Part A	(to)	(to)	(to)	
Part B	(to)	(to)	(to)	

Notes:

[1] - The minimum follow-up of 5-years was not achieved.

[2] - The minimum follow-up of 5-years was not achieved.

[3] - The minimum follow-up of 5-years was not achieved.

Statistical analyses

No statistical analyses for this end point

Secondary: Disease-Free Survival (DFS) per BICR in Contemporaneously Randomized Combination and Monotherapy Participants - Part B

End point title	Disease-Free Survival (DFS) per BICR in Contemporaneously Randomized Combination and Monotherapy Participants - Part B[4]

End point description:

Disease-Free Survival (DFS) is defined as the time from randomization to development of local disease recurrence (ie, recurrence of primary tumor in situ or occurrence of a secondary renal cell carcinoma (RCC) primary cancer), distance metastasis, or death, whichever came first per Blinded Independent Central Review (BICR) based on Kaplan-Meier estimates. Analyzed for all randomized combination and

monotherapy participants in Part B. Prespecified to be collected for Part B only. Arm B was prespecified to be excluded from the endpoint objective.

Note: 99999 - N/A (Insufficient number of participants with events)

End point type	Secondary

End point timeframe:

From randomization to development of local disease recurrence, distance metastasis, or death, whichever came first (up to an average of 72 months)

Notes:

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

End point values	Arm A: Nivo + Ipi	Arm C: Nivo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	206[5]	411[6]		
Units: Months				
median (confidence interval 95%)	99999 (36.17 to 99999)	99999 (99999 to 99999)		

Notes:

[5] - Part B

[6] - Part B

Statistical analyses

Statistical analysis title	Arm A vs Arm C
Comparison groups	Arm A: Nivo + Ipi v Arm C: Nivo
Number of subjects included in analysis	617
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Cox proportional hazard
Point estimate	1.22
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.89
upper limit	1.67

Secondary: Overall Survival (OS) in the Contemporaneously Randomized Combination and Monotherapy Participants - Part B

End point title	Overall Survival (OS) in the Contemporaneously Randomized Combination and Monotherapy Participants - Part B[7]

End point description:

Overall Survival (OS) is defined as the time between the date of randomization and the date of death. For participants without documentation of death, OS will be censored on the last date the participants was known to be alive. Based on Kaplan-Meier estimates. Analyzed for all randomized combination and monotherapy participants in Part B. Prespecified to be collected for Part B only. Arm B was prespecified to be excluded from the endpoint objective.

Note: 99999 - N/A (Insufficient number of participants with events)

End point type	Secondary

End point timeframe:

From randomization to the date of death (up to an average of 72 months)

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: Prespecified to only be collected for Part B.

End point values	Arm A: Nivo + Ipi	Arm C: Nivo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	206[8]	411[9]		
Units: Months				
median (confidence interval 95%)	99999 (99999 to 99999)	99999 (99999 to 99999)		

Notes:

[8] - Part B

[9] - Part B

Statistical analyses

Statistical analysis title	Arm A vs Arm C
Comparison groups	Arm A: Nivo + Ipi v Arm C: Nivo
Number of subjects included in analysis	617
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Cox proportional hazard
Point estimate	0.75
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.33
upper limit	1.68

Secondary: The Number of Participants with Adverse Events up to 30 Days After Last Dose of Study Therapy - Part A

End point title	The Number of Participants with Adverse Events up to 30 Days After Last Dose of Study Therapy - Part A[10]

End point description:

An Adverse Event (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. Graded according to NCI CTCAE (Version 4) guidelines where grade 1 = mild, grade 2 = moderate, grade 3 = severe, grade 4 = life threatening, grade 5 = death. Analyzed in all treated participants in Part A.

End point type	Secondary

End point timeframe:

From first dose to 30 days post last dose (up to approximately 40 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: Prespecified to only be collected for Part A.

End point values	Arm A: Nivo + Ipi	Arm B: Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	404	407		
Units: Participants				
Any Grade AE	392	362		
Grade 3-4 AE	154	44		
Grade 5 AE	1	0		
Any Grade Drug-Related AE	359	230		
Grade 3-4 Drug-Related AE	114	8		
Grade 5 Drug-Related AE	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: The Number of Participants with Adverse Events up to 30 Days After Last Dose of Study Therapy - Part B

End point title	The Number of Participants with Adverse Events up to 30 Days After Last Dose of Study Therapy - Part B

End point description:

An Adverse Event (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. Graded according to NCI CTCAE (Version 4) guidelines where grade 1 = mild, grade 2 = moderate, grade 3 = severe, grade 4 = life threatening, grade 5 = death. Analyzed in all treated participants in Part B.

End point type	Secondary

End point timeframe:

From first dose to 30 days post last dose (up to approximately 40 weeks)

End point values	Arm A: Nivo + Ipi	Arm B: Placebo	Arm C: Nivo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	204[11]	207[12]	408[13]	
Units: Participants				
Any Grade AE	193	182	362	
Grade 3-4 AE	59	31	70	
Grade 5 AE	1	1	0	
Any Grade Drug-Related AE	173	107	297	
Grade 3-4 Drug-Related AE	41	4	36	
Grade 5 Drug-Related AE	0	0	0	

Notes:

[11] - Part B

[12] - Part B

[13] - Part B

Statistical analyses

No statistical analyses for this end point

Secondary: The Number of Participants with Adverse Events up to 100 Days After Last Dose of Study Therapy - Part A

End point title	The Number of Participants with Adverse Events up to 100 Days After Last Dose of Study Therapy - Part A[14]

End point description:

An Adverse Event (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. Graded according to NCI CTCAE (Version 4) guidelines where grade 1 = mild, grade 2 = moderate, grade 3 = severe, grade 4 = life threatening, grade 5 = death. Analyzed in all treated participants in Part A.

End point type	Secondary

End point timeframe:

From first dose to 100 days post last dose (up to approximately 50 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: Prespecified to only be collected for Part A.

End point values	Arm A: Nivo + Ipi	Arm B: Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	404	407		
Units: Participants				
Any Grade AE	393	365		
Grade 3-4 AE	167	52		
Grade 5 AE	4	1		
Any Grade Drug-Related AE	361	230		
Grade 3-4 Drug-Related AE	128	9		
Grade 5 Drug-Related AE	2	0		

Statistical analyses

No statistical analyses for this end point

Secondary: The Number of Participants with Adverse Events up to 100 Days After Last Dose of Study Therapy - Part B

End point title	The Number of Participants with Adverse Events up to 100 Days After Last Dose of Study Therapy - Part B

End point description:

An Adverse Event (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. Graded according to NCI CTCAE (Version 4) guidelines where grade 1 = mild, grade 2 = moderate, grade 3 = severe, grade 4 = life threatening, grade 5 = death. Analyzed in all treated participants in Part B.

End point type	Secondary

End point timeframe:

From first dose to 100 days post last dose (up to approximately 50 weeks)

End point values	Arm A: Nivo + Ipi	Arm B: Placebo	Arm C: Nivo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	204	207	408	
Units: Participants				
Any Grade AE	196	182	367	
Grade 3-4 AE	68	32	85	
Grade 5 AE	5	2	2	
Any Grade Drug-Related AE	175	108	300	
Grade 3-4 Drug-Related AE	46	5	46	
Grade 5 Drug-Related AE	0	0	0	

Statistical analyses

No statistical analyses for this end point

Secondary: The Number of Participants Experiencing Laboratory Parameters by Worst CTC (Grade 3-4) that Worsened Relative to Baseline up to 30 days - Part A

End point title	The Number of Participants Experiencing Laboratory Parameters by Worst CTC (Grade 3-4) that Worsened Relative to Baseline up to 30 days - Part A[15]

End point description:

Graded by the National Cancer Institute [NCI] Common Terminology Criteria for Adverse Events [CTCAE, Version 4.0] where grade 3 = severe, and grade 4 = life-threatening. Baseline evaluations are defined as evaluations or events that occur before the date and time of the first dose of study treatment. Analyzed in all treated participants in Part A with a CTC graded laboratory result for the given parameter from both baseline and on-treatment.

Note: n = number of participants analyzed for each arm, LL = Local Lab, AT = Aminotransferase, ABS = Absolute.

End point type	Secondary

End point timeframe:

From first dose to 30 days post last dose (up to approximately 40 weeks)

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: Prespecified to only be collected for Part A.

End point values	Arm A: Nivo + Ipi	Arm B: Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	398	404		
Units: Participants				
HEMOGLOBIN (n = 398, n = 404)	1	1		
PLATELET COUNT (n = 398, n = 404)	1	0		
LEUKOCYTES, LL (n = 398, n = 404)	0	0		
LYMPHOCYTES (ABS), TOTAL (n = 398, n = 404)	6	3		

ABS NEUTROPHIL COUNT (n = 398, n = 404)	2	0		
ALKALINE PHOSPHATASE, LL (n = 397, n = 404)	3	0		
ASPARTATE AT, LL (n = 398, n = 404)	14	3		
ALANINE AT, LL (n = 398, n = 404)	16	5		
BILIRUBIN, TOTAL, LL (n = 395, n = 404)	1	0		
CREATININE, LL (n = 398, n = 404)	1	1		
HYPERNATREMIA (n = 398, n = 404)	0	0		
HYPONATREMIA (n = 398, n = 404)	28	7		
HYPERKALEMIA (n = 398, n = 404)	6	5		
HYPOKALEMIA (n = 398, n = 404)	3	1		
HYPERCALCEMIA (n = 381, n = 389)	3	0		
HYPOCALCEMIA (n = 381, n = 389)	1	0		
HYPERMAGNESEMIA (n = 392, n = 401)	1	1		
HYPOMAGNESEMIA (n = 392, n = 401)	1	0		
HYPERGLYCEMIA (n = 180, n = 179)	6	1		
HYPOGLYCEMIA (n = 391, n = 397)	1	0		

Statistical analyses

No statistical analyses for this end point

Secondary: The Number of Participants Experiencing Laboratory Parameters by Worst CTC (Grade 3-4) that Worsened Relative to Baseline up to 30 days - Part B

End point title	The Number of Participants Experiencing Laboratory Parameters by Worst CTC (Grade 3-4) that Worsened Relative to Baseline up to 30 days - Part B

End point description:

Graded by the National Cancer Institute [NCI] Common Terminology Criteria for Adverse Events [CTCAE, Version 4.0] where grade 3 = severe, and grade 4 = life-threatening. Baseline evaluations are defined as evaluations or events that occur before the date and time of the first dose of study treatment. Analyzed in all treated participants in Part B with a CTC graded laboratory result for the given parameter from both baseline and on-treatment.

Note: n = number of participants analyzed for each arm, LL = Local Lab, AT = Aminotransferase, ABS = Absolute.

End point type	Secondary

End point timeframe:

From first dose to 30 days post last dose (up to approximately 40 weeks)

End point values	Arm A: Nivo + Ipi	Arm B: Placebo	Arm C: Nivo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	201	205	406	
Units: Participants				
HEMOGLOBIN (n = 201, n =205, n = 406)	0	3	0	
PLATELET COUNT (n = 201, n =204, n = 406)	0	1	0	

LEUKOCYTES, LL (n = 201, n =205, n = 406)	0	0	1	
LYMPHOCYTES (ABS), TOTAL (n=201, n=205, n=406)	3	1	4	
ABS NEUTROPHIL COUNT (n = 201, n =205, n = 406)	0	0	1	
ALKALINE PHOSPHATASE, LL (n=201, n=205, n=404)	1	1	0	
ASPARTATE AT, LL (n = 201, n =205, n = 405)	4	4	5	
ALANINE AT, LL (n = 201, n =205, n = 405)	7	3	8	
BILIRUBIN, TOTAL, LL (n = 200, n =205, n = 405)	0	1	0	
CREATININE, LL (n = 201, n =205, n = 406)	3	0	0	
HYPERNATREMIA (n = 201, n =204, n = 405)	0	0	0	
HYPONATREMIA (n = 201, n =204, n = 405)	11	1	9	
HYPERKALEMIA (n = 201, n =205, n = 406)	1	2	2	
HYPOKALEMIA (n = 201, n =205, n = 406)	1	1	0	
HYPERCALCEMIA (n = 197, n =199, n = 396)	1	0	1	
HYPOCALCEMIA (n = 197, n =199, n = 396)	0	1	0	
HYPERMAGNESEMIA (n = 196, n =203, n = 404)	2	2	3	
HYPOMAGNESEMIA (n = 196, n =203, n = 404)	0	1	1	
HYPERGLYCEMIA (n = 99, n =109, n = 208)	3	1	3	
HYPOGLYCEMIA (n = 196, n =195, n = 401)	0	0	1	

Statistical analyses

No statistical analyses for this end point

Secondary: The Number of Participants Experiencing Laboratory Parameters by Worst CTC (Grade 3-4) that Worsened Relative to Baseline up to 100 days - Part A

End point title	The Number of Participants Experiencing Laboratory Parameters by Worst CTC (Grade 3-4) that Worsened Relative to Baseline up to 100 days - Part A[16]

End point description:

Graded by the National Cancer Institute [NCI] Common Terminology Criteria for Adverse Events [CTCAE, Version 4.0] where grade 3 = severe, and grade 4 = life-threatening. Baseline evaluations are defined as evaluations or events that occur before the date and time of the first dose of study treatment. Analyzed in all treated participants in Part A with a CTC graded laboratory result for the given parameter from both baseline and on-treatment.

Note: n = number of participants analyzed for each arm, LL = Local Lab, AT = Aminotransferase, ABS = Absolute.

End point type	Secondary

End point timeframe:

From first dose to 100 days post last dose (up to approximately 50 weeks)

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: Prespecified to only be collected for Part A.

End point values	Arm A: Nivo + Ipi	Arm B: Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	401	406		
Units: Participants				
HEMOGLOBIN (n = 401, n = 406)	1	1		
PLATELET COUNT (n = 401, n = 406)	1	0		
LEUKOCYTES, LL (n = 401, n = 406)	0	0		
LYMPHOCYTES (ABS), TOTAL (n = 401, n = 406)	11	3		
ABS NEUTROPHIL COUNT (n = 401, n = 406)	2	0		
ALKALINE PHOSPHATASE, LL (n = 400, n = 406)	5	0		
ASPARTATE AT, LL (n = 401, n = 406)	17	3		
ALANINE AT, LL (n = 401, n = 406)	20	6		
BILIRUBIN, TOTAL, LL (n = 399, n = 406)	3	0		
CREATININE, LL (n = 401, n = 406)	4	1		
HYPERNATREMIA (n = 401, n = 406)	0	0		
HYPONATREMIA (n = 401, n = 406)	30	7		
HYPERKALEMIA (n = 401, n = 406)	6	5		
HYPOKALEMIA (n = 401, n = 406)	5	1		
HYPERCALCEMIA (n = 384, n = 391)	3	0		
HYPOCALCEMIA (n = 384, n = 391)	1	0		
HYPERMAGNESEMIA (n = 395, n = 403)	1	1		
HYPOMAGNESEMIA (n = 395, n = 403)	1	0		
HYPERGLYCEMIA (n = 183, n = 179)	7	1		
HYPOGLYCEMIA (n = 394, n = 398)	1	0		

Statistical analyses

No statistical analyses for this end point

Secondary: The Number of Participants Experiencing Laboratory Parameters by Worst CTC (Grade 3-4) that Worsened Relative to Baseline up to 100 days - Part B

End point title	The Number of Participants Experiencing Laboratory Parameters by Worst CTC (Grade 3-4) that Worsened Relative to Baseline up to 100 days - Part B

End point description:

Graded by the National Cancer Institute [NCI] Common Terminology Criteria for Adverse Events [CTCAE, Version 4.0] where grade 3 = severe, and grade 4 = life-threatening. Baseline evaluations are defined as evaluations or events that occur before the date and time of the first dose of study treatment. Analyzed in all treated participants in Part A with a CTC graded laboratory result for the given parameter from both baseline and on-treatment.

Note: n = number of participants analyzed for each arm, LL = Local Lab, AT = Aminotransferase, ABS = Absolute.

End point type	Secondary

End point timeframe:

From first dose to 100 days post last dose (up to approximately 50 weeks)

End point values	Arm A: Nivo + Ipi	Arm B: Placebo	Arm C: Nivo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	203	205	407	
Units: Participants				
HEMOGLOBIN (n = 203, n =205, n = 407)	2	3	1	
PLATELET COUNT (n = 203, n =204, n = 407)	0	1	0	
LEUKOCYTES, LL (n = 203, n =205, n = 407)	0	0	2	
LYMPHOCYTES (ABS), TOTAL (n=203, n=205, n= 407)	3	2	7	
ABS NEUTROPHIL COUNT (n = 203, n =205, n = 407)	0	0	2	
ALKALINE PHOSPHATASE, LL (n=203, n=205, n=405)	2	1	0	
ASPARTATE AT, LL (n = 203, n =205, n = 406)	6	4	6	
ALANINE AT, LL (n = 203, n =205, n = 406)	9	3	10	
BILIRUBIN, TOTAL, LL (n = 202, n =205, n = 406)	0	1	0	
CREATININE, LL (n = 203, n =205, n = 407)	4	0	3	
HYPERNATREMIA (n = 203, n =204, n = 406)	0	0	0	
HYPONATREMIA (n = 203, n =204, n = 407)	12	1	13	
HYPERKALEMIA (n = 203, n =205, n = 407)	1	2	4	
HYPOKALEMIA (n = 203, n =205, n = 407)	1	2	2	
HYPERCALCEMIA (n = 199, n =199, n = 397)	1	0	1	
HYPOCALCEMIA (n = 199, n =199, n = 397)	0	1	1	
HYPERMAGNESEMIA (n = 198, n = 203, n = 405)	3	2	3	
HYPOMAGNESEMIA (n = 198, n = 203, n = 405)	0	1	1	
HYPERGLYCEMIA (n = 99, n = 109, n = 211)	3	1	4	
HYPOGLYCEMIA (n = 99, n = 195, n = 402)	0	0	1	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All-cause mortality was assessed from a participants first dose to their study completion (up to an average of 72 months) SAEs and Other AEs were assessed from first dose to 100 days following last dose (up to approximately 50 weeks).

Adverse event reporting additional description:

The number at Risk for All-Cause Mortality and Serious Adverse Events and Other (Not Including Serious) Adverse Events represents all participants that received at least 1 dose of study medication.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	26.1

Reporting groups

Reporting group title	Arm A: Nivo + Ipi

Reporting group description:

Nivolumab 240 mg every 2 weeks and ipilimumab 1 mg/kg every 6 weeks (or every third nivolumab dose if dosing is delayed).

Reporting group title	Arm C: Nivo

Reporting group description:

Nivolumab 240 mg every 2 weeks and ipilimumab Placebo every 6 weeks (or every third nivolumab dose if dosing is delayed).

Reporting group title	Arm B: Placebo

Reporting group description:

Placebo infusions at the same frequency of nivolumab and ipilimumab infusions.

Serious adverse events	Arm A: Nivo + Ipi	Arm C: Nivo	Arm B: Placebo
Total subjects affected by serious adverse events			
subjects affected / exposed	196 / 608 (32.24%)	56 / 408 (13.73%)	49 / 614 (7.98%)
number of deaths (all causes)	65	22	55
number of deaths resulting from adverse events	12	5	4
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Cervix carcinoma stage 0			
subjects affected / exposed	0 / 608 (0.00%)	0 / 408 (0.00%)	1 / 614 (0.16%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Basal cell carcinoma			
subjects affected / exposed	1 / 608 (0.16%)	0 / 408 (0.00%)	2 / 614 (0.33%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colon cancer			

subjects affected / exposed	0 / 608 (0.00%)	0 / 408 (0.00%)	1 / 614 (0.16%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Malignant melanoma			
subjects affected / exposed	0 / 608 (0.00%)	0 / 408 (0.00%)	1 / 614 (0.16%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Malignant neoplasm progression			
subjects affected / exposed	0 / 608 (0.00%)	0 / 408 (0.00%)	2 / 614 (0.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Uterine leiomyoma			
subjects affected / exposed	0 / 608 (0.00%)	1 / 408 (0.25%)	0 / 614 (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
Transitional cell carcinoma			
subjects affected / exposed	1 / 608 (0.16%)	0 / 408 (0.00%)	0 / 614 (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
Thyroid cancer			
subjects affected / exposed	1 / 608 (0.16%)	0 / 408 (0.00%)	0 / 614 (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
Renal cell carcinoma recurrent			
subjects affected / exposed	1 / 608 (0.16%)	0 / 408 (0.00%)	0 / 614 (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
Recurrent cancer			
subjects affected / exposed	2 / 608 (0.33%)	2 / 408 (0.49%)	3 / 614 (0.49%)
occurrences causally related to treatment / all	0 / 2	0 / 2	0 / 3
deaths causally related to treatment / all	0 / 1	0 / 1	0 / 1
Prostate cancer			

subjects affected / exposed	0 / 608 (0.00%)	0 / 408 (0.00%)	2 / 614 (0.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metastatic renal cell carcinoma			
subjects affected / exposed	0 / 608 (0.00%)	0 / 408 (0.00%)	1 / 614 (0.16%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Hypotension			
subjects affected / exposed	1 / 608 (0.16%)	0 / 408 (0.00%)	1 / 614 (0.16%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thrombophlebitis			
subjects affected / exposed	1 / 608 (0.16%)	0 / 408 (0.00%)	0 / 614 (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
Haematoma			
subjects affected / exposed	1 / 608 (0.16%)	0 / 408 (0.00%)	0 / 614 (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
Embolism			
subjects affected / exposed	0 / 608 (0.00%)	0 / 408 (0.00%)	1 / 614 (0.16%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Deep vein thrombosis			
subjects affected / exposed	1 / 608 (0.16%)	0 / 408 (0.00%)	0 / 614 (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
Aortic dissection			
subjects affected / exposed	1 / 608 (0.16%)	0 / 408 (0.00%)	0 / 614 (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
Hypertensive crisis			

subjects affected / exposed	0 / 608 (0.00%)	1 / 408 (0.25%)	0 / 614 (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
Surgical and medical procedures			
Assisted suicide			
subjects affected / exposed	1 / 608 (0.16%)	0 / 408 (0.00%)	0 / 614 (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
General disorders and administration site conditions			
Non-cardiac chest pain			
subjects affected / exposed	1 / 608 (0.16%)	0 / 408 (0.00%)	0 / 614 (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
Death			
subjects affected / exposed	1 / 608 (0.16%)	0 / 408 (0.00%)	0 / 614 (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
Disease recurrence			
subjects affected / exposed	0 / 608 (0.00%)	0 / 408 (0.00%)	1 / 614 (0.16%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Fatigue			
subjects affected / exposed	0 / 608 (0.00%)	1 / 408 (0.25%)	0 / 614 (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
General physical health deterioration			
subjects affected / exposed	1 / 608 (0.16%)	0 / 408 (0.00%)	0 / 614 (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
Influenza like illness			
subjects affected / exposed	2 / 608 (0.33%)	0 / 408 (0.00%)	0 / 614 (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

Malaise			
subjects affected / exposed	1 / 608 (0.16%)	1 / 408 (0.25%)	0 / 614 (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
Mucosal inflammation			
subjects affected / exposed	1 / 608 (0.16%)	0 / 408 (0.00%)	0 / 614 (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
Multiple organ dysfunction syndrome			
subjects affected / exposed	0 / 608 (0.00%)	1 / 408 (0.25%)	0 / 614 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Pyrexia			
subjects affected / exposed	4 / 608 (0.66%)	1 / 408 (0.25%)	0 / 614 (0.00%)
occurrences causally related to treatment / all	3 / 5	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sudden death			
subjects affected / exposed	1 / 608 (0.16%)	0 / 408 (0.00%)	0 / 614 (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
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	0 / 608 (0.00%)	1 / 408 (0.25%)	0 / 614 (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
Sarcoidosis			
subjects affected / exposed	2 / 608 (0.33%)	0 / 408 (0.00%)	0 / 614 (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
Reproductive system and breast disorders			
Benign prostatic hyperplasia			
subjects affected / exposed	0 / 608 (0.00%)	0 / 408 (0.00%)	1 / 614 (0.16%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Prostatitis			
subjects affected / exposed	1 / 608 (0.16%)	1 / 408 (0.25%)	0 / 614 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Uterine polyp			
subjects affected / exposed	0 / 608 (0.00%)	1 / 408 (0.25%)	0 / 614 (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, thoracic and mediastinal disorders			
Pulmonary embolism			
subjects affected / exposed	3 / 608 (0.49%)	1 / 408 (0.25%)	2 / 614 (0.33%)
occurrences causally related to treatment / all	1 / 3	0 / 1	0 / 3
deaths causally related to treatment / all	1 / 1	0 / 1	0 / 0
Pneumonitis			
subjects affected / exposed	7 / 608 (1.15%)	4 / 408 (0.98%)	1 / 614 (0.16%)
occurrences causally related to treatment / all	6 / 7	4 / 4	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune-mediated lung disease			
subjects affected / exposed	1 / 608 (0.16%)	0 / 408 (0.00%)	0 / 614 (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
Dyspnoea			
subjects affected / exposed	1 / 608 (0.16%)	1 / 408 (0.25%)	1 / 614 (0.16%)
occurrences causally related to treatment / all	1 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchospasm			
subjects affected / exposed	1 / 608 (0.16%)	0 / 408 (0.00%)	0 / 614 (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
Bronchiectasis			
subjects affected / exposed	1 / 608 (0.16%)	0 / 408 (0.00%)	0 / 614 (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

Psychiatric disorders			
Depression			
subjects affected / exposed	0 / 608 (0.00%)	1 / 408 (0.25%)	0 / 614 (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
Major depression			
subjects affected / exposed	0 / 608 (0.00%)	1 / 408 (0.25%)	0 / 614 (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
Panic attack			
subjects affected / exposed	1 / 608 (0.16%)	0 / 408 (0.00%)	0 / 614 (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
Suicidal ideation			
subjects affected / exposed	0 / 608 (0.00%)	1 / 408 (0.25%)	1 / 614 (0.16%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Suicide attempt			
subjects affected / exposed	0 / 608 (0.00%)	0 / 408 (0.00%)	1 / 614 (0.16%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Product issues			
Device breakage			
subjects affected / exposed	0 / 608 (0.00%)	1 / 408 (0.25%)	0 / 614 (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
Hepatobiliary disorders			
Autoimmune hepatitis			
subjects affected / exposed	2 / 608 (0.33%)	0 / 408 (0.00%)	0 / 614 (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
Cholecystitis			

subjects affected / exposed	1 / 608 (0.16%)	0 / 408 (0.00%)	0 / 614 (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
Cholecystitis acute			
subjects affected / exposed	0 / 608 (0.00%)	1 / 408 (0.25%)	0 / 614 (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
Drug-induced liver injury			
subjects affected / exposed	1 / 608 (0.16%)	1 / 408 (0.25%)	1 / 614 (0.16%)
occurrences causally related to treatment / all	1 / 1	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Subacute hepatic failure			
subjects affected / exposed	1 / 608 (0.16%)	0 / 408 (0.00%)	0 / 614 (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
Hepatic failure			
subjects affected / exposed	1 / 608 (0.16%)	1 / 408 (0.25%)	0 / 614 (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
Hepatic function abnormal			
subjects affected / exposed	2 / 608 (0.33%)	0 / 408 (0.00%)	0 / 614 (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
Hepatitis			
subjects affected / exposed	0 / 608 (0.00%)	0 / 408 (0.00%)	1 / 614 (0.16%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hydrocholecystis			
subjects affected / exposed	1 / 608 (0.16%)	0 / 408 (0.00%)	0 / 614 (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
Hypertransaminasaemia			

subjects affected / exposed	2 / 608 (0.33%)	0 / 408 (0.00%)	0 / 614 (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
Immune-mediated hepatitis			
subjects affected / exposed	2 / 608 (0.33%)	1 / 408 (0.25%)	0 / 614 (0.00%)
occurrences causally related to treatment / all	2 / 2	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatic cytolysis			
subjects affected / exposed	0 / 608 (0.00%)	1 / 408 (0.25%)	0 / 614 (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
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	3 / 608 (0.49%)	0 / 408 (0.00%)	0 / 614 (0.00%)
occurrences causally related to treatment / all	3 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General physical condition abnormal			
subjects affected / exposed	1 / 608 (0.16%)	0 / 408 (0.00%)	0 / 614 (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
Liver function test increased			
subjects affected / exposed	1 / 608 (0.16%)	0 / 408 (0.00%)	0 / 614 (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
Injury, poisoning and procedural complications			
Arterial injury			
subjects affected / exposed	0 / 608 (0.00%)	0 / 408 (0.00%)	1 / 614 (0.16%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Femur fracture			
subjects affected / exposed	0 / 608 (0.00%)	1 / 408 (0.25%)	1 / 614 (0.16%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Heat stroke			
subjects affected / exposed	1 / 608 (0.16%)	0 / 408 (0.00%)	0 / 614 (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
Hip fracture			
subjects affected / exposed	1 / 608 (0.16%)	0 / 408 (0.00%)	0 / 614 (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
Infusion related reaction			
subjects affected / exposed	2 / 608 (0.33%)	0 / 408 (0.00%)	0 / 614 (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
Open fracture			
subjects affected / exposed	0 / 608 (0.00%)	1 / 408 (0.25%)	0 / 614 (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
Post procedural complication			
subjects affected / exposed	0 / 608 (0.00%)	0 / 408 (0.00%)	1 / 614 (0.16%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Postoperative thoracic procedure complication			
subjects affected / exposed	0 / 608 (0.00%)	0 / 408 (0.00%)	1 / 614 (0.16%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Splenic injury			
subjects affected / exposed	1 / 608 (0.16%)	0 / 408 (0.00%)	0 / 614 (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
Traumatic fracture			
subjects affected / exposed	1 / 608 (0.16%)	0 / 408 (0.00%)	0 / 614 (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
Congenital, familial and genetic disorders			

Paraduodenal hernia			
subjects affected / exposed	1 / 608 (0.16%)	0 / 408 (0.00%)	0 / 614 (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			
Acute coronary syndrome			
subjects affected / exposed	1 / 608 (0.16%)	0 / 408 (0.00%)	1 / 614 (0.16%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute myocardial infarction			
subjects affected / exposed	2 / 608 (0.33%)	0 / 408 (0.00%)	0 / 614 (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
Cardiac arrest			
subjects affected / exposed	1 / 608 (0.16%)	0 / 408 (0.00%)	0 / 614 (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
Atrial fibrillation			
subjects affected / exposed	1 / 608 (0.16%)	2 / 408 (0.49%)	0 / 614 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial flutter			
subjects affected / exposed	1 / 608 (0.16%)	0 / 408 (0.00%)	0 / 614 (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
Angina pectoris			
subjects affected / exposed	1 / 608 (0.16%)	1 / 408 (0.25%)	0 / 614 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac failure			
subjects affected / exposed	1 / 608 (0.16%)	1 / 408 (0.25%)	0 / 614 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myocardial infarction			

subjects affected / exposed	1 / 608 (0.16%)	0 / 408 (0.00%)	0 / 614 (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
Myocardial injury			
subjects affected / exposed	1 / 608 (0.16%)	0 / 408 (0.00%)	0 / 614 (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
Myocarditis			
subjects affected / exposed	3 / 608 (0.49%)	1 / 408 (0.25%)	0 / 614 (0.00%)
occurrences causally related to treatment / all	3 / 3	1 / 1	0 / 0
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
Palpitations			
subjects affected / exposed	0 / 608 (0.00%)	0 / 408 (0.00%)	1 / 614 (0.16%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sinus node dysfunction			
subjects affected / exposed	0 / 608 (0.00%)	0 / 408 (0.00%)	1 / 614 (0.16%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Stress cardiomyopathy			
subjects affected / exposed	0 / 608 (0.00%)	0 / 408 (0.00%)	1 / 614 (0.16%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac tamponade			
subjects affected / exposed	1 / 608 (0.16%)	0 / 408 (0.00%)	0 / 614 (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			
Encephalitis autoimmune			
subjects affected / exposed	1 / 608 (0.16%)	0 / 408 (0.00%)	0 / 614 (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
Dizziness			

subjects affected / exposed	0 / 608 (0.00%)	0 / 408 (0.00%)	1 / 614 (0.16%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diabetic neuropathy			
subjects affected / exposed	1 / 608 (0.16%)	0 / 408 (0.00%)	0 / 614 (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
Cerebrovascular accident			
subjects affected / exposed	2 / 608 (0.33%)	0 / 408 (0.00%)	1 / 614 (0.16%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Cerebral infarction			
subjects affected / exposed	1 / 608 (0.16%)	0 / 408 (0.00%)	1 / 614 (0.16%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Carpal tunnel syndrome			
subjects affected / exposed	1 / 608 (0.16%)	0 / 408 (0.00%)	0 / 614 (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
Neurological decompensation			
subjects affected / exposed	0 / 608 (0.00%)	0 / 408 (0.00%)	1 / 614 (0.16%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ischaemic stroke			
subjects affected / exposed	0 / 608 (0.00%)	0 / 408 (0.00%)	1 / 614 (0.16%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ischaemic cerebral infarction			
subjects affected / exposed	1 / 608 (0.16%)	0 / 408 (0.00%)	0 / 614 (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
Immune-mediated encephalitis			

subjects affected / exposed	2 / 608 (0.33%)	1 / 408 (0.25%)	0 / 614 (0.00%)
occurrences causally related to treatment / all	2 / 2	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypoaesthesia			
subjects affected / exposed	1 / 608 (0.16%)	0 / 408 (0.00%)	0 / 614 (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
Hemiparesis			
subjects affected / exposed	1 / 608 (0.16%)	0 / 408 (0.00%)	0 / 614 (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
Peripheral sensory neuropathy			
subjects affected / exposed	2 / 608 (0.33%)	0 / 408 (0.00%)	0 / 614 (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
Haemorrhage intracranial			
subjects affected / exposed	1 / 608 (0.16%)	0 / 408 (0.00%)	0 / 614 (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
Guillain-Barre syndrome			
subjects affected / exposed	1 / 608 (0.16%)	0 / 408 (0.00%)	0 / 614 (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
Facial paralysis			
subjects affected / exposed	0 / 608 (0.00%)	1 / 408 (0.25%)	0 / 614 (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
Epilepsy			
subjects affected / exposed	0 / 608 (0.00%)	0 / 408 (0.00%)	1 / 614 (0.16%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osmotic demyelination syndrome			

subjects affected / exposed	0 / 608 (0.00%)	1 / 408 (0.25%)	0 / 614 (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
Headache			
subjects affected / exposed	3 / 608 (0.49%)	0 / 408 (0.00%)	0 / 614 (0.00%)
occurrences causally related to treatment / all	3 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tension headache			
subjects affected / exposed	1 / 608 (0.16%)	0 / 408 (0.00%)	0 / 614 (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
Syncope			
subjects affected / exposed	1 / 608 (0.16%)	1 / 408 (0.25%)	0 / 614 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal cord compression			
subjects affected / exposed	0 / 608 (0.00%)	0 / 408 (0.00%)	1 / 614 (0.16%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sciatica			
subjects affected / exposed	0 / 608 (0.00%)	0 / 408 (0.00%)	1 / 614 (0.16%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Polyneuropathy			
subjects affected / exposed	1 / 608 (0.16%)	0 / 408 (0.00%)	0 / 614 (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
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 608 (0.16%)	1 / 408 (0.25%)	0 / 614 (0.00%)
occurrences causally related to treatment / all	0 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Ear and labyrinth disorders			

Vertigo			
subjects affected / exposed	0 / 608 (0.00%)	0 / 408 (0.00%)	1 / 614 (0.16%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
Uveitis			
subjects affected / exposed	0 / 608 (0.00%)	1 / 408 (0.25%)	0 / 614 (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
Cataract			
subjects affected / exposed	1 / 608 (0.16%)	0 / 408 (0.00%)	0 / 614 (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
Diplopia			
subjects affected / exposed	0 / 608 (0.00%)	1 / 408 (0.25%)	0 / 614 (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
Orbital myositis			
subjects affected / exposed	0 / 608 (0.00%)	1 / 408 (0.25%)	0 / 614 (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
Retinal detachment			
subjects affected / exposed	0 / 608 (0.00%)	1 / 408 (0.25%)	0 / 614 (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
Retinal vein occlusion			
subjects affected / exposed	0 / 608 (0.00%)	0 / 408 (0.00%)	1 / 614 (0.16%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Serous retinal detachment			
subjects affected / exposed	0 / 608 (0.00%)	1 / 408 (0.25%)	0 / 614 (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
Gastrointestinal disorders			

Abdominal hernia			
subjects affected / exposed	0 / 608 (0.00%)	1 / 408 (0.25%)	0 / 614 (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
Abdominal pain			
subjects affected / exposed	4 / 608 (0.66%)	1 / 408 (0.25%)	1 / 614 (0.16%)
occurrences causally related to treatment / all	1 / 5	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal pain upper			
subjects affected / exposed	1 / 608 (0.16%)	0 / 408 (0.00%)	1 / 614 (0.16%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Autoimmune colitis			
subjects affected / exposed	1 / 608 (0.16%)	0 / 408 (0.00%)	0 / 614 (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
Colitis			
subjects affected / exposed	12 / 608 (1.97%)	1 / 408 (0.25%)	0 / 614 (0.00%)
occurrences causally related to treatment / all	12 / 12	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colitis ischaemic			
subjects affected / exposed	1 / 608 (0.16%)	0 / 408 (0.00%)	0 / 614 (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
Mesenteric panniculitis			
subjects affected / exposed	1 / 608 (0.16%)	0 / 408 (0.00%)	0 / 614 (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
Duodenal ulcer			
subjects affected / exposed	0 / 608 (0.00%)	1 / 408 (0.25%)	0 / 614 (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
Gastric ulcer			

subjects affected / exposed	0 / 608 (0.00%)	0 / 408 (0.00%)	2 / 614 (0.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastritis			
subjects affected / exposed	2 / 608 (0.33%)	1 / 408 (0.25%)	0 / 614 (0.00%)
occurrences causally related to treatment / all	2 / 2	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haematemesis			
subjects affected / exposed	2 / 608 (0.33%)	0 / 408 (0.00%)	0 / 614 (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
Immune-mediated enterocolitis			
subjects affected / exposed	6 / 608 (0.99%)	0 / 408 (0.00%)	0 / 614 (0.00%)
occurrences causally related to treatment / all	6 / 6	0 / 0	0 / 0
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
Intestinal perforation			
subjects affected / exposed	0 / 608 (0.00%)	0 / 408 (0.00%)	1 / 614 (0.16%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Diarrhoea			
subjects affected / exposed	16 / 608 (2.63%)	0 / 408 (0.00%)	1 / 614 (0.16%)
occurrences causally related to treatment / all	15 / 16	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nausea			
subjects affected / exposed	2 / 608 (0.33%)	0 / 408 (0.00%)	0 / 614 (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
Pancreatitis acute			
subjects affected / exposed	2 / 608 (0.33%)	0 / 408 (0.00%)	0 / 614 (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
Small intestinal obstruction			

subjects affected / exposed	2 / 608 (0.33%)	0 / 408 (0.00%)	0 / 614 (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
Upper gastrointestinal haemorrhage			
subjects affected / exposed	0 / 608 (0.00%)	0 / 408 (0.00%)	1 / 614 (0.16%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			
subjects affected / exposed	5 / 608 (0.82%)	0 / 408 (0.00%)	0 / 614 (0.00%)
occurrences causally related to treatment / all	5 / 5	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatitis			
subjects affected / exposed	3 / 608 (0.49%)	2 / 408 (0.49%)	0 / 614 (0.00%)
occurrences causally related to treatment / all	3 / 3	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Angioedema			
subjects affected / exposed	1 / 608 (0.16%)	0 / 408 (0.00%)	0 / 614 (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
Dermatitis			
subjects affected / exposed	0 / 608 (0.00%)	1 / 408 (0.25%)	0 / 614 (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
Drug eruption			
subjects affected / exposed	1 / 608 (0.16%)	0 / 408 (0.00%)	0 / 614 (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
Rash maculo-papular			
subjects affected / exposed	1 / 608 (0.16%)	0 / 408 (0.00%)	0 / 614 (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
Stevens-Johnson syndrome			

subjects affected / exposed	0 / 608 (0.00%)	1 / 408 (0.25%)	0 / 614 (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
Renal and urinary disorders			
Bladder hypertrophy			
subjects affected / exposed	0 / 608 (0.00%)	1 / 408 (0.25%)	0 / 614 (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
Acute kidney injury			
subjects affected / exposed	13 / 608 (2.14%)	2 / 408 (0.49%)	1 / 614 (0.16%)
occurrences causally related to treatment / all	8 / 13	1 / 2	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract obstruction			
subjects affected / exposed	2 / 608 (0.33%)	0 / 408 (0.00%)	0 / 614 (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
Tubulointerstitial nephritis			
subjects affected / exposed	2 / 608 (0.33%)	0 / 408 (0.00%)	0 / 614 (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
Nephropathy			
subjects affected / exposed	1 / 608 (0.16%)	0 / 408 (0.00%)	0 / 614 (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
Nephritis			
subjects affected / exposed	1 / 608 (0.16%)	1 / 408 (0.25%)	0 / 614 (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
Immune-mediated nephritis			
subjects affected / exposed	1 / 608 (0.16%)	0 / 408 (0.00%)	0 / 614 (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
Chronic kidney disease			

subjects affected / exposed	0 / 608 (0.00%)	1 / 408 (0.25%)	0 / 614 (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
Endocrine disorders			
Hypercalcaemia of malignancy			
subjects affected / exposed	0 / 608 (0.00%)	0 / 408 (0.00%)	1 / 614 (0.16%)
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	21 / 608 (3.45%)	3 / 408 (0.74%)	0 / 614 (0.00%)
occurrences causally related to treatment / all	24 / 24	3 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Adrenocortical insufficiency acute			
subjects affected / exposed	1 / 608 (0.16%)	0 / 408 (0.00%)	0 / 614 (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
Adrenocorticotropic hormone deficiency			
subjects affected / exposed	1 / 608 (0.16%)	0 / 408 (0.00%)	0 / 614 (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
Autoimmune thyroiditis			
subjects affected / exposed	1 / 608 (0.16%)	0 / 408 (0.00%)	0 / 614 (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
Hyperthyroidism			
subjects affected / exposed	2 / 608 (0.33%)	0 / 408 (0.00%)	0 / 614 (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
Hypophysitis			
subjects affected / exposed	12 / 608 (1.97%)	0 / 408 (0.00%)	0 / 614 (0.00%)
occurrences causally related to treatment / all	11 / 12	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypopituitarism			

subjects affected / exposed	4 / 608 (0.66%)	0 / 408 (0.00%)	0 / 614 (0.00%)
occurrences causally related to treatment / all	4 / 4	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypothyroidism			
subjects affected / exposed	2 / 608 (0.33%)	0 / 408 (0.00%)	0 / 614 (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
Lymphocytic hypophysitis			
subjects affected / exposed	1 / 608 (0.16%)	0 / 408 (0.00%)	0 / 614 (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	2 / 608 (0.33%)	0 / 408 (0.00%)	0 / 614 (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
Thyroiditis			
subjects affected / exposed	2 / 608 (0.33%)	0 / 408 (0.00%)	0 / 614 (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
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 608 (0.16%)	0 / 408 (0.00%)	0 / 614 (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
Rheumatoid arthritis			
subjects affected / exposed	1 / 608 (0.16%)	0 / 408 (0.00%)	0 / 614 (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
Rhabdomyolysis			
subjects affected / exposed	2 / 608 (0.33%)	1 / 408 (0.25%)	0 / 614 (0.00%)
occurrences causally related to treatment / all	2 / 2	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Polymyalgia rheumatica			

subjects affected / exposed	1 / 608 (0.16%)	0 / 408 (0.00%)	0 / 614 (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
Pain in extremity			
subjects affected / exposed	1 / 608 (0.16%)	0 / 408 (0.00%)	0 / 614 (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
Osteoarthritis			
subjects affected / exposed	1 / 608 (0.16%)	0 / 408 (0.00%)	0 / 614 (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
Myositis			
subjects affected / exposed	2 / 608 (0.33%)	0 / 408 (0.00%)	0 / 614 (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
Myalgia			
subjects affected / exposed	1 / 608 (0.16%)	0 / 408 (0.00%)	0 / 614 (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
Intervertebral disc protrusion			
subjects affected / exposed	0 / 608 (0.00%)	1 / 408 (0.25%)	0 / 614 (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
Immune-mediated myositis			
subjects affected / exposed	1 / 608 (0.16%)	0 / 408 (0.00%)	0 / 614 (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 / 608 (0.16%)	0 / 408 (0.00%)	0 / 614 (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
Back pain			

subjects affected / exposed	1 / 608 (0.16%)	0 / 408 (0.00%)	2 / 614 (0.33%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Abdominal sepsis			
subjects affected / exposed	0 / 608 (0.00%)	0 / 408 (0.00%)	1 / 614 (0.16%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Appendicitis			
subjects affected / exposed	0 / 608 (0.00%)	1 / 408 (0.25%)	1 / 614 (0.16%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
COVID-19			
subjects affected / exposed	1 / 608 (0.16%)	1 / 408 (0.25%)	1 / 614 (0.16%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
COVID-19 pneumonia			
subjects affected / exposed	0 / 608 (0.00%)	1 / 408 (0.25%)	0 / 614 (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
Hepatitis E			
subjects affected / exposed	0 / 608 (0.00%)	0 / 408 (0.00%)	1 / 614 (0.16%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cytomegalovirus colitis			
subjects affected / exposed	1 / 608 (0.16%)	0 / 408 (0.00%)	0 / 614 (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
Diverticulitis			
subjects affected / exposed	1 / 608 (0.16%)	0 / 408 (0.00%)	0 / 614 (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
Encephalitis			

subjects affected / exposed	1 / 608 (0.16%)	0 / 408 (0.00%)	0 / 614 (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
Enterocolitis infectious			
subjects affected / exposed	1 / 608 (0.16%)	0 / 408 (0.00%)	0 / 614 (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
Febrile infection			
subjects affected / exposed	1 / 608 (0.16%)	0 / 408 (0.00%)	0 / 614 (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
Gastrointestinal fungal infection			
subjects affected / exposed	1 / 608 (0.16%)	0 / 408 (0.00%)	0 / 614 (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
Clostridium difficile infection			
subjects affected / exposed	0 / 608 (0.00%)	1 / 408 (0.25%)	0 / 614 (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
Herpes zoster meningitis			
subjects affected / exposed	1 / 608 (0.16%)	0 / 408 (0.00%)	0 / 614 (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	4 / 608 (0.66%)	1 / 408 (0.25%)	0 / 614 (0.00%)
occurrences causally related to treatment / all	0 / 6	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Meningitis			
subjects affected / exposed	1 / 608 (0.16%)	0 / 408 (0.00%)	0 / 614 (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
Meningitis aseptic			

subjects affected / exposed	2 / 608 (0.33%)	0 / 408 (0.00%)	0 / 614 (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
Peritonitis			
subjects affected / exposed	0 / 608 (0.00%)	0 / 408 (0.00%)	1 / 614 (0.16%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	6 / 608 (0.99%)	1 / 408 (0.25%)	1 / 614 (0.16%)
occurrences causally related to treatment / all	0 / 6	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Postoperative wound infection			
subjects affected / exposed	1 / 608 (0.16%)	0 / 408 (0.00%)	1 / 614 (0.16%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyelonephritis			
subjects affected / exposed	0 / 608 (0.00%)	1 / 408 (0.25%)	0 / 614 (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
Sepsis			
subjects affected / exposed	1 / 608 (0.16%)	1 / 408 (0.25%)	2 / 614 (0.33%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Septic shock			
subjects affected / exposed	1 / 608 (0.16%)	1 / 408 (0.25%)	0 / 614 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Sinusitis			
subjects affected / exposed	0 / 608 (0.00%)	0 / 408 (0.00%)	1 / 614 (0.16%)
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 / 608 (0.16%)	0 / 408 (0.00%)	0 / 614 (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
Spontaneous bacterial peritonitis			
subjects affected / exposed	1 / 608 (0.16%)	0 / 408 (0.00%)	0 / 614 (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
Upper respiratory tract infection			
subjects affected / exposed	1 / 608 (0.16%)	0 / 408 (0.00%)	0 / 614 (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
Klebsiella sepsis			
subjects affected / exposed	1 / 608 (0.16%)	0 / 408 (0.00%)	0 / 614 (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
Vestibular neuronitis			
subjects affected / exposed	1 / 608 (0.16%)	0 / 408 (0.00%)	0 / 614 (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
Metabolism and nutrition disorders			
Type 2 diabetes mellitus			
subjects affected / exposed	0 / 608 (0.00%)	1 / 408 (0.25%)	0 / 614 (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
Type 1 diabetes mellitus			
subjects affected / exposed	4 / 608 (0.66%)	1 / 408 (0.25%)	0 / 614 (0.00%)
occurrences causally related to treatment / all	4 / 4	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyponatraemia			
subjects affected / exposed	6 / 608 (0.99%)	2 / 408 (0.49%)	0 / 614 (0.00%)
occurrences causally related to treatment / all	4 / 6	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypoglycaemia			

subjects affected / exposed	1 / 608 (0.16%)	0 / 408 (0.00%)	0 / 614 (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
Hyperkalaemia			
subjects affected / exposed	1 / 608 (0.16%)	1 / 408 (0.25%)	0 / 614 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperglycaemic hyperosmolar nonketotic syndrome			
subjects affected / exposed	1 / 608 (0.16%)	0 / 408 (0.00%)	0 / 614 (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
Hypercalcaemia			
subjects affected / exposed	2 / 608 (0.33%)	0 / 408 (0.00%)	0 / 614 (0.00%)
occurrences causally related to treatment / all	1 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gout			
subjects affected / exposed	1 / 608 (0.16%)	1 / 408 (0.25%)	0 / 614 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diabetic ketoacidosis			
subjects affected / exposed	3 / 608 (0.49%)	3 / 408 (0.74%)	0 / 614 (0.00%)
occurrences causally related to treatment / all	2 / 3	2 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diabetes mellitus inadequate control			
subjects affected / exposed	1 / 608 (0.16%)	0 / 408 (0.00%)	0 / 614 (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
Diabetes mellitus			
subjects affected / exposed	3 / 608 (0.49%)	0 / 408 (0.00%)	0 / 614 (0.00%)
occurrences causally related to treatment / all	3 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dehydration			

subjects affected / exposed	2 / 608 (0.33%)	0 / 408 (0.00%)	0 / 614 (0.00%)
occurrences causally related to treatment / all	3 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperglycaemia			
subjects affected / exposed	5 / 608 (0.82%)	3 / 408 (0.74%)	0 / 614 (0.00%)
occurrences causally related to treatment / all	2 / 5	3 / 3	0 / 0
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: Nivo + Ipi	Arm C: Nivo	Arm B: Placebo
Total subjects affected by non-serious adverse events			
subjects affected / exposed	544 / 608 (89.47%)	325 / 408 (79.66%)	469 / 614 (76.38%)
Vascular disorders			
Hypertension			
subjects affected / exposed	31 / 608 (5.10%)	21 / 408 (5.15%)	45 / 614 (7.33%)
occurrences (all)	36	24	58
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	72 / 608 (11.84%)	46 / 408 (11.27%)	55 / 614 (8.96%)
occurrences (all)	110	58	96
Fatigue			
subjects affected / exposed	189 / 608 (31.09%)	99 / 408 (24.26%)	158 / 614 (25.73%)
occurrences (all)	228	145	190
Pyrexia			
subjects affected / exposed	61 / 608 (10.03%)	13 / 408 (3.19%)	25 / 614 (4.07%)
occurrences (all)	77	15	29
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	36 / 608 (5.92%)	21 / 408 (5.15%)	38 / 614 (6.19%)
occurrences (all)	41	24	41
Cough			
subjects affected / exposed	66 / 608 (10.86%)	25 / 408 (6.13%)	67 / 614 (10.91%)
occurrences (all)	70	27	80
Psychiatric disorders			

Insomnia			
subjects affected / exposed	51 / 608 (8.39%)	25 / 408 (6.13%)	37 / 614 (6.03%)
occurrences (all)	54	25	39
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	74 / 608 (12.17%)	34 / 408 (8.33%)	24 / 614 (3.91%)
occurrences (all)	88	38	32
Aspartate aminotransferase increased			
subjects affected / exposed	60 / 608 (9.87%)	22 / 408 (5.39%)	15 / 614 (2.44%)
occurrences (all)	67	31	17
Blood creatinine increased			
subjects affected / exposed	82 / 608 (13.49%)	40 / 408 (9.80%)	59 / 614 (9.61%)
occurrences (all)	101	55	80
Nervous system disorders			
Headache			
subjects affected / exposed	102 / 608 (16.78%)	53 / 408 (12.99%)	89 / 614 (14.50%)
occurrences (all)	122	76	131
Dizziness			
subjects affected / exposed	37 / 608 (6.09%)	17 / 408 (4.17%)	38 / 614 (6.19%)
occurrences (all)	42	21	43
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	42 / 608 (6.91%)	21 / 408 (5.15%)	24 / 614 (3.91%)
occurrences (all)	54	30	34
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	40 / 608 (6.58%)	21 / 408 (5.15%)	44 / 614 (7.17%)
occurrences (all)	46	28	51
Constipation			
subjects affected / exposed	57 / 608 (9.38%)	29 / 408 (7.11%)	49 / 614 (7.98%)
occurrences (all)	68	34	52
Vomiting			
subjects affected / exposed	52 / 608 (8.55%)	27 / 408 (6.62%)	30 / 614 (4.89%)
occurrences (all)	66	37	43
Nausea			

subjects affected / exposed	102 / 608 (16.78%)	53 / 408 (12.99%)	73 / 614 (11.89%)
occurrences (all)	128	74	91
Dry mouth			
subjects affected / exposed	49 / 608 (8.06%)	20 / 408 (4.90%)	15 / 614 (2.44%)
occurrences (all)	51	20	17
Diarrhoea			
subjects affected / exposed	180 / 608 (29.61%)	77 / 408 (18.87%)	120 / 614 (19.54%)
occurrences (all)	272	114	187
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	131 / 608 (21.55%)	50 / 408 (12.25%)	57 / 614 (9.28%)
occurrences (all)	163	63	84
Rash maculo-papular			
subjects affected / exposed	51 / 608 (8.39%)	23 / 408 (5.64%)	6 / 614 (0.98%)
occurrences (all)	62	28	6
Pruritus			
subjects affected / exposed	213 / 608 (35.03%)	103 / 408 (25.25%)	103 / 614 (16.78%)
occurrences (all)	274	125	118
Dry skin			
subjects affected / exposed	47 / 608 (7.73%)	19 / 408 (4.66%)	30 / 614 (4.89%)
occurrences (all)	50	20	32
Endocrine disorders			
Adrenal insufficiency			
subjects affected / exposed	52 / 608 (8.55%)	13 / 408 (3.19%)	4 / 614 (0.65%)
occurrences (all)	59	13	4
Hyperthyroidism			
subjects affected / exposed	98 / 608 (16.12%)	47 / 408 (11.52%)	8 / 614 (1.30%)
occurrences (all)	104	47	9
Hypothyroidism			
subjects affected / exposed	131 / 608 (21.55%)	54 / 408 (13.24%)	28 / 614 (4.56%)
occurrences (all)	133	54	37
Musculoskeletal and connective tissue disorders			
Pain in extremity			
subjects affected / exposed	27 / 608 (4.44%)	22 / 408 (5.39%)	29 / 614 (4.72%)
occurrences (all)	29	22	34
Myalgia			

subjects affected / exposed	57 / 608 (9.38%)	39 / 408 (9.56%)	47 / 614 (7.65%)
occurrences (all)	66	49	52
Back pain			
subjects affected / exposed	45 / 608 (7.40%)	48 / 408 (11.76%)	66 / 614 (10.75%)
occurrences (all)	52	57	77
Arthralgia			
subjects affected / exposed	111 / 608 (18.26%)	58 / 408 (14.22%)	97 / 614 (15.80%)
occurrences (all)	141	72	107
Infections and infestations			
COVID-19			
subjects affected / exposed	15 / 608 (2.47%)	29 / 408 (7.11%)	19 / 614 (3.09%)
occurrences (all)	16	31	19
Metabolism and nutrition disorders			
Hyperglycaemia			
subjects affected / exposed	35 / 608 (5.76%)	27 / 408 (6.62%)	25 / 614 (4.07%)
occurrences (all)	51	38	33
Decreased appetite			
subjects affected / exposed	71 / 608 (11.68%)	15 / 408 (3.68%)	19 / 614 (3.09%)
occurrences (all)	80	15	20

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
22 March 2017	- Consider the placebo products as investigational products - Remove the bioequivalence language
06 April 2018	Reduce frequency of patient questionnaires, update exclusion criterion for serum creatinine, remove 42-day screening window, provide more flexibility in scheduling scans, update background data, and provide additional information and/or clarification to sections indicated.
01 November 2019	Add Part B to the study for evaluation of nivolumab monotherapy.
27 October 2020	Remove Interim Analysis 1 for disease-free survival (DFS), from both Part A and Part B, to delay Interim Analysis 2 for DFS in Part A, and for both Part A and Part B Overall Survival (OS) to be hierarchically analyzed at the same time as the interim or final analysis for DFS in the same group of subjects. This revision also incorporates several changes to provide additional information and/or clarification.
13 February 2022	Address the timing of interim and final disease-free survival (DFS) analyses in Part A, which were initially planned to occur within 6 months of each other. However, the earlier versions of the protocol did not capture the scenario to proceed directly to the final DFS analysis in Part A in the event that Part B enrollment is ongoing when the required number of events needed for interim analysis of DFS in Part A is achieved. With this amendment, the scenario with DFS final analysis only is pre-specified.
08 December 2022	Address the timing of interim and final disease-free survival (DFS) analyses in Part B, which were initially planned to occur at least 8 months of each other. However, the earlier versions of the protocol did not capture the scenario to proceed directly to the final DFS analysis in Part B in the event that the interim analysis and final analysis are projected in a shorter time interval (approximately within 6 months). With this amendment, the scenario with DFS final analysis only is explicitly stated. Also, the redundant OS interim analysis scenario in Part B is now omitted.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported