Clinical trial results:
A Double-Blind, Randomized, Two Arm Phase 2 Study of Nivolumab in Combination with Ipilimumab versus Nivolumab in Combination with Ipilimumab Placebo In Recurrent or Metastatic Squamous Cell Carcinoma of the Head and Neck (SCCHN) (CheckMate 714: CHECKpoint pathway and nivoluMAb clinical Trial Evaluation 714)

Summary

EudraCT number	2016-001645-64
Trial protocol	CZ ES IE BE NL SE NO GB FI IT
Global end of trial date	11 March 2022

Results information

Result version number	v1 (current)
This version publication date	28 March 2023
First version publication date	28 March 2023

Trial information

Trial identification

Sponsor protocol code	CA209-714

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02823574
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Bristol-Myers Squibb
Sponsor organisation address	Chaussee 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.gov

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	22 April 2022
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	11 March 2022
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To compare the ORR and assess the DOR of the treatment of nivolumab in combination with ipilimumab vs nivolumab in combination with ipilimumab placebo, as determined by a blinded independent central review (BICR) using Response Evaluation Criteria In Solid Tumors (RECIST 1.1) criteria, for first-line treatment of recurrent or metastatic SCCHN in the platinum refractory setting.

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 subjects were followed.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	22 September 2016
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: 1
Country: Number of subjects enrolled	Belgium: 12
Country: Number of subjects enrolled	Brazil: 45
Country: Number of subjects enrolled	Canada: 46
Country: Number of subjects enrolled	Chile: 1
Country: Number of subjects enrolled	Finland: 2
Country: Number of subjects enrolled	France: 79
Country: Number of subjects enrolled	Ireland: 10
Country: Number of subjects enrolled	Italy: 1
Country: Number of subjects enrolled	Mexico: 13
Country: Number of subjects enrolled	Netherlands: 13
Country: Number of subjects enrolled	Norway: 20
Country: Number of subjects enrolled	Romania: 37
Country: Number of subjects enrolled	Russian Federation: 10
Country: Number of subjects enrolled	South Africa: 1
Country: Number of subjects enrolled	Spain: 22
Country: Number of subjects enrolled	Sweden: 1
Country: Number of subjects enrolled	Turkey: 3
Country: Number of subjects enrolled	United Kingdom: 19

Country: Number of subjects enrolled	United States: 69
Country: Number of subjects enrolled	Czechia: 20
Worldwide total number of subjects	425
EEA total number of subjects	217

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)	301
From 65 to 84 years	122
85 years and over	2

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

425 randomized and 423 participants treated.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Treatment A - Platinum Refractory Subgroup

Arm description:

Participants with histologically confirmed Squamous Cell Carcinoma of the Head and Neck (SCCHN) that has recurred during or less than 6 months after completion of previous platinum-based chemotherapy. Treated with Nivolumab 3 mg/kg Q2W + Ipilimumab 1 mg/kg Q6W

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

Dosage and administration details:

100mg (10mg/mL)

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:

200mg (5mg/mL)

Arm title	Treatment B - Platinum Refractory Subgroup

Arm description:

Participants with histologically confirmed Squamous Cell Carcinoma of the Head and Neck (SCCHN) that has recurred during or less than 6 months after completion of previous platinum-based chemotherapy. Treated with Nivolumab 3 mg/kg Q2W + Ipilimumab-Placebo Q6W

Arm type	Experimental
Investigational medicinal product name	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 injection or 5% dextrose injection

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

Dosage and administration details:

100mg (10mg/mL)

Arm title	Treatment A - Platinum Eligible Subgroup

Arm description:

Participants with histologically confirmed Squamous Cell Carcinoma of the Head and Neck (SCCHN) who are platinum naive or have recurred 6 months or more after completion of previous platinum-based chemotherapy. Treated with Nivolumab 3 mg/kg Q2W + Ipilimumab 1 mg/kg Q6W

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:

200mg (5mg/mL)

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

Dosage and administration details:

100mg (10mg/mL)

Arm title	Treatment B - Platinum Eligible Subgroup

Arm description:

Participants with histologically confirmed Squamous Cell Carcinoma of the Head and Neck (SCCHN) who are platinum naive or have recurred 6 months or more after completion of previous platinum-based chemotherapy. Treated with Nivolumab 3 mg/kg Q2W + Ipilimumab-Placebo Q6W

Arm type	Experimental
Investigational medicinal product name	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 injection or 5% dextrose injection

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

Dosage and administration details:

100mg (10mg/mL)

Number of subjects in period 1	Treatment A - Platinum Refractory Subgroup	Treatment B - Platinum Refractory Subgroup	Treatment A - Platinum Eligible Subgroup
Started	159	82	123
Completed	158	82	122
Not completed	1	0	1
AE unrelated to Study Drug	1	-	-
Disease Progression	-	-	1

Number of subjects in period 1	Treatment B - Platinum Eligible Subgroup
Started	61
Completed	61
Not completed	0
AE unrelated to Study Drug	-
Disease Progression	-

Period 2

Period 2 title	Treatment Period
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Arms

Are arms mutually exclusive?	Yes
Arm title	Treatment A - Platinum Refractory Subgroup

Arm description:

Participants with histologically confirmed Squamous Cell Carcinoma of the Head and Neck (SCCHN) that has recurred during or less than 6 months after completion of previous platinum-based chemotherapy. Treated with Nivolumab 3 mg/kg Q2W + Ipilimumab 1 mg/kg Q6W

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:

200mg (5mg/mL)

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

Dosage and administration details:

100mg (10mg/mL)

Arm title	Treatment B - Platinum Refractory Subgroup

Arm description:

Participants with histologically confirmed Squamous Cell Carcinoma of the Head and Neck (SCCHN) that has recurred during or less than 6 months after completion of previous platinum-based chemotherapy. Treated with Nivolumab 3 mg/kg Q2W + Ipilimumab-Placebo Q6W

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

Dosage and administration details:

100mg (10mg/mL)

Investigational medicinal product name	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 injection or 5% dextrose injection

Arm title	Treatment A - Platinum Eligible Subgroup

Arm description:

Participants with histologically confirmed Squamous Cell Carcinoma of the Head and Neck (SCCHN) who are platinum naive or have recurred 6 months or more after completion of previous platinum-based chemotherapy. Treated with Nivolumab 3 mg/kg Q2W + Ipilimumab 1 mg/kg Q6W

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:

200mg (5mg/mL)

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

Dosage and administration details:

100mg (10mg/mL)

Arm title	Treatment B - Platinum Eligible Subgroup

Arm description:

Participants with histologically confirmed Squamous Cell Carcinoma of the Head and Neck (SCCHN) who are platinum naive or have recurred 6 months or more after completion of previous platinum-based chemotherapy. Treated with Nivolumab 3 mg/kg Q2W + Ipilimumab-Placebo Q6W

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

Dosage and administration details: 100mg (10mg/mL)	
Investigational medicinal product name	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 injection or 5% dextrose injection

Number of subjects in period 2	Treatment A - Platinum Refractory Subgroup	Treatment B - Platinum Refractory Subgroup	Treatment A - Platinum Eligible Subgroup
Started	158	82	122
Completed	0	0	0
Not completed	158	82	122
Adverse event, serious fatal	-	-	3
Participant withdrew consent	4	-	-
Poor/Non Compliance	1	-	-
Participant request to discontinue	5	-	3
Maximum Clinical Benefit	8	4	7
Adverse Event unrelated to to study Drug	10	2	9
Participant no longer meets study criterai	-	-	1
Other reasons	5	9	3
Study Drug Toxicity	11	2	14
Lost to follow-up	1	1	-
Disease Progression	113	64	82

Number of subjects in period 2	Treatment B - Platinum Eligible Subgroup
Started	61
Completed	0
Not completed	61
Adverse event, serious fatal	1
Participant withdrew consent	1
Poor/Non Compliance	1
Participant request to discontinue	2
Maximum Clinical Benefit	1
Adverse Event unrelated to to study Drug	2
Participant no longer meets study criterai	-
Other reasons	6

Study Drug Toxicity	4
Lost to follow-up	-
Disease Progression	43

Baseline characteristics

Reporting groups	
Reporting group title	Treatment A - Platinum Refractory Subgroup
Reporting group description:	
Participants with histologically confirmed Squamous Cell Carcinoma of the Head and Neck (SCCHN) that has recurred during or less than 6 months after completion of previous platinum-based chemotherapy. Treated with Nivolumab 3 mg/kg Q2W + Ipilimumab 1 mg/kg Q6W	
Reporting group title	Treatment B - Platinum Refractory Subgroup
Reporting group description:	
Participants with histologically confirmed Squamous Cell Carcinoma of the Head and Neck (SCCHN) that has recurred during or less than 6 months after completion of previous platinum-based chemotherapy. Treated with Nivolumab 3 mg/kg Q2W + Ipilimumab-Placebo Q6W	
Reporting group title	Treatment A - Platinum Eligible Subgroup
Reporting group description:	
Participants with histologically confirmed Squamous Cell Carcinoma of the Head and Neck (SCCHN) who are platinum naive or have recurred 6 months or more after completion of previous platinum-based chemotherapy. Treated with Nivolumab 3 mg/kg Q2W + Ipilimumab 1 mg/kg Q6W	
Reporting group title	Treatment B - Platinum Eligible Subgroup
Reporting group description:	
Participants with histologically confirmed Squamous Cell Carcinoma of the Head and Neck (SCCHN) who are platinum naive or have recurred 6 months or more after completion of previous platinum-based chemotherapy. Treated with Nivolumab 3 mg/kg Q2W + Ipilimumab-Placebo Q6W	

Reporting group values	Treatment A - Platinum Refractory Subgroup	Treatment B - Platinum Refractory Subgroup	Treatment A - Platinum Eligible Subgroup
Number of subjects	159	82	123
Age Categorical Units: participants			
<=18 years	0	0	0
Between 18 and 65 years	119	63	79
>=65 years	40	19	44
Age continuous Units: years			
arithmetic mean	58.2	57.9	61.8
full range (min-max)	24 to 82	36 to 77	37 to 88
Sex: Female, Male Units: participants			
Female	29	18	18
Male	130	64	105
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	3	1	0
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	2	3	2
White	141	75	120
More than one race	0	0	0
Unknown or Not Reported	13	3	1
Ethnicity (NIH/OMB)			

Units: Subjects			
Hispanic or Latino	10	7	6
Not Hispanic or Latino	56	23	66
Unknown or Not Reported	93	52	51

Reporting group values	Treatment B - Platinum Eligible Subgroup	Total	
Number of subjects	61	425	
Age Categorical Units: participants			
<=18 years	0	0	
Between 18 and 65 years	40	301	
>=65 years	21	124	
Age continuous Units: years			
arithmetic mean	60.8		
full range (min-max)	33 to 79	-	
Sex: Female, Male Units: participants			
Female	14	79	
Male	47	346	
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0	0	
Asian	1	5	
Native Hawaiian or Other Pacific Islander	0	0	
Black or African American	1	8	
White	58	394	
More than one race	0	0	
Unknown or Not Reported	1	18	
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	6	29	
Not Hispanic or Latino	25	170	
Unknown or Not Reported	30	226	

End points

End points reporting groups

Reporting group title	Treatment A - Platinum Refractory Subgroup
Reporting group description:	
Participants with histologically confirmed Squamous Cell Carcinoma of the Head and Neck (SCCHN) that has recurred during or less than 6 months after completion of previous platinum-based chemotherapy. Treated with Nivolumab 3 mg/kg Q2W + Ipilimumab 1 mg/kg Q6W	
Reporting group title	Treatment B - Platinum Refractory Subgroup
Reporting group description:	
Participants with histologically confirmed Squamous Cell Carcinoma of the Head and Neck (SCCHN) that has recurred during or less than 6 months after completion of previous platinum-based chemotherapy. Treated with Nivolumab 3 mg/kg Q2W + Ipilimumab-Placebo Q6W	
Reporting group title	Treatment A - Platinum Eligible Subgroup
Reporting group description:	
Participants with histologically confirmed Squamous Cell Carcinoma of the Head and Neck (SCCHN) who are platinum naive or have recurred 6 months or more after completion of previous platinum-based chemotherapy. Treated with Nivolumab 3 mg/kg Q2W + Ipilimumab 1 mg/kg Q6W	
Reporting group title	Treatment B - Platinum Eligible Subgroup
Reporting group description:	
Participants with histologically confirmed Squamous Cell Carcinoma of the Head and Neck (SCCHN) who are platinum naive or have recurred 6 months or more after completion of previous platinum-based chemotherapy. Treated with Nivolumab 3 mg/kg Q2W + Ipilimumab-Placebo Q6W	
Reporting group title	Treatment A - Platinum Refractory Subgroup
Reporting group description:	
Participants with histologically confirmed Squamous Cell Carcinoma of the Head and Neck (SCCHN) that has recurred during or less than 6 months after completion of previous platinum-based chemotherapy. Treated with Nivolumab 3 mg/kg Q2W + Ipilimumab 1 mg/kg Q6W	
Reporting group title	Treatment B - Platinum Refractory Subgroup
Reporting group description:	
Participants with histologically confirmed Squamous Cell Carcinoma of the Head and Neck (SCCHN) that has recurred during or less than 6 months after completion of previous platinum-based chemotherapy. Treated with Nivolumab 3 mg/kg Q2W + Ipilimumab-Placebo Q6W	
Reporting group title	Treatment A - Platinum Eligible Subgroup
Reporting group description:	
Participants with histologically confirmed Squamous Cell Carcinoma of the Head and Neck (SCCHN) who are platinum naive or have recurred 6 months or more after completion of previous platinum-based chemotherapy. Treated with Nivolumab 3 mg/kg Q2W + Ipilimumab 1 mg/kg Q6W	
Reporting group title	Treatment B - Platinum Eligible Subgroup
Reporting group description:	
Participants with histologically confirmed Squamous Cell Carcinoma of the Head and Neck (SCCHN) who are platinum naive or have recurred 6 months or more after completion of previous platinum-based chemotherapy. Treated with Nivolumab 3 mg/kg Q2W + Ipilimumab-Placebo Q6W	
Subject analysis set title	Treatment A
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
Participants in both Platinum Refractory Subgroup and Platinum Eligible Subgroup treated with Nivolumab 3 mg/kg Q2W + Ipilimumab 1 mg/kg Q6W	
Subject analysis set title	Treatment B
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
Participants in both Platinum Refractory Subgroup and Platinum Eligible Subgroup treated with Nivolumab 3 mg/kg Q2W + Ipilimumab-Placebo Q6W	

Primary: Time to Response (TTR) as determined by Blinded Independent Central Review (BIRC) - Platinum refractory subgroup

End point title	Time to Response (TTR) as determined by Blinded Independent Central Review (BIRC) - Platinum refractory subgroup[1][2]

End point description:

Time to Response (TTR) for participants demonstrating a response (either CR or PR) was defined as the time from the date of randomization to the date of the first confirmed response.

Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes(whether target or non-target) must have reduction in short axis to < 10 mm.

Partial Response (PR): At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.

End point type	Primary

End point timeframe:

Approximately up to 30 months (from FPFV to Data base lock)

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Endpoints are specific for subgroups not baseline period

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

End point values	Treatment A - Platinum Refractory Subgroup	Treatment B - Platinum Refractory Subgroup		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	21	15		
Units: Months				
median (full range (min-max))	2.56 (1.1 to 6.6)	1.51 (1.2 to 7.7)		

Statistical analyses

No statistical analyses for this end point

Primary: Objective Response Rate (ORR) as determined by Blinded Independent Central Review (BIRC) - Platinum refractory subgroup

End point title	Objective Response Rate (ORR) as determined by Blinded Independent Central Review (BIRC) - Platinum refractory subgroup[3]

End point description:

ORR is defined as best overall response (BOR) of a complete response (CR) or partial response (PR) divided by the number of randomized participants for each treatment group.

Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes(whether target or non-target) must have reduction in short axis to < 10 mm.

Partial Response (PR): At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.

End point type	Primary

End point timeframe:

Approximately up to 30 months (from FPFV to Data base lock)

Notes:

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

End point values	Treatment A - Platinum Refractory Subgroup	Treatment B - Platinum Refractory Subgroup		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	159	82		
Units: percentage of participants				
number (confidence interval 95%)	13.2 (8.4 to 19.5)	18.3 (10.6 to 28.4)		

Statistical analyses

Statistical analysis title	Statistical Analysis
Statistical analysis description: Treatment A over Treatment B	
Comparison groups	Treatment A - Platinum Refractory Subgroup v Treatment B - Platinum Refractory Subgroup
Number of subjects included in analysis	241
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.2897
Method	Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Point estimate	0.68
Confidence interval	
level	95.5 %
sides	2-sided
lower limit	0.33
upper limit	1.43

Primary: Duration of Response (DOR) as determined by Blinded Independent Central Review (BIRC) - Platinum refractory subgroup

End point title	Duration of Response (DOR) as determined by Blinded Independent Central Review (BIRC) - Platinum refractory subgroup[4][5]

End point description:

The time between the date of first confirmed response to the date of the first documented tumor progression, or death due to any cause, whichever occurs first.

Here "99999" signifies NA

End point type	Primary

End point timeframe:

Approximately up to 30 months (from FPFV to Data base lock)

Notes:

[4] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Endpoints are specific for subgroups not baseline period

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

End point values	Treatment A - Platinum Refractory Subgroup	Treatment B - Platinum Refractory Subgroup		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	21	15		
Units: Months				
median (confidence interval 95%)	99999 (11.01 to 99999)	11.07 (4.14 to 99999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Objective Response Rate (ORR) as determined by Blinded Independent Central Review (BIRC) - Platinum Eligible subgroup

End point title	Objective Response Rate (ORR) as determined by Blinded Independent Central Review (BIRC) - Platinum Eligible subgroup[6]

End point description:

ORR is defined as percentage of participants with a complete response (CR) or partial response (PR)

Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes(whether target or non-target) must have reduction in short axis to < 10 mm.

Partial Response (PR): At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.

End point type	Secondary

End point timeframe:

From randomization to end of study. Approximately 63 Months

Notes:

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

End point values	Treatment A - Platinum Eligible Subgroup	Treatment B - Platinum Eligible Subgroup		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	123	61		
Units: percentage of participants				
number (confidence interval 95%)	20.3 (13.6 to 28.5)	29.5 (18.5 to 42.6)		

Statistical analyses

No statistical analyses for this end point

Secondary: Progression Free Survival (PFS) as determined by Blinded Independent Central Review (BIRC) - Platinum Eligible subgroup

End point title	Progression Free Survival (PFS) as determined by Blinded Independent Central Review (BIRC) - Platinum Eligible subgroup[7]

End point description:

the time from randomization to the date of first documented disease progression, or death due to any cause, whichever occurs first.

Progressive Disease (PD): At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progression).

End point type	Secondary

End point timeframe:

From randomization to disease progression or death. Approximately 63 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: Endpoints are specific for subgroups not baseline period

End point values	Treatment A - Platinum Eligible Subgroup	Treatment B - Platinum Eligible Subgroup		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	123	61		
Units: Months				
median (confidence interval 95%)	2.76 (1.64 to 4.17)	2.86 (1.51 to 5.65)		

Statistical analyses

Statistical analysis title	Statistical Analysis
Comparison groups	Treatment A - Platinum Eligible Subgroup v Treatment B - Platinum Eligible Subgroup
Number of subjects included in analysis	184
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Hazard ratio (HR)
Point estimate	1.12
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.8
upper limit	1.59

Secondary: Progression Free Survival (PFS) as determined by Blinded Independent Central Review (BIRC) - Platinum Refractory subgroup

End point title	Progression Free Survival (PFS) as determined by Blinded Independent Central Review (BIRC) - Platinum Refractory subgroup[8]

End point description:

The time from randomization to the date of first documented disease progression, or death due to any cause, whichever occurs first.

Progressive Disease (PD): At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progression).

End point type	Secondary

End point timeframe:

From randomization to disease progression or death. Approximately 63 Months

Notes:

[8] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Endpoints are specific for subgroups not baseline period

End point values	Treatment A - Platinum Refractory Subgroup	Treatment B - Platinum Refractory Subgroup		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	159	82		
Units: Months				
median (confidence interval 95%)	2.50 (1.45 to 2.76)	2.60 (1.54 to 3.38)		

Statistical analyses

Statistical analysis title	Statistical Analysis
Comparison groups	Treatment A - Platinum Refractory Subgroup v Treatment B - Platinum Refractory Subgroup
Number of subjects included in analysis	241
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Hazard ratio (HR)
Point estimate	1.05
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.78
upper limit	1.41

Secondary: Duration of Response (DOR) as determined by Blinded Independent Central Review (BIRC) - Platinum Eligible subgroup

End point title	Duration of Response (DOR) as determined by Blinded Independent Central Review (BIRC) - Platinum Eligible

	subgroup[9]

End point description:

The time between the date of first confirmed response to the date of the first documented tumor progression, or death due to any cause, whichever occurs first.

Here "99999" signifies NA

End point type	Secondary

End point timeframe:

From randomization to disease progression or death. Approximately 63 Months

Notes:

[9] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Endpoints are specific for subgroups not baseline period

End point values	Treatment A - Platinum Eligible Subgroup	Treatment B - Platinum Eligible Subgroup		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	25	18		
Units: Months				
median (confidence interval 95%)	27.04 (11.01 to 99999)	24.61 (6.90 to 99999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival (OS) - Platinum Refractory Subgroup

End point title	Overall Survival (OS) - Platinum Refractory Subgroup[10]

End point description:

Overall survival was defined as the time from randomization to the date of death from any cause. Participants were censored at the date they were last known to be alive and at the date of randomization if they were randomized but had no follow-up.

End point type	Secondary

End point timeframe:

From randomization to death. Approximately 63 Months

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: Endpoints are specific for subgroups not baseline period

End point values	Treatment A - Platinum Refractory Subgroup	Treatment B - Platinum Refractory Subgroup		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	159	82		
Units: Months				
median (confidence interval 95%)	9.76 (6.51 to 11.37)	9.59 (7.13 to 14.26)		

Statistical analyses

Statistical analysis title	Statistical Analysis
Comparison groups	Treatment A - Platinum Refractory Subgroup v Treatment B - Platinum Refractory Subgroup
Number of subjects included in analysis	241
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Hazard ratio (HR)
Point estimate	1.08
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.81
upper limit	1.45

Secondary: Overall Survival (OS)

End point title	Overall Survival (OS)

End point description:

Overall survival was defined as the time from randomization to the date of death from any cause. Participants were censored at the date they were last known to be alive and at the date of randomization if they were randomized but had no follow-up.

End point type	Secondary

End point timeframe:

From randomization to death. Approximately 63 Months

End point values	Treatment A	Treatment B		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	282	143		
Units: Months				
median (confidence interval 95%)	9.76 (7.52 to 11.47)	11.30 (8.48 to 14.00)		

Statistical analyses

Statistical analysis title	Statistical Analysis
Comparison groups	Treatment A v Treatment B

Number of subjects included in analysis	425
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Hazard ratio (HR)
Point estimate	1.09
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.87
upper limit	1.36

Secondary: ORR - Platinum Eligible Subgroup based on HPV p-16 status

End point title	ORR - Platinum Eligible Subgroup based on HPV p-16 status[11]

End point description:

ORR is defined as percentage of participants with a complete response (CR) or partial response (PR)

Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes(whether target or non-target) must have reduction in short axis to < 10 mm.

Partial Response (PR): At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.

End point type	Secondary

End point timeframe:

From randomization to end of study. Approximately 63 Months

Notes:

[11] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Endpoints are specific for subgroups not baseline period

End point values	Treatment A - Platinum Eligible Subgroup	Treatment B - Platinum Eligible Subgroup		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	123	61		
Units: percentage of participants				
number (confidence interval 95%)				
Positive	20.0 (8.4 to 36.9)	41.2 (18.4 to 67.1)		
Negative	20.5 (12.6 to 30.4)	25.0 (13.2 to 40.3)		

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival (OS) - Platinum Eligible Subgroup

End point title	Overall Survival (OS) - Platinum Eligible Subgroup[12]

End point description:

Overall survival was defined as the time from randomization to the date of death from any cause. Participants were censored at the date they were last known to be alive and at the date of randomization if they were randomized but had no follow-up.

End point type	Secondary

End point timeframe:

From randomization to death. Approximately 63 Months

Notes:

[12] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Endpoints are specific for subgroups not baseline period

End point values	Treatment A - Platinum Eligible Subgroup	Treatment B - Platinum Eligible Subgroup		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	123	61		
Units: Months				
median (confidence interval 95%)	9.71 (7.43 to 12.62)	12.91 (9.33 to 22.01)		

Statistical analyses

Statistical analysis title	Statistical Analysis
Comparison groups	Treatment A - Platinum Eligible Subgroup v Treatment B - Platinum Eligible Subgroup
Number of subjects included in analysis	184
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Cox proportional hazard
Point estimate	1.14
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.81
upper limit	1.61

Secondary: ORR - Platinum Refractory Subgroup based on HPV p-16 Status

End point title	ORR - Platinum Refractory Subgroup based on HPV p-16

End point description:

ORR is defined as percentage of participants with a complete response (CR) or partial response (PR)

Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes(whether target or non-target) must have reduction in short axis to < 10 mm.

Partial Response (PR): At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.

End point type	Secondary

End point timeframe:

From randomization to end of study. Approximately 63 Months

Notes:

[13] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Endpoints are specific for subgroups not baseline period

End point values	Treatment A - Platinum Refractory Subgroup	Treatment B - Platinum Refractory Subgroup		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	159	82		
Units: percentage of participants				
number (confidence interval 95%)				
OROPHARYNGEAL HPV P-16 POSITIVE	23.3 (9.9 to 42.3)	37.5 (15.2 to 64.6)		
OROPHARYNGEAL HPV P-16 NEGATIVE/ NON-OROPHARYNGEAL	12.4 (7.3 to 19.4)	16.7 (8.6 to 27.9)		

Statistical analyses

No statistical analyses for this end point

Secondary: ORR - Platinum Eligible Subgroup based on Tumor Mutation Burden (TMB) Biomarker

End point title	ORR - Platinum Eligible Subgroup based on Tumor Mutation Burden (TMB) Biomarker[14]

End point description:

ORR is defined as percentage of participants with a complete response (CR) or partial response (PR)

Tumor Mutational Burden (TMB) refers to the number of nonsynonymous somatic mutations that exist within a tumor’s genome as measured by the Foundation One CDx panel at Foundation Medicine. The analysis was done on subjects with baseline tumor mutation burden by a cutoff of 7 mutations/megabase (mut/Mb) and 10 mut/Mb

Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes(whether target or non-target) must have reduction in short axis to < 10 mm.

Partial Response (PR): At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.

End point type	Secondary

End point timeframe:

From randomization to end of study. Approximately 63 Months

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: Endpoints are specific for subgroups not baseline period

End point values	Treatment A - Platinum Eligible Subgroup	Treatment B - Platinum Eligible Subgroup		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	123	61		
Units: percentage of participants				
number (confidence interval 95%)				
TMB < 7	10.2 (3.8 to 20.8)	30.8 (14.3 to 51.8)		
TMB ≥ 7	34.2 (19.6 to 51.4)	28.6 (11.3 to 52.2)		
TMB < 10	17.3 (9.8 to 27.3)	28.6 (14.6 to 46.3)		
TMB ≥ 10	31.3 (11.0 to 58.7)	33.3 (9.9 to 65.1)		
TMB Not Reported	23.1 (9.0 to 43.6)	28.6 (8.4 to 58.1)		

Statistical analyses

No statistical analyses for this end point

Secondary: ORR - Platinum Refractory Subgroup based on Tumor Mutation Burden (TMB) Biomarker

End point title	ORR - Platinum Refractory Subgroup based on Tumor Mutation Burden (TMB) Biomarker[15]

End point description:

ORR is defined as percentage of participants with a complete response (CR) or partial response (PR)

Tumor Mutational Burden (TMB) refers to the number of nonsynonymous somatic mutations that exist within a tumor's genome as measured by the Foundation One CDx panel at Foundation Medicine. The analysis was done on subjects with baseline tumor mutation burden by a cutoff of 7 mutations/megabase (mut/Mb) and 10 mut/Mb

Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes(whether target or non-target) must have reduction in short axis to < 10 mm.

Partial Response (PR): At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.

End point type	Secondary

End point timeframe:

From randomization to end of study. Approximately 63 Months

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: Endpoints are specific for subgroups not baseline period

End point values	Treatment A - Platinum Refractory Subgroup	Treatment B - Platinum Refractory Subgroup		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	159	82		
Units: percentage of participants				
number (confidence interval 95%)				

TMB < 7	9.0 (3.4 to 18.5)	20.5 (9.3 to 36.5)		
TMB ≥ 7	23.3 (11.8 to 38.6)	19.0 (5.4 to 41.9)		
TMB < 10	11.0 (5.4 to 19.3)	22.4 (11.8 to 36.6)		
TMB ≥ 10	31.6 (12.6 to 56.6)	18.2 (2.3 to 51.8)		
TMB Not Reported	14.3 (5.9 to 27.2)	18.2 (5.2 to 40.3)		

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Response (DOR) - Platinum Refractory subgroup based on HPV p-16 Status

End point title	Duration of Response (DOR) - Platinum Refractory subgroup based on HPV p-16 Status[16]

End point description:

The time between the date of first confirmed response to the date of the first documented tumor progression, or death due to any cause, whichever occurs first.

Here "99999" signifies NA

End point type	Secondary

End point timeframe:

From randomization to disease progression or death. Approximately 63 Months

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: Endpoints are specific for subgroups not baseline period

End point values	Treatment A - Platinum Refractory Subgroup	Treatment B - Platinum Refractory Subgroup		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	21	15		
Units: Months				
median (confidence interval 95%)				
HPV p-16 Positive	99999 (6.87 to 99999)	11.10 (4.17 to 14.9)		
HPV p-16 Negative	39.43 (26.71 to 99999)	8.34 (2.79 to 99999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Response (DOR) - Platinum Refractory subgroup based on Tumor Mutation Burden (TMB) Status

End point title	Duration of Response (DOR) - Platinum Refractory subgroup based on Tumor Mutation Burden (TMB) Status[17]

End point description:

The time between the date of first confirmed response to the date of the first documented tumor progression, or death due to any cause, whichever occurs first.

Here "99999" signifies NA
Tumor Mutational Burden (TMB) refers to the number of nonsynonymous somatic mutations that exist within a tumor's genome as measured by the Foundation One CDx panel at Foundation Medicine. The analysis was done on subjects with baseline tumor mutation burden by a cutoff of 7 mutations/megabase (mut/Mb) and 10 mut/Mb

End point type	Secondary

End point timeframe:

From randomization to disease progression or death. Approximately 63 Months

Notes:

[17] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Endpoints are specific for subgroups not baseline period

End point values	Treatment A - Platinum Refractory Subgroup	Treatment B - Platinum Refractory Subgroup		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	21	15		
Units: Months				
median (confidence interval 95%)				
TMB: <7	99999 (11.01 to 99999)	11.14 (2.69 to 99999)		
TMB ≥ 7	38.67 (3.06 to 39.43)	8.59 (2.79 to 99999)		
TMB: <10	99999 (3.06 to 99999)	11.14 (4.17 to 99999)		
TMB: ≥ 10	38.67 (6.87 to 38.67)	7.54 (2.79 to 12.29)		
TMB: Not Reported	26.71 (6.93 to 26.71)	8.21 (4.14 to 14.29)		

Statistical analyses

No statistical analyses for this end point

Secondary: Progression Free Survival (PFS) - Platinum Refractory subgroup based on HPV p-16 Status

End point title	Progression Free Survival (PFS) - Platinum Refractory subgroup based on HPV p-16 Status[18]

End point description:

the time from randomization to the date of first documented disease progression, or death due to any cause, whichever occurs first.

Progressive Disease (PD): At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progression).

End point type	Secondary

End point timeframe:

From randomization to disease progression or death. Approximately 63 Months

Notes:

[18] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Endpoints are specific for subgroups not baseline period

End point values	Treatment A - Platinum Refractory Subgroup	Treatment B - Platinum Refractory Subgroup		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	159	82		
Units: Months				
median (confidence interval 95%)				
Postive	4.11 (1.81 to 8.31)	6.70 (1.28 to 13.67)		
Negative	1.84 (1.41 to 2.63)	1.94 (1.41 to 3.02)		

Statistical analyses

No statistical analyses for this end point

Secondary: Progression Free Survival (PFS) - Platinum Refractory subgroup Based on Tumor Mutation Burden (TMB) Status

End point title	Progression Free Survival (PFS) - Platinum Refractory subgroup Based on Tumor Mutation Burden (TMB) Status[19]

End point description:

the time from randomization to the date of first documented disease progression, or death due to any cause, whichever occurs first.

Tumor Mutational Burden (TMB) refers to the number of nonsynonymous somatic mutations that exist within a tumor’s genome as measured by the Foundation One CDx panel at Foundation Medicine. The analysis was done on subjects with baseline tumor mutation burden by a cutoff of 7 mutations/megabase (mut/Mb) and 10 mut/Mb

Progressive Disease (PD): At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progression).

End point type	Secondary

End point timeframe:

From randomization to disease progression or death. Approximately 63 Months

Notes:

[19] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Endpoints are specific for subgroups not baseline period

End point values	Treatment A - Platinum Refractory Subgroup	Treatment B - Platinum Refractory Subgroup		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	159	82		
Units: Months				
median (confidence interval 95%)				
TMB: < 7	1.45 (1.38 to 2.60)	2.50 (1.41 to 5.26)		
TMB: ≥ 7	2.76 (1.45 to 4.11)	1.54 (1.25 to 4.07)		
TMB: < 10	1.68 (1.41 to 2.60)	2.50 (1.41 to 4.24)		
TMB: ≥ 10	2.81 (1.38 to 9.69)	1.41 (1.25 to 4.07)		
TMB: Not Reported	2.66 (1.45 to 2.92)	2.92 (1.28 to 7.00)		

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival (OS) - Platinum Refractory Subgroup based on HPV p-16 status

End point title	Overall Survival (OS) - Platinum Refractory Subgroup based on HPV p-16 status[20]

End point description:

Overall survival was defined as the time from randomization to the date of death from any cause. Participants were censored at the date they were last known to be alive and at the date of randomization if they were randomized but had no follow-up.

End point type	Secondary

End point timeframe:

From randomization to death. Approximately 63 Months

Notes:

[20] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Endpoints are specific for subgroups not baseline period

End point values	Treatment A - Platinum Refractory Subgroup	Treatment B - Platinum Refractory Subgroup		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	159	82		
Units: Months				
median (confidence interval 95%)				
Positive	13.93 (5.98 to 33.81)	14.32 (6.28 to 44.88)		
Negative	9.36 (5.98 to 10.87)	9.59 (6.93 to 13.40)		

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival (OS) - Platinum Refractory Subgroup based on Tumor Mutation Burden (TMB) status

End point title	Overall Survival (OS) - Platinum Refractory Subgroup based on Tumor Mutation Burden (TMB) status[21]

End point description:

Overall survival was defined as the time from randomization to the date of death from any cause. Participants were censored at the date they were last known to be alive and at the date of randomization if they were randomized but had no follow-up.

Tumor Mutational Burden (TMB) refers to the number of nonsynonymous somatic mutations that exist within a tumor's genome as measured by the Foundation One CDx panel at Foundation Medicine. The analysis was done on subjects with baseline tumor mutation burden by a cutoff of 7 mutations/megabase (mut/Mb) and 10 mut/Mb

End point type	Secondary

End point timeframe:

From randomization to death. Approximately 63 Months

Notes:

[21] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Endpoints are specific for subgroups not baseline period

End point values	Treatment A - Platinum Refractory Subgroup	Treatment B - Platinum Refractory Subgroup		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	159	82		
Units: Months				
median (confidence interval 95%)				
TMB: <7	5.78 (3.45 to 9.76)	8.77 (4.14 to 16.66)		
TMB: ≥ 7	11.37 (6.41 to 16.95)	7.16 (6.28 to 12.29)		
TMB: < 10	7.52 (4.96 to 11.27)	8.31 (4.90 to 13.04)		
TMB: ≥10	6.51 (2.50 to 41.33)	9.26 (1.35 to 17.51)		
Not Reported	13.86 (9.53 to 17318)	20.01 (7.56 to 23.46)		

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival (OS) - Platinum Eligible Subgroup based on HPV p-16 status

End point title	Overall Survival (OS) - Platinum Eligible Subgroup based on HPV p-16 status[22]

End point description:

Overall survival was defined as the time from randomization to the date of death from any cause. Participants were censored at the date they were last known to be alive and at the date of randomization if they were randomized but had no follow-up.

Here "99999" signifies NA

End point type	Secondary

End point timeframe:

From randomization to death. Approximately 63 Months

Notes:

[22] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Endpoints are specific for subgroups not baseline period

End point values	Treatment A - Platinum Eligible Subgroup	Treatment B - Platinum Eligible Subgroup		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	123	61		
Units: Months				
median (confidence interval 95%)				
Positive	16.66 (8.54 to 28.06)	33.74 (12.91 to 99999)		
Negative	7.79 (5.06 to 12.39)	9.46 (5.32 to 14.00)		

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival (OS) - Platinum Eligible Subgroup based on Tumor Mutation Burden (TMB) status

End point title	Overall Survival (OS) - Platinum Eligible Subgroup based on Tumor Mutation Burden (TMB) status[23]

End point description:

Overall survival was defined as the time from randomization to the date of death from any cause. Participants were censored at the date they were last known to be alive and at the date of randomization if they were randomized but had no follow-up.

Here "99999" signifies NA

Tumor Mutational Burden (TMB) refers to the number of nonsynonymous somatic mutations that exist within a tumor’s genome as measured by the Foundation One CDx panel at Foundation Medicine. The analysis was done on subjects with baseline tumor mutation burden by a cutoff of 7 mutations/megabase (mut/Mb) and 10 mut/Mb

End point type	Secondary

End point timeframe:

From randomization to death. Approximately 63 Months

Notes:

[23] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Endpoints are specific for subgroups not baseline period

End point values	Treatment A - Platinum Eligible Subgroup	Treatment B - Platinum Eligible Subgroup		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	123	61		
Units: Months				
median (confidence interval 95%)				
TMB: <7	7.56 (4.83 to 12.25)	18.27 (4.04 to 33.74)		
TMB: ≥ 7	16.30 (9.43 to 36.30)	13.08 (8.28 to 38.11)		
TMB: < 10	9.99 (6.41 to 12.62)	15.01 (7.62 to 27.47)		
TMB: ≥10	16.72 (4.47 to 99999)	14.77 (2.83 to 99999)		
Not Reported	8.00 (3.84 to 26.12)	9.71 (2.56 to 18.79)		

Statistical analyses

No statistical analyses for this end point

Secondary: Progression Free Survival (PFS) - Platinum Eligible subgroup Based on Tumor Mutation Burden (TMB) Status

End point title	Progression Free Survival (PFS) - Platinum Eligible subgroup Based on Tumor Mutation Burden (TMB) Status[24]

End point description:

the time from randomization to the date of first documented disease progression, or death due to any cause, whichever occurs first.

Tumor Mutational Burden (TMB) refers to the number of nonsynonymous somatic mutations that exist within a tumor’s genome as measured by the Foundation One CDx panel at Foundation Medicine. The analysis was done on subjects with baseline tumor mutation burden by a cutoff of 7 mutations/megabase (mut/Mb) and 10 mut/Mb

Progressive Disease (PD): At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progression).

Here "99999" signifies NA

End point type	Secondary

End point timeframe:

From randomization to disease progression or death. Approximately 63 Months

Notes:

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

Justification: Endpoints are specific for subgroups not baseline period

End point values	Treatment A - Platinum Eligible Subgroup	Treatment B - Platinum Eligible Subgroup		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	123	61		
Units: Months				
median (confidence interval 95%)				
TMB: < 7	2.63 (1.45 to 3.06)	2.92 (1.38 to 9.59)		
TMB: ≥ 7	5.82 (1.45 to 12.42)	2.83 (1.41 to 13.01)		
TMB: < 10	2.63 (1.45 to 3.06)	2.99 (1.41 to 13.01)		
TMB: ≥ 10	6.97 (1.41 to 99999)	2.76 (0.72 to 27.60)		
TMB: Not Reported	2.71 (1.45 to 8.48)	3.10 (1.38 to 9.82)		

Statistical analyses

No statistical analyses for this end point

Secondary: Progression Free Survival (PFS) - Platinum Eligible subgroup based on HPV p-16 Status

End point title	Progression Free Survival (PFS) - Platinum Eligible subgroup based on HPV p-16 Status[25]

End point description:

the time from randomization to the date of first documented disease progression, or death due to any cause, whichever occurs first.

Progressive Disease (PD): At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progression).

End point type	Secondary

End point timeframe:

From randomization to disease progression or death. Approximately 63 Months

Notes:

[25] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Endpoints are specific for subgroups not baseline period

End point values	Treatment A - Platinum Eligible Subgroup	Treatment B - Platinum Eligible Subgroup		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	123	61		
Units: Months				
median (confidence interval 95%)				

Postive	2.92 (1.41 to 6.60)	6.83 (1.38 to 49.84)		
Negative	2.66 (1.51 to 4.14)	2.83 (1.51 to 4.24)		

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Response (DOR) - Platinum Eligible subgroup based on HPV p-16 Status

End point title	Duration of Response (DOR) - Platinum Eligible subgroup based on HPV p-16 Status[26]

End point description:

The time between the date of first confirmed response to the date of the first documented tumor progression, or death due to any cause, whichever occurs first.

Progressive Disease (PD): At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progression).

Here "99999" signifies NA

End point type	Secondary

End point timeframe:

From randomization to disease progression or death. Approximately 63 Months

Notes:

[26] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Endpoints are specific for subgroups not baseline period

End point values	Treatment A - Platinum Eligible Subgroup	Treatment B - Platinum Eligible Subgroup		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	25	18		
Units: Months				
median (confidence interval 95%)				
Positive	33.84 (4.14 to 99999)	48.49 (5.49 to 99999)		
Negative	27.04 (10.97 to 99999)	19.32 (4.11 to 99999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Response (DOR) - Platinum Eligible subgroup based on Tumor Mutation Burden (TMB) Status

End point title	Duration of Response (DOR) - Platinum Eligible subgroup based on Tumor Mutation Burden (TMB) Status[27]

End point description:

The time between the date of first confirmed response to the date of the first documented tumor progression, or death due to any cause, whichever occurs first.

Tumor Mutational Burden (TMB) refers to the number of nonsynonymous somatic mutations that exist within a tumor's genome as measured by the Foundation One CDx panel at Foundation Medicine. The analysis was done on subjects with baseline tumor mutation burden by a cutoff of 7 mutations/megabase (mut/Mb) and 10 mut/Mb.

Progressive Disease (PD): At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progression).

Here "99999" signifies NA

End point type	Secondary

End point timeframe:

From randomization to disease progression or death. Approximately 63 Months

Notes:

[27] - 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: Endpoints are specific for subgroups not baseline period

End point values	Treatment A - Platinum Eligible Subgroup	Treatment B - Platinum Eligible Subgroup		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	25	18		
Units: Months				
median (confidence interval 95%)				
TMB: <7	10.97 (4.14 to 35.55)	99999 (5.52 to 99999)		
TMB ≥ 7	24.11 (10.97 to 99999)	19.32 (5.49 to 24.61)		
TMB: <10	13.67 (8.28 to 35.55)	99999 (5.52 to 99999)		
TMB: ≥ 10	99999 (5.78 to 99999)	19.32 (5.49 to 24.61)		
TMB: Not Reported	99999 (27.04 to 99999)	48.49 (4.11 to 99999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Response (DOR) - Platinum Refractory subgroup based on PD-L1 Status

End point title	Duration of Response (DOR) - Platinum Refractory subgroup based on PD-L1 Status[28]

End point description:

The time between the date of first confirmed response to the date of the first documented tumor progression, or death due to any cause, whichever occurs first.

Tumor PD-L1 expression was defined as the percent of tumor cell membrane staining in a minimum of 100 evaluable tumor cells per validated Dako PD-L1 IHC assay.

Progressive Disease (PD): At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progression).

Here "99999 and -99999" signifies NA

Here "9999" signifies not calculated

End point type	Secondary

End point timeframe:

From randomization to disease progression or death. Approximately 63 Months

Notes:

[28] - 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: Endpoints are specific for subgroups not baseline period

End point values	Treatment A - Platinum Refractory Subgroup	Treatment B - Platinum Refractory Subgroup		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	21	15		
Units: Months				
median (confidence interval 95%)				
PD-L1: ≥ 1%	39.43 (11.01 to 99999)	8.34 (2.79 to 99999)		
PD-L1: < 25%	39.43 (6.87 to 99999)	11.10 (4.17 to 38.51)		
PD-L1: ≥ 25%	9999 (6.93 to 99999)	8.34 (2.79 to 99999)		
PD-L1: <50%	9999 (26.71 to 99999)	11.14 (4.17 to 38.51)		
PD-L1: > 50%	9999 (6.93 to 99999)	6.24 (4.14 to 8.34)		
PD-L1: 1 - < 25%	39.43 (3.06 to 39.43)	9999 (4.17 to 99999)		
PD-L1: Unquantifiable	38.67 (-99999 to 99999)	9999 (-99999 to 99999)		

Statistical analyses

No statistical analyses for this end point

Secondary: ORR - Platinum Refractory Subgroup based on PD-L1 Expression

End point title	ORR - Platinum Refractory Subgroup based on PD-L1 Expression[29]

End point description:

ORR is defined as percentage of participants with a complete response (CR) or partial response (PR)

Tumor PD-L1 expression was defined as the percent of tumor cell membrane staining in a minimum of 100 evaluable tumor cells per validated Dako PD-L1 IHC assay

Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes(whether target or non-target) must have reduction in short axis to < 10 mm.

Partial Response (PR): At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.

Here "9999" signifies not calculated

End point type	Secondary

End point timeframe:

From randomization to end of study. Approximately 63 Months

Notes:

[29] - 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: Endpoints are specific for subgroups not baseline period

End point values	Treatment A - Platinum Refractory Subgroup	Treatment B - Platinum Refractory Subgroup		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	159	82		
Units: Percentage of Participants				
number (confidence interval 95%)				
<1%	7.7 (2.1 to 18.5)	25.8 (11.9 to 44.6)		
PD-L1: ≥ 1%	19.6 (12.0 to 29.1)	19.6 (9.4 to 33.9)		
PD-L1: < 25%	11.1 (6.1 to 18.3)	21.1 (11.4 to 33.9)		
PD-L1: ≥ 25%	33.3 (16.5 to 54.0)	25.0 (8.7 to 49.1)		
PD-L1: <50%	13.2 (7.9 to 20.3)	22.7 (13.3 to 34.7)		
PD-L1: > 50%	33.3 (11.8 to 61.6)	18.2 (2.3 to 51.8)		
PD-L1: 1 - < 25%	13.8 (6.5 to 24.7)	15.4 (4.4 to 34.9)		
without quantifiable PD-L1 expression at baseline	9999 (-9999 to 99999)	9999 (-99999 to 99999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival (OS) - Platinum Refractory Subgroup based on PD-L1 status

End point title	Overall Survival (OS) - Platinum Refractory Subgroup based on PD-L1 status[30]

End point description:

Overall survival was defined as the time from randomization to the date of death from any cause. Participants were censored at the date they were last known to be alive and at the date of randomization if they were randomized but had no follow-up.

Tumor PD-L1 expression was defined as the percent of tumor cell membrane staining in a minimum of 100 evaluable tumor cells per validated Dako PD-L1 IHC assay

End point type	Secondary

End point timeframe:

From randomization to death. Approximately 63 Months

Notes:

[30] - 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: Endpoints are specific for subgroups not baseline period

End point values	Treatment A - Platinum Refractory Subgroup	Treatment B - Platinum Refractory Subgroup		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	159	82		
Units: Months				
median (confidence interval 95%)				
<1%	9.53 (6.31 to 12.62)	12.29 (6.08 to 20.27)		
PD-L1: ≥ 1%	10.22 (5.95 to 14.52)	9.02 (6.74 to 13.34)		
PD-L1: < 25%	9.95 (7.26 to 11.37)	8.77 (6.28 to 14.78)		
PD-L1: ≥ 25%	5.78 (2.43 to 48.69)	10.23 (7.03 to 16.66)		
PD-L1: <50%	9.76 (6.51 to 11.37)	10.61 (6.74 to 14.26)		
PD-L1: > 50%	26.02 (2.43 to 48.69)	7.33 (1.51 to 16.66)		
PD-L1: 1 - < 25%	10.32 (5.98 to 14.32)	7.56 (4.86 to 17.51)		
Without quantifiable PD-L1 expression at baseline	6.93 (1.71 to 14.16)	28.09 (7.56 to 44.88)		

Statistical analyses

No statistical analyses for this end point

Secondary: Progression Free Survival (PFS) - Platinum Refractory subgroup based on PD-L1 Status

End point title	Progression Free Survival (PFS) - Platinum Refractory subgroup based on PD-L1 Status[31]

End point description:

The time from randomization to the date of first documented disease progression, or death due to any cause, whichever occurs first.

Tumor PD-L1 expression was defined as the percent of tumor cell membrane staining in a minimum of 100 evaluable tumor cells per validated Dako PD-L1 IHC assay.

Progressive Disease (PD): At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progression).

Here "99999" signifies NA

End point type	Secondary

End point timeframe:

From randomization to disease progression or death. Approximately 63 Months

Notes:

[31] - 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: Endpoints are specific for subgroups not baseline period

End point values	Treatment A - Platinum Refractory Subgroup	Treatment B - Platinum Refractory Subgroup		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	159	82		
Units: Months				
median (confidence interval 95%)				
<1%	2.60 (1.41 to 2.86)	2.96 (1.38 to 5.32)		
PD-L1: ≥ 1%	2.60 (1.45 to 2.83)	2.60 (1.41 to 4.11)		
PD-L1: < 25%	2.60 (1.45 to 2.83)	2.79 (1.41 to 4.01)		
PD-L1: ≥ 25%	2.12 (1.38 to 13.77)	1.54 (1.25 to 7.03)		
PD-L1: <50%	2.60 (1.45 to 2.79)	2.79 (1.54 to 4.07)		
PD-L1: > 50%	2.79 (0.59 to 13.77)	1.54 (0.66 to 7.03)		
PD-L1: 1 - < 25%	2.66 (1.45 to 2.83)	2.60 (1.38 to 4.07)		
Without Quantifiable PD-L1 expression at Baseline	2.17 (1.08 to 2.66)	1.71 (1.22 to 99999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Response (DOR) - Platinum Eligible subgroup based on PD-L1 Status

End point title	Duration of Response (DOR) - Platinum Eligible subgroup based on PD-L1 Status[32]

End point description:

The time between the date of first confirmed response to the date of the first documented tumor progression, or death due to any cause, whichever occurs first.

Tumor PD-L1 expression was defined as the percent of tumor cell membrane staining in a minimum of 100 evaluable tumor cells per validated Dako PD-L1 IHC assay

Progressive Disease (PD): At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progression).

Here "99999" signifies NA

End point type	Secondary

End point timeframe:

From randomization to disease progression or death. Approximately 63 Months

Notes:

[32] - 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: Endpoints are specific for subgroups not baseline period

End point values	Treatment A - Platinum Eligible Subgroup	Treatment B - Platinum Eligible Subgroup		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	25	18		
Units: Months				
median (confidence interval 95%)				
PD-L1: ≥ 1%	33.84 (8.28 to 99999)	24.61 (4.11 to 99999)		
PD-L1: < 25%	13.17 (4.17 to 35.55)	12.42 (4.11 to 99999)		
PD-L1: ≥ 25%	99999 (8.28 to 99999)	99999 (24.61 to 99999)		
PD-L1: <50%	13.67 (5.78 to 35.55)	15.87 (4.11 to 99999)		
PD-L1: > 50%	99999 (33.84 to 99999)	99999 (24.61 to 99999)		
PD-L1: 1 - < 25%	13.13 (4.14 to 99999)	6.21 (4.11 to 12.42)		
PD-L1: Unquantifiable	99999 (27.04 to 99999)	28.99 (9.49 to 48.49)		

Statistical analyses

No statistical analyses for this end point

Secondary: ORR - Platinum Eligible Subgroup based on PD-L1 Expression

End point title	ORR - Platinum Eligible Subgroup based on PD-L1

End point description:

ORR is defined as percentage of participants with a complete response (CR) or partial response (PR)

Tumor PD-L1 expression was defined as the percent of tumor cell membrane staining in a minimum of 100 evaluable tumor cells per validated Dako PD-L1 IHC assay
Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes(whether target or non-target) must have reduction in short axis to < 10 mm.

Partial Response (PR): At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.

Here "99999" signifies NA

End point type	Secondary

End point timeframe:

From randomization to end of study. Approximately 63 Months

Notes:

[33] - 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: Endpoints are specific for subgroups not baseline period

End point values	Treatment A - Platinum Eligible Subgroup	Treatment B - Platinum Eligible Subgroup		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	123	61		
Units: percentage of participants				
number (confidence interval 95%)				
<1%	15.7 (7.0 to 28.6)	21.7 (7.5 to 43.7)		
PD-L1: ≥ 1%	21.5 (12.3 to 33.5)	30.3 (15.6 to 48.7)		
PD-L1: < 25%	14.9 (8.2 to 24.2)	24.3 (11.8 to 41.2)		
PD-L1: ≥ 25%	31.0 (15.3 to 50.8)	31.6 (12.6 to 56.6)		
PD-L1: <50%	16.7 (9.8 to 25.6)	24.4 (12.4 to 40.3)		
PD-L1: > 50%	30.0 (11.9 to 54.3)	33.3 (11.8 to 61.6)		
PD-L1: 1 - < 25%	13.9 (4.7 to 29.5)	28.6 (8.4 to 58.1)		
Without quantifiable PD-L1 expression at baseline	99999 (99999 to 99999)	99999 (99999 to 99999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival (OS) - Platinum Eligible Subgroup based on PD-L1 status

End point title	Overall Survival (OS) - Platinum Eligible Subgroup based on PD-L1 status[34]

End point description:

Overall survival was defined as the time from randomization to the date of death from any cause. Participants were censored at the date they were last known to be alive and at the date of randomization if they were randomized but had no follow-up.

Tumor PD-L1 expression was defined as the percent of tumor cell membrane staining in a minimum of 100 evaluable tumor cells per validated Dako PD-L1 IHC assay

Here "99999" signifies NA

End point type	Secondary

End point timeframe:

From randomization to death. Approximately 63 Months

Notes:

[34] - 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: Endpoints are specific for subgroups not baseline period

End point values	Treatment A - Platinum Eligible Subgroup	Treatment B - Platinum Eligible Subgroup		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	123	61		
Units: months				
median (confidence interval 95%)				
<1%	12.52 (8.21 to 17.68)	11.17 (3.42 to 21.52)		
PD-L1: ≥ 1%	7.56 (5.06 to 11.24)	14.00 (7.62 to 23.66)		
PD-L1: < 25%	8.72 (5.91 to 12.25)	11.17 (5.32 to 21.52)		
PD-L1: ≥ 25%	12.39 (5.06 to 36.30)	14.00 (6.34 to 38.74)		
PD-L1: <50%	9.10 (6.57 to 12.62)	9.92 (4.04 to 18.79)		
PD-L1: > 50%	9.40 (4.11 to 36.30)	15.01 (7.62 to 99999)		
PD-L1: 1 - < 25%	6.16 (4.57 to 8.11)	8.48 (2.83 to 22.41)		
Without quantifiable PD-L1 expression at baseline	26.12 (1.64 to 99999)	33.74 (5.72 to 99999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Progression Free Survival (PFS) - Platinum Eligible subgroup based on PD-L1 Status

End point title	Progression Free Survival (PFS) - Platinum Eligible subgroup based on PD-L1 Status[35]

End point description:

The time from randomization to the date of first documented disease progression, or death due to any cause, whichever occurs first.

Tumor PD-L1 expression was defined as the percent of tumor cell membrane staining in a minimum of 100 evaluable tumor cells per validated Dako PD-L1 IHC assay

Progressive Disease (PD): At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progression).

Here "99999" signifies NA

End point type	Secondary

End point timeframe:

From randomization to disease progression or death. Approximately 63 Months

Notes:

[35] - 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: Endpoints are specific for subgroups not baseline period

End point values	Treatment A - Platinum Eligible Subgroup	Treatment B - Platinum Eligible Subgroup		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	123	61		
Units: Months				
median (confidence interval 95%)				
<1%	2.61 (1.38 to 5.78)	2.73 (1.41 to 9.82)		
PD-L1: ≥ 1%	2.89 (1.51 to 4.21)	2.99 (1.38 to 5.65)		
PD-L1: < 25%	2.37 (1.41 to 2.76)	2.76 (1.41 to 5.65)		
PD-L1: ≥ 25%	5.75 (3.71 to 16.59)	2.99 (1.38 to 99999)		
PD-L1: <50%	2.55 (1.45 to 2.89)	2.76 (1.41 to 5.65)		
PD-L1: > 50%	4.21 (2.79 to 99999)	2.99 (1.38 to 99999)		
PD-L1: 1 - < 25%	1.51 (1.41 to 2.86)	3.10 (1.28 to 8.28)		
Without quantifiable PD-L1 expression at baseline	6.47 (1.51 to 99999)	13.73 (1.28 to 49.84)		

Statistical analyses

No statistical analyses for this end point

Post-hoc: Objective Response Rate (ORR) as determined by Blinded Independent Central Review (BIRC) - Platinum refractory subgroup - Post Hoc Analysis

End point title	Objective Response Rate (ORR) as determined by Blinded Independent Central Review (BIRC) - Platinum refractory subgroup - Post Hoc Analysis[36]

End point description:

ORR is defined as percentage of participants with a complete response (CR) or partial response (PR)

Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes(whether target or non-target) must have reduction in short axis to < 10 mm.

Partial Response (PR): At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.

End point type	Post-hoc

End point timeframe:

From randomization to end of study. Approximately 63 Months

Notes:

[36] - 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: Endpoints are specific for subgroups not baseline period

End point values	Treatment A - Platinum Refractory Subgroup	Treatment B - Platinum Refractory Subgroup		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	159	82		
Units: percentage of participants				
number (confidence interval 95%)	14.5 (9.4 to 20.9)	20.7 (12.6 to 31.1)		

Statistical analyses

Statistical analysis title	Statistical Analysis
Statistical analysis description: Treatment A over Treatment B	
Comparison groups	Treatment A - Platinum Refractory Subgroup v Treatment B - Platinum Refractory Subgroup
Number of subjects included in analysis	241
Analysis specification	Post-hoc
Analysis type	
Method	Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Point estimate	0.64
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.32
upper limit	1.29

Post-hoc: Time to Response (TTR) as determined by Blinded Independent Central Review (BIRC) - Platinum refractory subgroup - Post Hoc Analysis

End point title	Time to Response (TTR) as determined by Blinded Independent Central Review (BIRC) - Platinum refractory subgroup - Post Hoc Analysis[37]

End point description:

Time to Response (TTR) for participants demonstrating a response (either CR or PR) was defined as the time from the date of randomization to the date of the first confirmed response.

Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes(whether target or non-target) must have reduction in short axis to < 10 mm.

Partial Response (PR): At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.

End point type	Post-hoc

End point timeframe:

From randomization to a confirmed response. Approximately 35 Months

Notes:

[37] - 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: Endpoints are specific for subgroups not baseline period

End point values	Treatment A - Platinum Refractory Subgroup	Treatment B - Platinum Refractory Subgroup		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	23	17		
Units: Months				
median (full range (min-max))	2.63 (1.1 to 34.3)	1.71 (1.2 to 7.7)		

Statistical analyses

No statistical analyses for this end point

Post-hoc: Duration of Response (DOR) as determined by Blinded Independent Central Review (BIRC) - Platinum refractory subgroup - Post Hoc Analysis

End point title	Duration of Response (DOR) as determined by Blinded Independent Central Review (BIRC) - Platinum refractory subgroup - Post Hoc Analysis[38]

End point description:

The time between the date of first confirmed response to the date of the first documented tumor progression, or death due to any cause, whichever occurs first.

Progressive Disease (PD): At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progression).

Here "99999" signifies NA

End point type	Post-hoc

End point timeframe:

From randomization to disease progression or death. Approximately 63 Months

Notes:

[38] - 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: Endpoints are specific for subgroups not baseline period

End point values	Treatment A - Platinum Refractory Subgroup	Treatment B - Platinum Refractory Subgroup		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	23	17		
Units: Months				
median (confidence interval 95%)	39.43 (26.71 to 99999)	11.07 (4.17 to 38.51)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse Events and Serious Adverse Events: Approximately 32 months

All-Cause mortality: Approximately 65 months

Adverse event reporting additional description:

Adverse Event and Serious Adverse Events are measured from first dose to last dose + 100 days.

All-Cause mortality will be measured from the time of randomization to the end of study.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	24.1

Reporting groups

Reporting group title	Treatment A - Platinum Refractory Subgroup

Reporting group description:

Participants with histologically confirmed Squamous Cell Carcinoma of the Head and Neck (SCCHN) that has recurred during or less than 6 months after completion of previous platinum-based chemotherapy. Treated with Nivolumab 3 mg/kg Q2W + Ipilimumab 1 mg/kg Q6W

Reporting group title	Treatment B - Platinum Eligible Subgroup

Reporting group description:

Participants with histologically confirmed Squamous Cell Carcinoma of the Head and Neck (SCCHN) who are platinum naive or have recurred 6 months or more after completion of previous platinum-based chemotherapy. Treated with Nivolumab 3 mg/kg Q2W + Ipilimumab-Placebo Q6W

Reporting group title	Treatment A - Platinum Eligible Subgroup

Reporting group description:

Participants with histologically confirmed Squamous Cell Carcinoma of the Head and Neck (SCCHN) who are platinum naive or have recurred 6 months or more after completion of previous platinum-based chemotherapy. Treated with Nivolumab 3 mg/kg Q2W + Ipilimumab 1 mg/kg Q6W

Reporting group title	Treatment B - Platinum Refractory Subgroup

Reporting group description:

Participants with histologically confirmed Squamous Cell Carcinoma of the Head and Neck (SCCHN) that has recurred during or less than 6 months after completion of previous platinum-based chemotherapy. Treated with Nivolumab 3 mg/kg Q2W + Ipilimumab-Placebo Q6W

Serious adverse events	Treatment A - Platinum Refractory Subgroup	Treatment B - Platinum Eligible Subgroup	Treatment A - Platinum Eligible Subgroup
Total subjects affected by serious adverse events			
subjects affected / exposed	103 / 159 (64.78%)	35 / 61 (57.38%)	89 / 123 (72.36%)
number of deaths (all causes)	131	49	102
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Cancer pain			

subjects affected / exposed[1]	1 / 158 (0.63%)	0 / 61 (0.00%)	1 / 122 (0.82%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Basal cell carcinoma			
subjects affected / exposed[2]	1 / 158 (0.63%)	0 / 61 (0.00%)	1 / 122 (0.82%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatocellular carcinoma			
subjects affected / exposed[3]	0 / 158 (0.00%)	0 / 61 (0.00%)	1 / 122 (0.82%)
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[4]	61 / 158 (38.61%)	16 / 61 (26.23%)	47 / 122 (38.52%)
occurrences causally related to treatment / all	0 / 63	0 / 16	0 / 48
deaths causally related to treatment / all	0 / 58	0 / 16	0 / 45
Malignant pleural effusion			
subjects affected / exposed[5]	0 / 158 (0.00%)	0 / 61 (0.00%)	1 / 122 (0.82%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metastases to bone			
subjects affected / exposed[6]	1 / 158 (0.63%)	0 / 61 (0.00%)	0 / 122 (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
Second primary malignancy			
subjects affected / exposed[7]	0 / 158 (0.00%)	1 / 61 (1.64%)	0 / 122 (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
Tumour associated fever			
subjects affected / exposed[8]	0 / 158 (0.00%)	0 / 61 (0.00%)	1 / 122 (0.82%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tumour haemorrhage			

subjects affected / exposed[9]	2 / 158 (1.27%)	0 / 61 (0.00%)	1 / 122 (0.82%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tumour pain			
subjects affected / exposed[10]	0 / 158 (0.00%)	0 / 61 (0.00%)	0 / 122 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Hypovolaemic shock			
subjects affected / exposed[11]	0 / 158 (0.00%)	0 / 61 (0.00%)	0 / 122 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemorrhage			
subjects affected / exposed[12]	1 / 158 (0.63%)	0 / 61 (0.00%)	2 / 122 (1.64%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 2
Embolism			
subjects affected / exposed[13]	0 / 158 (0.00%)	0 / 61 (0.00%)	0 / 122 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lymphoedema			
subjects affected / exposed[14]	1 / 158 (0.63%)	0 / 61 (0.00%)	0 / 122 (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 venous disease			
subjects affected / exposed[15]	0 / 158 (0.00%)	0 / 61 (0.00%)	2 / 122 (1.64%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Superior vena cava syndrome			
subjects affected / exposed[16]	1 / 158 (0.63%)	0 / 61 (0.00%)	0 / 122 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			

Hyperthermia			
subjects affected / exposed[17]	1 / 158 (0.63%)	0 / 61 (0.00%)	0 / 122 (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
Generalised oedema			
subjects affected / exposed[18]	1 / 158 (0.63%)	0 / 61 (0.00%)	0 / 122 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General physical health deterioration			
subjects affected / exposed[19]	0 / 158 (0.00%)	0 / 61 (0.00%)	3 / 122 (2.46%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fatigue			
subjects affected / exposed[20]	0 / 158 (0.00%)	0 / 61 (0.00%)	1 / 122 (0.82%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Face oedema			
subjects affected / exposed[21]	1 / 158 (0.63%)	0 / 61 (0.00%)	0 / 122 (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
Drug intolerance			
subjects affected / exposed[22]	1 / 158 (0.63%)	0 / 61 (0.00%)	0 / 122 (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[23]	0 / 158 (0.00%)	1 / 61 (1.64%)	0 / 122 (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
Chest pain			
subjects affected / exposed[24]	0 / 158 (0.00%)	0 / 61 (0.00%)	0 / 122 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Swelling			

subjects affected / exposed[25]	1 / 158 (0.63%)	0 / 61 (0.00%)	0 / 122 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sudden death			
subjects affected / exposed[26]	0 / 158 (0.00%)	0 / 61 (0.00%)	3 / 122 (2.46%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 3
Pyrexia			
subjects affected / exposed[27]	1 / 158 (0.63%)	0 / 61 (0.00%)	1 / 122 (0.82%)
occurrences causally related to treatment / all	0 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Impaired healing			
subjects affected / exposed[28]	0 / 158 (0.00%)	0 / 61 (0.00%)	1 / 122 (0.82%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mucosal inflammation			
subjects affected / exposed[29]	1 / 158 (0.63%)	0 / 61 (0.00%)	2 / 122 (1.64%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Malaise			
subjects affected / exposed[30]	0 / 158 (0.00%)	1 / 61 (1.64%)	1 / 122 (0.82%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Inflammation			
subjects affected / exposed[31]	0 / 158 (0.00%)	0 / 61 (0.00%)	1 / 122 (0.82%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pain			
subjects affected / exposed[32]	0 / 158 (0.00%)	0 / 61 (0.00%)	1 / 122 (0.82%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune system disorders			
Drug hypersensitivity			

subjects affected / exposed[33]	0 / 158 (0.00%)	0 / 61 (0.00%)	1 / 122 (0.82%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Autoimmune lung disease			
subjects affected / exposed[34]	1 / 158 (0.63%)	0 / 61 (0.00%)	0 / 122 (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 obstructive pulmonary disease			
subjects affected / exposed[35]	0 / 158 (0.00%)	0 / 61 (0.00%)	1 / 122 (0.82%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyspnoea			
subjects affected / exposed[36]	4 / 158 (2.53%)	1 / 61 (1.64%)	4 / 122 (3.28%)
occurrences causally related to treatment / all	0 / 4	0 / 1	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemoptysis			
subjects affected / exposed[37]	0 / 158 (0.00%)	0 / 61 (0.00%)	3 / 122 (2.46%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypoxia			
subjects affected / exposed[38]	0 / 158 (0.00%)	0 / 61 (0.00%)	0 / 122 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Laryngeal dyspnoea			
subjects affected / exposed[39]	0 / 158 (0.00%)	0 / 61 (0.00%)	0 / 122 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung disorder			
subjects affected / exposed[40]	0 / 158 (0.00%)	0 / 61 (0.00%)	1 / 122 (0.82%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Laryngeal oedema			

subjects affected / exposed[41]	0 / 158 (0.00%)	0 / 61 (0.00%)	1 / 122 (0.82%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Laryngeal obstruction			
subjects affected / exposed[42]	1 / 158 (0.63%)	0 / 61 (0.00%)	0 / 122 (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
Laryngeal haemorrhage			
subjects affected / exposed[43]	0 / 158 (0.00%)	1 / 61 (1.64%)	1 / 122 (0.82%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nasal obstruction			
subjects affected / exposed[44]	0 / 158 (0.00%)	1 / 61 (1.64%)	0 / 122 (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
Obstructive airways disorder			
subjects affected / exposed[45]	0 / 158 (0.00%)	0 / 61 (0.00%)	1 / 122 (0.82%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pharyngeal oedema			
subjects affected / exposed[46]	0 / 158 (0.00%)	0 / 61 (0.00%)	1 / 122 (0.82%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pleural effusion			
subjects affected / exposed[47]	3 / 158 (1.90%)	0 / 61 (0.00%)	0 / 122 (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
Pneumonitis			
subjects affected / exposed[48]	1 / 158 (0.63%)	1 / 61 (1.64%)	2 / 122 (1.64%)
occurrences causally related to treatment / all	1 / 1	0 / 1	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumothorax			

subjects affected / exposed[49]	0 / 158 (0.00%)	0 / 61 (0.00%)	2 / 122 (1.64%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary embolism			
subjects affected / exposed[50]	1 / 158 (0.63%)	1 / 61 (1.64%)	0 / 122 (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
Respiratory distress			
subjects affected / exposed[51]	1 / 158 (0.63%)	0 / 61 (0.00%)	0 / 122 (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
Respiratory failure			
subjects affected / exposed[52]	3 / 158 (1.90%)	1 / 61 (1.64%)	2 / 122 (1.64%)
occurrences causally related to treatment / all	0 / 3	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Psychiatric disorders			
Insomnia			
subjects affected / exposed[53]	0 / 158 (0.00%)	0 / 61 (0.00%)	1 / 122 (0.82%)
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 leakage			
subjects affected / exposed[54]	2 / 158 (1.27%)	0 / 61 (0.00%)	2 / 122 (1.64%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Device dislocation			
subjects affected / exposed[55]	0 / 158 (0.00%)	2 / 61 (3.28%)	0 / 122 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Weight decreased			
subjects affected / exposed[56]	1 / 158 (0.63%)	0 / 61 (0.00%)	0 / 122 (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

Platelet count decreased			
subjects affected / exposed[57]	0 / 158 (0.00%)	0 / 61 (0.00%)	0 / 122 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Creatinine renal clearance decreased			
subjects affected / exposed[58]	0 / 158 (0.00%)	0 / 61 (0.00%)	1 / 122 (0.82%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Head injury			
subjects affected / exposed[59]	0 / 158 (0.00%)	0 / 61 (0.00%)	1 / 122 (0.82%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Hand fracture			
subjects affected / exposed[60]	0 / 158 (0.00%)	0 / 61 (0.00%)	0 / 122 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Foot fracture			
subjects affected / exposed[61]	0 / 158 (0.00%)	0 / 61 (0.00%)	0 / 122 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Femur fracture			
subjects affected / exposed[62]	0 / 158 (0.00%)	0 / 61 (0.00%)	1 / 122 (0.82%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Accidental overdose			
subjects affected / exposed[63]	0 / 158 (0.00%)	0 / 61 (0.00%)	1 / 122 (0.82%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infusion related reaction			
subjects affected / exposed[64]	0 / 158 (0.00%)	0 / 61 (0.00%)	1 / 122 (0.82%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Spinal compression fracture			
subjects affected / exposed[65]	1 / 158 (0.63%)	0 / 61 (0.00%)	0 / 122 (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
Post procedural haemorrhage			
subjects affected / exposed[66]	0 / 158 (0.00%)	0 / 61 (0.00%)	1 / 122 (0.82%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Overdose			
subjects affected / exposed[67]	1 / 158 (0.63%)	0 / 61 (0.00%)	0 / 122 (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
Toxicity to various agents			
subjects affected / exposed[68]	1 / 158 (0.63%)	0 / 61 (0.00%)	0 / 122 (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
Tracheal haemorrhage			
subjects affected / exposed[69]	0 / 158 (0.00%)	0 / 61 (0.00%)	2 / 122 (1.64%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper limb fracture			
subjects affected / exposed[70]	0 / 158 (0.00%)	1 / 61 (1.64%)	1 / 122 (0.82%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vasoplegia syndrome			
subjects affected / exposed[71]	0 / 158 (0.00%)	0 / 61 (0.00%)	1 / 122 (0.82%)
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 disorders			
Cardiac failure congestive			
subjects affected / exposed[72]	0 / 158 (0.00%)	0 / 61 (0.00%)	1 / 122 (0.82%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Arrhythmia			

subjects affected / exposed[73]	0 / 158 (0.00%)	0 / 61 (0.00%)	0 / 122 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac arrest			
subjects affected / exposed[74]	1 / 158 (0.63%)	0 / 61 (0.00%)	0 / 122 (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
Cardiac failure			
subjects affected / exposed[75]	0 / 158 (0.00%)	0 / 61 (0.00%)	1 / 122 (0.82%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute myocardial infarction			
subjects affected / exposed[76]	0 / 158 (0.00%)	0 / 61 (0.00%)	0 / 122 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pericardial effusion			
subjects affected / exposed[77]	2 / 158 (1.27%)	0 / 61 (0.00%)	1 / 122 (0.82%)
occurrences causally related to treatment / all	1 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myocardial infarction			
subjects affected / exposed[78]	1 / 158 (0.63%)	0 / 61 (0.00%)	0 / 122 (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			
Carotid aneurysm rupture			
subjects affected / exposed[79]	0 / 158 (0.00%)	0 / 61 (0.00%)	0 / 122 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ischaemic stroke			
subjects affected / exposed[80]	0 / 158 (0.00%)	0 / 61 (0.00%)	0 / 122 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebrovascular accident			

subjects affected / exposed[81]	0 / 158 (0.00%)	0 / 61 (0.00%)	1 / 122 (0.82%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebral ischaemia			
subjects affected / exposed[82]	0 / 158 (0.00%)	0 / 61 (0.00%)	0 / 122 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorder			
subjects affected / exposed[83]	0 / 158 (0.00%)	0 / 61 (0.00%)	1 / 122 (0.82%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Syncope			
subjects affected / exposed[84]	1 / 158 (0.63%)	0 / 61 (0.00%)	1 / 122 (0.82%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neuropathy peripheral			
subjects affected / exposed[85]	0 / 158 (0.00%)	0 / 61 (0.00%)	1 / 122 (0.82%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed[86]	1 / 158 (0.63%)	0 / 61 (0.00%)	1 / 122 (0.82%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lymph node pain			
subjects affected / exposed[87]	1 / 158 (0.63%)	0 / 61 (0.00%)	0 / 122 (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
Neutropenia			
subjects affected / exposed[88]	0 / 158 (0.00%)	0 / 61 (0.00%)	1 / 122 (0.82%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Febrile bone marrow aplasia			

subjects affected / exposed[89]	2 / 158 (1.27%)	0 / 61 (0.00%)	0 / 122 (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
Ear and labyrinth disorders			
Vestibular disorder			
subjects affected / exposed[90]	1 / 158 (0.63%)	0 / 61 (0.00%)	0 / 122 (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 disorders			
Ascites			
subjects affected / exposed[91]	1 / 158 (0.63%)	0 / 61 (0.00%)	0 / 122 (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
Abdominal distension			
subjects affected / exposed[92]	0 / 158 (0.00%)	0 / 61 (0.00%)	1 / 122 (0.82%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal pain upper			
subjects affected / exposed[93]	0 / 158 (0.00%)	1 / 61 (1.64%)	0 / 122 (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
Diarrhoea			
subjects affected / exposed[94]	3 / 158 (1.90%)	0 / 61 (0.00%)	4 / 122 (3.28%)
occurrences causally related to treatment / all	3 / 3	0 / 0	2 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Constipation			
subjects affected / exposed[95]	0 / 158 (0.00%)	0 / 61 (0.00%)	0 / 122 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colitis			
subjects affected / exposed[96]	1 / 158 (0.63%)	1 / 61 (1.64%)	0 / 122 (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
Autoimmune colitis			

subjects affected / exposed[97]	2 / 158 (1.27%)	0 / 61 (0.00%)	0 / 122 (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
Duodenitis			
subjects affected / exposed[98]	0 / 158 (0.00%)	0 / 61 (0.00%)	1 / 122 (0.82%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haematemesis			
subjects affected / exposed[99]	0 / 158 (0.00%)	0 / 61 (0.00%)	1 / 122 (0.82%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal haemorrhage			
subjects affected / exposed[100]	1 / 158 (0.63%)	0 / 61 (0.00%)	0 / 122 (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
Gastric ulcer			
subjects affected / exposed[101]	1 / 158 (0.63%)	0 / 61 (0.00%)	0 / 122 (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
Dysphagia			
subjects affected / exposed[102]	3 / 158 (1.90%)	0 / 61 (0.00%)	5 / 122 (4.10%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hernial eventration			
subjects affected / exposed[103]	0 / 158 (0.00%)	0 / 61 (0.00%)	0 / 122 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune-mediated enterocolitis			
subjects affected / exposed[104]	3 / 158 (1.90%)	1 / 61 (1.64%)	2 / 122 (1.64%)
occurrences causally related to treatment / all	3 / 3	1 / 1	3 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Impaired gastric emptying			

subjects affected / exposed[105]	0 / 158 (0.00%)	0 / 61 (0.00%)	0 / 122 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mouth haemorrhage			
subjects affected / exposed[106]	2 / 158 (1.27%)	1 / 61 (1.64%)	1 / 122 (0.82%)
occurrences causally related to treatment / all	0 / 3	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Small intestinal perforation			
subjects affected / exposed[107]	0 / 158 (0.00%)	0 / 61 (0.00%)	1 / 122 (0.82%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatitis			
subjects affected / exposed[108]	0 / 158 (0.00%)	1 / 61 (1.64%)	1 / 122 (0.82%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Palatal disorder			
subjects affected / exposed[109]	1 / 158 (0.63%)	0 / 61 (0.00%)	0 / 122 (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
Oesophageal fistula			
subjects affected / exposed[110]	0 / 158 (0.00%)	0 / 61 (0.00%)	0 / 122 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nausea			
subjects affected / exposed[111]	0 / 158 (0.00%)	0 / 61 (0.00%)	0 / 122 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mouth ulceration			
subjects affected / exposed[112]	0 / 158 (0.00%)	0 / 61 (0.00%)	0 / 122 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Stomatitis			

subjects affected / exposed[113]	0 / 158 (0.00%)	0 / 61 (0.00%)	0 / 122 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			
subjects affected / exposed[114]	6 / 158 (3.80%)	0 / 61 (0.00%)	2 / 122 (1.64%)
occurrences causally related to treatment / all	2 / 6	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Autoimmune hepatitis			
subjects affected / exposed[115]	0 / 158 (0.00%)	1 / 61 (1.64%)	1 / 122 (0.82%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholecystitis			
subjects affected / exposed[116]	0 / 158 (0.00%)	0 / 61 (0.00%)	1 / 122 (0.82%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatitis			
subjects affected / exposed[117]	0 / 158 (0.00%)	1 / 61 (1.64%)	0 / 122 (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
Hepatotoxicity			
subjects affected / exposed[118]	0 / 158 (0.00%)	0 / 61 (0.00%)	0 / 122 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune-mediated hepatitis			
subjects affected / exposed[119]	0 / 158 (0.00%)	0 / 61 (0.00%)	1 / 122 (0.82%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Pruritus			
subjects affected / exposed[120]	1 / 158 (0.63%)	0 / 61 (0.00%)	0 / 122 (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
Rash			

subjects affected / exposed[121]	2 / 158 (1.27%)	0 / 61 (0.00%)	1 / 122 (0.82%)
occurrences causally related to treatment / all	2 / 2	0 / 0	1 / 1
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
Rash maculo-papular			
subjects affected / exposed[122]	1 / 158 (0.63%)	0 / 61 (0.00%)	0 / 122 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed[123]	2 / 158 (1.27%)	1 / 61 (1.64%)	0 / 122 (0.00%)
occurrences causally related to treatment / all	1 / 2	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal failure			
subjects affected / exposed[124]	1 / 158 (0.63%)	0 / 61 (0.00%)	2 / 122 (1.64%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endocrine disorders			
Adrenal insufficiency			
subjects affected / exposed[125]	0 / 158 (0.00%)	0 / 61 (0.00%)	2 / 122 (1.64%)
occurrences causally related to treatment / all	0 / 0	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypophysitis			
subjects affected / exposed[126]	0 / 158 (0.00%)	0 / 61 (0.00%)	2 / 122 (1.64%)
occurrences causally related to treatment / all	0 / 0	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Adrenocortical insufficiency acute			
subjects affected / exposed[127]	0 / 158 (0.00%)	1 / 61 (1.64%)	0 / 122 (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
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed[128]	1 / 158 (0.63%)	0 / 61 (0.00%)	0 / 122 (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

Neck pain			
subjects affected / exposed[129]	1 / 158 (0.63%)	0 / 61 (0.00%)	0 / 122 (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
Spinal pain			
subjects affected / exposed[130]	0 / 158 (0.00%)	0 / 61 (0.00%)	1 / 122 (0.82%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pathological fracture			
subjects affected / exposed[131]	1 / 158 (0.63%)	0 / 61 (0.00%)	1 / 122 (0.82%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteonecrosis			
subjects affected / exposed[132]	0 / 158 (0.00%)	0 / 61 (0.00%)	1 / 122 (0.82%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Abscess neck			
subjects affected / exposed[133]	1 / 158 (0.63%)	0 / 61 (0.00%)	0 / 122 (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
Bacteraemia			
subjects affected / exposed[134]	1 / 158 (0.63%)	0 / 61 (0.00%)	0 / 122 (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
Cellulitis			
subjects affected / exposed[135]	2 / 158 (1.27%)	0 / 61 (0.00%)	0 / 122 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Encephalitis			
subjects affected / exposed[136]	0 / 158 (0.00%)	0 / 61 (0.00%)	0 / 122 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Empyema			

subjects affected / exposed[137]	0 / 158 (0.00%)	1 / 61 (1.64%)	0 / 122 (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
Influenza			
subjects affected / exposed[138]	0 / 158 (0.00%)	0 / 61 (0.00%)	1 / 122 (0.82%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lower respiratory tract infection			
subjects affected / exposed[139]	1 / 158 (0.63%)	0 / 61 (0.00%)	0 / 122 (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
Ludwig angina			
subjects affected / exposed[140]	0 / 158 (0.00%)	0 / 61 (0.00%)	1 / 122 (0.82%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endocarditis			
subjects affected / exposed[141]	0 / 158 (0.00%)	0 / 61 (0.00%)	0 / 122 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Epiglottitis			
subjects affected / exposed[142]	0 / 158 (0.00%)	0 / 61 (0.00%)	1 / 122 (0.82%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Focal peritonitis			
subjects affected / exposed[143]	0 / 158 (0.00%)	0 / 61 (0.00%)	1 / 122 (0.82%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis			
subjects affected / exposed[144]	0 / 158 (0.00%)	0 / 61 (0.00%)	1 / 122 (0.82%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatic infection bacterial			

subjects affected / exposed[145]	0 / 158 (0.00%)	0 / 61 (0.00%)	1 / 122 (0.82%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Herpes zoster			
subjects affected / exposed[146]	1 / 158 (0.63%)	0 / 61 (0.00%)	0 / 122 (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
Infective myositis			
subjects affected / exposed[147]	0 / 158 (0.00%)	1 / 61 (1.64%)	0 / 122 (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
Lymph node abscess			
subjects affected / exposed[148]	0 / 158 (0.00%)	1 / 61 (1.64%)	0 / 122 (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
Neutropenic sepsis			
subjects affected / exposed[149]	0 / 158 (0.00%)	0 / 61 (0.00%)	0 / 122 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oral infection			
subjects affected / exposed[150]	0 / 158 (0.00%)	1 / 61 (1.64%)	0 / 122 (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
Pneumococcal sepsis			
subjects affected / exposed[151]	0 / 158 (0.00%)	0 / 61 (0.00%)	0 / 122 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis syndrome			
subjects affected / exposed[152]	1 / 158 (0.63%)	0 / 61 (0.00%)	0 / 122 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia aspiration			

subjects affected / exposed[153]	2 / 158 (1.27%)	1 / 61 (1.64%)	3 / 122 (2.46%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Pneumonia pseudomonal			
subjects affected / exposed[154]	0 / 158 (0.00%)	0 / 61 (0.00%)	1 / 122 (0.82%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			
subjects affected / exposed[155]	1 / 158 (0.63%)	1 / 61 (1.64%)	0 / 122 (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
Pneumonia			
subjects affected / exposed[156]	18 / 158 (11.39%)	4 / 61 (6.56%)	10 / 122 (8.20%)
occurrences causally related to treatment / all	0 / 19	0 / 5	0 / 13
deaths causally related to treatment / all	0 / 6	0 / 1	0 / 0
Septic shock			
subjects affected / exposed[157]	0 / 158 (0.00%)	1 / 61 (1.64%)	0 / 122 (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
Sinusitis			
subjects affected / exposed[158]	0 / 158 (0.00%)	0 / 61 (0.00%)	0 / 122 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin infection			
subjects affected / exposed[159]	0 / 158 (0.00%)	1 / 61 (1.64%)	1 / 122 (0.82%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Staphylococcal bacteraemia			
subjects affected / exposed[160]	0 / 158 (0.00%)	0 / 61 (0.00%)	0 / 122 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Staphylococcal scalded skin syndrome			

subjects affected / exposed[161]	0 / 158 (0.00%)	0 / 61 (0.00%)	1 / 122 (0.82%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Subcutaneous abscess			
subjects affected / exposed[162]	0 / 158 (0.00%)	0 / 61 (0.00%)	0 / 122 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tracheitis			
subjects affected / exposed[163]	2 / 158 (1.27%)	0 / 61 (0.00%)	0 / 122 (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
Tracheobronchitis			
subjects affected / exposed[164]	1 / 158 (0.63%)	0 / 61 (0.00%)	0 / 122 (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
Viral myocarditis			
subjects affected / exposed[165]	0 / 158 (0.00%)	0 / 61 (0.00%)	0 / 122 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular access site infection			
subjects affected / exposed[166]	1 / 158 (0.63%)	0 / 61 (0.00%)	0 / 122 (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[167]	1 / 158 (0.63%)	1 / 61 (1.64%)	2 / 122 (1.64%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Tracheostomy infection			
subjects affected / exposed[168]	0 / 158 (0.00%)	1 / 61 (1.64%)	1 / 122 (0.82%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper respiratory tract infection			

subjects affected / exposed[169]	0 / 158 (0.00%)	0 / 61 (0.00%)	1 / 122 (0.82%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Viral upper respiratory tract infection			
subjects affected / exposed[170]	1 / 158 (0.63%)	0 / 61 (0.00%)	0 / 122 (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			
Diabetes mellitus			
subjects affected / exposed[171]	0 / 158 (0.00%)	0 / 61 (0.00%)	2 / 122 (1.64%)
occurrences causally related to treatment / all	0 / 0	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dehydration			
subjects affected / exposed[172]	4 / 158 (2.53%)	0 / 61 (0.00%)	2 / 122 (1.64%)
occurrences causally related to treatment / all	0 / 4	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Failure to thrive			
subjects affected / exposed[173]	0 / 158 (0.00%)	0 / 61 (0.00%)	1 / 122 (0.82%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Electrolyte imbalance			
subjects affected / exposed[174]	0 / 158 (0.00%)	0 / 61 (0.00%)	1 / 122 (0.82%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Feeding disorder			
subjects affected / exposed[175]	1 / 158 (0.63%)	0 / 61 (0.00%)	0 / 122 (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[176]	0 / 158 (0.00%)	0 / 61 (0.00%)	0 / 122 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperglycaemia			

subjects affected / exposed[177]	0 / 158 (0.00%)	0 / 61 (0.00%)	1 / 122 (0.82%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypercalcaemia			
subjects affected / exposed[178]	6 / 158 (3.80%)	1 / 61 (1.64%)	1 / 122 (0.82%)
occurrences causally related to treatment / all	0 / 6	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Malnutrition			
subjects affected / exposed[179]	1 / 158 (0.63%)	0 / 61 (0.00%)	0 / 122 (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
Hyponatraemia			
subjects affected / exposed[180]	2 / 158 (1.27%)	1 / 61 (1.64%)	0 / 122 (0.00%)
occurrences causally related to treatment / all	0 / 2	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypokalaemia			
subjects affected / exposed[181]	1 / 158 (0.63%)	0 / 61 (0.00%)	0 / 122 (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
Hypernatraemia			
subjects affected / exposed[182]	0 / 158 (0.00%)	0 / 61 (0.00%)	1 / 122 (0.82%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1

Serious adverse events	Treatment B - Platinum Refractory Subgroup		
Total subjects affected by serious adverse events			
subjects affected / exposed	52 / 82 (63.41%)		
number of deaths (all causes)	71		
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Cancer pain			

subjects affected / exposed[1]	0 / 82 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Basal cell carcinoma				
subjects affected / exposed[2]	0 / 82 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hepatocellular carcinoma				
subjects affected / exposed[3]	0 / 82 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Malignant neoplasm progression				
subjects affected / exposed[4]	25 / 82 (30.49%)			
occurrences causally related to treatment / all	0 / 25			
deaths causally related to treatment / all	0 / 25			
Malignant pleural effusion				
subjects affected / exposed[5]	0 / 82 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Metastases to bone				
subjects affected / exposed[6]	0 / 82 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Second primary malignancy				
subjects affected / exposed[7]	0 / 82 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Tumour associated fever				
subjects affected / exposed[8]	0 / 82 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Tumour haemorrhage				

subjects affected / exposed[9]	1 / 82 (1.22%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Tumour pain				
subjects affected / exposed[10]	1 / 82 (1.22%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Vascular disorders				
Hypovolaemic shock				
subjects affected / exposed[11]	1 / 82 (1.22%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Haemorrhage				
subjects affected / exposed[12]	1 / 82 (1.22%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Embolism				
subjects affected / exposed[13]	1 / 82 (1.22%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Lymphoedema				
subjects affected / exposed[14]	0 / 82 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Peripheral venous disease				
subjects affected / exposed[15]	0 / 82 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Superior vena cava syndrome				
subjects affected / exposed[16]	0 / 82 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
General disorders and administration site conditions				

Hyperthermia				
subjects affected / exposed[17]	0 / 82 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Generalised oedema				
subjects affected / exposed[18]	0 / 82 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
General physical health deterioration				
subjects affected / exposed[19]	0 / 82 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Fatigue				
subjects affected / exposed[20]	0 / 82 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Face oedema				
subjects affected / exposed[21]	0 / 82 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Drug intolerance				
subjects affected / exposed[22]	0 / 82 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Death				
subjects affected / exposed[23]	0 / 82 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Chest pain				
subjects affected / exposed[24]	1 / 82 (1.22%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Swelling				

subjects affected / exposed[25]	0 / 82 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Sudden death				
subjects affected / exposed[26]	0 / 82 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pyrexia				
subjects affected / exposed[27]	1 / 82 (1.22%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Impaired healing				
subjects affected / exposed[28]	0 / 82 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Mucosal inflammation				
subjects affected / exposed[29]	0 / 82 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Malaise				
subjects affected / exposed[30]	0 / 82 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Inflammation				
subjects affected / exposed[31]	0 / 82 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pain				
subjects affected / exposed[32]	0 / 82 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Immune system disorders				
Drug hypersensitivity				

subjects affected / exposed[33]	0 / 82 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Autoimmune lung disease			
subjects affected / exposed[34]	0 / 82 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Chronic obstructive pulmonary disease			
subjects affected / exposed[35]	0 / 82 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Dyspnoea			
subjects affected / exposed[36]	3 / 82 (3.66%)		
occurrences causally related to treatment / all	1 / 4		
deaths causally related to treatment / all	0 / 0		
Haemoptysis			
subjects affected / exposed[37]	0 / 82 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hypoxia			
subjects affected / exposed[38]	1 / 82 (1.22%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Laryngeal dyspnoea			
subjects affected / exposed[39]	1 / 82 (1.22%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Lung disorder			
subjects affected / exposed[40]	1 / 82 (1.22%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Laryngeal oedema			

subjects affected / exposed[41]	0 / 82 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Laryngeal obstruction				
subjects affected / exposed[42]	0 / 82 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Laryngeal haemorrhage				
subjects affected / exposed[43]	1 / 82 (1.22%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Nasal obstruction				
subjects affected / exposed[44]	0 / 82 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Obstructive airways disorder				
subjects affected / exposed[45]	0 / 82 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pharyngeal oedema				
subjects affected / exposed[46]	0 / 82 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pleural effusion				
subjects affected / exposed[47]	1 / 82 (1.22%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pneumonitis				
subjects affected / exposed[48]	2 / 82 (2.44%)			
occurrences causally related to treatment / all	1 / 3			
deaths causally related to treatment / all	0 / 0			
Pneumothorax				

subjects affected / exposed[49]	1 / 82 (1.22%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pulmonary embolism			
subjects affected / exposed[50]	0 / 82 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Respiratory distress			
subjects affected / exposed[51]	0 / 82 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Respiratory failure			
subjects affected / exposed[52]	0 / 82 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Insomnia			
subjects affected / exposed[53]	0 / 82 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Product issues			
Device leakage			
subjects affected / exposed[54]	0 / 82 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Device dislocation			
subjects affected / exposed[55]	0 / 82 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Investigations			
Weight decreased			
subjects affected / exposed[56]	1 / 82 (1.22%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Platelet count decreased				
subjects affected / exposed[57]	1 / 82 (1.22%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Creatinine renal clearance decreased				
subjects affected / exposed[58]	0 / 82 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Injury, poisoning and procedural complications				
Head injury				
subjects affected / exposed[59]	0 / 82 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hand fracture				
subjects affected / exposed[60]	1 / 82 (1.22%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Foot fracture				
subjects affected / exposed[61]	1 / 82 (1.22%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Femur fracture				
subjects affected / exposed[62]	0 / 82 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Accidental overdose				
subjects affected / exposed[63]	0 / 82 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Infusion related reaction				
subjects affected / exposed[64]	0 / 82 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			

Spinal compression fracture				
subjects affected / exposed[65]	0 / 82 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Post procedural haemorrhage				
subjects affected / exposed[66]	1 / 82 (1.22%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Overdose				
subjects affected / exposed[67]	0 / 82 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Toxicity to various agents				
subjects affected / exposed[68]	0 / 82 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Tracheal haemorrhage				
subjects affected / exposed[69]	0 / 82 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Upper limb fracture				
subjects affected / exposed[70]	0 / 82 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Vasoplegia syndrome				
subjects affected / exposed[71]	0 / 82 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cardiac disorders				
Cardiac failure congestive				
subjects affected / exposed[72]	0 / 82 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Arrhythmia				

subjects affected / exposed[73]	1 / 82 (1.22%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Cardiac arrest				
subjects affected / exposed[74]	0 / 82 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cardiac failure				
subjects affected / exposed[75]	0 / 82 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Acute myocardial infarction				
subjects affected / exposed[76]	1 / 82 (1.22%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pericardial effusion				
subjects affected / exposed[77]	0 / 82 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Myocardial infarction				
subjects affected / exposed[78]	0 / 82 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Nervous system disorders				
Carotid aneurysm rupture				
subjects affected / exposed[79]	1 / 82 (1.22%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Ischaemic stroke				
subjects affected / exposed[80]	1 / 82 (1.22%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cerebrovascular accident				

subjects affected / exposed[81]	0 / 82 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cerebral ischaemia				
subjects affected / exposed[82]	1 / 82 (1.22%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Nervous system disorder				
subjects affected / exposed[83]	0 / 82 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Syncope				
subjects affected / exposed[84]	0 / 82 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Neuropathy peripheral				
subjects affected / exposed[85]	0 / 82 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Blood and lymphatic system disorders				
Anaemia				
subjects affected / exposed[86]	1 / 82 (1.22%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Lymph node pain				
subjects affected / exposed[87]	0 / 82 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Neutropenia				
subjects affected / exposed[88]	0 / 82 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Febrile bone marrow aplasia				

subjects affected / exposed[89]	0 / 82 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Ear and labyrinth disorders			
Vestibular disorder			
subjects affected / exposed[90]	0 / 82 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Ascites			
subjects affected / exposed[91]	0 / 82 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Abdominal distension			
subjects affected / exposed[92]	0 / 82 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Abdominal pain upper			
subjects affected / exposed[93]	0 / 82 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Diarrhoea			
subjects affected / exposed[94]	1 / 82 (1.22%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Constipation			
subjects affected / exposed[95]	1 / 82 (1.22%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Colitis			
subjects affected / exposed[96]	0 / 82 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Autoimmune colitis			

subjects affected / exposed[97]	0 / 82 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Duodenitis				
subjects affected / exposed[98]	0 / 82 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Haematemesis				
subjects affected / exposed[99]	0 / 82 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal haemorrhage				
subjects affected / exposed[100]	0 / 82 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Gastric ulcer				
subjects affected / exposed[101]	0 / 82 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Dysphagia				
subjects affected / exposed[102]	0 / 82 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hernial eventration				
subjects affected / exposed[103]	1 / 82 (1.22%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Immune-mediated enterocolitis				
subjects affected / exposed[104]	1 / 82 (1.22%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Impaired gastric emptying				

subjects affected / exposed[105]	1 / 82 (1.22%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Mouth haemorrhage				
subjects affected / exposed[106]	0 / 82 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Small intestinal perforation				
subjects affected / exposed[107]	0 / 82 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pancreatitis				
subjects affected / exposed[108]	0 / 82 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Palatal disorder				
subjects affected / exposed[109]	0 / 82 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Oesophageal fistula				
subjects affected / exposed[110]	1 / 82 (1.22%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Nausea				
subjects affected / exposed[111]	2 / 82 (2.44%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 0			
Mouth ulceration				
subjects affected / exposed[112]	1 / 82 (1.22%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Stomatitis				

subjects affected / exposed[113]	1 / 82 (1.22%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Vomiting				
subjects affected / exposed[114]	3 / 82 (3.66%)			
occurrences causally related to treatment / all	2 / 3			
deaths causally related to treatment / all	0 / 1			
Hepatobiliary disorders				
Autoimmune hepatitis				
subjects affected / exposed[115]	0 / 82 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cholecystitis				
subjects affected / exposed[116]	0 / 82 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hepatitis				
subjects affected / exposed[117]	0 / 82 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hepatotoxicity				
subjects affected / exposed[118]	1 / 82 (1.22%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Immune-mediated hepatitis				
subjects affected / exposed[119]	0 / 82 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Skin and subcutaneous tissue disorders				
Pruritus				
subjects affected / exposed[120]	0 / 82 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Rash				

subjects affected / exposed[121]	0 / 82 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Rash maculo-papular			
subjects affected / exposed[122]	0 / 82 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed[123]	0 / 82 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Renal failure			
subjects affected / exposed[124]	0 / 82 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Endocrine disorders			
Adrenal insufficiency			
subjects affected / exposed[125]	0 / 82 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hypophysitis			
subjects affected / exposed[126]	0 / 82 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Adrenocortical insufficiency acute			
subjects affected / exposed[127]	0 / 82 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed[128]	1 / 82 (1.22%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Neck pain				
subjects affected / exposed[129]	0 / 82 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Spinal pain				
subjects affected / exposed[130]	0 / 82 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pathological fracture				
subjects affected / exposed[131]	0 / 82 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Osteonecrosis				
subjects affected / exposed[132]	0 / 82 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Infections and infestations				
Abscess neck				
subjects affected / exposed[133]	0 / 82 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Bacteraemia				
subjects affected / exposed[134]	0 / 82 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cellulitis				
subjects affected / exposed[135]	0 / 82 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Encephalitis				
subjects affected / exposed[136]	1 / 82 (1.22%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Empyema				

subjects affected / exposed[137]	0 / 82 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Influenza				
subjects affected / exposed[138]	0 / 82 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Lower respiratory tract infection				
subjects affected / exposed[139]	1 / 82 (1.22%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Ludwig angina				
subjects affected / exposed[140]	0 / 82 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Endocarditis				
subjects affected / exposed[141]	1 / 82 (1.22%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Epiglottitis				
subjects affected / exposed[142]	0 / 82 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Focal peritonitis				
subjects affected / exposed[143]	0 / 82 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Gastroenteritis				
subjects affected / exposed[144]	0 / 82 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hepatic infection bacterial				

subjects affected / exposed[145]	0 / 82 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Herpes zoster				
subjects affected / exposed[146]	0 / 82 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Infective myositis				
subjects affected / exposed[147]	0 / 82 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Lymph node abscess				
subjects affected / exposed[148]	0 / 82 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Neutropenic sepsis				
subjects affected / exposed[149]	1 / 82 (1.22%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Oral infection				
subjects affected / exposed[150]	0 / 82 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pneumococcal sepsis				
subjects affected / exposed[151]	1 / 82 (1.22%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Sepsis syndrome				
subjects affected / exposed[152]	0 / 82 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pneumonia aspiration				

subjects affected / exposed[153]	0 / 82 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pneumonia pseudomonal				
subjects affected / exposed[154]	0 / 82 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Sepsis				
subjects affected / exposed[155]	0 / 82 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pneumonia				
subjects affected / exposed[156]	5 / 82 (6.10%)			
occurrences causally related to treatment / all	0 / 6			
deaths causally related to treatment / all	0 / 1			
Septic shock				
subjects affected / exposed[157]	0 / 82 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Sinusitis				
subjects affected / exposed[158]	1 / 82 (1.22%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Skin infection				
subjects affected / exposed[159]	1 / 82 (1.22%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Staphylococcal bacteraemia				
subjects affected / exposed[160]	2 / 82 (2.44%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Staphylococcal scalded skin syndrome				

subjects affected / exposed[161]	0 / 82 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Subcutaneous abscess				
subjects affected / exposed[162]	1 / 82 (1.22%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Tracheitis				
subjects affected / exposed[163]	0 / 82 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Tracheobronchitis				
subjects affected / exposed[164]	0 / 82 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Viral myocarditis				
subjects affected / exposed[165]	1 / 82 (1.22%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Vascular access site infection				
subjects affected / exposed[166]	0 / 82 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Urinary tract infection				
subjects affected / exposed[167]	0 / 82 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Tracheostomy infection				
subjects affected / exposed[168]	0 / 82 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Upper respiratory tract infection				

subjects affected / exposed[169]	2 / 82 (2.44%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Viral upper respiratory tract infection				
subjects affected / exposed[170]	0 / 82 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Metabolism and nutrition disorders				
Diabetes mellitus				
subjects affected / exposed[171]	0 / 82 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Dehydration				
subjects affected / exposed[172]	0 / 82 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Failure to thrive				
subjects affected / exposed[173]	0 / 82 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Electrolyte imbalance				
subjects affected / exposed[174]	0 / 82 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Feeding disorder				
subjects affected / exposed[175]	0 / 82 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hyperkalaemia				
subjects affected / exposed[176]	1 / 82 (1.22%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Hyperglycaemia				

subjects affected / exposed[177]	0 / 82 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hypercalcaemia			
subjects affected / exposed[178]	2 / 82 (2.44%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Malnutrition			
subjects affected / exposed[179]	0 / 82 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hyponatraemia			
subjects affected / exposed[180]	2 / 82 (2.44%)		
occurrences causally related to treatment / all	2 / 3		
deaths causally related to treatment / all	0 / 0		
Hypokalaemia			
subjects affected / exposed[181]	0 / 82 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hypernatraemia			
subjects affected / exposed[182]	0 / 82 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Notes:

[1] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.
Justification: Number exposed is reflecting all randomized participants

[2] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.
Justification: Number exposed is reflecting all randomized participants

[3] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.
Justification: Number exposed is reflecting all randomized participants

[4] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.
Justification: Number exposed is reflecting all randomized participants

[5] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.
Justification: Number exposed is reflecting all randomized participants

[6] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.
Justification: Number exposed is reflecting all randomized participants

[7] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.
Justification: Number exposed is reflecting all randomized participants

[8] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.
Justification: Number exposed is reflecting all randomized participants

[9] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.
Justification: Number exposed is reflecting all randomized participants

[10] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.
Justification: Number exposed is reflecting all randomized participants

[11] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.
Justification: Number exposed is reflecting all randomized participants

[12] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.
Justification: Number exposed is reflecting all randomized participants

[13] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.
Justification: Number exposed is reflecting all randomized participants

[14] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.
Justification: Number exposed is reflecting all randomized participants

[15] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.
Justification: Number exposed is reflecting all randomized participants

[16] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.
Justification: Number exposed is reflecting all randomized participants

[17] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.
Justification: Number exposed is reflecting all randomized participants

[18] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.
Justification: Number exposed is reflecting all randomized participants

[19] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.
Justification: Number exposed is reflecting all randomized participants

[20] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.
Justification: Number exposed is reflecting all randomized participants

[21] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.
Justification: Number exposed is reflecting all randomized participants

[22] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.
Justification: Number exposed is reflecting all randomized participants

[23] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.
Justification: Number exposed is reflecting all randomized participants

[24] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.
Justification: Number exposed is reflecting all randomized participants

[25] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.
Justification: Number exposed is reflecting all randomized participants

[26] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.
Justification: Number exposed is reflecting all randomized participants

[27] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.
Justification: Number exposed is reflecting all randomized participants

[28] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.
Justification: Number exposed is reflecting all randomized participants

[29] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.
Justification: Number exposed is reflecting all randomized participants

[30] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.
Justification: Number exposed is reflecting all randomized participants

[31] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.
Justification: Number exposed is reflecting all randomized participants

[32] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.
Justification: Number exposed is reflecting all randomized participants

[33] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.
Justification: Number exposed is reflecting all randomized participants

[34] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.
Justification: Number exposed is reflecting all randomized participants

[35] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.
Justification: Number exposed is reflecting all randomized participants

[36] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.
Justification: Number exposed is reflecting all randomized participants

[37] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.
Justification: Number exposed is reflecting all randomized participants

[38] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.
Justification: Number exposed is reflecting all randomized participants

[39] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.
Justification: Number exposed is reflecting all randomized participants

[40] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.
Justification: Number exposed is reflecting all randomized participants

[41] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.
Justification: Number exposed is reflecting all randomized participants

[42] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.
Justification: Number exposed is reflecting all randomized participants

[43] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.
Justification: Number exposed is reflecting all randomized participants

[44] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.
Justification: Number exposed is reflecting all randomized participants

[45] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.
Justification: Number exposed is reflecting all randomized participants

[46] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.
Justification: Number exposed is reflecting all randomized participants

[47] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.
Justification: Number exposed is reflecting all randomized participants

[48] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.
Justification: Number exposed is reflecting all randomized participants

[49] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.
Justification: Number exposed is reflecting all randomized participants

[50] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.
Justification: Number exposed is reflecting all randomized participants

[51] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.
Justification: Number exposed is reflecting all randomized participants

[52] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.
Justification: Number exposed is reflecting all randomized participants

[53] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.
Justification: Number exposed is reflecting all randomized participants

[54] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.
Justification: Number exposed is reflecting all randomized participants

[55] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.
Justification: Number exposed is reflecting all randomized participants

[56] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.
Justification: Number exposed is reflecting all randomized participants

[57] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.
Justification: Number exposed is reflecting all randomized participants

[58] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.
Justification: Number exposed is reflecting all randomized participants

[59] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.
Justification: Number exposed is reflecting all randomized participants

[60] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.
Justification: Number exposed is reflecting all randomized participants

[61] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.
Justification: Number exposed is reflecting all randomized participants

[62] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.
Justification: Number exposed is reflecting all randomized participants

[63] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.
Justification: Number exposed is reflecting all randomized participants

[64] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.
Justification: Number exposed is reflecting all randomized participants

[65] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.
Justification: Number exposed is reflecting all randomized participants

[66] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.
Justification: Number exposed is reflecting all randomized participants

[67] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.
Justification: Number exposed is reflecting all randomized participants

[68] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.
Justification: Number exposed is reflecting all randomized participants

[69] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.
Justification: Number exposed is reflecting all randomized participants

[70] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.
Justification: Number exposed is reflecting all randomized participants

[71] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.
Justification: Number exposed is reflecting all randomized participants

[72] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.
Justification: Number exposed is reflecting all randomized participants

[73] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.
Justification: Number exposed is reflecting all randomized participants

[74] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.
Justification: Number exposed is reflecting all randomized participants

[75] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.
Justification: Number exposed is reflecting all randomized participants

[76] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.
Justification: Number exposed is reflecting all randomized participants

[77] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.
Justification: Number exposed is reflecting all randomized participants

[78] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.
Justification: Number exposed is reflecting all randomized participants

[79] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.
Justification: Number exposed is reflecting all randomized participants

[80] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.
Justification: Number exposed is reflecting all randomized participants

[81] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.
Justification: Number exposed is reflecting all randomized participants

[82] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.
Justification: Number exposed is reflecting all randomized participants

[83] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.
Justification: Number exposed is reflecting all randomized participants

[84] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.
Justification: Number exposed is reflecting all randomized participants

[85] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.
Justification: Number exposed is reflecting all randomized participants

[86] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.
Justification: Number exposed is reflecting all randomized participants

[87] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.
Justification: Number exposed is reflecting all randomized participants

[88] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.
Justification: Number exposed is reflecting all randomized participants

[89] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.
Justification: Number exposed is reflecting all randomized participants

[90] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.
Justification: Number exposed is reflecting all randomized participants

[91] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.
Justification: Number exposed is reflecting all randomized participants

[92] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.
Justification: Number exposed is reflecting all randomized participants

[93] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.
Justification: Number exposed is reflecting all randomized participants

[94] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.
Justification: Number exposed is reflecting all randomized participants

[95] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.
Justification: Number exposed is reflecting all randomized participants

[96] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.
Justification: Number exposed is reflecting all randomized participants

[97] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.
Justification: Number exposed is reflecting all randomized participants

[98] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.
Justification: Number exposed is reflecting all randomized participants

[99] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.
Justification: Number exposed is reflecting all randomized participants

[100] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.
Justification: Number exposed is reflecting all randomized participants

[101] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.
Justification: Number exposed is reflecting all randomized participants

[102] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.
Justification: Number exposed is reflecting all randomized participants

[103] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.
Justification: Number exposed is reflecting all randomized participants

[104] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.
Justification: Number exposed is reflecting all randomized participants

[105] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.
Justification: Number exposed is reflecting all randomized participants

[106] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.
Justification: Number exposed is reflecting all randomized participants

[107] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.
Justification: Number exposed is reflecting all randomized participants

[108] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.
Justification: Number exposed is reflecting all randomized participants

[109] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.
Justification: Number exposed is reflecting all randomized participants

[110] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.
Justification: Number exposed is reflecting all randomized participants

[111] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.
Justification: Number exposed is reflecting all randomized participants

[112] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.
Justification: Number exposed is reflecting all randomized participants

[113] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.
Justification: Number exposed is reflecting all randomized participants

[114] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.
Justification: Number exposed is reflecting all randomized participants

[115] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.
Justification: Number exposed is reflecting all randomized participants

[116] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.
Justification: Number exposed is reflecting all randomized participants

[117] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.
Justification: Number exposed is reflecting all randomized participants

[118] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.
Justification: Number exposed is reflecting all randomized participants

[119] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.
Justification: Number exposed is reflecting all randomized participants

[120] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.
Justification: Number exposed is reflecting all randomized participants

[121] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.
Justification: Number exposed is reflecting all randomized participants

[122] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.
Justification: Number exposed is reflecting all randomized participants

[123] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.
Justification: Number exposed is reflecting all randomized participants

[124] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.
Justification: Number exposed is reflecting all randomized participants

[125] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.
Justification: Number exposed is reflecting all randomized participants

[126] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.
Justification: Number exposed is reflecting all randomized participants

[127] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.
Justification: Number exposed is reflecting all randomized participants

[128] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.
Justification: Number exposed is reflecting all randomized participants

[129] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.
Justification: Number exposed is reflecting all randomized participants

[130] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.
Justification: Number exposed is reflecting all randomized participants

[131] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.
Justification: Number exposed is reflecting all randomized participants

[132] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.
Justification: Number exposed is reflecting all randomized participants

[133] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.
Justification: Number exposed is reflecting all randomized participants

[134] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.
Justification: Number exposed is reflecting all randomized participants

[135] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.
Justification: Number exposed is reflecting all randomized participants

[136] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.
Justification: Number exposed is reflecting all randomized participants

[137] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.
Justification: Number exposed is reflecting all randomized participants

[138] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.
Justification: Number exposed is reflecting all randomized participants

[139] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.
Justification: Number exposed is reflecting all randomized participants

[140] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.
Justification: Number exposed is reflecting all randomized participants

[141] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.
Justification: Number exposed is reflecting all randomized participants

[142] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.
Justification: Number exposed is reflecting all randomized participants

[143] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.
Justification: Number exposed is reflecting all randomized participants

[144] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.
Justification: Number exposed is reflecting all randomized participants

[145] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.
Justification: Number exposed is reflecting all randomized participants

[146] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.
Justification: Number exposed is reflecting all randomized participants

[147] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.
Justification: Number exposed is reflecting all randomized participants

[148] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.
Justification: Number exposed is reflecting all randomized participants

[149] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.
Justification: Number exposed is reflecting all randomized participants

[150] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.
Justification: Number exposed is reflecting all randomized participants

[151] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.
Justification: Number exposed is reflecting all randomized participants

[152] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.
Justification: Number exposed is reflecting all randomized participants

[153] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.
Justification: Number exposed is reflecting all randomized participants

[154] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.
Justification: Number exposed is reflecting all randomized participants

[155] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.
Justification: Number exposed is reflecting all randomized participants

[156] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.
Justification: Number exposed is reflecting all randomized participants

[157] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.
Justification: Number exposed is reflecting all randomized participants

[158] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.
Justification: Number exposed is reflecting all randomized participants

[159] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.
Justification: Number exposed is reflecting all randomized participants

[160] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.
Justification: Number exposed is reflecting all randomized participants

[161] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.
Justification: Number exposed is reflecting all randomized participants

[162] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.
Justification: Number exposed is reflecting all randomized participants

[163] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.
Justification: Number exposed is reflecting all randomized participants

[164] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.
Justification: Number exposed is reflecting all randomized participants

[165] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.
Justification: Number exposed is reflecting all randomized participants

[166] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.
Justification: Number exposed is reflecting all randomized participants

[167] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.
Justification: Number exposed is reflecting all randomized participants

[168] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.
Justification: Number exposed is reflecting all randomized participants

[169] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.
Justification: Number exposed is reflecting all randomized participants

[170] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.
Justification: Number exposed is reflecting all randomized participants

[171] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.
Justification: Number exposed is reflecting all randomized participants

[172] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.
Justification: Number exposed is reflecting all randomized participants

[173] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.
Justification: Number exposed is reflecting all randomized participants

[174] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.
Justification: Number exposed is reflecting all randomized participants

[175] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.
Justification: Number exposed is reflecting all randomized participants

[176] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.
Justification: Number exposed is reflecting all randomized participants

[177] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.
Justification: Number exposed is reflecting all randomized participants

[178] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.
Justification: Number exposed is reflecting all randomized participants

[179] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.
Justification: Number exposed is reflecting all randomized participants

[180] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.
Justification: Number exposed is reflecting all randomized participants

[181] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.
Justification: Number exposed is reflecting all randomized participants

[182] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.
Justification: Number exposed is reflecting all randomized participants

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

Non-serious adverse events	Treatment A - Platinum Refractory Subgroup	Treatment B - Platinum Eligible Subgroup	Treatment A - Platinum Eligible Subgroup
Total subjects affected by non-serious adverse events			
subjects affected / exposed	139 / 159 (87.42%)	54 / 61 (88.52%)	118 / 123 (95.93%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			

Cancer pain			
subjects affected / exposed[183]	3 / 158 (1.90%)	4 / 61 (6.56%)	2 / 122 (1.64%)
occurrences (all)	3	4	2
Vascular disorders			
Hypotension			
subjects affected / exposed[184]	6 / 158 (3.80%)	6 / 61 (9.84%)	5 / 122 (4.10%)
occurrences (all)	7	6	7
Hypertension			
subjects affected / exposed[185]	2 / 158 (1.27%)	4 / 61 (6.56%)	5 / 122 (4.10%)
occurrences (all)	2	4	5
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed[186]	27 / 158 (17.09%)	7 / 61 (11.48%)	13 / 122 (10.66%)
occurrences (all)	42	13	18
Chills			
subjects affected / exposed[187]	2 / 158 (1.27%)	0 / 61 (0.00%)	7 / 122 (5.74%)
occurrences (all)	3	0	7
Face oedema			
subjects affected / exposed[188]	9 / 158 (5.70%)	2 / 61 (3.28%)	7 / 122 (5.74%)
occurrences (all)	9	3	7
Fatigue			
subjects affected / exposed[189]	29 / 158 (18.35%)	22 / 61 (36.07%)	46 / 122 (37.70%)
occurrences (all)	31	22	55
Mucosal inflammation			
subjects affected / exposed[190]	9 / 158 (5.70%)	2 / 61 (3.28%)	8 / 122 (6.56%)
occurrences (all)	9	2	9
Pyrexia			
subjects affected / exposed[191]	15 / 158 (9.49%)	5 / 61 (8.20%)	15 / 122 (12.30%)
occurrences (all)	16	8	20
Oedema peripheral			
subjects affected / exposed[192]	7 / 158 (4.43%)	1 / 61 (1.64%)	10 / 122 (8.20%)
occurrences (all)	7	1	10
Respiratory, thoracic and mediastinal disorders			
Productive cough			
subjects affected / exposed[193]	9 / 158 (5.70%)	7 / 61 (11.48%)	6 / 122 (4.92%)
occurrences (all)	12	8	6

Dyspnoea			
subjects affected / exposed[194]	17 / 158 (10.76%)	9 / 61 (14.75%)	20 / 122 (16.39%)
occurrences (all)	17	12	22
Cough			
subjects affected / exposed[195]	20 / 158 (12.66%)	9 / 61 (14.75%)	20 / 122 (16.39%)
occurrences (all)	22	13	21
Psychiatric disorders			
Insomnia			
subjects affected / exposed[196]	13 / 158 (8.23%)	5 / 61 (8.20%)	5 / 122 (4.10%)
occurrences (all)	14	5	7
Anxiety			
subjects affected / exposed[197]	9 / 158 (5.70%)	4 / 61 (6.56%)	2 / 122 (1.64%)
occurrences (all)	9	4	2
Investigations			
Aspartate aminotransferase increased			
subjects affected / exposed[198]	9 / 158 (5.70%)	5 / 61 (8.20%)	11 / 122 (9.02%)
occurrences (all)	15	8	27
Amylase increased			
subjects affected / exposed[199]	4 / 158 (2.53%)	3 / 61 (4.92%)	10 / 122 (8.20%)
occurrences (all)	7	6	19
Alanine aminotransferase increased			
subjects affected / exposed[200]	8 / 158 (5.06%)	6 / 61 (9.84%)	7 / 122 (5.74%)
occurrences (all)	9	9	17
Blood alkaline phosphatase increased			
subjects affected / exposed[201]	7 / 158 (4.43%)	3 / 61 (4.92%)	9 / 122 (7.38%)
occurrences (all)	17	4	16
Weight decreased			
subjects affected / exposed[202]	20 / 158 (12.66%)	5 / 61 (8.20%)	25 / 122 (20.49%)
occurrences (all)	22	5	25
Lipase increased			
subjects affected / exposed[203]	13 / 158 (8.23%)	5 / 61 (8.20%)	11 / 122 (9.02%)
occurrences (all)	18	10	17
Blood thyroid stimulating hormone increased			
subjects affected / exposed[204]	4 / 158 (2.53%)	4 / 61 (6.56%)	5 / 122 (4.10%)
occurrences (all)	6	6	8
Blood creatinine increased			

subjects affected / exposed[205]	11 / 158 (6.96%)	5 / 61 (8.20%)	7 / 122 (5.74%)
occurrences (all)	20	6	17
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed[206]	1 / 158 (0.63%)	4 / 61 (6.56%)	2 / 122 (1.64%)
occurrences (all)	1	5	3
Nervous system disorders			
Headache			
subjects affected / exposed[207]	14 / 158 (8.86%)	6 / 61 (9.84%)	11 / 122 (9.02%)
occurrences (all)	16	6	16
Dizziness			
subjects affected / exposed[208]	8 / 158 (5.06%)	4 / 61 (6.56%)	5 / 122 (4.10%)
occurrences (all)	8	4	6
Blood and lymphatic system disorders			
Lymphopenia			
subjects affected / exposed[209]	12 / 158 (7.59%)	2 / 61 (3.28%)	0 / 122 (0.00%)
occurrences (all)	16	2	0
Anaemia			
subjects affected / exposed[210]	41 / 158 (25.95%)	15 / 61 (24.59%)	30 / 122 (24.59%)
occurrences (all)	50	18	39
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed[211]	8 / 158 (5.06%)	4 / 61 (6.56%)	10 / 122 (8.20%)
occurrences (all)	14	4	15
Dysphagia			
subjects affected / exposed[212]	16 / 158 (10.13%)	7 / 61 (11.48%)	18 / 122 (14.75%)
occurrences (all)	17	7	19
Nausea			
subjects affected / exposed[213]	31 / 158 (19.62%)	13 / 61 (21.31%)	28 / 122 (22.95%)
occurrences (all)	41	18	38
Stomatitis			
subjects affected / exposed[214]	2 / 158 (1.27%)	1 / 61 (1.64%)	6 / 122 (4.92%)
occurrences (all)	2	1	7
Vomiting			
subjects affected / exposed[215]	18 / 158 (11.39%)	5 / 61 (8.20%)	14 / 122 (11.48%)
occurrences (all)	23	12	25

Dyspepsia			
subjects affected / exposed[216]	6 / 158 (3.80%)	3 / 61 (4.92%)	7 / 122 (5.74%)
occurrences (all)	7	4	7
Abdominal pain upper			
subjects affected / exposed[217]	7 / 158 (4.43%)	5 / 61 (8.20%)	4 / 122 (3.28%)
occurrences (all)	8	6	4
Constipation			
subjects affected / exposed[218]	24 / 158 (15.19%)	9 / 61 (14.75%)	26 / 122 (21.31%)
occurrences (all)	32	10	28
Dry mouth			
subjects affected / exposed[219]	11 / 158 (6.96%)	3 / 61 (4.92%)	9 / 122 (7.38%)
occurrences (all)	12	3	9
Diarrhoea			
subjects affected / exposed[220]	33 / 158 (20.89%)	15 / 61 (24.59%)	27 / 122 (22.13%)
occurrences (all)	52	20	39
Skin and subcutaneous tissue disorders			
Dry skin			
subjects affected / exposed[221]	10 / 158 (6.33%)	1 / 61 (1.64%)	6 / 122 (4.92%)
occurrences (all)	10	1	6
Pruritus			
subjects affected / exposed[222]	33 / 158 (20.89%)	10 / 61 (16.39%)	24 / 122 (19.67%)
occurrences (all)	46	13	29
Rash			
subjects affected / exposed[223]	32 / 158 (20.25%)	6 / 61 (9.84%)	19 / 122 (15.57%)
occurrences (all)	49	7	25
Erythema			
subjects affected / exposed[224]	3 / 158 (1.90%)	1 / 61 (1.64%)	8 / 122 (6.56%)
occurrences (all)	3	2	9
Endocrine disorders			
Hyperthyroidism			
subjects affected / exposed[225]	12 / 158 (7.59%)	1 / 61 (1.64%)	11 / 122 (9.02%)
occurrences (all)	13	1	11
Hypothyroidism			
subjects affected / exposed[226]	28 / 158 (17.72%)	12 / 61 (19.67%)	23 / 122 (18.85%)
occurrences (all)	29	15	23
Musculoskeletal and connective tissue disorders			

Neck pain			
subjects affected / exposed[227]	18 / 158 (11.39%)	9 / 61 (14.75%)	7 / 122 (5.74%)
occurrences (all)	23	12	7
Myalgia			
subjects affected / exposed[228]	5 / 158 (3.16%)	3 / 61 (4.92%)	8 / 122 (6.56%)
occurrences (all)	5	4	8
Back pain			
subjects affected / exposed[229]	10 / 158 (6.33%)	5 / 61 (8.20%)	12 / 122 (9.84%)
occurrences (all)	10	5	13
Arthralgia			
subjects affected / exposed[230]	20 / 158 (12.66%)	10 / 61 (16.39%)	18 / 122 (14.75%)
occurrences (all)	21	10	21
Infections and infestations			
Pneumonia			
subjects affected / exposed[231]	10 / 158 (6.33%)	2 / 61 (3.28%)	8 / 122 (6.56%)
occurrences (all)	13	3	9
Oral candidiasis			
subjects affected / exposed[232]	9 / 158 (5.70%)	2 / 61 (3.28%)	1 / 122 (0.82%)
occurrences (all)	9	2	1
Nasopharyngitis			
subjects affected / exposed[233]	2 / 158 (1.27%)	4 / 61 (6.56%)	6 / 122 (4.92%)
occurrences (all)	2	6	8
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed[234]	21 / 158 (13.29%)	8 / 61 (13.11%)	25 / 122 (20.49%)
occurrences (all)	22	8	29
Hypercalcaemia			
subjects affected / exposed[235]	18 / 158 (11.39%)	4 / 61 (6.56%)	11 / 122 (9.02%)
occurrences (all)	21	5	12
Hyperglycaemia			
subjects affected / exposed[236]	5 / 158 (3.16%)	4 / 61 (6.56%)	5 / 122 (4.10%)
occurrences (all)	6	5	7
Hyperkalaemia			
subjects affected / exposed[237]	7 / 158 (4.43%)	1 / 61 (1.64%)	0 / 122 (0.00%)
occurrences (all)	7	2	0
Hypokalaemia			

subjects affected / exposed[238]	5 / 158 (3.16%)	3 / 61 (4.92%)	12 / 122 (9.84%)
occurrences (all)	5	3	16
Hypomagnesaemia			
subjects affected / exposed[239]	8 / 158 (5.06%)	6 / 61 (9.84%)	9 / 122 (7.38%)
occurrences (all)	8	10	13
Hyponatraemia			
subjects affected / exposed[240]	11 / 158 (6.96%)	5 / 61 (8.20%)	14 / 122 (11.48%)
occurrences (all)	21	7	18

Non-serious adverse events	Treatment B - Platinum Refractory Subgroup		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	76 / 82 (92.68%)		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Cancer pain			
subjects affected / exposed[183]	1 / 82 (1.22%)		
occurrences (all)	1		
Vascular disorders			
Hypotension			
subjects affected / exposed[184]	2 / 82 (2.44%)		
occurrences (all)	2		
Hypertension			
subjects affected / exposed[185]	3 / 82 (3.66%)		
occurrences (all)	4		
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed[186]	14 / 82 (17.07%)		
occurrences (all)	16		
Chills			
subjects affected / exposed[187]	0 / 82 (0.00%)		
occurrences (all)	0		
Face oedema			
subjects affected / exposed[188]	3 / 82 (3.66%)		
occurrences (all)	3		
Fatigue			

subjects affected / exposed[189]	21 / 82 (25.61%)		
occurrences (all)	22		
Mucosal inflammation			
subjects affected / exposed[190]	4 / 82 (4.88%)		
occurrences (all)	5		
Pyrexia			
subjects affected / exposed[191]	9 / 82 (10.98%)		
occurrences (all)	12		
Oedema peripheral			
subjects affected / exposed[192]	6 / 82 (7.32%)		
occurrences (all)	6		
Respiratory, thoracic and mediastinal disorders			
Productive cough			
subjects affected / exposed[193]	2 / 82 (2.44%)		
occurrences (all)	2		
Dyspnoea			
subjects affected / exposed[194]	11 / 82 (13.41%)		
occurrences (all)	12		
Cough			
subjects affected / exposed[195]	8 / 82 (9.76%)		
occurrences (all)	13		
Psychiatric disorders			
Insomnia			
subjects affected / exposed[196]	7 / 82 (8.54%)		
occurrences (all)	9		
Anxiety			
subjects affected / exposed[197]	4 / 82 (4.88%)		
occurrences (all)	4		
Investigations			
Aspartate aminotransferase increased			
subjects affected / exposed[198]	4 / 82 (4.88%)		
occurrences (all)	5		
Amylase increased			
subjects affected / exposed[199]	5 / 82 (6.10%)		
occurrences (all)	13		
Alanine aminotransferase increased			

subjects affected / exposed[200] occurrences (all)	4 / 82 (4.88%) 5		
Blood alkaline phosphatase increased subjects affected / exposed[201] occurrences (all)	9 / 82 (10.98%) 13		
Weight decreased subjects affected / exposed[202] occurrences (all)	9 / 82 (10.98%) 10		
Lipase increased subjects affected / exposed[203] occurrences (all)	4 / 82 (4.88%) 4		
Blood thyroid stimulating hormone increased subjects affected / exposed[204] occurrences (all)	1 / 82 (1.22%) 2		
Blood creatinine increased subjects affected / exposed[205] occurrences (all)	10 / 82 (12.20%) 20		
Injury, poisoning and procedural complications Fall subjects affected / exposed[206] occurrences (all)	1 / 82 (1.22%) 1		
Nervous system disorders Headache subjects affected / exposed[207] occurrences (all)	5 / 82 (6.10%) 7		
Dizziness subjects affected / exposed[208] occurrences (all)	2 / 82 (2.44%) 2		
Blood and lymphatic system disorders Lymphopenia subjects affected / exposed[209] occurrences (all)	3 / 82 (3.66%) 6		
Anaemia subjects affected / exposed[210] occurrences (all)	33 / 82 (40.24%) 45		
Gastrointestinal disorders			

Abdominal pain			
subjects affected / exposed[211]	5 / 82 (6.10%)		
occurrences (all)	8		
Dysphagia			
subjects affected / exposed[212]	10 / 82 (12.20%)		
occurrences (all)	16		
Nausea			
subjects affected / exposed[213]	18 / 82 (21.95%)		
occurrences (all)	34		
Stomatitis			
subjects affected / exposed[214]	5 / 82 (6.10%)		
occurrences (all)	5		
Vomiting			
subjects affected / exposed[215]	9 / 82 (10.98%)		
occurrences (all)	18		
Dyspepsia			
subjects affected / exposed[216]	0 / 82 (0.00%)		
occurrences (all)	0		
Abdominal pain upper			
subjects affected / exposed[217]	0 / 82 (0.00%)		
occurrences (all)	0		
Constipation			
subjects affected / exposed[218]	14 / 82 (17.07%)		
occurrences (all)	16		
Dry mouth			
subjects affected / exposed[219]	4 / 82 (4.88%)		
occurrences (all)	5		
Diarrhoea			
subjects affected / exposed[220]	17 / 82 (20.73%)		
occurrences (all)	30		
Skin and subcutaneous tissue disorders			
Dry skin			
subjects affected / exposed[221]	5 / 82 (6.10%)		
occurrences (all)	11		
Pruritus			

subjects affected / exposed[222]	6 / 82 (7.32%)		
occurrences (all)	9		
Rash			
subjects affected / exposed[223]	9 / 82 (10.98%)		
occurrences (all)	14		
Erythema			
subjects affected / exposed[224]	3 / 82 (3.66%)		
occurrences (all)	4		
Endocrine disorders			
Hyperthyroidism			
subjects affected / exposed[225]	4 / 82 (4.88%)		
occurrences (all)	4		
Hypothyroidism			
subjects affected / exposed[226]	10 / 82 (12.20%)		
occurrences (all)	11		
Musculoskeletal and connective tissue disorders			
Neck pain			
subjects affected / exposed[227]	11 / 82 (13.41%)		
occurrences (all)	12		
Myalgia			
subjects affected / exposed[228]	3 / 82 (3.66%)		
occurrences (all)	3		
Back pain			
subjects affected / exposed[229]	11 / 82 (13.41%)		
occurrences (all)	12		
Arthralgia			
subjects affected / exposed[230]	9 / 82 (10.98%)		
occurrences (all)	11		
Infections and infestations			
Pneumonia			
subjects affected / exposed[231]	5 / 82 (6.10%)		
occurrences (all)	6		
Oral candidiasis			
subjects affected / exposed[232]	2 / 82 (2.44%)		
occurrences (all)	2		
Nasopharyngitis			

subjects affected / exposed[233]	1 / 82 (1.22%)		
occurrences (all)	3		
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed[234]	17 / 82 (20.73%)		
occurrences (all)	18		
Hypercalcaemia			
subjects affected / exposed[235]	10 / 82 (12.20%)		
occurrences (all)	13		
Hyperglycaemia			
subjects affected / exposed[236]	4 / 82 (4.88%)		
occurrences (all)	4		
Hyperkalaemia			
subjects affected / exposed[237]	8 / 82 (9.76%)		
occurrences (all)	11		
Hypokalaemia			
subjects affected / exposed[238]	2 / 82 (2.44%)		
occurrences (all)	2		
Hypomagnesaemia			
subjects affected / exposed[239]	6 / 82 (7.32%)		
occurrences (all)	6		
Hyponatraemia			
subjects affected / exposed[240]	11 / 82 (13.41%)		
occurrences (all)	14		

Notes:

[183] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.
Justification: Number exposed is reflecting all randomized participants

[184] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.
Justification: Number exposed is reflecting all randomized participants

[185] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.
Justification: Number exposed is reflecting all randomized participants

[186] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.
Justification: Number exposed is reflecting all randomized participants

[187] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.
Justification: Number exposed is reflecting all randomized participants

[188] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.
Justification: Number exposed is reflecting all randomized participants

[189] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.
Justification: Number exposed is reflecting all randomized participants

[190] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.
Justification: Number exposed is reflecting all randomized participants

[191] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.
Justification: Number exposed is reflecting all randomized participants

[192] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.
Justification: Number exposed is reflecting all randomized participants

[193] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.
Justification: Number exposed is reflecting all randomized participants

[194] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.
Justification: Number exposed is reflecting all randomized participants

[195] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.
Justification: Number exposed is reflecting all randomized participants

[196] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.
Justification: Number exposed is reflecting all randomized participants

[197] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.
Justification: Number exposed is reflecting all randomized participants

[198] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.
Justification: Number exposed is reflecting all randomized participants

[199] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.
Justification: Number exposed is reflecting all randomized participants

[200] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.
Justification: Number exposed is reflecting all randomized participants

[201] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.
Justification: Number exposed is reflecting all randomized participants

[202] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.
Justification: Number exposed is reflecting all randomized participants

[203] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.
Justification: Number exposed is reflecting all randomized participants

[204] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.
Justification: Number exposed is reflecting all randomized participants

[205] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.
Justification: Number exposed is reflecting all randomized participants

[206] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.
Justification: Number exposed is reflecting all randomized participants

[207] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.
Justification: Number exposed is reflecting all randomized participants

[208] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.
Justification: Number exposed is reflecting all randomized participants

[209] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.
Justification: Number exposed is reflecting all randomized participants

[210] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.
Justification: Number exposed is reflecting all randomized participants

[211] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.
Justification: Number exposed is reflecting all randomized participants

[212] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.
Justification: Number exposed is reflecting all randomized participants

[213] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.
Justification: Number exposed is reflecting all randomized participants

[214] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.
Justification: Number exposed is reflecting all randomized participants

[215] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.
Justification: Number exposed is reflecting all randomized participants

[216] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.
Justification: Number exposed is reflecting all randomized participants

[217] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.
Justification: Number exposed is reflecting all randomized participants

[218] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.
Justification: Number exposed is reflecting all randomized participants

[219] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.
Justification: Number exposed is reflecting all randomized participants

[220] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.
Justification: Number exposed is reflecting all randomized participants

[221] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.
Justification: Number exposed is reflecting all randomized participants

[222] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.
Justification: Number exposed is reflecting all randomized participants

[223] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.
Justification: Number exposed is reflecting all randomized participants

[224] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.
Justification: Number exposed is reflecting all randomized participants

[225] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.
Justification: Number exposed is reflecting all randomized participants

[226] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.
Justification: Number exposed is reflecting all randomized participants

[227] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.
Justification: Number exposed is reflecting all randomized participantsNumber exposed is reflecting all randomized participants

[228] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.
Justification: Number exposed is reflecting all randomized participants

[229] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.
Justification: Number exposed is reflecting all randomized participants

[230] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.
Justification: Number exposed is reflecting all randomized participants

[231] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.
Justification: Number exposed is reflecting all randomized participants

[232] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.
Justification: Number exposed is reflecting all randomized participants

[233] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.
Justification: Number exposed is reflecting all randomized participants

[234] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.
Justification: Number exposed is reflecting all randomized participants

[235] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.
Justification: Number exposed is reflecting all randomized participants

[236] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.
Justification: Number exposed is reflecting all randomized participants

[237] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.
Justification: Number exposed is reflecting all randomized participants

[238] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.
Justification: Number exposed is reflecting all randomized participants

[239] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.
Justification: Number exposed is reflecting all randomized participants

[240] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.
Justification: Number exposed is reflecting all randomized participants

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
19 July 2016	PK and IMG Follow up visit samples no longer required to be collected; Updated Biomarker sample collection schedule; Updated Contraceptive language; Updated Algorithms for Renal, Hepatic, Pulmonary and Skin to match with updated Nivolumab IB v15 (includes Nivo IB 15 erratum update). Other minor edits, clarifications, corrections
27 June 2017	1. Increase in the size of the platinum eligible population in order to provide greater statistical precision 2. Alignment of protocol with responses to regulatory authorities 3. Minor changes to eligibility criteria and study processes 4. Clarification of outstanding issues and correction of typographical errors
14 November 2017	To clarify additional detail about existing endpoints To provide clarity on the planned interim descriptive analyses for the platinum eligible cohort. Necessary window shortened in light of evolving data on radiotherapy plus immuno-oncology agents. Clarification of applicability to palliative and curative settings. To provide clarity, eliminate redundancy, and to align with the nivolumab program standards.

25 May 2018	Tumor mutational burden has been shown to be a predictive biomarker of efficacy for checkpoint inhibitors in several tumors. Therefore, it is important to elevate this endpoint To establish the methods which will be used to analyze the primary and secondary objective of the study. Provide clarification to sites regarding time permitted for treatment beyond progression, to align with recent evidence (CA209153) indicating limited activity of retreatment. Myocarditis is a potential serious adverse event for immunooncology agents. This guidance was included to reduce the risk of serious outcomes for subjects. To provide clarity that the sponsor will remain blinded to both cohorts until the time of the interim analysis.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported